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High-resolution CT predictors of hypersensitivity pneumonitis

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Abstract. *Background:* The purpose of this study was to evaluate the use of high-resolution chest computed tomography (HRCT) to distinguish hypersensitivity pneumonitis (HP) from other diffuse parenchymal lung diseases (DPLDs). *Methods:* We examined 130 consecutive patients admitted to our hospital with DPLDs proved by HRCT. Patients underwent clinical and paraclinical examinations. Two readers interpreted 111 HRCT scans using predefined criteria. *Results:* The findings in patients with HP were compared to those with other DPLDs (non-HP) by univariate and multivariate analyses. Five independent radiological predictors were identified and were given a weight according to their regression coefficient: ground-glass attenuation nodules (4 points), homogeneous ground-glass opacity (3 points), patchy ground-glass opacity (2 points), absence of adenopathy (2 points), and absence of linear/reticular patterns (2 points). A total score (that we called "diagnostic index") of 5 offered the best trade-off between sensitivity and specificity. At this point of the ROC curve, the sensitivity, specificity, and likelihood ratio were 74%, 90% and 7.7, respectively. Given a pre-test probability of HP of 34% (i.e., 38 HP / 111 patients), the post-test probability was 79%. *Conclusion:* Our results provide evidence that HRCT can accurately distinguish HP from other DPLDs. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 117-123)*

Key words: HRCT, Hypersensitivity pneumonitis, diagnostic procedures

Introduction

Hypersensitivity pneumonitis (HP) is a granulomatous lung disorder resulting from repeated inhalation of organic antigens. HP is one of the main conditions identified in differential diagnoses of diffuse parenchymal lung diseases (DPLDs) which consist of disorders of known causes as well as disorders of unknown causes. HP is generally classified into acute, subactute and chronic forms (1-2). Several criteria are generally proposed for the diagnosis of HP, including exposure to a potential offending antigen, specific findings on clinical examination, lymphocytosis at bronchoalveolar lavage (BAL), impaired respiratory lung function, positive serum precipitins and pulmonary infiltrates on chest radiographs. Clinical independent predictors were identified in a prospective multicenter cohort study (3). Environmental exposure to sensitizing antigens appeared as the strongest clinical predictor of HP.

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High-resolution chest tomodensitometry (HRCT) is commonly used to investigate DPLDs (4-7) and is considered to be a better tool than chest radiography for the diagnosis of HP (8). The main features of HRCT described in the literature are ground-glass opacities, centrilobular nodules and air trapping (9-10). However, the diagnostic value of these findings has never been quantified. Although HRCT may often differentiate chronic HP from other chronic DPLDs, atypical idiopathic pulmonary fibrosis may be mistaken and only results of lung biopsy can distinguish the histological patterns (11-12). It may also be used to predict a poor outcome in patients with chronic HP (13-14).

Since the prevalence of HP is high in Doubs (France), we performed a prospective study to determine to what extent HRCT findings could be useful in addition to clinical findings to distinguish HP from other DPLDs.

Material and methods

Study design

We conducted a prospective study using consecutive patients admitted for DPLDs proved by HRCT between January 1998 and November 2002 in the Department of Respiratory Diseases, University Hospital of Besançon (Besançon, France), a French center labelled as a "competence center for rare pulmonary diseases in adults". Some of them were included in the HP study (3). This study was conducted in accordance with the amended Declaration of Helsinki. In France in 1998, the agreement of the University Hospital of Besançon ethics committee was not required for this type of study. The patients systematically underwent a clinical examination and lung function tests including spirometry, measurement of lung volume and diffusing capacity of the lung for carbon monoxide, BAL, precipitin tests, blood gas analysis and HRCT. Bronchial, transbronchial and lung biopsies were not protocol-based and left to the physician's assessment.

Diagnostic criteria

Final diagnoses were obtained by integrating clinical, biological, functional and imaging criteria and, when necessary, results of BAL and/or lung biopsy. In the absence of a unique gold standard, the following characteristics were used to diagnose acute/subacute HP: (1) compatible clinical manifestations, (2) chronic exposure to a known offending antigens, (3) BAL lymphocytosis (> 30% for non- and ex-smokers and > 20% for current smokers (15)), (4) decreased DLCO, and (5) positive serum precipitins against a panel of antigens locally validated (16). Chronic HP was diagnosed when these characteristics were present with emphysema and/or fibrosis on HRCT. We did not define gold standard for non-HP diseases and diagnosis was left to the physician's assessment. Final diagnoses of HP and non HP were validated during agreement meetings.

High-resolution CT

HRCT were performed in the department of radiology of the university hospital of Besançon according to the standardized procedure used for incident cases of interstitial lung diseases. Before 2000, a single detector incremental CT scanner (GE CT-pace, Milwaukee, Wisconsin, US) was used with the following 2 protocols: 12 high resolution incremental slices (1.0-mm collimation 30 mm intervals, 120 kV, 160 mA, 1 second) from apices to lung bases and additional thick incremental slices (7.0-mm collimation, 6.0-mm intervals, 120 kV, 160 mA, 1 second) throughout the whole thorax. From the year 2000, we used a single-detector helical CT scanner (GE Hispeed, Milwaukee, Wisconsin, US) with the following protocol: 1.0-mm collimation, 0,8 pitch, 140 kV, 200-280 mA, 1 second.

HRCT reading was performed retrospectively on dedicated workstations by two independent readers with more than ten years experience: a pneumologist (JCP) and a thoracic radiologist (PM) blinded from clinical, biological and pathological features and from the final diagnosis (HP or not-HP). Disagreement was resolved by consensus or by consulting a second thoracic radiologist (FL).

We defined *a priori* criteria for the description of the main radiological features, their location and their distribution within the lung parenchyma. The features were defined in accordance with the Fleischner Society's glossary of terms for thoracic imaging (17). The following HRCT characteristics were examined: (1) nodular pattern (size, density and dis-

tribution in the lobule), (2) linear or reticular patterns, (3) high-attenuation patterns (consolidations, ground-glass opacities and crazy-paving pattern), (4) low-attenuation patterns (cavity, centrilobular emphysema, mosaic-attenuation pattern, cavitated nodules, or air trapping), (5) honeycombing, (6) bronchial anomalies, (7) pleural anomalies and (8) adenopathy. All features were scored as "present" or "absent". The distribution of each feature was also classified as unilateral or bilateral, and symmetric or asymmetric. The predominant location of the main features was assessed in the cephalocaudal, antero-posterior, and the sub-pleural to perihilar directions. The profusion of findings within the lung parenchyma was quantified as follows: ≤25%, 26 - 50%, 51% - 75%, ≥75%.

Analysis

Patients were classified in two categories: HP or non-HP. We first performed univariate analyses (Chi-squared tests) to compare the prevalence of radiological features and their location and distribution in the HP and non-HP groups. From these analyses, we then incorporated the variables found significant at the 0.05 level in a stepwise logistic regression model. The independent radiological predictors identified from this multivariate model were given a weight according to the regression coefficient that we rounded to the nearest integer. For each HRCT scan, a global "diagnostic index" was calculated from the sum of the weights of the different predictors. Also, for each significant predictor and for each possible "diagnostic index", we computed the associated sensitivity, specificity, diagnostic accuracy (i.e., true positive + true negative/total number of patients) and likelihood ratio (i.e., true positive rate/false positive rate). We also constructed a receiver operating characteristic (ROC) curve in order to determine the threshold that provided the best sensitivity/specificity ratio for the diagnosis of HP. Using the Fagan's nomogram (18), we estimated the post-test probability of HP at this threshold from the pre-test probability that we determined from the prevalence of HP in our cohort of patients.

Results

One hundred and thirty consecutive patients with DPLDs were admitted to our hospital between January 1998 and November 2002. We excluded 19 HRCT of poor quality, leaving 111 scans to be examined by the two independent physicians.

Diagnoses

The final diagnosis was HP in 38 patients (including mainly acute/subacute farmer's lung (n=32), chronic farmer's lung (n=3) and bird fancier's disease (n=3)); the prevalence of HP was therefore 38/111 (34%). The non-HP group (n=73) included the following diagnoses: idiopathic pulmonary fibrosis, non-specific interstitial pneumonitis, and fibrosis associated with connective tissue disorders (n=23), acute eosinophilic pneumonia (n = 3), cryptogenic organizing pneumonia (n=4), Langerhans cell histiocytosis (n=3), pneumoconiosis (n=4), drug-induced lung toxicity (n=10), sarcoidosis (n=14), infectious pneumonia (n=2), carcinomatous lymphangitis (n= 2), bronchiolitis (n=2), severe form of organic dust toxic syndrom (n=1), lymphoid interstitial pneumonia (n=1), pneumocystosis (n=1), chronic eosinophilic pneumonia (n=1), exogenous lipoid pneumonia (n=1), and eosinophilic granulomatosis with polyangeitis (n=1).

HRCT features: results of the univariate analyses

Nodular, low and high-attenuation patterns were significantly associated with HP, whereas linear or reticular patterns, honeycombing, pleural abnormalities and the presence of enlarged adenopathies were more frequent in the non-HP group (Table 1).

With only 3 exceptions (Table 2), we found no difference in the patterns of distribution of abnormalities between the two groups. The distribution was found to be bilateral (HP group: n=36/36; non-HP group: n=69/72) and symmetric (HP group: n=29/36; non-HP group: n= 4/72), diffuse in the anteroposterior direction (HP group: n=34/36; non-HP group, n=62/72), diffuse from the sub-pleural to hilar direction (HP group: n=33/36; non-HP group, n=38/72), diffuse in the cephalocaudal direction (HP group, n=30/36; non-HP group, n=41/72).

HRCT features: results of the multivariate analyses

We found five independent predictors of HP to which we assigned an HRCT score based on the

regression coefficients (Table 3). The total "diagnostic index" ranged from 0 (all predictors absent) to 13 (all predictors present). The associated ROC curve is presented in the Figure 1. The area under the ROC curve was 0.89. A diagnostic index of 5 best discriminated HP from non-HP. For instance,

Table 1. HRCT features: results of the univariate analysis

HRCT features	HP n=38	Non-HP n=73	p
Nodular pattern	16 (42.1%)	24 (32.9)	0.33
Size			
Micronodules	15 (39.5%)	22 (30.1%)	0.32
Nodules	16 (42.1%)	24 (32.9%)	0.33
Density			
Soft-tissue attenuation	1 (2.6%)	23 (31.5%)	<0.001
Ground-glass attenuation	15 (39.5%)	1 (1.4%)	<0.001
Distribution			
Centrilobular	14 (36.8%)	11 (15%)	0.02
Linear/reticular pattern	6 (15.8%)	47 (64.4%)	<0.001
High-attenuation pattern	31 (81.6%)	35 (47.9%)	<0.001
Ground-glass opacity*	31 (81.6%)	32 (43.8%)	<0.001
Diffuse	29 (76.3%)	18 (24.7%)	<0.001
Patchy	16 (42.1%)	10 (13.7%)	<0.001
Homogenous	10 (26.3%)	5 (6.8%)	<0.01
Consolidation	1 (2.6%)	11 (15.1%)	<0.05
Crazy-paving pattern	0	0	-
Low-attenuation pattern	23 (60.5%)	24 (32.5%)	<0.05
Mosaïc-attenuation pattern	2 (5.3%)	1 (1.4%)	0.5
Air trapping	18 (47.5%)	10 (13.7%)	<0.001
Emphysema	4 (10.5%)	8 (11%)	0.8
Cavity	0	9 (12.3%)	0.058
Honeycombing	2 (5.3%)	40 (54.8%)	<0.001
Bronchial abnormalities	3 (7.9%)	6 (8.2%)	0.75
Pleural abnormalities	0	10 (13.7%)	0.04
Adenopathy	5 (13.2%)	30 (41.1%)	<0.01

* More that 1 pattern could be found in a single patient

Table 2. Distribution of the main features in the lung parenchyma: results of the univariate analyses

	HP	Non HP	P
Sparing of lung bases	29/36 (80.6%)	34/71 (47.9%)	0.001
Sparing sub-pleural fields	31/36 (86.1%)	25/71 (35.2%)	< 0.0001
> 75% impairement of the lung parenchyma	25/38 (65.7%)	14/73 (19.1%)	< 0.0001

Table 3. Results of the multivariate analysis

Semiological features	OR	CI 95%	Regression coefficient	HRCT Score
Intercept	-	-	-5.0877	-
Ground-glass attenuation nodules	71	3.7 - >999	4.2627	4
Homogeneous ground-glass opacity	15.8	2.38 - 104	2.7608	3
Patchy ground-glass opacity	12.1	2.84 - 51.7	2.4951	2
Absence of adenopathy	6.2	1.21 - 31.8	1.8257	2
Absence of linear/reticular patterns	9.2	2.35 - 36.3	2.2258	2

The HRCT score is based on the regression coefficient. OR: odds ratio, CI: confidence interval

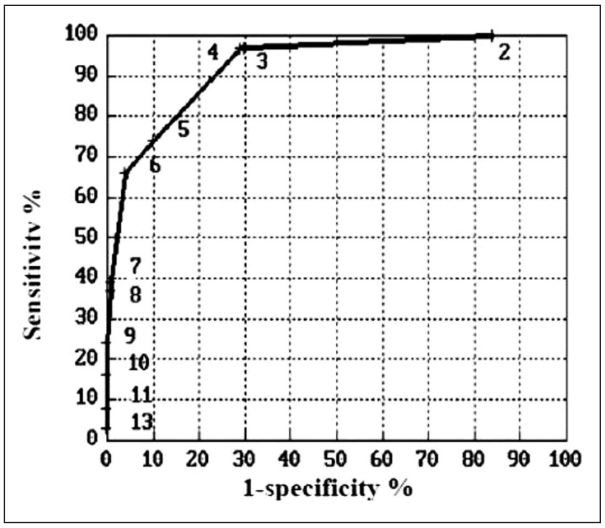

Fig. 1. Receiver operating characteristic (ROC) curve. The ROC curve was based on the HRCT scores. The HRCT index is the sum of the HRCT scores

Table 4. Result-specific likelihood ratios

Diagnostic index	Sensitivity (%)	Specificity (%)	Diagnostic accuracy (%)	Likelihood ratio
0	100	0	34	1
2	100	16	45	1.2
3	97	70	79	3.2
4	97	71	80	3.4
5	74	90	85	7.7
6	66	96	86	16.0
7	39	99	78	28.8
8	37	99	77	26.9
9	24	100	74	∞
10	16	100	71	∞
11	8	100	68	∞
13	3	100	67	∞

a set of predictors to obtain a diagnostic index of 5 in an individual patient would be a combination of "homogeneous ground-glass opacity" (3 points) and "absence of linear/reticular patterns" (2 points). At this point of the ROC curve, the sensitivity, specificity and likelihood ratio were 74%, 90% and 7.7, respectively, and the diagnostic accuracy was 85%. Result-specific likelihood ratios are reported in Table 4. Using the Fagan's nomogram (Figure 2), given a pre-test probability of 34% and a diagnostic index of 5, the post-test probability was 79%.

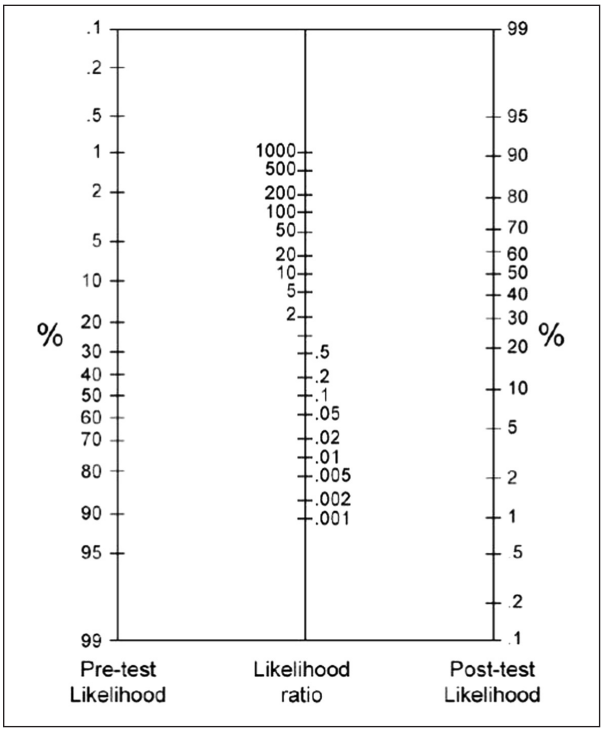

Fig. 2. Nomogram for interpreting diagnostic test results. Adapted from Fagan (18). This involves an estimate of the prevalence of the disease (pre-test probability) and the knowledge of the likelihood ratio corresponding to a given test result. Example: Using 45% as the pre-HRCT probability of HP, a diagnostic index of 6, which is associated to a likelihood ratio of 16, the result of the HRCT would bring the post-HRCT probability of HP to 93% when using the nomogram of Fagan

Discussion

HRCT is one of the cornerstones in the investigation of DPLDs (6-8). Typical patterns of HRCT findings may guide clinicians in the diagnosis of DPLDs without the necessity of BAL or lung biopsy. In this regard, it is currently accepted that a combined "clinical and radiological" diagnostic approach is useful for the diagnosis of idiopathic pulmonary fibrosis (19-21). The results of our study add to the interest of HRCT as a diagnostic tool when acute or subacute HP is suspected.

We described acute or subacute HP as a diffuse and symmetrical lung disease, with an impairment covering more than 75% of the lung parenchyma. The main abnormalities were ground-glass opacities (either patchy or homogeneous), nodules with a centrilobular distribution, and air trapping. These

features spared the sub-pleural fields and the lung bases. In this regard, the results of our study confirmed those published in the literature (8-9). The original contribution of our study is that it quantifies the diagnostic value of HRCT findings in HP.

To diagnose acute or subacute HP with higher level of confidence without BAL or biopsy, our model could be improved by including clinical predictors of the disease in the analyses. Combining the independent predictor "exposure to a known offending antigen" (which was the strongest predictor of HP in the HP study (3)) with the HRCT index that we describe may be the best approach to diagnose acute or subacute HP in our region. A simple but more sophisticated approach would be to estimate the pre-test probability of HP from the results of the HP study (3). For instance, in a farmer presenting with recurrent episodes of respiratory symptoms, inspiratory crackles and testing negative for the corresponding precipitating antibodies, the clinical probability of HP would be 45%. Further investigation would be mandated if HP was still considered in the differential diagnosis. In this patient, the combination of patchy ground-glass opacity" (2 points) in the absence of hilar or mediastinal adenopathies (2 points) or linear/reticular markings (2 points) would result in a diagnostic index of 6, which is associated to a likelihood ratio of 16.0 (Table 4). Using 45% as the pre-HRCT probability of HP and the nomogram of Fagan (18), the result of the HRCT would bring the post-HRCT probability of HP to 93%. This would secure the diagnosis of HP, without resorting to surgical lung biopsy. This approach could also be refined by incorporating the result of site-specific serum precipitins (16).

It has been suggested that a post-test probability ≥ 90% or ≤ 10% should be sufficient in most cases to respectively rule in or rule out HP, especially in areas of high or low prevalence of HP respectively (3). However, the « test threshold » (i.e., the probability below which a clinician would dismiss the diagnosis and order no further test) and the « treatment threshold » (i.e., the probability above which a clinician could consider the diagnosis confirmed and would stop testing) are likely to differ according to the clinical implications of the diagnosis (22). A clinician and his/her patient may be more likely to accept the diagnosis of bird fancier's disease when the offending antigen is a pet, even if the probability of HP is 75%. In this patient, antigen avoidance would be appropriate, and further investigation would be required only if the clinical course is unusual. On the other hand, a clinician and his/her patient will want to secure the diagnosis of farmer's lung even if the probability of HP is around 90%, given the implications of such a diagnosis (23).

Our study has however some limitations. First, it was performed in an area with a high prevalence of farmer's lung and included mainly acute or subacute cases of farmer's lung. Second, our model may not be appropriate for screening chronic HP or other types of HP and for discriminating chronic HP from other chronic diffuse interstitial lung disease because we compared mostly acute/subacute HP with an heterogenous group of non HP lung diseases. Our model was not validated in an independent cohort. Also, we did not formally assess the concordance between the two readers.

Conclusion

HRCT is a good tool for discriminating HP, especially acute/subacute farmer's lung, from other DPLD, in a region where HP is highly prevalent. A combined approach using clinical, laboratory and HRCT criteria may be effective in diagnosing HP without resorting to invasive procedures.

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References

1. Lacasse Y, Girard M, Cormier Y. Recent advances in hypersensitivity pneumonitis. Chest 2012; 142: 208-17.

2. Selman M, Pardo A, King TE. Hypersensitivity pneumonitis: insights in diagnosis and pathobiology. Am J Respir Crit Care Med 2012; 186: 314-24.
3. Lacasse Y, Selman M, Costabel U, Dalphin JC, Ando M, Morell F, et al. Clinical diagnosis of hypersensitivity pneumonitis. Am J Respir Crit Care Med 2003; 168: 952-8.
4. Cormier Y, Brown M, Worthy S, Racine G, Muller NL. High-resolution computed tomographic characteristics in acute farmer's lung and in its follow-up. Eur Respir J 2000; 16: 56-60.
5. Lynch DA, Travis WD, Muller NL, Galvin JR, Hansell DM, Grenier PA, et al. Idiopathic interstitial pneumonias: CT features. Radiology 2005; 236: 10-21.
6. Brauner M, Brillet P. Pathophysiological approach to infiltrative lung diseases on CT. J Radiol 2009; 90: 1841-53.
7. Hobbs S, Lynch D. The idiopathic interstitial pneumonias: an update and review. Radiol Clin North Am 2014; 52: 105-20.
8. Lynch DA, Rose CS, Way D, King TE. Hypersensitivity pneumonitis: sensitivity of high-resolution CT in a population-based study. AJR Am J Roentgenol 1992; 159: 469-72.
9. Silva CI, Churg A, Muller NL. Hypersensitivity pneumonitis: spectrum of high-resolution CT and pathologic findings. AJR Am J Roentgenol 2007; 188: 334-44.
10. Hirschmann JV, Pipavath SN, Godwin JD. Hypersensitivity pneumonitis: a historical, clinical, and radiologic review. Radiographics 2009; 29: 1921-38.
11. Lynch DA, Newell JD, Logan PM, King TE, Muller NL. Can CT distinguish hypersensitivity pneumonitis from idiopathic pulmonary fibrosis? AJR Am J Roentgenol 1995; 165: 807-11.
12. Silva CI, Muller NL, Lynch DA, Curran-Everett D, Brown KK, Lee KS, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 2008; 246: 288-97.
13. Hanak V, Golbin JM, Hartman TE, Ryu JH. High-resolution CT findings of parenchymal fibrosis correlate with prognosis in hypersensitivity pneumonitis. Chest 2008; 134: 133-8.
14. Mooney JJ, Elicker BM, Urbania TH, Agarwal MR, Ryerson CJ, Nguyen ML, et al. Radiographic fibrosis score predicts survival in hypersensitivity pneumonitis. Chest 2013; 144: 586-92.
15. The_BAL_Cooperative_Group_Steering_Committee. Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. Am Rev Respir Dis 1990; 141: S169-202.
16. Fenoglio CM, Reboux G, Sudre B, Mercier M, Roussel S, Cordier JF, et al. Diagnostic value of serum precipitins to mould antigens in active hypersensitivity pneumonitis. Eur Respir J 2007; 29: 706-12.
17. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008; 246: 697-722.
18. Fagan TJ. Letter: Nomogram for Bayes theorem. N Engl J Med 1975; 293: 257.
19. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-824.
20. Raghu G. Idiopathic pulmonary fibrosis: guidelines for diagnosis and clinical management have advanced from consensus-based in 2000 to evidence-based in 2011. Eur Respir J 2011; 37: 743-6.
21. Hodnett PA, Naidich DP. Fibrosing interstitial lung disease. A practical high-resolution computed tomography-based approach to diagnosis and management and a review of the literature. Am J Respir Crit Care Med 2013; 188: 141-9.
22. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. N Engl J Med 1980; 302: 1109-17.
23. Bouchard S, Morin F, Bedard G, Gauthier J, Paradis J, Cormier Y. Farmer's lung and variables related to the decision to quit farming. Am J Respir Crit Care Med 1995; 152: 997-1002.