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Clinical profile of unclassifiable interstitial lung disease: Comparison with chronic fibrosing idiopathic interstitial pneumonias

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Abstract

Objective: Unclassifiable interstitial lung disease (ILD) is a common problem in clinical practice. These patients pose a distinct challenge with regard to appropriate evaluation and management. We investigated the clinical features and prognosis of unclassifiable ILD and compared its clinical profile with that of idiopathic pulmonary fibrosis (IPF) and idiopathic nonspecific interstitial pneumonia (NSIP).

Methods: Patients with IPF (n = 40), NSIP (n = 14), and unclassifiable ILD (n = 27) were selected from an ongoing database. Baseline clinical features, pulmonary function, and the extent of fibrosis on high-resolution computed tomography (HRCT) were evaluated. Mortality was estimated based on the ILD–Gender, Age, Physiology (ILD-GAP) index and composite physiologic index (CPI).

Results: IPF was associated with the worst survival (hazard ratio [HR] = 4.361 compared with NSIP), followed by unclassifiable cases (HR = 1.251 compared with NSIP). Increasing mortality was significantly impacted by age (HR = 1.04 per 1-year increase), lower carbon monoxide diffusing capacity of the lung (HR = 0.97), HRCT interstitial score (HR = 1.119 per 1-point increase), ILD-GAP score (HR = 1.570 per 1-point increase), and CPI (HR = 1.039 per 1-point increase).

Conclusions: Patients with unclassifiable ILD had an intermediate prognosis between that of IPF and NSIP. Patients at high risk of mortality can be identified using baseline clinical, physiological, and radiological features.

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Introduction

Idiopathic interstitial pneumonias (IIPs) are a heterogeneous subset of diffuse parenchymal lung disorders of unknown etiology. Characterized by inflammation and/or fibrosis of the pulmonary parenchyma, IIP entities are individualized through specific clinicopathological features.

According to the current classification, IIPs are grouped into three categories: major, rare, and unclassifiable. Major IIPs comprise chronic fibrosing IIPs (idiopathic pulmonary fibrosis [IPF], idiopathic nonspecific interstitial pneumonia [NSIP]), smoking-related IIPs (respiratory bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia), and acute/subacute IIPs (cryptogenic organizing pneumonia, acute interstitial pneumonia).[1]

Chronic fibrosing IIPs are by far the most common entities, with IPF accounting for up to 65% and NSIP accounting for 14% to 36% of patients with IIPs.[2]

IPF is characterized by a clinical syndrome associated with the morphologic pattern of usual interstitial pneumonia (UIP) and is most prevalent in middle-aged and elderly patients; the median age at diagnosis is 66 years.[3] The clinical course of IPF can vary considerably. While most patients follow a relatively slow clinical and functional decline even in the absence of effective medical treatment, a few patients experience rapid physiologic deterioration and progression to death. Idiopathic acute worsening (acute exacerbations) can occur at any point during the course of IPF and are associated with substantial morbidity and mortality.[4] With a median life expectancy of approximately 3 years after diagnosis, IPF carries the worst prognosis among all IIPs.[5]

NSIP is histopathologically characterized by a temporally uniform interstitial process with varying proportions of interstitial inflammation and fibrosis. Idiopathic NSIP is a specific clinicopathologic entity with highly heterogeneous clinical progression; some patients remain stable or improve with treatment, but some evolve to end-stage fibrosis and eventually die of the disease.[6-8] Distinction between IPF and NSIP is important because in general, the prognosis of NSIP is substantially better than that of IPF.

An accurate and specific diagnosis of ILD requires an integrated approach involving pulmonologists, radiologists, and pathologists. However, because of inadequate data or major discordance among clinical, radiological, or pathological findings, many patients cannot be classified into one of the existing ILD entities. Unclassifiable cases are considered to represent a heterogeneous collection of fibrotic ILDs such as IPF, idiopathic NSIP, chronic hypersensitivity pneumonitis, and connective tissue disease-associated ILD. In one large cohort of patients with ILD, the prognosis was found to be intermediate between IPF and non-IPF ILDs, with a reported 5-year mortality rate of 31%.[9]

Materials and methods

Study patients

This was a single-center, retrospective, observational study including all consecutive patients enrolled in the ILD database of the Clinical Hospital of Infectious Disease and Pneumophysiology, University of Medicine and Pharmacy

"Dr. Victor Babes," Timisoara from January 2005 to December 2015.

Among 173 patients enrolled in our database during this period, a diagnosis of ILD was confirmed in 152 patients based on a review of the clinical history, pulmonary function test results, thin-section high-resolution computed tomography (HRCT) images of the lungs, and surgical lung biopsy reports. Twenty-one patients with incomplete medical records were excluded.

Patients with chronic fibrosing IIPs (IPF and idiopathic NSIP) and unclassifiable fibrotic ILD were selected for the analysis. The diagnosis of IPF and idiopathic NSIP was made according to the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) 2013 guidelines.[1] The diagnosis of IPF was confirmed by the presence of a UIP pattern on HRCT in the appropriate clinical setting or by a combination of HRCT and characteristic findings on surgical lung biopsy.

Idiopathic NSIP was confirmed in the presence of characteristic histological and radiological features with no identified causative factor. Patients with unclassifiable fibrotic ILD were defined as those without a specific ILD diagnosis following a multidisciplinary review of their clinical, radiologic, and pathologic data.

The study was approved by the ethics board of the Clinical Hospital of Infectious Disease and Pneumophysiology of the University of Medicine and Pharmacy "Dr. Victor Babes," Timisoara.

Measurements

Spirometry and assessment of the carbon monoxide diffusing capacity of the lung (DL_{CO}) were performed using standardized procedures.[10,11]

Baseline HRCT scans were evaluated in all patients for patterns of UIP (UIP, possible UIP, or inconsistent with UIP) according to the ATS/ERS/JRS/ALAT IPF guidelines 2011.[5]

The extent of disease on HRCT was evaluated using the semiquantitative scoring system proposed by Kazerooni et al.[12] The HRCT alveolar score (extent of ground-glass attenuation) and HRCT interstitial score (extent of reticulation and honeycombing) were estimated for each lobe on a scale of 0 to 5 (0% to <5%, 5% to <25%, 25% to <50%, 50% to <75%, and >75% lobe involvement). Emphysema was quantified as none, mild (present but scant), moderate (notable or equivalent in extent to the fibrosis), or severe (the predominant abnormality).

Mortality was estimated at baseline using two validated prognostic models: the ILD–Gender, Age, Physiology (ILD-GAP) index and composite physiologic index (CPI). The ILD-GAP model stratifies patients with chronic ILD into disease categories with significantly different prognoses. It incorporates the ILD subtype, gender, age, and two lung physiology variables (forced vital capacity [FVC] and DL_{CO}).[13] The CPI, which uses the forced expiratory volume in 1 second (FEV1), FVC, and DL_{CO}, quantifies functional impairment specifically due to pulmonary fibrosis, removing the confounding functional effects of coexistent emphysema.[14]

Statistical analysis

Data were collected using SPSS v.17 (SPSS Inc., Chicago, IL, USA). The results are presented as mean ± standard deviation for continuous variables with Gaussian distribution, median (interquartile range) for continuous variables without Gaussian distribution, and percentage for categorical variables. The survival analysis data are presented as hazard ratios (HRs) and plotted using Kaplan–Meier diagrams.

To assess the significance of differences between groups, we performed analysis of variance (means, Gaussian populations), the Kruskal–Wallis test (medians, non-Gaussian

populations), the chi-square test for trends (proportions), and the log-rank test (differences between survival curves and HRs). Post-hoc tests were performed to evaluate the differences between pairs of groups. Distributions of continuous variables were tested for normality using the Shapiro–Wilk test and for equality of variances using Levene's test. Cox proportional-hazards models were built to evaluate the involvement of more confounding factors in time-related risk. The acceptance of a predictor in the equation was performed according to the backward Wald principle, having an entry probability threshold of 0.05 and removal probability threshold of 0.10.

A P value of <0.05 was considered statistically significant.

Results

Patient characteristics

In total, 152 patients with ILD were identified from our database (Figure 1). IPF was the most common specific ILD diagnosis (26.3%, 40 patients) followed by sarcoidosis (17.1%, 26 patients), connective tissue disease-associated ILD (15.8%, 14 patients), and idiopathic NSIP (9.2%, 14 patients). Twenty-seven patients (17.8%) were considered to have unclassifiable ILD, which made these nonspecific diagnoses the second most common in our cohort.

The main reason for the inclusion of patients in the unclassified category was the inability to obtain pathological information. Surgical lung biopsy was not performed in patients for whom the risks were likely to outweigh the benefits: patients with stable or mild disease (6 patients) and those with severe lung impairment or significant comorbidities (11 patients). Six patients declined to undergo surgical procedures. Surgical lung biopsy was performed in only four (15%) patients with unclassifiable ILD in whom the disease remained unclassifiable due to discrepancies among the clinical, radiological, and histopathological features.

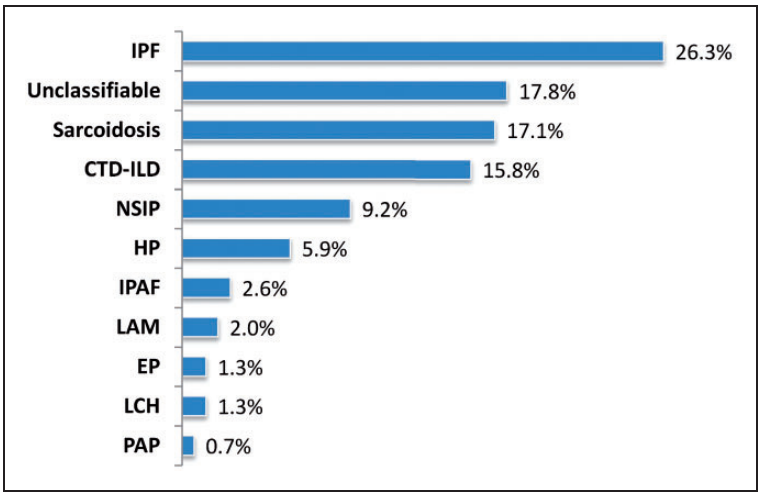

Figure 1. Population of patients with interstitial lung disease (ILD) (152 patients). IPF: idiopathic pulmonary fibrosis, CTD-ILD: connective tissue disease-associated ILD, NSIP: idiopathic nonspecific interstitial pneumonia, HP: hypersensitivity pneumonitis, IPAF: interstitial pneumonia with autoimmune features, LAM: lymphangioleiomyomatosis, EP: idiopathic eosinophilic pneumonia, LCH: Langerhans cell histiocytosis, PAP: pulmonary alveolar proteinosis.

Table 1. Baseline clinical characteristics and pulmonary function.

Variable	IPF (n = 40)	NSIP (n = 14)	Unclassifiable (n = 27)	*P* value
Age, years	64.7 ± 10.1	57.4 ± 12.2	53.0 ± 14.6	<0.001*
Gender				
Male	27 (67.5)	9 (64.3)	9 (33.3)	0.017*
Female	13 (32.5)	5 (35.7)	18 (66.7)	
Body mass index, kg/m^2	27.3 ± 4.8	30.4 ± 4.1	26.6 ± 5.4	0.061
Smoking history				
Ever smoked	22 (55.0)	5 (35.7)	8 (29.6)	0.099
Pack-years	15.8 ± 19.9	10.1 ± 20.8	9.5 ± 17.0	0.365
Pulmonary function				
FVC, L	2.5 ± 0.9	2.3 ± 0.5	2.5 ± 0.9	0.630
FVC, % pred	71.4 ± 18.8	67.3 ± 14.6	73.4 ± 22.7	0.655
FEV1, L	2.1 ± 0.6	2.0 ± 0.5	2.0 ± 0.6	0.600
FEV1, % pred	77.5 ± 20.3	70.3 ± 14.2	69.9 ± 18.3	0.234
FEV1/FVC, %	86.0 ± 5.4	84.9 ± 7.0	81.3 ± 10.2	0.066
DL_{CO}, mL/min−1/mmHg−1	11.4 ± 4.8	10.8 ± 2.6	12.3 ± 4.6	0.580
DL_{CO}, % pred	44.8 ± 17.7	42.3 ± 8.0	47.4 ± 16.1	0.624
K_{CO}, mL/min−1/mmHg−1/L	3.0 ± 1.0	3.2 ± 0.6	3.5 ± 1.2	0.164
K_{CO}, % pred	73.8 ± 21.4	73.1 ± 10.2	69.9 ± 26.0	0.790
Prognostic models				
ILD-GAP	3.6 ± 1.7	1.5 ± 0.9	2.3 ± 1.6	<0.001*
CPI	50.6 ± 14.2	51.7 ± 8.0	45.1 ± 12.3	0.187

Data are presented as average ± standard deviation or n (%).

*Differences are statistically significant.

IPF: idiopathic pulmonary fibrosis, NSIP: idiopathic nonspecific interstitial pneumonia, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, DL_{CO}: diffusing capacity of lung for carbon monoxide, K_{CO}: diffusing capacity of lung for carbon monoxide corrected for alveolar volume, ILD-GAP: Interstitial Lung Disease–Gender, Age, Physiology index, CPI: composite physiologic index.

The baseline clinical characteristics and pulmonary function test results in the IPF, NSIP, and unclassifiable groups are shown in Table 1. There were no significant differences in restrictive ventilatory defects or an impaired diffusing capacity of the lung among these patient groups.

The HRCT findings are summarized in Table 2. An inconsistent UIP pattern was present in all patients with NSIP and in most patients with unclassifiable ILD (88.9%). Patients with IPF had higher HRCT interstitial scores and less ground-glass attenuation than patients with NSIP and unclassifiable ILD.

Emphysematous changes were more commonly found in patients with unclassifiable ILD (41.7%) than in patients with IPF (27.5%) and NSIP (0.0%). Severe emphysema was observed only in patients with unclassifiable ILD (4 patients, 14.8%).

Comparison among ILD categories

The comparison analysis revealed several significant associations between the type of ILD and studied parameters. The diagnosis of IPF was significantly associated with a higher age at diagnosis (64.7 years) when compared with NSIP (57.4 years) and

Table 2. HRCT characteristics of patients.

Variable	IPF (n = 40)	Idiopathic NSIP (n = 14)	Unclassifiable ILD (n = 27)	*P* value
HRCT pattern				
UIP	36 (90.0)	0 (0.0)	0 (0.0)	<0.001*
Possible UIP	4 (10.0)	0 (0.0)	3 (11.1)	
Inconsistent UIP	0 (0.0)	14 (100.0)	24 (88.9)	
HRCT scores				
Alveolar score	1.25 ± 2.40	12.29 ± 4.97	9.11 ± 8.15	<0.001*
Interstitial score	11.75 ± 3.85	3.50 ± 2.98	4.04 ± 4.15	<0.001*
Emphysema				
None	29 (72.5)	14 (100.0)	16 (59.3)	0.033*
Mild	8 (20.0)	0 (0.0)	6 (22.2)	
Moderate	3 (7.5)	0 (0.0)	1 (3.7)	
Severe	0 (0.0)	0 (0.0)	4 (14.8)	

Data are presented as average ± standard deviation or n (%).
*Differences are statistically significant.
HRCT: high-resolution computed tomography, IPF: idiopathic pulmonary fibrosis, NSIP: idiopathic nonspecific interstitial pneumonia, ILD: interstitial lung disease, UIP: usual interstitial pneumonia.

unclassifiable ILD (53.0 years) ($P = 0.001$). The proportion of males was significantly higher in patients with IPF (67.5%) and NSIP (64.3%) than unclassifiable ILD (33.3%) ($P = 0.017$). The variance in the body mass index (BMI) among the three groups was only marginally significant; however, the Bonferroni post-hoc analysis showed that NSIP was associated with a significantly higher BMI (30.4 kg/m^2) than both IPF (27.4 kg/m^2) and unclassifiable ILD (26.6 kg/m^2); the difference between IPF and ILD was not statistically significant. Significant variations among the three groups were observed in the HRCT alveolar score ($P < 0.001$), HRCT interstitial score ($P < 0.001$), and ILD-GAP score ($P < 0.001$).

Survival analysis

The Kaplan–Meier survival analysis (Figure 2) revealed that IPF was associated with the worst survival (HR = 4.361 compared with NSIP, $P = 0.019$), followed by unclassifiable cases (HR = 1.251 compared with NSIP, $P = 0.019$). The average survival duration, considering censored cases, was 5.2 years (95% confidence interval [CI], 4.2–6.2 years) for patients with IPF, 7.0 years (95% CI, 5.7–8.2 years) for patients with unclassifiable ILD, and 8.6 years (95% CI, 7.1–10.2 years) for patients with NSIP.

The role of multiple factors in the risk of mortality was analyzed using a multivariate (Stepwise, Wald, backward) Cox regression model, stratified with respect to the disease category (IPF, NSIP, or unclassifiable) and having the following step 1 covariates: age, gender, BMI, DL_{CO}, FVC, and FEV1. According to the backward Wald method and with an entry probability threshold of 0.05 and removal probability threshold of 0.10, the final equation was obtained after six removal steps. The final predictors accepted in the hazard equation were the age at diagnosis and DL_{CO}. The excluded covariates proved to be neither significant nor marginally significant, having a *P* value for the HR of > 0.10.

According to our model, higher age (HR = 1.04 per 1-year increase, $P = 0.008$)

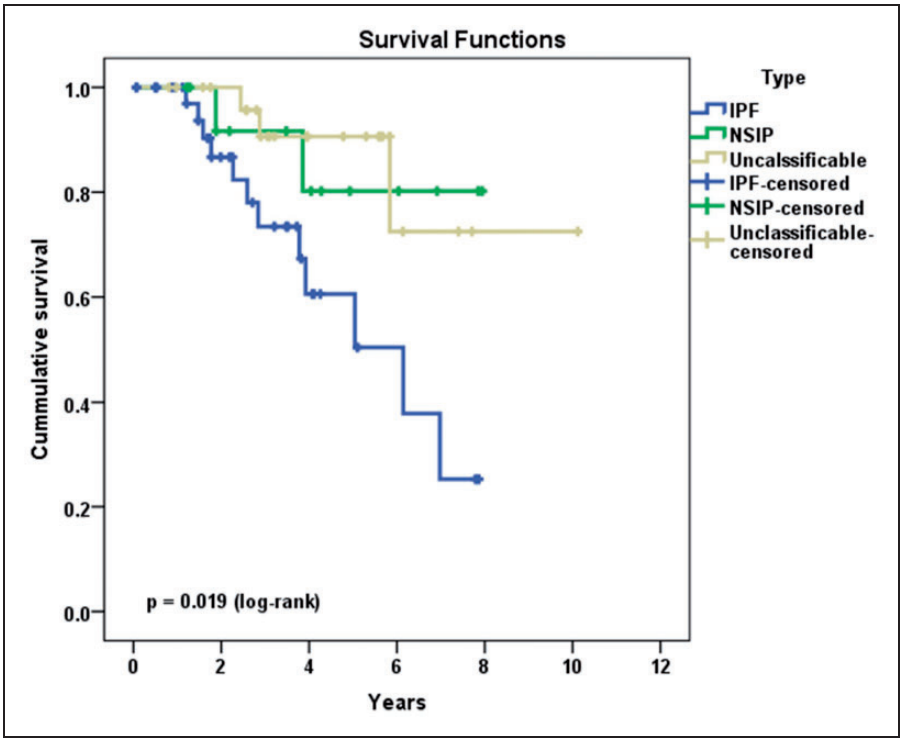

Figure 2. Kaplan–Meier survival analysis. IPF: idiopathic pulmonary fibrosis, NSIP: idiopathic nonspecific interstitial pneumonia.

and lower DL_{CO} (HR = 0.97, $P = 0.005$) had a significant impact on the risk of mortality in the studied patients.

We analyzed the prognostic significance of the HRCT, ILD-GAP, and CPI scores in our studied cohort. The HRCT interstitial score (HR = 1.119 per 1-point increase, $P = 0.008$), ILD-GAP score (HR = 1.570 per 1-point increase, $P = 0.004$), and CPI (HR = 1.039 per 1-point increase, $P = 0.047$) had a significant impact on mortality. The HRCT alveolar score did not have a significant impact (HR = 1.061 per 1-point increase).

Discussion

Recent advances in the classification of IIPs and the development of multidisciplinary approaches have improved the diagnostic accuracy in most cases. Nevertheless, a significant proportion of patients with ILD remain unclassifiable in clinical practice, with a reported prevalence ranging from 10% to 25% in the published literature.[9,15–20] This wide variation is due to inconsistent definitions of unclassifiable cases among studies, mainly differing on whether a surgical lung biopsy was required in the diagnostic work-up.

In our cohort, unclassifiable ILD accounted for 17.8% of cases, making this the second most common diagnosis after IPF. Most of these patients with unclassifiable ILD did not undergo a lung biopsy; thus, a specific diagnosis of ILD could not be confidently established based only on clinical data.

Unclassifiable ILD represents a heterogeneous collection of ILDs, including both

IPF and non-IPF conditions. In this series, the majority of unclassifiable patients did not have radiologic features of UIP; 88.9% were inconsistent with a UIP pattern and in a possible UIP pattern was found in only 11.1%. In addition to the significantly lower age at diagnosis compared with IPF, these findings suggest that most of our cohort of patients with unclassifiable ILD had non-IPF conditions.

The baseline spirometry and gas exchange variables showed similar lung function impairment among unclassifiable ILD, IPF, and NSIP, typically with mild restriction and moderately reduced DL_{CO}. Based on the CPI, which excludes functional impairment due to emphysema, patients with unclassified disease had less functional impairment ascribable to interstitial disease.

Survival in our cohort was significantly different among the groups. Patients with unclassifiable ILD had lower mortality than those with IPF and higher mortality than those with NSIP. These results are consistent with the outcome of unclassifiable ILD reported in the literature as intermediate between that of IPF and non-IPF ILD.[9,16,19]

Several baseline clinical, physiological, and radiological features indicated that patients with unclassifiable disease were at high risk of death, similar to patients with IPF and NSIP. A higher age at diagnosis, lower baseline DL_{CO}, and higher degree of fibrosis on HRCT were independent predictors of mortality. The ILD-GAP index and CPI provided a valuable prognostic assessment at disease presentation.

Our study has several limitations. This was a retrospective single-center review that included a relatively small number of patients. Most patients with unclassifiable disease had not undergone a surgical lung biopsy. Thus, the accuracy of the multidisciplinary review could have been influenced by the absence of histological data and by the experience level of the multidisciplinary team.

The 2013 ATS/ERS guidelines proposed disease behavior classification as complementary to the IIP classification and a useful approach in unclassifiable cases. Classifying patients according to the clinical behavior of their disease (self-limited, stable, reversible, progressive, and irreversible) is useful in guiding monitoring strategies and selecting appropriate treatment approaches. Based on the association of the DL_{CO} and HRCT fibrosis score with survival, these clinical and radiological variables as well as the clinical risk prediction models have shown utility in helping to anticipate the disease behavior.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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