Development and Validation of Diffuse Idiopathic Pulmonary Neuroendocrine Hyperplasia Diagnostic Criteria

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ABSTRACT

Introduction: Diffuse idiopathic pulmonary neuroendocrine hyperplasia (DIPNECH) is a rare condition that is likely underdiagnosed owing to the lack of established and validated diagnostic criteria. These clinical guidelines are empirical and created on the basis of a limited number of studies. This study was designed to validate the existing criteria and to identify new clinical parameters that can accurately diagnose DIPNECH.

Methods: Patients with DIPNECH were identified from a cohort that underwent surgical lung resection for pulmonary carcinoids. The study cohort included a total of 105 consecutive cases with neuroendocrine lesions. Initial diagnostic predictors of DIPNECH were selected from the literature. We employed univariate and multivariate models to evaluate the association of clinical, pathologic, radiologic variables with the likelihood of DIPNECH.

Results: Univariate analysis identified age, sex, chronic obstructive pulmonary disease diagnosis, obstructive abnormalities, pulmonary nodules, mosaicism, absolute numbers of pulmonary neuroendocrine lesions (PNELs), and the number of tumorlets as significant DIPNECH predictors (for \( p < 0.05 \)). After adjustment for sampling variations, the ratio of the total number of PNELs to the number of bronchioles was found to be considerably higher in DIPNECH category. Multivariate analysis identified the total number of PNELs and multiple pulmonary nodules (>10) as independent predictors of DIPNECH. The performance of our criteria revealed an accuracy of 76% in detecting DIPNECH cases.

Conclusions: We proposed a set of diagnostic criteria for DIPNECH on the basis of an expert-panel approach integrating pathological features, radiology, and clinical data. Our findings will help identify DIPNECH patients, without a pathological confirmation of a neuroendocrine lesion. Before the implementation of these criteria in clinical practice, they require further validation in multi-institutional cohorts.

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Introduction

Diffuseidiopathic pulmonary neuroendocrine hyperplasia (DIPNECH) is defined as “a generalized proliferation of pulmonary neuroendocrine cells that are potentially confined to the mucosa of the airways and may either invade locally to form tumorlets, or develop into carcinoid tumors,” according to the WHO classification. It is an underdiagnosed condition with only a few series of cases reported in the literature. Patients with DIPNECH frequently receive medical attention because of pulmonary nodules on computed tomography (CT) scans or nonspecific respiratory symptoms such as chronic cough and dyspnea. Obstructive symptoms can vary in severity, with a small number of patients exhibiting a considerable deterioration in pulmonary function that can ultimately evolve into respiratory insufficiency. Pulmonary nodules are indicative of a well-differentiated neuroendocrine proliferation that encompasses the foci of pulmonary neuroendocrine cells hyperplasia (PNECH), tumorlet, and carcinoid tumors.

Clinical symptoms of DIPNECH overlap with those of several other common pulmonary conditions, including asthma, and chronic obstructive pulmonary disease, which can make the diagnosis of DIPNECH challenging in a clinical setting. Accordingly, a review study found that the average time between the onset of symptoms and confirmation of the diagnosis was around 8.6 years, which is likely explained by the lack of clear clinical diagnostic criteria. The histologic finding of pulmonary neuroendocrine proliferation alone is currently considered to be suboptimal for a definitive diagnosis of DIPNECH, given the difficulty in distinguishing idiopathic pulmonary neuroendocrine proliferations from reactive lesions. However, evidence supports that neuroendocrine proliferation related to DIPNECH or associated with carcinoids are often more florid. A more recent study suggested histologic criteria to diagnose DIPNECH on the basis of the number of foci of neuroendocrine proliferations. However, the conclusions related to DIPNECH diagnoses were on the basis of a correlation with carcinoid co-occurrence with no defined established criterion. In addition, the study lacked any standardization for sampling variations.

Identifying the appropriate clinical criteria for the diagnosis of DIPNECH represents an obstacle to improving our understanding of this condition. Currently, there is no consensus on whether a histologic examination alone can be used to establish the diagnosis of DIPNECH cases. Previous studies that have attempted to propose DIPNECH clinical diagnostic criteria on the basis of a combination of symptoms, biochemical, and pulmonary function tests, radiologic data, and histologic examination were all empirical. Furthermore, none of the proposed criteria have been evaluated in an independent cohort. In addition, there is a lack of substantive research on how to integrate the histologic diagnosis with radiologic features, clinical symptoms, and pulmonary function tests to improve diagnostic accuracy. The lack of robust clinical or pathologic diagnostic criteria for DIPNECH cases poses an important problem in routine practice. On the basis of this premise, this study was designed to develop diagnostic criteria for the diagnosis of DIPNECH by employing univariate and multivariate models.

Materials and Methods

Participants and Data Source

The study included a retrospective cohort of consecutive cases of surgical pulmonary resections for low-grade and intermediate-grade neuroendocrine pulmonary tumors (typical and atypical carcinoids), tumorlets, and pulmonary neuroendocrine hyperplasia diagnosed at The Québec Heart and Lung Institute of Québec City (Canada) from 2000 to 2017. Cases were retrieved from the pathology department and biobank databases of our institution. This study was conducted in accordance with the amended Declaration of Helsinki. Surgical specimens were obtained from the Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec site of the Québec Respiratory Health Network Tissue Bank (www.tissuebank.ca). The local Institutional Ethics Review Board approved the protocol, and written informed consent was obtained from all patients at the time of lung resection or biopsy (#21250). Clinical presentation and radiologic data were not considered as part of the inclusion criteria. Cases were excluded when pathologic material was lacking. The study design is outlined in Figure 1.

Variables Collection

Clinical Parameters. Clinical data were retrieved by internal medicine, pathology, and radiology residents (Drs. Beland, Sazonova, and Hamel) from electronic medical files. This information included age, sex, and medical history (including tobacco use, symptoms, duration of symptoms, and physical examination findings). Shortness of breath symptoms were graded using the Medical Research Council scale. Pulmonary function tests and spirometry results were reevaluated by a pulmonologist (Dr. Provencher) under blinded conditions. Any signs of small and large airway obstruction (defined as the ratio of forced expiratory volume in 1 s and forced vital capacity <0.70), air trapping (residual lung volume >150% of predicted), and impaired
diffusing capacity of the lungs for carbon monoxide (defined as diffusing capacity for carbon monoxide [DLCO] <80% of predicted), measured according to contemporary guidelines,\(^1,2\) were recorded.\(^{17,18}\)

**Pathologic Parameters.** For all cases, archival hematoxylin and eosin–stained slides of the lung parenchyma from pulmonary resection specimens were reviewed by a thoracic pathologist (Dr. Joubert) and a pathology resident (Dr. Sazonova). When deemed necessary, additional immunohistochemistry stains, including chromogranin, CD56, or synaptophysin were performed to confirm the presence or absence of neuroendocrine lesions. The number of tumorlets and sites of PNECH were evaluated, although blinded to any other patient information. To better account for sampling variations, the number of bronchioles was counted on each slide. This is expressed as a total number of pulmonary neuroendocrine lesions (PNELs) (calculated as the sum of tumorlets \([t]\) and foci of PNECH) per total number of bronchioles \([br]\). Then, the logarithmic conversion of the above ratio was calculated to facilitate statistical analysis. The above ratio was expressed as the logarithm of the total number of PNELs per total number of bronchioles, given as \(\ln([t+\text{PNECH}] / \text{br})\).

**Radiologic Parameters.** CT scans were reviewed by a thoracic radiologist and a radiology resident (Drs. Levèque and Hamel), which were characterized for the following: (1) the number of nodules (<5, 5–10, >10), their location (central or peripheral; apices or bases), their shape (oval, round, speculated, or other), the largest size of nodules present (in mm), and presence of calcification; (2) the number of segments with mosaicism (<5, 5–10, >10), their location (central or peripheral), and gradient (apices or bases); (3) presence of bronchiectasis; and (4) presence of bronchial thickening.

**Diagnosis Review**

The final diagnoses were determined by an expert panel comprising a pneumologist, a thoracic radiologist, and a thoracic pathologist. Cases with more than a single lesion on preoperative thoracic radiology and pulmonary neuroendocrine hyperplasia detected by pathologic evaluation or abnormal pulmonary function tests were all reviewed by the expert panel on an individual basis. The remaining cases were classified as DIPNECH-free by the expert panel without further review. Committee members had access to the recorded clinical, radiologic, and pathologic parameters but were blinded to the final diagnosis found in the medical files. They used four
diagnostic categories: (1) definitive (expert panel members could diagnose with certitude); (2) probable (expert panel members tended to diagnose DIPNECH, but some elements were missing; thus, the diagnosis was less certain); (3) possible DIPNECH (there were a few DIPNECH features but considered insufficient for diagnosis by expert panel members); and (4) absence of DIPNECH (expert panel members could confidently rule out DIPNECH with high certainty). The definitive and probable DIPNECH categories were combined into a DIPNECH-positive group, whereas possible DIPNECH and absence of DIPNECH categories were considered a DIPNECH-negative group. Disagreement among committee members was resolved through a plenary discussion, and if disagreement persisted, the case was put to vote to determine a final diagnosis (Fig. 1).

Statistical Analyses
The quantitative variables were described as means (SD) for normally distributed variables. The qualitative variables were defined by frequencies and percentages. The logarithm-transformed data for the ratio of PNEL per number of bronchioles (expressed as \( \ln[\text{PNEL}/\text{br}] \)) was used to facilitate statistical analysis. For continuous values, the Mann-Whitney-Wilcoxon test was used to compare two groups, whereas the Kruskal-Wallis test was used to compare multiple groups. Pearson chi-square or the Fisher exact tests were used for categorical values. The fitted models were evaluated for crude and adjusted odds ratios and 95% confidence interval. Receiver operating characteristic (ROC) curve analysis was performed to detect the cutoff for the number of positive minor DIPNECH criteria known from the literature to predict DIPNECH (minor DIPNECH criteria include the following: woman, aged 45–67 years, cough \( \pm \) dyspnea for 5–10 years, increased residual volume, total leucocyte count, fixed obstruction, low DLCO corrected with alveolar volume, diffuse pulmonary nodules 4–10 mm, >20 nodules mosaic attenuation or air trapping >50% of lung, the proliferation of pulmonary neuroendocrine cells, and elevated serum chromogranin A levels). Statistical analyses were performed using Statistical Analysis System Software version 9.4 (SAS Institute, Cary, North Carolina) and R Statistical Software version 3.3.3 with a two-sided significance level set at \( p < 0.05 \).

The predictors used in diagnostic criteria were chosen based on the literature. They were divided into three groups: clinical, radiologic, and pathologic criteria.\(^3\) Univariate analyses of clinical, radiologic, and pathologic parameters were conducted independently to evaluate their associations with DIPNECH categories. Next, a multivariate logistic regression model was employed with the response variable for the predictive model as the absence/presence of DIPNECH.

Results
The study cohort included a total of 105 consecutive cases with neuroendocrine lesions. The demographics are summarized in Table 1. Of the 105 cases, 17 were missing pulmonary function tests. Four of those 17 cases had earlier reports available that were used to supplement the data. In one case, data were missing on diffusion and pulmonary volumes only. However, in that case, spirometry data were reviewed and interpreted to be consistent with a restrictive pattern. A total of 52% of patients had at least one nodule on their CT scans, and 31% presented pulmonary mosaicism (Table 2). The primary tumor variable indicates the dominant lesion for which surgical resection was performed, and \( n \) represents the number of such lesions. A total of 28 cases had missing CT scans. Expiratory CT images were not available in our cohort. Radiology reports of CT scans were used as substitutes for missing data. Of the 105 cases analyzed, 27 were diagnosed as DIPNECH. In six of them, PNELs were histologically confirmed in at least two different anatomical lung locations, which complied with the WHO DIPNECH definition of the generalized proliferation of neuroendocrine cells.\(^1\)

Univariate Analysis
The diagnostic criteria included clinical, radiologic, and pathologic variables listed in Tables 1 to 3 (column 1), respectively. The results of the univariate model using clinical, pathologic, and radiologic variables are presented in Tables 1 to 3. OR greater than 1 implies that patients are at a relatively higher risk of being classified as DIPNECH. Of the 27 clinical factors, we found nine variables to be statistically significant for a \( p \) value of 5%. We found age, male sex, previous chronic obstructive pulmonary disease diagnosis, obstructive abnormalities on pulmonary function tests (Table 1) along with radiologic evidence of pulmonary nodules and mosaicism (Table 2) as significant predictors (\( p < 0.05 \)) of DIPNECH status in this sample. In addition, among the pathologic variables, absolute numbers of PNELs, including the number of bronchioles affected by PNECH, and the number of tumorlets were substantially higher in the DIPNECH category. In addition, after adjustment for sampling variations, the ratio of the total number of PNELs to the number of bronchioles remained considerably higher in the DIPNECH category (Table 3).

Multivariate Analysis
The following variables were retained for the multivariate analysis: age, sex, air trapping, multiple
pulmonary nodules (>10), mosaicism, and logarithm of the total number of PNELs per total number of bronchioles. Employing a multivariate model on the above-mentioned variables resulted in a logarithm of the total number of PNELs and multiple pulmonary nodules as independent predictors of DIPNECH cases (Table 4).

**ROC Curve Analysis**

The ROC curve analysis revealed that the presence of greater than or equal to four positive, minor DIPNECH clinical and radiologic criteria (listed previously) was sufficient to predict DIPNECH with an accuracy of 76%, a sensitivity of 70%, and a specificity of 78%. In addition, the cutoff value for the ratio of the total number of PNELs to the number of bronchioles was tested in the multivariate model as a continuous value. The ROC curve analysis using this variable revealed that a cutoff of 0.1277 exhibited a sensitivity of 96% and a specificity of 95% to predict the DIPNECH (not reported in the article).

**Discussion**

DIPNECH remains a condition difficult to diagnose owing to the lack of validated diagnostic criteria. In this study, we identified air trapping and multiple pulmonary nodules to be specific predictors of DIPNECH in the presence of neuroendocrine lesions, as exhibited by the pathological abnormalities-based test. In addition, it was reported that given adequate sampling, pathological assessment alone could diagnose DIPNECH with fairly high levels of sensitivity and specificity. Therefore, this study refines the criteria for diagnosing DIPNECH and provides actuarial criteria for using clinicopathologic data to guide decision-making in such cases.

In a pathological-based setting, usually in the context of carcinoids, DIPNECH is defined by the presence of neuroendocrine cell hyperplasia and tumorlets. However, the presence of a neuroendocrine lesion on a small biopsy is insufficient by itself for diagnosing DIPNECH as sporadic neuroendocrine tumors are more typically seen, and reactive neuroendocrine lesions such as neuroendocrine hyperplasia has also been described in several contexts. Furthermore, the proliferation of neuroendocrine cells can be scattered in lung parenchyma that is adjacent to the tumor; however, this largely depends on the number of samples taken for histologic examination. Earlier studies identified demographic, clinical, and radiologic parameters related to DIPNECH and multiple carcinoid tumors. Some
studies have evaluated histologic criteria but without consideration of clinical and radiologic characteristics. Attempts were made to propose a more comprehensive set of diagnostic criteria for DIPNECH on the basis of a set of clinical parameters. However, the criteria that emerged from these studies were provisional and non-validated. Moreover, there is no consensus on the minimum criteria required to diagnose DIPNECH cases. Our study introduced an expert-panel approach that established a reference standard given the lack of a single definitive standard test. The conclusions from the expert panel were used as reference to determine a diagnosis for each case in the cohort. The basis of this approach is to unify and standardize the clinical expertise of physicians from multiple relevant fields. This approach has been reported to be valid for studies in which multiple diagnostic predictors need to be considered and in which there is no established consensus on the diagnostic criteria.

In this study, we comprehensively assessed the association of clinical, pathologic, and radiologic variables with the occurrence of DIPNECH. To the best of our knowledge, this is the largest single-institution cohort of DIPNECH cases on which the proposed criteria have been evaluated. To achieve this, we employed univariate and multivariate models. We found that age, female sex, the presence of symptoms of air trapping, the presence of multiple pulmonary nodules, mosaicism, and bronchial thickening were important characteristics of patients with DIPNECH, which is in line with the findings from other studies in the literature. Using radiologic data, we found pulmonary nodules and mosaicism as significant predictors ($p < 0.05$) of DIPNECH diagnosis. Among the pathologic variables, we found the absolute numbers of PNELs and the number of tumorlets as significant predictors ($p < 0.05$) for the diagnosis of DIPNECH cases. Using a multivariate model, we found the total number of PNELs and multiple pulmonary nodules as independent predictors of DIPNECH cases. The performance of our selected set of criteria (variables presented in Tables 1–3), revealed an accuracy of 76% (with a sensitivity of 70% and specificity of 78%). This analysis was performed using only the clinical and radiologic minor DIPNECH criteria in the ROC curve analyses. On the basis of this premise, our

### Table 2. Radiologic Characteristics of Patients With DIPNECH Versus Non-DIPNECH

| Characteristic                  | All n = 77, n (%) | DIPNECH n = 23, n (%) | Non-DIPNECH n = 54, n (%) | OR (95% CI) | p Value |
|--------------------------------|-------------------|-----------------------|----------------------------|-------------|---------|
| **Primary tumor**              |                   |                       |                            |             |         |
|                                | 64 (61.0)         | 45 (70.3)             | 19 (64.0)                  | 1.0 (0.3-3.5) | 0.9377  |
| **Pulmonary nodules presence** |                   |                       |                            |             |         |
| 0                              | 41 (39.0)         | 39 (95.1)             | 2 (4.9)                    |             | <0.0001 |
| 1-10                           | 34 (32.4)         | 22 (64.7)             | 12 (35.3)                  |             |         |
| >10                            | 15 (14.3)         | 3 (20.0)              | 12 (80.0)                  |             |         |
| **Localization**               |                   |                       |                            |             |         |
| Bilateral                      | 29 (27.6)         | 11 (37.9)             | 18 (62.1)                  | 28.6 (5.7-143.3) | 0.0027 |
| Inferior third                 | 8 (7.6)           | 5 (62.5)              | 3 (37.5)                   | 10.2 (1.4-76.9) | 0.0004 |
| Middle third                   | 3 (2.9)           | 2 (66.7)              | 1 (33.3)                   | 8.5 (0.5-138.7) | 0.0022 |
| Upper third                    | 4 (3.8)           | 3 (75)                | 1 (25)                     | 5.7 (0.4-82.2) | 0.0001 |
| No gradient third              | 26 (24.8)         | 10 (38.5)             | 16 (61.5)                  | 27.2 (5.3-138.8) | 0.0001 |
| **Shape**                      |                   |                       |                            |             |         |
| Round                          | 25 (23.8)         | 12 (48.0)             | 13 (52.0)                  | 15.3 (3.4-70.0) | 0.0022 |
| Oval                           | 14 (13.3)         | 6 (42.9)              | 8 (57.1)                   | 18.6 (3.5-99.1) | 0.0022 |
| Irregular                      | 1 (1.0)           | 1 (100)               | 0 (0)                      | 4.0 (0.0-543.5) | 0.0001 |
| **Density**                    |                   |                       |                            |             |         |
| Solid                          | 34 (32.4)         | 16 (47.1)             | 18 (52.9)                  | 19.7 (4.1-95.2) | 0.0001 |
| GGO                            | 3 (2.9)           | 2 (66.7)              | 1 (33.3)                   | 8.8 (0.5-142.6) | 0.0001 |
| Mixed                          | 3 (2.9)           | 1 (33.3)              | 2 (66.7)                   | 35.0 (2.2-570.6) | 0.0001 |
| Size of the biggest nodule, mm (mean + SD) | 3.4 (4.3) | 1.9 (3.3) | 7.0 (4.4) | 1.4 (1.2-1.6) | 0.0001 |
| **Mosaicism**                  |                   |                       |                            |             |         |
| 28 (26.7)                      | 12 (42.9)         | 16 (57.1)             | 6.9 (2.5-19.0)             |             |         |
| Mosaicism localization         |                   |                       |                            |             |         |
| Bilateral                      | 29 (27.6)         | 11 (37.9)             | 18 (62.1)                  |             |         |
| Unilateral                     | 11 (10.5)         | 8 (72.7)              | 3 (27.3)                   |             |         |
| Bronchiectasis                 | 3 (2.9)           | 1 (33.3)              | 2 (66.7)                   | 5.1 (0.4-58.7) | 0.0001 |
| Bronchial thickening           | 18 (17.1)         | 7 (38.9)              | 11 (61.1)                  | 6.2 (2.0-19.3) | 0.0001 |

Note: Values are given in number (%) unless indicated otherwise.

CI, confidence interval; DIPNECH, diffuse idiopathic pulmonary neuroendocrine hyperplasia; GGO, ground-glass opacity.
findings can help identify a possible diagnosis of DIPNECH without requiring a pathological confirmation of a neuroendocrine lesion. However, a larger cohort of studies is warranted to confirm this finding, which can eventually improve the clinical management of DIPNECH cases. Our results reveal that histologic diagnosis from the pulmonary resections with adequate sampling is a strong predictor of DIPNECH. Our data are, thus, consistent with those of other studies reporting that higher numbers of neuroendocrine lesions in a specimen yield a greater likelihood of DIPNECH cases. Our results reveal that histologic findings consistent with neuroendocrine lesions increases the likelihood of finding consistent lesions.

In addition, we validated the criteria proposed by Carr et al., on our cohort, which is the largest assembled data set from a single institution. These diagnostic criteria were derived from a cohort of 30 patients and diagnosed DIPNECH on the basis of patient demographics, clinical features, pulmonary function tests, CT scans, transbronchial and surgical lung biopsy findings along with serum markers (i.e., chromogranin A). In this study, the chromogranin A levels were not considered because most of our patients had pulmonary carcinoid tumors known to contribute to the chromogranin A elevation, which diminished the meaningfulness of the marker results. The minor criteria, as defined by Carr et al., exhibited an accuracy of 68% (with a sensitivity of 81% and specificity of 63%). These minor criteria proved to be more sensitive but less specific and had lower accuracy in performance than our selected criteria.

The limitations of this study are summarized below. First, patient selection may have introduced a selection bias, which is a frequent drawback of retrospective study designs. Second, these patients were surgically resected cases with a diagnosis of neuroendocrine lesions. Hence, it should be emphasized that the studied cohort included only cases with DIPNECH-related or non-DIPNECH-related neuroendocrine lesions. The external validity of our results in patients for whom a PNEL has not been histologically confirmed remains unknown. Third, expert panel members had access to all the data, including pathologic reports, which may have introduced a bias in the study design. However, this approach has been widely adopted by other studies and, in our opinion, provides the best evidence given the current state of knowledge. Fourth, the limited number of cases might have precluded the identification of some independent variables in the multiple regression tests and decision tree, which may have resulted in the loss of some predictors in the diagnostic criteria and a lower level of sensitivity. Finally, although missing data are inevitable in most retrospective studies, every effort has been made to retrieve all relevant patient characteristics, and so only a few cases remained with missing data. We believe that these missing data minimally affected the conclusions of this article because there were no missing data among cases identified as DIPNECH by the expert panel committee.

### Table 3. Histologic Characteristics of Pulmonary Tissue Samples From Patients With DIPNECH Versus Non-DIPNECH

| Characteristic                              | All | Mean (95% CI) without DIPNECH | Mean (95% CI) with DIPNECH | OR (95% CI) | p Value |
|---------------------------------------------|-----|-------------------------------|----------------------------|------------|---------|
| No. of carcinoid tumors at presentation     | 105 | 0.99 (0.96–1.01)              | 1.41 (0.69–2.13)           | 2.38 (0.61–9.31) | 0.2143  |
| No. of tumorlets                            | 105 | 0.04 (–0.01 to 0.08)          | 2.89 (1.69–4.09)           | 17.73 (4.17–75.45) | <0.0001 |
| No. of bronchioles with PNECH              | 105 | 0.25 (0.05–0.44)              | 11.78 (7.71–15.84)         | 2.59 (1.63–4.11) | <0.0001 |
| No. of bronchioles counted                  | 105 | 24.88 (20.94–28.83)           | 58.22 (41.36–75.09)        | 1.05 (1.02–1.07) | <0.0001 |
| No. of PNEL                                 | 105 | 0.30 (0.06–0.53)              | 14.81 (9.51–20.12)         | 2.20 (1.52–3.19) | <0.0001 |
| ln((t + PNECH)/br)                         | 105 | –6.30 (–6.66 to 5.93)         | –1.47 (–1.94 to –1.01)     | 3.17 (1.86–5.41) | <0.0001 |

CI, confidence interval; DIPNECH, diffuse idiopathic pulmonary neuroendocrine hyperplasia; ln(PNEL/br), logarithmic conversion of the total number of PNEL calculated as a sum of tumorlets and bronchioles with PNECH per total number of bronchioles; PNECH, pulmonary neuroendocrine cell hyperplasia; PNEL, pulmonary neuroendocrine lesion.

### Table 4. Multivariate Analysis With Stepwise Selection for the Ensemble of Predictors

| Step | Entered | DF | NumberIn | χ² Value | p Value |
|------|---------|----|-----------|----------|---------|
| 1    | ln((t + PNECH)/br) | 1 | 1 | 54.5763 | <0.0001 |
| 2    | Multiple nodules (>10) | 2 | 2 | 9.1019 | 0.0106 |

DF, degrees of freedom; ln((t + PNECH)/br): logarithmic conversion of the total number of PNELs calculated as a sum of tumorlets and bronchioles with PNECH per total number of bronchioles; PNECH, pulmonary neuroendocrine cell hyperplasia; PNEL, pulmonary neuroendocrine lesion.
Conclusions

Overall, introducing a reference standard with robust statistical analyses allowed developing diagnostic criteria on the basis of a scientific approach and evaluating performance parameters such as sensitivity, specificity, and accuracy. The study identified the logarithm of the total number of PNELs and multiple pulmonary nodules (>10) as independent predictors of DIPNECH cases in the presence of histologically confirmed neuroendocrine lesions. We also reported that, with adequate sampling, pathological assessment alone could diagnose DIPNECH. Owing to study limitations and the use of a cohort from a single institution, the validation of diagnostic criteria should be performed on external cohorts before they can be implemented in routine clinical practice.

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