CLINICAL SCIENCE

Severity classification for idiopathic pulmonary fibrosis by using fuzzy logic

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OBJECTIVE: To set out a severity classification for idiopathic pulmonary fibrosis (IPF) based on the interaction of pulmonary function parameters with high resolution computed tomography (CT) findings.

INTRODUCTION: Despite the contribution of functional and radiological methods in the study of IPF, there are few classification proposals for the disease based on these examinations.

METHODS: A cross-sectional study was carried out, in which 41 non-smoking patients with IPF were evaluated. The following high resolution CT findings were quantified using a semi-quantitative scoring system: reticular abnormality, honeycombing and ground-glass opacity. The functional variables were measured by spirometry, forced oscillation technique, helium dilution method, as well as the single-breath method of diffusing capacity of carbon monoxide. With the interaction between functional indexes and high resolution CT scores through fuzzy logic, a classification for IPF has been built.

RESULTS: Out of 41 patients studied, 26 were male and 15 female, with a mean age of 70.8 years. Volume measurements were the variables which showed the best interaction with the disease extension on high resolution CT, while the forced vital capacity showed the lowest estimative errors in comparison to total lung capacity. A classification for IPF was suggested based on the 95% confidence interval of the forced vital capacity %: mild group ($\geq$92.7); moderately mild (76.9–92.6); moderate (64.3–76.8%); moderately severe (47.1–64.2); severe (24.3–47.0); and very severe ($<$24.3).

CONCLUSION: Through fuzzy logic, an IPF classification was built based on forced vital capacity measurement with a simple practical application.

KEYWORDS: Fuzzy logic; Idiopathic pulmonary fibrosis; Respiratory function tests; Respiratory mechanics; Tomography, X-ray computed.

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial fibrosing disease and, by definition, of unknown etiology, limited to the lung. It is classified as one of the idiopathic interstitial pneumonia forms, characterized by the usual interstitial pneumonia (UIP) histologic pattern.[1]

Imaging methods and respiratory function tests are the most commonly used exams in IPF cases. Surgical lung biopsy, although essential to define a UIP diagnosis, is an invasive method. Therefore, it is not indicated during follow-up and evaluation of the therapeutic response.[1–3]

There are few classification proposals for IPF based on radiologic and functional methods. Regarding high resolution computed tomography (HRCT), there were some attempts to standardize its use in IPF. Müller et al.[4] categorized HRCT according to the predominant type of lesion. On the other hand, Chan et al., also using HRCT, created a grading system based on the intensity of the reticular pattern.[5] However, both classification proposals were before the currently accepted definition of IPF based on standard histological UIP.[1]

Concerning lung function, the most used severity classification for restrictive disturbance is based on the percentage values either of total lung capacity (TLC) or forced vital capacity (FVC).[6] However, such measurements

do not consider another important exam in clinical practice, or take into account the underlying restrictive disease, used for both intrapulmonary causes and extra-pulmonary restriction causes.

An IPF classification may allow a better follow-up of this disease and the development of new treatment protocols.[7] Moreover, the categorization of these patients is critical for adequate lung transplantation indication.[8] Nevertheless, the study of the interaction between the several IPF follow-up methods is the key to establishing classification of the disease.

This study aims to set out a classification for IPF based on the interaction of pulmonary function parameters with HRCT findings using fuzzy logic.

MATERIALS AND METHODS

Patients

From March 2005 to July 2007, a descriptive cross-sectional study was conducted, evaluating 55 non-smoking patients diagnosed with IPF who were referred to the Laboratory of Respiratory Physiology and to the Division of Radiology of the State University of Rio de Janeiro, Brazil. Considering the aims of the study, the inclusion criterion was a surgical lung biopsy consistent with UIP diagnosis. Smokers and former smokers were excluded, as were individuals with asthma and those with a history of another pleura-pulmonary disease or congestive heart failure. After applying these criteria, 14 patients were excluded from the study; 6 for having associate asthma, 5 for possible hypersensitivity pneumonitis diagnosis or collagen disease, and 3 for possible associated pulmonary tuberculosis sequel. Thus, the final sample consisted of 41 IPF patients.

According to the World Medical Association Declaration of Helsinki, the protocol was approved by the Research and Ethics Committee of the University of the State of Rio de Janeiro and written informed consent was obtained from all participants.

Measurements

Pulmonary function tests were performed using spirometry, forced oscillation technique (FOT), helium dilution method and single breath determination of carbon monoxide diffusing capacity (DLco). FOT was performed using an impedance analyzer to measure the dynamic respiratory compliance (Crs.dyn). The remaining tests were carried out by using the Collins Plus Pulmonary Function Testing Systems (Warren E. Collins, Inc., Braintree, MA, USA), following the Brazilian Thoracic Society's standardization and interpretation.[9] Results were expressed in percent of the predicted values.[10–12]

The following technique was used for HRCT: General Eletric equipment, HISPEED model; 1-mm thick slices, at 1.5 s intervals and increased by 10 mm; image reconstruction with a 512×512 pixel matrix, using a high resolution algorithm; 1000 HU width window; -700 HU medium window level. Interpretation of computed tomography (CT) findings was performed according to a consensus among four radiologists with extensive experience in interstitial disease. The HRCT was evaluated as to the extent and intensity of interstitial lung involvement, considering five cut-off levels: 1) origin of major vessels; 2) aortic arch level; 3) carina; 4) confluence of pulmonary veins; and, 5) 1 cm above the right diaphragm.[13] Through a semi-quantitative evaluation system in both right and left levels (right and left, separately, totaling 10 levels), the score of reticular abnormality and honeycombing extent, as well as the score of ground-glass opacity extent were analyzed. The following values were attributed to the score of ground-glass opacity extent: 0) no ground-glass opacity extent; 1) ground-glass opacity involving ≤5% of the area; 2) ground-glass opacity involving 6–25% of the area; 3) ground-glass opacity involving 26–49% of the area; 4) ground-glass opacity involving 50–75% of the area; and, 5) ground-glass opacity involving > 75% of the area. The following values were given to the score of reticular abnormality and honeycombing extent: 0) no reticular abnormality or honeycombing; 1) reticular abnormality and no honeycombing; 2) honeycombing (with or without reticular abnormality) involving < 25% of the area; 3) honeycombing involving 25–49% of the area; 4) honeycombing involving 50–75% of the area; 5) honeycombing involving > 75% of the area.[1]

For the analysis of CT findings, estimated pulmonary involvement was obtained using an influence factor to correct, at each level, different pulmonary volumes, as follows: 1) origin of major vessels—weight = 0.129; 2) aortic arch level—weight = 0.190; 3) carina—weight = 0.222; 4) confluence of pulmonary veins—weight = 0.228; and, 5) 1 cm above the right diaphragm—weight = 0.230.[13] Reticular abnormality/honeycombing and ground-grass opacity levels were obtained by totaling the scores for each level.

Data analysis and study design

SAS version 6.11 for Windows (SAS Institute, Inc, Cary, NC, USA) was used for data analysis with the level of significance set at $p<0.05$.

An IPF classification was built by the interaction between functional indexes and radiological scores through fuzzy logic.

The set of relative input variables in the fuzzy logic system has been split in two models: 1) the CT one, established to score the ground-glass opacity extent and to score the reticular abnormality and honeycombing extent; and, 2) the pulmonary function one, formed by volume variables (FVC and TLC), DLco and Crs.dyn. The input of variable measurements standardizing was performed in standard deviation units. The fuzzification of the input variable was obtained in the function of Zadeh's Extension Principle, a basic concept in the fuzzy set theory that extends crisp domains of mathematical expressions to fuzzy domains.[14] The fuzzy domains of mathematical expressions were on the basis of ellipsoidal signals and Mahalanobis distance.[15] The ellipsoidal signals allowed to obtain, for each variable, the marginal pertinence functions, while Mahalanobis distance made the calculation of the combined pertinence value possible.[16] To define the fuzzy set degree of pertinence, the fuzzy logic operators used in this study were the minimum and the maximum.[15–16] The four possible scenarios studied in the fuzzy logic system are shown in Table 1. True modeling was based on identifying classes of patients with the same functional and radiologic features, that is, the recognition of patterns that reflect the peculiarity of the disease.

In the present study, groupings were carried out according to the graphical display in the three-dimensional shape, matching the pertinence of each model and totalling their

Table 1 - Possible scenarios studied in the fuzzy logic system between computed tomography (CT) scores and functional indexes in idiopathic pulmonary fibrosis (IPF) patients.

Possible scenario		Model	Data sheet*
1	CT scores	GGO	min [μ_{GGO}; $\mu_{GGO;RAH}$]
		RAH	min [μ_{RAH}; $\mu_{GGO;RAH}$]
	Pulmonary function	Volumes	mahalanobis distance
2	CT scores	GGO	mahalanobis distance
		RAH	mahalanobis distance
	Pulmonary function	Volumes	mahalanobis distance
3	CT scores	GGO	mahalanobis distance
		RAH	mahalanobis distance
	Pulmonary function	Volumes	min [μ_{GGO}; $\mu_{TLC;FVC}$] min [μ_{RAH}; $\mu_{TLC;FVC}$]
4	CT scores	GGO	mahalanobis distance
		RAH	mahalanobis distance
	Pulmonary function	Volumes	[μ_{RAH}; $\mu_{TLC;FVC}$]. [$\mu_{TLC;FVC}$] max [μ_{TLC}; μ_{FVC}] max [μ_{GGO}; μ_{RAH}]

*Pertinence values intervals according to functional and radiological features and measure of variability (Mahalanobis distance).
μ: pertinence value replicated to all studied pulmonary function variables, GGO: score of the ground-glass opacity extent, RAH: score of the reticular abnormality and honeycombing extent, TLC: total lung capacity, FVC: forced vital capacity.

combined pertinence. At this stage, it was possible to determine the classes, outlined by the elliptical signals constitution. The ellipses were drawn in line with the Mahalanobis distance, fixing the groups according to the proximity of the points projected on the Cartesian plane. The next step was defuzzification through the centroid method, which allowed both the attainment of the weighted average and the standard deviation values of each grouping.[15–16]

Classification was generated through the estimated mean with a 95% confidence interval, based on the standard error of the mean from the Student's *t* test. In this stage, three considerations were undertaken to decide the classification: 1) lack of 95% confidence intervals superposition; 2) the presence of at least three classes (mild, moderate and severe) so as to ensure the discriminative power of the classification; and, 3) minimization of estimation errors.[17]

RESULTS

Table 2 summarizes the main demographic, respiratory function and radiologic characteristics of the patients studied. Restrictive syndrome was diagnosed in 92.7% of the sample, and none of the evaluated patients presented airflow limitation. The DLco was at the lowest limit of normality in 95.1% of the patients.

In determining homogeneous classes to identify the interaction between functional indexes and CT scores, only the fuzzy scenario 4, which used a multiplicity of operators, was able to recognize a pattern.

In scenario 4, three compositions were carried out for the CT model interaction with the pulmonary function model: 1) CT model and volume; 2) CT model and diffusion; and, 3) CT model and dynamic compliance. The visualization of such compositions was performed by a three-dimensional graphical representation that shows, in one axis, the

Table 2 - Demographic, respiratory function and radiological data for all idiopathic pulmonary fibrosis (IPF) patients.

Variables	Values
Male gender, n (%)	26 (63.4)
Age (years)	70.8 (9.4)
FVC %	63.0 (17.3)
TLC %	60.2 (16.9)
DLco %	44.2 (18.7)
Crs.dyn* (L/cmH_2O)	0.0097 (0.0046)
Ground-glass opacity, n (%)	22.0 (53.7)
Reticular abnormality, n (%)	41.0 (100.0)
Honeycombing, n (%)	40.0 (97.6)
Score of ground-glass opacity extent	1.80 (0.61)
Score of extent of reticular abnormality and honeycombing	4.00 (1.80)

Values expressed as mean (SD), unless otherwise stated. FVC %: predicted forced vital capacity, TLC %: predicted total lung capacity, DLco %: predicted carbon monoxide diffusing capacity, Crs.dyn: dynamic respiratory compliance.

combined pertinence for the two variables, and in the other two, the maximum pertinence of each model. The only composition that matched the CT model with the volume measurements discriminated classes of patients.

Table 3 shows the interaction between functional indexes and CT scores through 95% confidence interval (95% CI) and standard error of the mean (SEM). Interaction between DLco and CT scores showed acceptable SEM; yet, there was a 95% CI overlap between the moderate and severe classes. Interaction between Crs.dyn and CT scores pointed to three classes with apparently low SEM; however, from the perspective of relative error (error/mean), the severe class presented a value equal to 143%, affecting the 95% CI.

On the other hand, the interaction between the volume measurements (FVC and TLC) and CT scores showed small estimative errors, and the FVC had lower values than the TLC. Moreover, several 95% CI volume measurements showed no overlap, discriminating degrees of classification.

Thus, our proposed IPF severity classification considers the various 95% CI for the mild, moderate and severe FVC% classes, based on interaction with the HRCT findings, as shown in Table 4.

DISCUSSION

We observed that restrictive defect occurred in 92.7% of cases. In contrast to the findings of other studies, in which, by virtue of not excluding smokers or former smokers, pulmonary volumes were found to be relatively preserved in a significant portion of the study samples.[18,19] Such a difference is as a result of the effect of emphysema which, through air trapping and hyperinflation of the lungs, can ultimately mask the effect of fibrosis in decreased pulmonary volumes.[1] Regarding DLco, it is more sensitive than other tests performed at rest, and can be decreased even when static volumes are still preserved.[1]

There are no normal FOT values for dynamic compliance. However, the extent of the effect of fibrosis on the Crs.dyn of the studied patients can be easily evaluated, considering the mean found in the present study (10 mL/cmH_2O) and the mean values previously reported for normal individuals in Brazil (40 mL/cmH_2O).[20]

Table 3 - Interaction between functional indexes and computed tomography (CT) scores expressed through the parameters of lung function in idiopathic pulmonary fibrosis (IPF) patients.

Variables	Classes	95% CI			SEM
		Lower limit	Mean	Upper limit	
FVC %	Mild	92.7	95.4	98.2	2.74
	Moderate	64.3	70.5	76.8	6.21
	Severe	24.3	35.7	47.0	11.3
TLC %	Mild	73.9	97.1	120.2	23.1
	Moderate	59.9	64.7	69.5	4.85
	Severe	27.2	39.2	51.2	12.0
DLco %	Mild	77.7	83.3	88.9	5.62
	Moderate	37.4	52.0	66.6	14.6
	Severe	34.3	39.6	45.0	5.33
Crs.dyn*	Mild	0.0104	0.0114	0.0124	0.0010
(L/cmH_2O)	Moderate	0.0056	0.0063	0.0070	0.0007
	Severe	0.0009	0.0037	0.0090	0.0053

95% CI: 95% confidence interval, SEM: standard error of the mean (SEM), FVC %: predicted forced vital capacity, TLC %: predicted total lung capacity, DLco %: predicted carbon monoxide diffusing capacity, Crs.dyn: dynamic respiratory compliance.

In IPF, no other test facilitated diagnostic evaluation as much as HRCT, which allows the acquisition of detailed images close to macroscopic anatomy. Moreover, the extent of fibrosis on the HRCT in patients with IPF has proven to be one of the most reliable prognostic indexes.[1,21] In our study sample, we observed the presence of honeycombing in 97.6% of the cases, in accordance with Lynch et al.[22], who diagnosed honeycombing in 95.4% of patients. A ground-glass pattern was a less common finding, and, when present, the areas were not very extensive.

Over the last few decades, some IPF classification systems have been proposed in an attempt to assess its severity and predict its course.[4,5,6] However, none of them took into account the association between patients' different follow-up methods. Thus, our classification suggestion took, as a basis, the interaction among the functional indexes and the type and extent of tomographic lesions using fuzzy logic.

Fuzzy logic has been depicted in the literature as an artificial intelligence technology, capable of understanding and organizing information with a reduced number of observations and without clear organization, converting it to a numeric format, easily manipulated via computer.[16] Currently, fuzzy logic is widely used in various areas of knowledge such as pattern recognition. In medicine, in particular, several published studies used fuzzy logic. By measuring heart rate, tidal volume, respiratory rate and oxygen saturation, Nemoto et al.[22] developed an algorithm to control a mechanical ventilator in the intensive care unit. Brown et al.[23] created an automated system for detecting lung micronodules on HRCT. More recently, Koçer used fuzzy logic to propose a classification of electromyography signals observed in individuals with neuromuscular diseases.[24]

Table 4 - Severity classification for idiopathic pulmonary fibrosis (IPF) according to the values of predicted forced vital capacity (FVC) %.

Degree of severity	FVC %
Mild	≥92.7
Moderately mild	76.9–92.6
Moderate	64.3–76.8
Moderately severe	47.1–64.2
Severe	24.3–47.0
Very severe	<24.3

In our study, from the perspective of the interactive composition of the CT model with the pulmonary function model, it was seen, through fuzzy logic, that lung volume measurements were those that most contributed to the patients' classes discrimination. Just as it increased the classification gradation, the tomography model interacted with the volume measurements.

Our IPF severity classification proposal considers the various 95% CI measures of FVC %, as they best discriminated the severity of the disease. This result is in strict accordance with previous studies that also showed the superiority of FVC over other functional indexes used in IPF.[25,26] It is also interesting to observe that the upper limit for establishing the severe group (47.0%) is very near to the one suggested by the American Thoracic Society, which is 50%.[6] Among the many advantages of this classification, the severity of the disease is evaluated from the interaction between the functional assessment tests and the HRCT, which are the main tests used in IPF follow-up.

A critical analysis of the results obtained in the present study and its limitations is requested. We carefully eliminated the effects of tobacco on pulmonary function tests, so only non-smokers were analyzed. Similarly, individuals with concomitant asthma were excluded, as airflow limitation is one of the characteristics of the disease. However, by excluding those patients, the proposed classification system cannot be generalized for all IPF patients. Another limitation is that the proposed classification should be replicated in another cohort to seek validation. Thus, an extended validation cohort of IPF patients is under way.

To summarize, the present study provides an IPF classification proposal of simple practical application based on FVC measurement. This classification was built from the functional indexes interaction with HRCT findings by using fuzzy logic.

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