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New York Heart Association class associated with imaging is a prognostic mortality risk predictor in interstitial lung diseases

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Abstract. – OBJECTIVE: Mortality risk factors as forced vital capacity, diffuse lung capacity for carbon monoxide, and 6-minutes' walk test were studied in clinical trials monitoring patients affected by interstitial lung diseases (ILD). However, these parameters showed scarce accuracy. Our aim was to identify New York Heart Association (NHYA) class, in association with high resolution computed tomography (HRCT) and somatostatin receptor scintigraphy (Octreoscan), as a prognostic mortality risk factor in ILD patients.

PATIENTS AND METHODS: Study population comprised 128 ILD patients (78 Males and 50 Females). Histological diagnosis was usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) and granulomatous lung disease in 59, 19 and 50 patients, respectively. Patients were monitored by NYHA class, HRCT and Octreoscan at baseline and every 3 years up to a 10-year follow up. Overall survival was calculated from the date of diagnosis until death or last follow-up update. Statistical analysis was performed using Kaplan-Meier, log-rank test (LRT), multivariate analysis with Cox proportional hazard regression model, and log-likelihood ratio test.

RESULTS: Overall median survival was 89.3 months (7.4 years) with the poorer survival rate observed in UIP patients. NYHA class came out as a reliable prognostic mortality risk factor in each group of patients and prognosis was progressively worse with NYHA class increase (LRT $p<0.001$). A strong correlation was found between NYHA class and age, CT-score, and Octreoscan in UIP patients ($p<0.001$).

CONCLUSIONS: The determination of NYHA class can therefore be recommended as an additional prognostic mortality risk factor in ILD patients.

Key Words:
Interstitial Lung Disease, New York Heart Association, Idiopathic Pulmonary Fibrosis, Mortality predictors, Granulomatous Diseases.

Introduction

Interstitial lung diseases (ILD) represent a large group of diffuse parenchymal acute and chronic diseases with variable degrees of pulmonary inflammation and fibrosis[1].

Major accomplishments in understanding ILD findings have partially improved clinical diagnostic approach, whereas therapy has still to show relevant improvements, particularly in idiopathic pulmonary fibrosis (IPF). Therefore, patients with ILD generally have a poor survival rate, even though various studies[2-6] have shown different survival patterns between non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP). Patients affected by UIP represent the largest subgroup of ILD cases and have the poorer prognosis although their survival may be improved by lung transplantation[1,7,8].

Recently, a possible correlation between COVID-19 infection, causing respiratory distress syndrome and severe hypoxemia, and ILD onset has been reported. However, at present, little is known about the mechanisms underlying the development of COVID-19 associated ILD. For this reason, the latter can be misdiagnosed in clinical assessment of COVID-19 infected patients. HRCT scan could be an important procedure for the early diagnosis of acute ILD in the course of COVID-19 infection[9].

Several clinical research trials have examined many prognostic factors with the aim of identifying a reasonably reliable marker, sensitive to the presence of disease and prognostic of its progression over time. Such a marker would ease off the need of performing diagnostic biopsies, decrease unjustified reliance on highly variable clinical tests measuring disease severity and reduce prognostic uncertainty. Accordingly, recent studies[6,10-14] on prognostic factors in ILD have

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been focused on radiological and pulmonary function tests, timed walk tests and their progression, trying to find a relation between disease severity (and progression) and long-term outcome. Moreover, it has been reported that some serum biomarkers may be related to the prognosis of the disease and that multidimensional scales may represent a clinically useful method to predict mortality risk[15]. However, to our present knowledge, previous studies have not paid adequate attention to cardiac function parameters and little is known about their possible prognostic role. Tools such as the New York Heart Association (NYHA) class are simple, informative, and easy to recall. In our opinion, such stratifying information could be routinely collected in patients with ILD, and then, used as a prognostic factor[16].

Aims of present study were: 1) to evaluate differences in mortality rate of cases with different ILD, distinguishing between UIP, NSIP, and other granulomatous interstitial lung diseases (OILD); 2) to assess the prognostic value of NYHA class in association with radiological imaging.

Patients and Methods

This retrospective study comprised 128 patients (78 males and 50 females) from Northwest Italy who were enrolled between January 2005 and December 2014. All patients had a histological confirmed diagnosis of ILD: 59 cases were diagnosed with UIP (46.1%), 19 with cellular NSIP (14.8%), and the remaining 50 cases (39.1%) with granulomatous disease defined as other interstitial lung diseases (OILD). The latter group included 24 sarcoidosis, 16 granulomatosis with polyangiitis, and 10 extrinsic allergic alveolitis patients. Life status was last updated on 15.12.2014 (end of follow-up). Baseline evaluations included: age at diagnosis (<50, 50-59, 60-69 and > 70 years), gender (male/female), smoking habits (yes/no), chest X-ray, High Resolution Computer Tomography (HRCT) Score of the lung (CT-Score: levels 1 to 4), somatostatin receptor scintigraphy (Octreoscan) uptake index (U.I.), New York Heart Association class determination (negative, I, II, III and IV). All patients were monitored with HRCT, Octreoscan and NYHA class every 3 years up to a 10-year follow up. Baseline patients' characteristics are listed in Table I.

The research was conducted according to the principles of the Declaration of Helsinki and written informed consent for diagnostic procedures was obtained from all patients.

The approval from the Institutional Review Board (IRB) has not been requested as the study is retrospective and observational.

Table I. Interstitial lung disease patients' characteristics.

Characteristic	Categories	No. of patients	%
Diagnosis	UIP	59	46.1
	NSIP	19	14.8
	OILD	50	39.1
Gender	Female	50	39.1
	Male	78	60.9
Age (years)	Median (range)	58 (27-79)	
	<50	36	28.1
	50-60	34	26.6
	60-70	33	25.8
	≥70	25	19.5
Smoking habits	No smokers	82	64.1
	Smokers	46	35.9
NYHA	Negative	29	22.7
	Mild (I)	46	35.9
	Moderate (34)	34	26.6
	Severe[1] (III-IV)	19	14.8
Octreoscan U.I.	Median (range)	10.4 (9.3-23.1)	
	≤10 (Normal)	59	46.1
	>10 (Pathological)	69	53.9
CT score	1+2+3	45	35.1
	4	59	46.1
	Missing	24	18.8

[1]Two subjects with highly severe score are included.

Radiological Imaging Protocol

Several authors[17-19] have established different severity degrees of HRCT findings. The presence of ground glass has proven to be a valuable predictor both of response to therapy, as well as overall prognosis[20]. Wells et al[18] found that the presence of ground glass opacity associated with findings of fibrosis was related to prognosis and likelihood of response to treatment. In that study, HRCT abnormalities were interpreted as predominantly ground glass (group 1), mixed ground glass opacity and reticular pattern (group 2), or opacities that were predominantly reticular pattern (group 3). We determined HRCT appearances in predicting prognosis utilising a CT score similar to the standard definitions described by Wells et al[18] and Lynch[21]. Lung parenchymal abnormalities were grouped into four levels: predominantly ground-glass pattern (level 1), ground glass and nodular cavities (level 2), mixed (ground glass and reticular pattern) (level 3), or predominantly reticular pattern and honeycombing (level 4).

For statistical reasons, in most of the analyses, the levels have been re-grouped comparing levels 1 to 3 with the level 4. Two radiologists and two respiratory physicians met regularly and evaluated independently chest X-rays and HRCT findings. HRCT (General Electric, Milwaukee, WI, USA) were performed without intravenous contrast media and proceeding at 1.0 or 1.5 mm-thick sections taken at 1-cm intervals through the entire thorax.

Patients with sarcoidosis underwent a chest X-ray and were staged according to the Scadding Criteria (stage 0-IV). Patients with a normal chest X-ray, but a clinical suspicion of sarcoidosis were evaluated with HRCT[22].

Octreoscan Protocol

Somatostatin receptor scintigraphy (Octreoscan®, Mallinckrodt Medical, Petten, The Netherlands) whole-body scans were obtained at 4 and 24-hours after the administration of 5 mCi of [^{111}In-DTPA- D-Phe1]-Octreotide. Thoracic images were obtained with Single Photon Emission Computed Tomography (SPECT) at the same intervals after injecting the tracer. The whole-body acquisition (in 25 minutes) included anterior and posterior views of head, thorax, abdomen, pelvis and legs. Scintigraphic images were acquired with a double-head camera (Prism 2000, Picker Int., Cleveland, OH, USA).

The camera had a medium-energy parallel-hole collimator using a 256 x 1024 or a 256 x 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 x 64 matrix; slices were reconstructed after back projection, using a Butterworth (low pass) filter. The Octreoscan U.I., defined as the ratio between normalised accumulation of the tracer in the lungs and thigh, was evaluated in correlation with the diagnosis, and conventional imaging. Normal values of U.I. on 4-h (best statistics) and 24-h were obtained. According to these data, the normal value of U.I. at 24-h was fixed at $\leq$ 10 U.I.[22,23].

Statistical Analysis

Comparisons of baseline characteristics were made using unpaired *t*-tests and ANOVA (for normally distributed variables) and Chi-squared test for proportions. The statistical methodology applied in this study is that generally performed to analyze survival time data and the time endpoint of interest is date of mortality. Overall survival was calculated from the date of diagnosis until death or last follow-up update[24]. Survival curves were generated using the Kaplan-Meier method and differences in survival functions between groups were assessed by way of the log-rank test (LRT), (univariate analysis), and using parameters as categorical variables[25].The simultaneous effect of each prognostic factor was assessed in a multivariate analysis using Cox proportional hazard regression model, estimating hazard ratios and 95% confidence intervals. Cox proportional hazard model was constructed *via* forward addiction of variables in the model[26]. Statistical null hypotheses on each factor and whole model were assessed by the log-likelihood ratio test (LLR). Analysis were carried out using SPSS (SPSS Inc., Armonk, NY, USA) (descriptive statistics and Kaplan-Meier method), and STATA (Cox regression) statistical packages.

Results

Median survival was 89.3 months (7.4 years) and 79.4 percent of the cases were alive 3 years after diagnosis. UIP cases had a statistically significant older age, higher CT-score and NYHA class and lower Octreoscan U.I. (all $p<0.001$) with respect to NSIP and OILD cases (Table II). Among UIP patients, CT-score 4 had the worst

Table II. Patients characteristics according to histopathologic group.

Characteristic	UIP (n=59)	NSIP (n=19)	OILD (n=50)	*p*-value
Gender				
Male	34	9	35	0.177
Female	25	10	15	
Age (year)				
Mean ± SD	64 ± 9.5	51 ± 11.5	50 ± 12.8	<0.001
Range	27-79	28-75	30-78	
Smoking habits				
No smokers	40	10	32	0.488
Smokers	19	9	18	
NYHA				
Negative	0	1	28	<0.001
Mild	14	12	20	
Moderate	29	4	1	
Severe[1]	16	2	1	
Octreoscan U.I.				
Mean ± SD	9.5 ± 0.1	10.6 ± 0.4	17.4 ± 3.5	<0.001
Range	9.3-9.8	10.3-11.7	12.5-23.1	
CT score[2]				
1	0	9	0	<0.001
2	0	0	26	
3	0	10	0	
4	59	0	0	

[1]Two subjects with highly severe score are included.
[2]24 OILD cases did not have a HRCT scan evaluation.

survival compared with CT-scores 1 to 3 (LRT p <0.001) (Figure 1A) and survival probability was poorer when Octreoscan U.I. was lower than or equal to 10 (LRT p<0.001) (Figure 1B).

Univariate comparison of survival curves showed differences among diagnostic groups (Table III). The survival of UIP patients was poorer than that of NSIP patients and even poorer in OILD patients (LRT p<0.001) (Figure 2A). Survival rates were significantly decreasing with age increase (LRT p<0.001) (Figure 2B).

Focusing on NYHA, when all patients were analyzed, no deaths were observed among patients with negative NYHA and the prognosis was getting worse with increasing NYHA categories (LRT p<0.001) (Figure 2C). When only UIP patients were analyzed, NYHA indicated to be a good prognostic factor, as the survival of cases with moderate

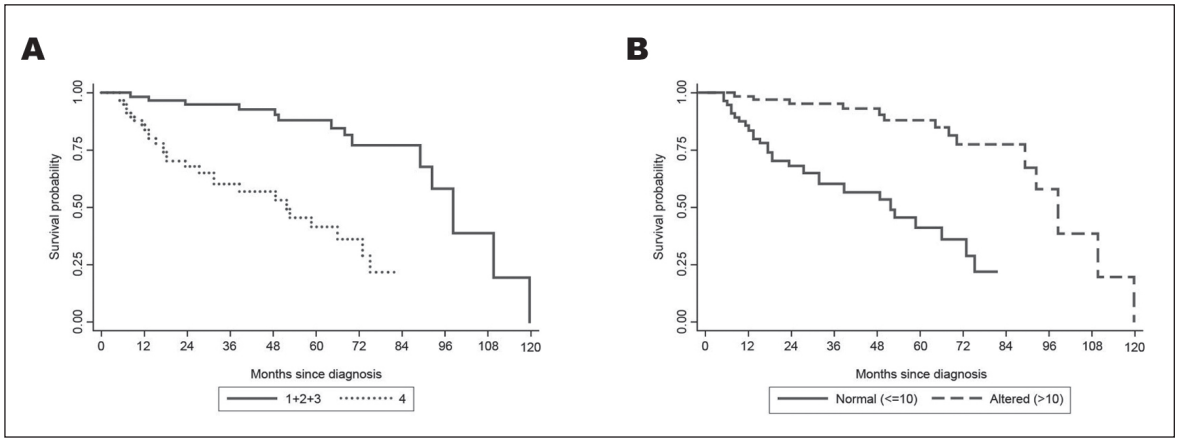

Figure 1. Survival probability of UIP patients enrolled in the study stratified by HRCT score (**A**) and octreoscan uptake index (**B**).

Table III. Univariate analysis of prognostic variables.

Variable	Categories	Events	Censored	Median survival (months)	3-year survival (%)	Log-rank test	*p*-value
Overall		42	86	89.3	79.4	–	–
Diagnosis	UIP	28	31	52	59.4	32.57	<0.001
	NSIP	5	14	50	85.7		
	OILD	9	41	98	98.0		
Gender	Female	19	31	92	76.1	0.36	0.547
	Male	23	55	89	81.3		
Age (year)	<50	3	33	–	96.9	49.96	<0.001
	50-60	5	29	98	89.1		
	60-70	11	22	73	85.9		
	≥70	23	2	27	39.0		
NYHA	Negative	0	29	–	100.0	77.80	<0.001
	Mild	8	38	110	97.7		
	Moderate	15	19	50	71.7		
	Severe	19	0	18	26.3		
CT score[1]	1+2+3	13	34	89	92.3	10.93	<0.001
	4	28	31	52	59.4		
Smoking habits	No smokers	28	54	92	78.9	0.06	0.804
	Smokers	14	32	89	80.2		
Octreoscan U.I.	≤10	28	31	52	59.4	28.52	<0.001
	>10	14	55	98	95.2		

[1]24 missing cases were excluded from the analysis.

level was lower than that experienced by mild and, moreover, negative ones (p<0.01) (Table III and Figure 2D). Multivariate analysis detected the independence of age and NYHA (LLR test p<0.001) as prognostic factors (Table IV). According to NYHA classification, cases with moderate and se-

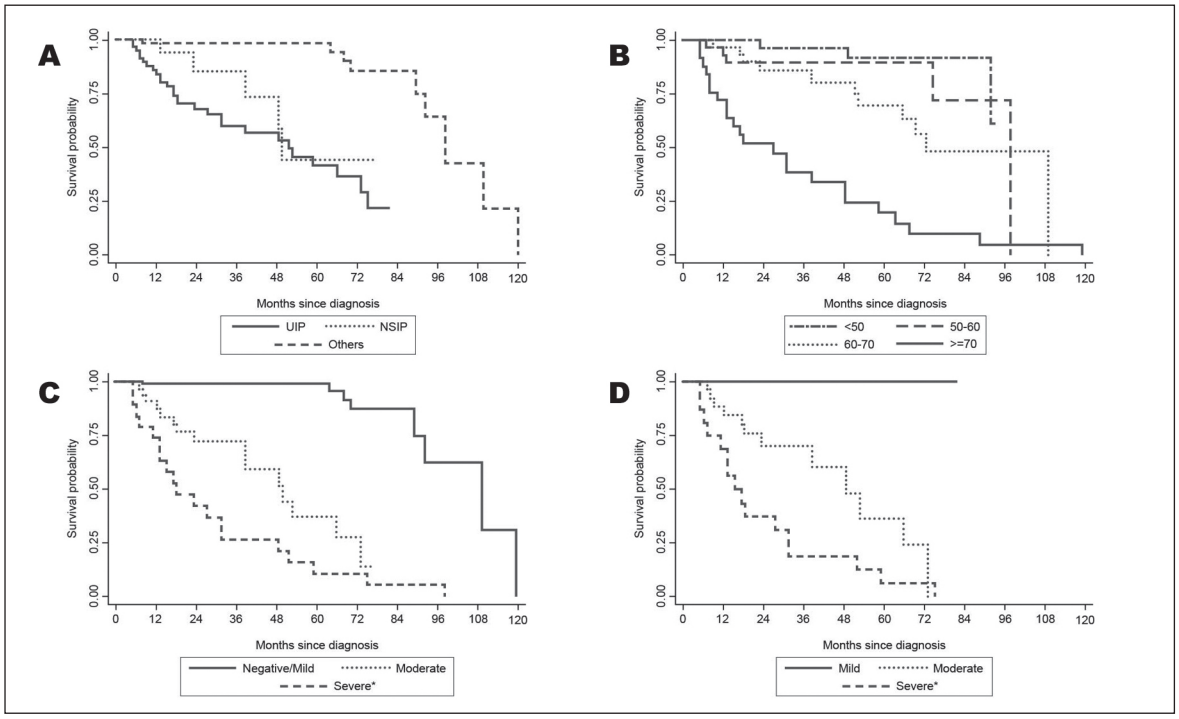

Figure 2. Survival probability of all ILD patients enrolled in the study stratified by disease categories (**A**), age (**B**), NYHA class (**C**), and NYHA class in UIP patients (**D**). *NYHA III and IV class are evaluated in only one group

Table IV. Multivariate analysis of prognostic factors.

Factors	Levels	Hazard Ratio	[95% Interval] Conf.		LLR-test	*p*-value
Diagnosis*					34.27	<0.001
	OILD	1	(Ref.)			
	UIP	1.606	.399	6.469		
	NSIP	1.338	.274	6.535		
Age					39.19	<0.001
	<50	1	(Ref.)			
	50-60	.756	.1416	4.040		
	60-70	1.565	.361	6.794		
	≥70	4.570	1.09	19.112		
NYHA					40.40	<0.001
	Mild	1	(Ref.)			
	Moderate	6.908	1.970	24.224		
	Severe	10.107	2.915	35.042		

*29 cases with negative NYHA are not included in the model (1 NSIP, 20 OILDS).

vere levels showed a significantly higher risks than mild cases (6.9 and 10.1, respectively).

Finally, age category showed a peculiar shape of HR distribution: the risk appeared lower among 50-60 aged cases with respect to the reference category (<50), and then, it increased to 1.6 (not significant) and 4.6 (significant) in oldest categories (60-70 and >70, respectively).

Representative HRCT scans of a typical IPF with advanced reticular and honeycombing pattern at diagnosis and end stage lung fibrosis are showed in Figure 3.

Discussion

The main finding of the present study is the close correlation between NYHA class and mortality in ILD patients. NYHA class and survival rates were compared prospectively for IPF and NSIP, as well as for OILD. Previous studies[2-5,10-13,16] suffered from a series of limitations, as all were retrospective, focused exclusively on Idiopathic Interstitial Pneumonia (IIP) cases, without any consideration of granulomatous lung diseases, and histological diagnosis was not

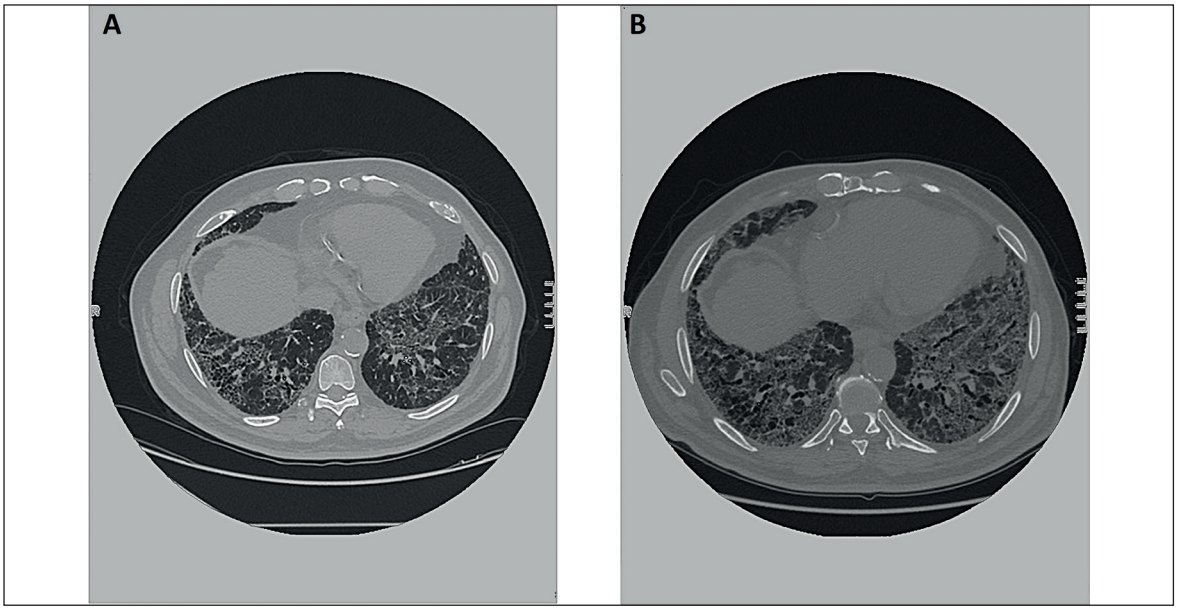

Figure 3. HRCT scans showing advanced reticular and honeycombing pattern at the basis of the lungs at diagnosis (**A**) evolving in end stage lung fibrosis after three months (**B**).

performed in all cases. Notably, some of them reported[10,12,27,28] a low median observation time and none included the NYHA class among possible prognostic factors.

Additionally, among 104 patients with IPF[2] who were diagnosed by open lung biopsy, those with the NSIP subtype had a better prognosis than patients with UIP (survival rate of 63 and 41 months, respectively)[27]. However, while the mortality rate at two years of follow-up was linked to the histopathologic difference between NSIP and UIP, prognosis at 12 months was better determined by serial pulmonary function trends while the histological distinction had no additional prognostic value. Flaherty et al[11] followed 80 patients with UIP and 29 patients with NSIP for baseline pulmonary function tests and HRCT. They found that a 6-month change in forced vital capacity gave additional prognostic information in IIP patients. In addition, Lama et al[28] reported that the level of desaturation during a 6-MWT was of prognostic value for patients with UIP and NSIP. Collard et al[10] followed 81 UIP patients for 6-months changes in physiologic variables, such as dyspnoea score (DS) total lung capacity (TLC), thoracic gas volume, forced vital capacity (FVC), forced respiratory volume in one second (FEV1), diffusion lung capacity for carbon monoxide (DLCO), partial pressure of arterial oxygen (PaO2), oxygen saturation and alveolar-arterial oxygen gradient. Fifty-one patients were re-evaluated at 12-months demonstrating that changes in DS, TLC, FVC, PaO2, oxygen saturation and alveolar-arterial oxygen gradient were all predictive of survival time after adjustment for baseline values. A multivariate analysis of 131 patients with UIP and 48 with NSIP (41 fibrotic and 7 cellular) showed that histologic subtype, patient age, and diffusion capacity at the beginning of follow-up were important survival prognostic factors, while changes in FVC and diffusion capacity measured at the beginning of follow up (but not the histologic subtype), remained the only prognostic factors for survival after 6 months[11].

In our study we indicated the strong prognostic value of histological diagnosis. In fact, UIP patients showed a dramatically poorer survival at 3-years (59%) compared to cellular NSIP (85%). The 3-year survival of OILD patients (98%) resulted higher than that of both IIP subgroups however, as it has not often been compared with IIP in other studies, we have no reliable comparison terms.

When baseline prognostic factors were evaluated by univariate analysis log-rank test showed no predictive value for sex and smoking status whereas age and HRCT score were good survival predictors. In fact, patients aged more than 60 showed a lower survival rate than younger patients and those having HRCT scores between 1 and 3 had a better survival with respect to those with score 4. Moreover, there was a strict correlation between CT-score and diagnosis, as all UIP patients scored at level 4 had a significantly lower survival rate compared to levels 1-3 (median survival 52 and 89 months respectively). The correlation between HRCT result and IIP diagnosis has been already reported in the literature, even if not with this strength[29].

Octreoscan analysis, has been recently confirmed as a good diagnostic tool providing additional information to radiological imaging in sarcoidosis and IPF. In particular, an increase in octreotide lung uptake index by somatostatin subtype 2 receptors has been reported in IPF showing a good correlation with HRCT score[23,30,31]. Interestingly, octreotide has been proposed as a safe treatment to slow down the progression of lung fibrosis in IPF patients[32].

In our patients, all cases with UIP had a U.I. value lower (or equal) to 10, all NSIP cases had an U.I. value between 10 and 12 and OILD cases had an O.I. value higher than 12. Of interest, the survival cases with an O.I. value $\leq$ 10 was lower than that of cases with an U.I. value $\geq$ than 10 (3-year survival of 59.4 and 95.4 months, respectively).

The results obtained by univariate analysis were confirmed for main factors by the multivariate analysis (Cox proportional hazard model). Importantly, multivariate analysis allows identification of those factors that are independently and significantly related to outcome (survival), while controlling for the other factors in the model. The best model was built up stepwise (forward selection method), i.e., including at each step the variable which showed the largest significance in the univariate analysis. Improvement in the overall significance of multivariate model was assessed using the likelihood ratio test. Hazard ratios estimated for diagnosis type, age class and NYHA resulting from the best model are reported in Table IV. Moreover, full models including sex and smoking habits have been performed, returning more or less the same results, with no improvement in the overall significance of the model. Unfortunately, the strong correlation between diagnosis and Octreoscan U.I. measures and scores of HRCT prevented us to include these latter prognostic factors in the model, as their effect was not estimable due

to the co-linearity with diagnosis itself. Finally, the exclusion of 29 cases with negative NYHA class did not alter the estimates of HR for diagnosis and age classes, but allowed to estimate HR for NYHA classes, as no case with negative NYHA has died during the follow-up period.

Of note, NYHA class came out as a reliable prognostic factor in each analysis setting it was tested. In fact, the log-rank test showed significant differences among NYHA classes, as cases included in the severe level showed the worst survival probability and no death was observed when NYHA class was negative. Moreover, the prognostic value of NYHA class was showed by multivariate analysis, as the survival probability resulted significantly different among levels even after adjustment for the other variables included in the model. Finally, NYHA prognostic value was once again revealed when the analysis was limited to UIP cases. These findings are in agreement with data of the international registry CORONA reporting that NYHA class IV is an independent predictor of survival in patients with IIP and pulmonary hypertension[33]. They also agree with the detection of a more severe lung fibrosis in ILD patients affected by systemic sclerosis or mixed connective tissue disease belonging to NYHA class III/IV[34,35]. The overall follow-up observation time covered was ample enough to give strong support to the data of mortality analysis.

Conclusions

Collectively, the results of our study are in agreement with previous ones[8,10,26,27] evaluating the survival of ILD patients confirming that UIP cases have a worse prognosis than NSIP cases. Moreover, they add the finding that OILD cases have a better prognosis than IIP cases. The main novelty of the present work is that NYHA class severity evaluation associated with imaging and Octreoscan may be regarded as an additional predictive mortality factor for both IIP and OILD. Therefore, we suggest that the determination of NYHA class could be routinely included in the prognostic mortality risk evaluation of patients affected by interstitial lung diseases.

Ethics Approval

The approval from the Institutional Review Board (IRB) has not been requested as the study is retrospective and observational.

Consent to Participate

The research was conducted according to the principles of the Declaration of Helsinki ad written informed consent for diagnostic procedures was obtained from all patients.

Consent for Publication

All Authors consent for publication.

Availability of Data and Material

Data are available.

Code Availability

Not applicable.

Authors' Contributions

RGC conceptualization and investigation; PP supervision; AM statistical analysis; GB validation of data; FP validation of data, reviewing and editing.

Conflict of Interests

Authors do not have any conflict of interest to declare.

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