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New York Heart Association class and pulmonary artery pressure as prognostic factors of interstitial lung disease survival

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Abstract. – OBJECTIVE: The aim of this study was to evaluate New York Heart Association (NYHA) class and systolic pulmonary artery pressure (sPAP) as survival predictors in major interstitial lung diseases (ILD) including idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP) and hypersensitivity pneumonitis (HP) and in other ILD like granulomatosis with polyangiitis (GPA).

PATIENTS AND METHODS: We analyzed survival, NYHA class, sPAP, and Octreoscan uptake index (UI) in 104 ILD patients (59 IPF, 19 NSIP, 10 HP and 16 GPA; median age 60.5 years) all referred to a single centre.

RESULTS: Median survival was 68 months, with 1- and 2-year survival of 91% and 78%, respectively. Survival was lower among IPF and NSIP *vs.* HP and GPA patients (p=0.01). NYHA class 3-4 was more frequent among IPF (76.3%) *vs.* NSIP patients (31.6%; p<0.001). HP and GPA had NYHA class 1-2. NYHA class was negatively associated with survival (class 1=90.3 months *vs.* class 3=18.3 months and class 4=5.1 months; p=0.001). sPAP was >55 mmHg in 76.3% of patients with IPF and 35-55 mmHg in 63.2% of patients with NSIP. Patients with HP and GPA had sPAP < 55 mmHg. Among patients with IPF, NYHA and sPAP were negatively associated with survival (p<0.01) both showed a parallel trend. High-resolution computed tomography and survival were worse among IPF and NSIP *vs.* HP and GPA patients (p<0.001). Octreoscan UI was <10, 10-12, and >12 in IPF, NSIP, HP and GPA, respectively. Octreoscan UI was negatively associated with survival (p=0.002).

CONCLUSIONS: NYHA class and sPAP are comparable ILD survival predictors. NYHA class is correlated with worse prognosis for IPF and NSIP *vs.* HP and GPA patients.

Key Words:
New York Heart Association, Pulmonary artery pressure, Interstitial lung disease, High resolution computed tomography, Octreoscan.

Introduction

Despite currently available anti-fibrotic treatments that slow down disease progression, survival and prognosis of interstitial lung disease (ILD) remain poor[1].

To date, the only treatment proven effective in prolonging the survival of the major ILD subset with a lower survival time, i.e., idiopathic pulmonary fibrosis (IPF) with advanced disease, is lung transplantation. Post-transplant, 5-year survival for IPF patients is approximately 40% and median waiting time for transplant is approximately 46 months. As consequence, more than 30% IPF patients listed die before receiving a transplant. Therefore, considering the limited organ donor pool, efforts should be focused on limiting transplantation to subjects with the highest probability of successful outcome[2-4].

Currently available multiple score systems for ILD are incomplete, as they do not include all probable predictors of poor outcome and patient monitoring covers a limited period.

To select IPF patients, King et al[5] applied a multiple baseline scoring system which consists in clinical, radiological, and physiological measurements (CRP score) and demonstrated that it was an accurate predictor of survival among this group of patients. However, it required both a de-

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tailed radiographic analysis and exercise physiologic measurements, which may not be readily available to every physician.

A composite physiologic index (CPI), where IPF patients were evaluated by high resolution computed tomography (HRCT) and pulmonary functional tests [forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV1) and diffusing capacity for carbon monoxide (DLCO)], was developed by Wells et al[6]. The strength of the CPI method lies in the fact that it does not require a complete exercise test or experienced radiologists for the interpretation of HRCT. This index could be used as a clinical guide for staging disease severity and predicting outcome in ILD patients. The drawback of CPI lies in its complexity and difficulty to be applied in clinical practice as it is feasible only in specialized ILD centres.

A further scoring system based on four readily ascertainable predictors (i.e., age, history of respiratory hospitalization, predicted FVC, and 24-week change in predicted FVC) to assess mortality risk in IPF patients has been proposed[7]. However, this system does not consider several other important predictors like DLco, HRCT and pulmonary hypertension (PH).

A multidimensional index and staging system for IPF including as variables gender, age, FVC and DLco has been developed[8] and known as GAP. It is simple-to-use, may improve prognosis and management of IPF patients, but lacks information about imaging and other functional parameters like PH, and New York Heart Association (NYHA) class.

Interestingly, Suzuki et al[9] evaluated FVC, DLco, GAP, artery oxygen partial pressure (PaO_2), fractional inspired oxygen (FiO_2), and P/F ratio in a large cohort of IPF patients with acute exacerbations. The authors demonstrated that lower FVC and P/F were predictors of poor prognosis with respect to DLco and GAP.

Therefore, an easy and early prognostic system to predict survival in cardio-pulmonary disease is needed.

Aims of the study were: i) to investigate New York Heart Association (NYHA) class and systolic pulmonary artery pressure (sPAP) as survival prognostic factors in major ILD including IPF, non-specific interstitial pneumonia (NSIP) and hypersensivity pneumonitis (HP) as well as in other ILD like granulomatosis with polyangiitis (GPA)[10]; ii) to identify an early accurate marker of disease progression in heart failure associated with cor pulmonale; iii) to simplify the monitoring of ILD and cardio-pulmonary disease saving resources.

Patients and Methods

This retrospective study included 104 ILD patients (59 males and 45 females), median age 60.5 years (range 27-79), affected by IPF (59), NSIP (19), HP (10), and GPA (16), consecutively referred to a single centre between January 2005 and October 2014. ILD diagnosis was performed according to Cottin et al[10] and histologically confirmed. The observation period was 120 months. Patients' characteristics are summarized in Table I. Parameters analysed were age, gender, smoking habit, NYHA class, sPAP, HRCT of the lung, pulmonary function tests, Octreoscan uptake index (UI). NYHA was assessed according to current guidelines[11]. Systolic pulmonary artery pressure (sPAP) was detected by trans-thoracic doppler-echocardiography that is recognized as a safe, suitable and cost-effective screening population procedure alternative to right heart catheterization[12-14]. The observation period of the study began in 2005, therefore the cut-off point used to diagnose PH was ≤25 mmHg according to the ESC/ERS 2015 Guidelines[11] with cut-offs of ≤35, 35-55, and >55 mmHg[15,16]. Mixed venous saturation (SvO_2, normal value 60-80%), that represents the percentage of oxygen bound to hemoglobin in blood returning to the right side of the heart and reflects the amount of oxygen after tissue removing, was determined in 18 patients by central venous catheter. HRCT score was determined assessing the extent of ground glass opacities, reticulation, honeycombing and traction bronchiectasis using a semi-quantitative scale (0=none, 1=1-25%, 2=26-50%, 3=51-75%, 4=76-100%)[17]. Pulmonary function tests including total lung capacity (TLC), forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLco) showed restrictive lung disease in all patients and are not reported in Results. Six-minute walk test was not performed as it is not included in ILD diagnostic algorithm[10]. Octreoscan was performed by a standardized protocol[18-20]. Octreoscan is a In^{111} labelled somatostatin receptor (Octreotide) scintigraphy that was previously studied in literature as marker of activity in neuro-endocrine tumours. Subsequently, Octreoscan has been evaluated[18-20] in ILD showing better accuracy and lower radiation exposition than $Gallium^{67}$ scintigraphy in identifying lung inflammation. According to Lebthai et al[18,19] Oc-

treoscan UI <10 indicates fibrotic ILD and Octreoscan UI >10 suggests inflammatory ILD.

Statistical Analysis

Survival was calculated in all patient groups. The Mann-Whitney or the Kruskal-Wallis test were used. Survival curves were determined using Kaplan-Meier method with the time period calculated from the date of diagnosis. The log-rank test (LRT) was used to evaluate differences between survival curves and to compare survivor functions across groups. The Cox proportional hazard regression analysis was used to quantify the relationship between survival time and the covariates considered in the study and to identify which prognostic factors significantly influenced survival. A value of 0.05 was defined as statistically significant. Data analysis was performed using SAS 9.1 (SAS, Cary, NC, USA).

Results

Median survival time was 68 months (95% CI: 54.8-81.1) with 1- and 2- year survival rates of 91% and 78%, respectively. Age was a negative

Table I. Characteristics of ILD patients.

	Number	Percentage
Sex		
Male	59	56.7
Female	45	43.3
Smoking		
No smokers	67	64.4
Smokers	37	35.6
HRCT		
1	9	8.6
2	26	25.0
3	10	9.7
4	59	56.7
NYHA class		
0	16	15.4
1	37	35.5
2	33	31.7
3-4	18	17.4
sPAP mmHg		
≤ 35	16	15.4
35 - 55	37	35.6
> 55	51	49.0
Octreoscan UI		
<10	47	45.2
10 -12	18	17.3
>12	39	37.5
Histology		
IPF	59	56.7
NSIP	19	18.3
GPA	16	15.4
HP	10	9.6
Status		
Alive	63	60.6
Died	41	39.4

High resolution computed tomography (HRCT), New York Heart Association (NYHA), uptake index (UI), systolic pulmonary artery pressure (sPAP), idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), hypersensivity pneumonitis (HP), granulomatosis with polyangiitis (GPA).

Table II. Survival according to different variables.

	Median (months)	95% CI	*p*-value
Overall	68	54.8-81.1	
Histology			
UIP	51.8	30.7-72.8	
NSIP	49.7	47.3-52.1	
GPA	90.3	68.8-111.8	
HP	100% alive	0.01	
HRCT score			
1	69 (mean)	55.6-82.3	
2	90.3	69.9-111.7	
3	48.7	11.3-86.1	
4	51.8	30.7-72.8	0.001
NYHA			
0	100% alive		
1	90.3	69-111.6	
2	48.7	32.2-65.2	
3	18.3	6.4-30.3	
4	6.1 (mean)	4.1-8.1	
	<0.001		
Octreoscan UI			
≤ 10	51.8	30.7-72.8	
10 - 12	49.7	47.3-52.1	
>12	90.3	68.9-11.7	0.002
Age (years)			
≤ 50	73.5 (mean)	57-90	
50 - 62	70.0	60.8-79.2	
> 62	48.7	32.8-64.6	0.05

High resolution computed tomography (HRCT), New York Heart Association (NYHA), idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), hypersensivity pneumonitis (HP), granulomatosis with polyangiitis (GPA), uptake index (UI), usual interstitial pneumonia (UIP).

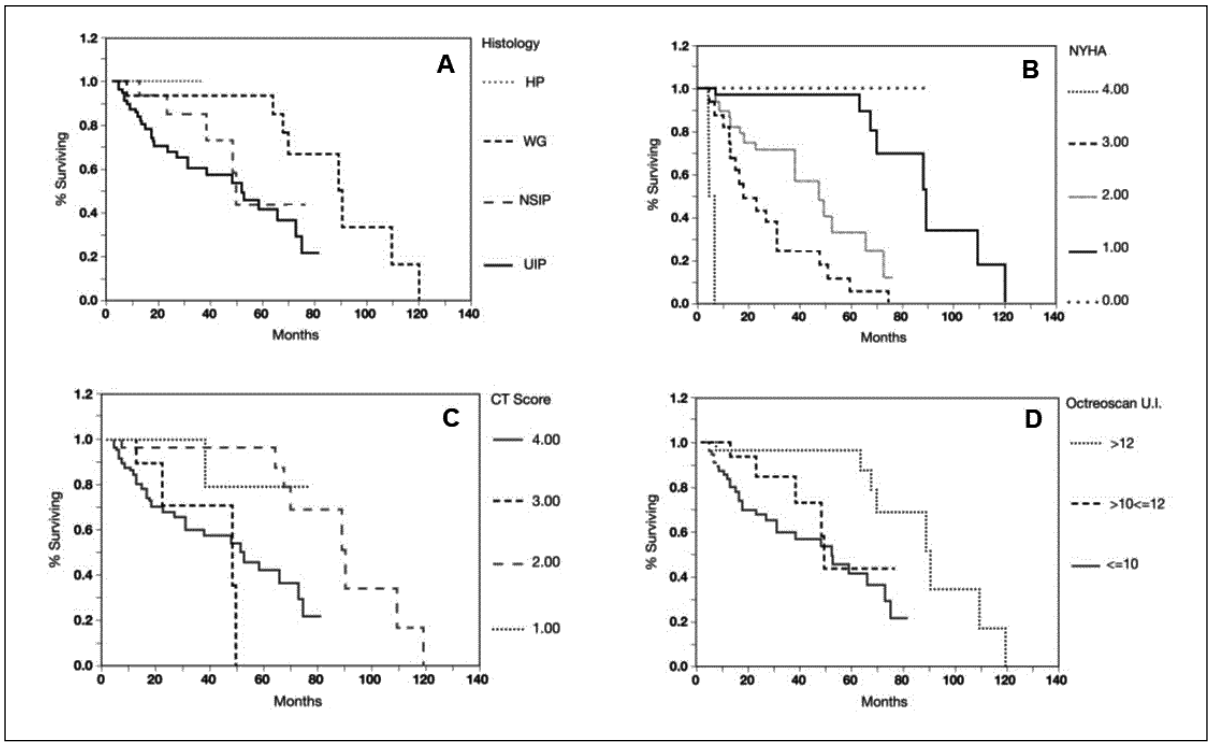

Figure 1. Survival of ILD patients according to histology (**A**), NYHA class (**B**), CT score (**C**) and Octreoscan UI (**D**).

prognostic factor of survival (p=0.05). NSIP and IPF had a lower median survival (49.7 and 51.8 months, respectively) than GPA (90.3 months; p=0.01). All HP were alive after 120 months. During the study period 41 (39.4%) patients died (Table II and Figure 1A).

The percentage of patients with severe NYHA class (3-4) was higher in IPF than in NSIP (76.3 and 31.6%, respectively; p<0.001). All patients with GPA or HP belonged to mild-moderate NYHA class (1-2). A negative association was found between survival and higher NYHA class (90.3 months for class 1 *vs.* 18.3 for class 3 and 5.1 for class 4; p=0.001) (Table II and Figure 1B).

The percentage of patients with severe sPAP (>55 mmHg) was higher in IPF (76.3%) than in NSIP (31.6%), conversely the percentage of patients with moderate sPAP (35-55 mmHg) was higher in NSIP (63.2%) than in IPF (23.7%). All patients with GPA or HP had sPAP values <55 mmHg (Table III). SvO_2 was under the normal limit in 16 IPF and 2 NSIP with elevated sPAP values further confirming the severe prognosis for these patients. A negative association was found between survival and higher sPAP value in IPF patients (LRT 53.34; p<0.01) (Figure 2). An analogous correlation was detected between NYHA class and survival (LTR 51.99; p<0.01) (Figure 2).

Multivariate analysis showed that NYHA class was a negative and independent prognostic factor for survival [Relative hazard ratio (RHR)=4.9; 95% CI: 2.8-8.7; p<0.001] (Table IV). Univariate analysis showed that both sPAP and NYHA class were negative prognostic factors for survival (LRT 77.80 and LRT 80.72, respectively; p<0.001) (Table V).

IPF and NSIP had a worse HRCT score (Figure 1C) and survival rate than GPA and HP (Table II; p<0.001).

Octreoscan UI was <10, between 10 and 12, and >12 in IPF, NSIP, and GPA and HP, respectively. The finding suggested fibrotic or inflammatory histological type. A negative association was found between survival and Octreoscan UI (51.8 months for UI ≤10 *vs.* 90.3 for UI >12; p=0.002) (Table II and Figure 1D).

Discussion

In this study we evaluated NYHA class and sPAP as survival prognostic factors in major interstitial lung diseases IPF, NSIP and HP as well as in other rare ILD conditions like GPA[21] to identify

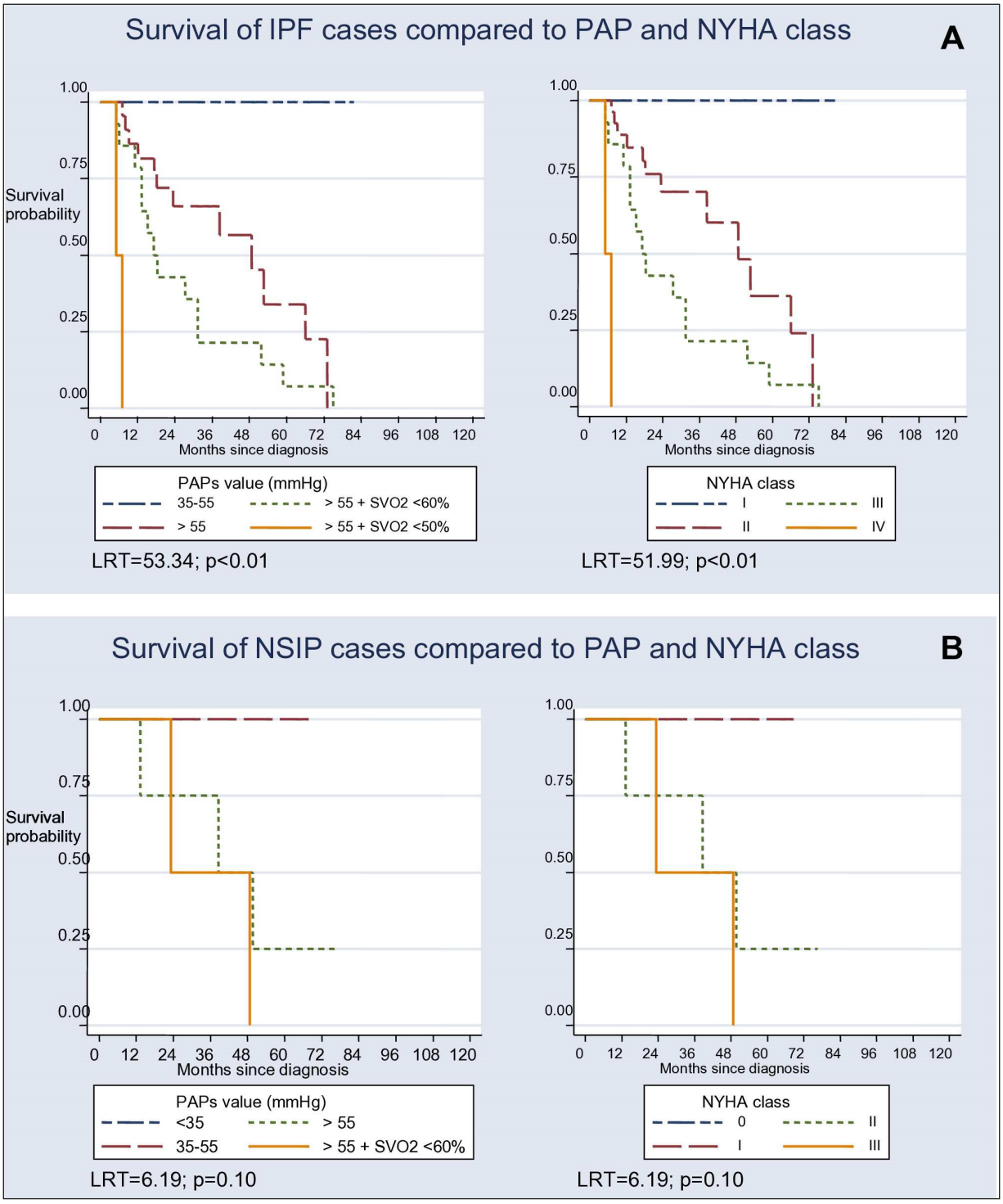

Figure 2. Survival of IPF (**A**) and NSIP (**B**) patients according to PAP value and NYHA class.

an early accurate marker of disease progression in heart failure associated with cor pulmonale.

Results showed that the median survival of NSIP and IPF patients (47.9 and 51.8 months, respectively) was lower than GPA patients (90.3 months). The poor survival of NSIP patients is attributable to the inhomogeneous composition of NSIP group and to the inclusion of patients with advanced disease. Furthermore, most NSIP patients had histological fibrotic NSIP, which yields

Table III. Systolic pulmonary artery pressure of ILD subsets.

Diagnosis	sPAP (mmHg)	Number	Percentage
IPF	≤ 35	0	0
	35-55	14	23.7
	>55	45	76.3
NSIP	≤ 35	1	5.3
	35-55	12	63.2
	>55	6	31.5
GPA	≤ 35	8	50.0
	35-55	8	50.0
	>55	0	0
HP	≤ 35	7	70.0
	35-55	3	30.0
	>55	0	0

Systolic pulmonary artery pressure (sPAP), idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), hypersensivity pneumonitis (HP), granulomatosis with polyangiitis (GPA), interstitial lung diseases (ILD).

a worse survival with only a smaller number of histological cellular NSIP yielding a better prognosis[20]. All HP patients were alive at the end of the 120 months observation period. However, due to the small number of HP patients, their survival is not comparable to that reported in a large Danish registry[22] (about 78% alive at 144 months).

Notably, severe NYHA class was more frequently found in IPF and in lower percentage in NSIP, whereas mild-moderate NYHA class was always detected in GPA and HP.

NYHA class is known as fundamental tool for risk stratification in chronic heart failure. This study showed that NYHA and sPAP trends were similar with respect to survival in the whole ILD group. However, only NYHA class was significantly predictive of worse survival and prognosis in multivariate analysis. Both NYHA and sPAP significantly correlated with disease severity in univariate analysis and sPAP was significantly predictive of worse survival in IPF patients. Therefore, NYHA class may be considered an accurate and easily feasible low-cost marker to simplify, on a global scale, right heart monitoring to predict survival and mortality after interstitial lung disease damage. This finding could be useful in clinical practice to overcome the difficulties in pulmonary hypertension diagnosis especially in the elderly population[23]. Notably, the importance of evaluating right ventricular function in left heart failure is well documented and this concept has been emphasized in the most recent heart failure guidelines[24]. Interestingly, a recent paper[25] indicated ischemic heart disease, diabetes, COPD, and chronic kidney as major comorbidities associated with chronic heart failure, but ILD is not included.

Table IV. Multivariate analysis.

Variables	Relative hazard ratio	95% CI	*p*-value
Gender	1.04	0.7-1.4	0.8
Age	1.03	0.6-1.8	0.9
Histology	0.69	0.1-4.7	0.7
HRCT score	1.13	0.4-3.1	0.8
NYHA	4.94	2.8-8.7	<0.001
Octreoscan UI	1.18	0.9-1.5	0.2

High resolution computed tomography (HRCT), New York Heart Association (NYHA), uptake index (UI).

Furthermore, we report that Octreoscan is an accurate tracer capable to distinguish and monitor ILD subsets. Age was significantly correlated with survival but at lower level than NYHA and sPAP. We can argue that ILD deaths were related to the increase of age but more closely to sPAP severity and NYHA class.

Limitations

The study has some limitations. The investigation was conducted in a single centre and results should be confirmed by a larger prospective multicentre study. Direct measurement of pulmonary artery pressure using right heart catheterization could improve the accuracy of the results. Confirmation of NYHA class as a prognostic factor in patients with ILD undergoing anti-fibrotic treatment would reinforce the quality of the study.

Contribution to the Field

This study demonstrates for the first time that: 1) New York Heart Association class can be used not only as sensitive parameter in heart failure assessment but also as an effective substitute of pulmonary artery pressure in the evaluation of interstitial lung disease survival and prognosis; 2) NYHA class severity is a major co-morbidity parameter in ILD; 3) Additionally, the study highlights that ILD mortality is mainly linked to histological findings rather than to patients' age.

Conclusions

New York Heart Association class is a well-known and sensitive parameter to assess heart failure. This study highlighted that NYHA class

Table V. Univariate analysis.

Variable	Categories	Events	Censored	Median survival (months)	3-year survival (%)	Log-rank test	*p*-value
NYHA class	**0**	0	29	-	100.0	77.80	<0.001
	1	8	44	110	97.7		
	2	15	13	50	71.2		
	3-4	19	0	18	26.3		
sPAP mmHg	**≤ 25**	0	29	-	100.0	80.72	< 0.0001
	≤ 35	8	44	110	97.9		
	35-55	15	13	49	68.2		
	> 55	19	0	18	26.3		

New York Heart Association (NYHA), systolic pulmonary artery pressure (sPAP).

can be also used as an effective substitute of systolic pulmonary artery pressure in interstitial lung disease and in the study of cor pulmonale showing that both parameters have a similar progression rate related with the severity of the disease.

Data also indicate that NYHA and sPAP worsening reflect worse survival and prognosis in major interstitial lung disease. Lastly, mortality was mainly linked to histological ILD findings rather than to the age of patients.

Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Approval
Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements.

Informed Consent
Not applicable due to the retrospective nature of the study.

Authors' Contributions
RGC and FP participated in the conception of the study design. RGC, FP and SN recruited patients and collected data. DP contributed to radiological imaging. RAF analyzed the data. AM reviewed and revised the manuscript. All authors participated in the interpretation of the results.

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