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Original Contribution

Micropapillary adenocarcinoma of lung: Morphological criteria and diagnostic reproducibility among pulmonary pathologists

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ABSTRACT

Context: Invasive micropapillary adenocarcinoma (MPC) is an aggressive variant of lung adenocarcinoma, frequently manifesting with advanced stage lymph node metastasis and decreased survival.
Objective: Identification of this morphology is important, as it is strongly correlated with poor prognosis regardless of the amount of MPC component. To date, no study has investigated the morphological criteria used to objectively diagnose it.
Design: Herein, we selected 30 cases of potential MPC of lung, and distributed 2 digital images per case among 15 pulmonary pathology experts. Reviewers were requested to diagnostically interpret, assign the percentage of MPC component, and record the morphological features they identified. The noted features included: columnar cells, elongated slender cell nests, extensive stromal retraction, lumen formation with internal epithelial tufting, epithelial signet ring-like forms, intracytoplasmic vacuolization, multiple nests in the same alveolar space, back-to-back lacunar spaces, epithelial nest anastomosis, marked pleomorphism, peripherally oriented nuclei, randomly distributed nuclei, small/medium/large tumor nest size, fibrovascular cores, and spread through airspaces (STAS).
Results: Cluster analysis revealed three subgroups with the following diagnoses: “MPC”, “combined papillary and MPC”, and “others”. The subgroups correlated with the reported median percentage of MPC. Intracytoplasmic vacuolization, epithelial nest anastomosis/confluence, multiple nests in the same alveolar space, and small/medium tumor nest size were the most common criteria identified in the cases diagnosed as MPC. Peripherally oriented nuclei and epithelial signet ring-like forms were frequently identified in both the “MPC” and “combined papillary and MPC” groups.
Conclusions: Our study provides objective diagnostic criteria to diagnose MPC of lung.

1. Introduction

Among carcinomas, micropapillary patterns have been recognized as aggressive variants in organs such as breast, bladder, salivary gland, and colon [1-10]. Invasive adenocarcinoma with a micropapillary pattern has also been identified in the lung, and the majority of lesions

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have been determined to be primary tumors rather than metastatic lesions, with both cytokeratin 7 (CK7) and thyroid transcription factor (TTF1) reactivity [11]. Invasive micropapillary adenocarcinoma (MPC) has also been reported to have adverse prognosis in the lung [12-17]. Studies have shown that both intra- and extra- pulmonary metastasis as well as lymphovascular invasion (LVI) are common; and the 5 year survival rate after diagnosis is significantly lower compared to patients with other morphological variants and the same tumor stage [11,18-23]. Recurrence is more frequent in patients with MPC of lung compared to other patterns such as acinar or papillary [20,24-28]. Thus, overall, MPC of lung has been recognized as a distinct morphological marker with poor prognosis, even when it is present in small amounts [8,11]. Interestingly, the prognostic findings are similar regardless of the percentage of MPC found within the primary tumor [8,11].

To date, the precise morphological criteria to diagnose MPC of lung have not been objectively determined. Furthermore, diagnostic accuracy in equivocal cases has not been thoroughly assessed. Several research groups have proposed adherence to arbitrary definitions in breast, urinary bladder, lung, and other organs; nonetheless, these studies lack objectiveness in criteria selection [6,10,29-32]. Morphological features that have been described in MPCs of lung include: small papillary tufts freely lying within alveolar spaces/encased within thin walls of connective tissue spaces, few or no fibrovascular cores, spaces with flat endothelial or no lining, micropapillary tufts in lymphovascular spaces, and variants consisting of micropapillary tufts floating within cystic spaces lined with tumor cells [8,11,17,19,33]. Stromal retraction was also noted in many cases [18]. Size variation, including very small nests, has been a controversial topic, and researchers have studied consecutive sections of paraffin-embedded blocks to determine when cellular tufts extend or disappear in consecutive cuts (to address the size concern: small vs. medium or large nests) [19]. However, diagnostic reproducibility using specific criteria has not been thoroughly evaluated, and we continue to find inconsistencies in the studies reporting MPC of lung. For example, in 4 studies of lung adenocarcinoma (including > 200 patients), the average number of patients diagnosed with the micropapillary variant was markedly different; the average ranged between 3.4 and 41% among the studies [34-37]. The aforementioned findings indicate lack of diagnostic consistency, which should be addressed in our opinion.

Given the clinical needs, in our study, we aimed to evaluate the diagnostic interpretations among pulmonary pathologists in both unequivocal cases of MPC of lung and challenging ones where diagnosis was not straightforward. Furthermore, our intention was to determine the morphological features identified in cases that were diagnosed as MPC of lung with high percentage of agreement on diagnoses among reviewers.

2. Materials and methods

A total of 30 cases of adenocarcinoma of lung (only one to two slides per case), submitted by all the coauthors, were reviewed and selected by two of the authors (RM, JR). The selected cases included tumors with unequivocal areas of MPC morphology, others with areas of mixed histological patterns including MPC (but also papillary, acinar, etc.), and cases with areas that could be classified as “non-diagnostic for MPC” (Fig. 1A–F). Only cases with wedge resection, segmentectomy, lobectomy or pneumonectomy were included; biopsies were excluded from the study. A digital survey, consisting of three questions and two digital still images per case, was distributed to 15 pulmonary pathologists. Our goal was to determine if specific morphological criteria- reproducible among pathologists- were present to diagnose this entity, even when limited amount of tissue was available. The 15 participating pathologists (ACR, AC, RB, PC, YG, HDT, MLS, BTL, LMS, MBB, AB, KR, AA, RM, JR) were from 10 different institutions, including experts that have practiced outside the United States. Each pathologist was assigned a numerical code (1 to 15) to secure anonymity of the individual responses.

The digital survey involved interpretation of two static images of hematoxylin- and eosin- stained slides. The images included areas of parenchyma and others near the periphery. The criteria chosen for the study were selected by two authors (RM, JR), according to those established by the 2015 WHO Lung Tumor Classification, and relevant criteria identified in other cancer types where micropapillary patterns have been extensively described [5-10,11]. The images were chosen for illustrative purposes to solicit potential diversity in opinions; they were representative of parts of the tumors selected, an included a high power (40-60X) and a low power (10-20X) in each case. The remainder of the slide was not included for complete review. The survey comprised three questions addressing the following: diagnostic interpretation, percentage of MPC component observed in the images (quantitative assessment), and determination of the morphological criteria used to make a diagnosis, initially recorded in diagnostic interpretation (Table 1). Pathologists were given several weeks to answer the survey, and the survey could be interrupted and continued at any moment during the period of time provided (to prevent bias based on the survey including 30 cases with multiple choices available for each question). Given our study design, we predicted that we would be able to identify morphological criteria used by the pathologist to diagnose MPC and other types of adenocarcinoma such as papillary, acinar, and others.

Statistical analyses were performed using the R software for statistical computing (http://www.r-project.org/). The relationships of the pathologists' diagnostic interpretations and mean percentage of morphological criteria reported by case were assessed using unsupervised hierarchical clustering with Euclidean distance and complete linkage. The clustering analysis of the tumor cases, with the morphological criteria and diagnostic impressions, was visualized on a heatmap dendrogram using the “heatmap.2” function in the R package “gplots”. Weighted kappa was used to compare contingency tables with the subgrouping cluster, predicted by morphological criteria and diagnostic classification.

Additionally, the participating pathologists were separated in 2 groups, based on their years of experience in the field. The groups were designated as “less than 15 years” vs. “15 years or more”. Using heatmap dendrograms, we compared the diagnostic impressions and inter-observer reproducibility among each group. Overall percent of agreement (OPA) values were used to assess inter-observer reproducibility; OPA values were calculated by comparing each possible permutation between reviewers (pathologists) data and sub-groups. An analysis-of-variance (ANOVA) model was created to determine differences in the median MPC percentage and morphological criteria in each subgroup, as reported by the pathologists in the hierarchical subgroups. Differences between groups were assessed with a Tukey-Kramer pairwise comparison test. All statistics were two-sided, and a p-value < 0.05 was considered statistically significant.

3. Results

Hierarchical clustering analysis of the diagnostic interpretations among pulmonary pathologists (addressed in the first question of the survey) resulted in three subgroups with different predominant diagnoses: “others”, “mixed papillary with MPC”, and “MPC” (Fig. 2A). The aforementioned subgroups were designated as MPC0, MPC1, and MPC2, respectively, depending on the total amount of MPC component. The overall diagnostic percentage of agreement among all reviewers and all cases was 45.0% (CI, 43.2–46.7). The overall percent of agreement that the reviewers reached within the subgroups was 11.3% (CI, 10.6–11.9) for the 9 cases of MP0; 47.9% (CI, 47.3–48.6) for the 8 cases of MP1; and 57.5% (CI, 56.8–58.2) for 13 cases of MP2 (Fig. 2B). The median percentage of the MPC component identified among cases in each subgroup correlated with the diagnostic impressions initially recorded (addressed in the second question of the survey, Fig. 2C).

We calculated the average percentage reported for each criterion in

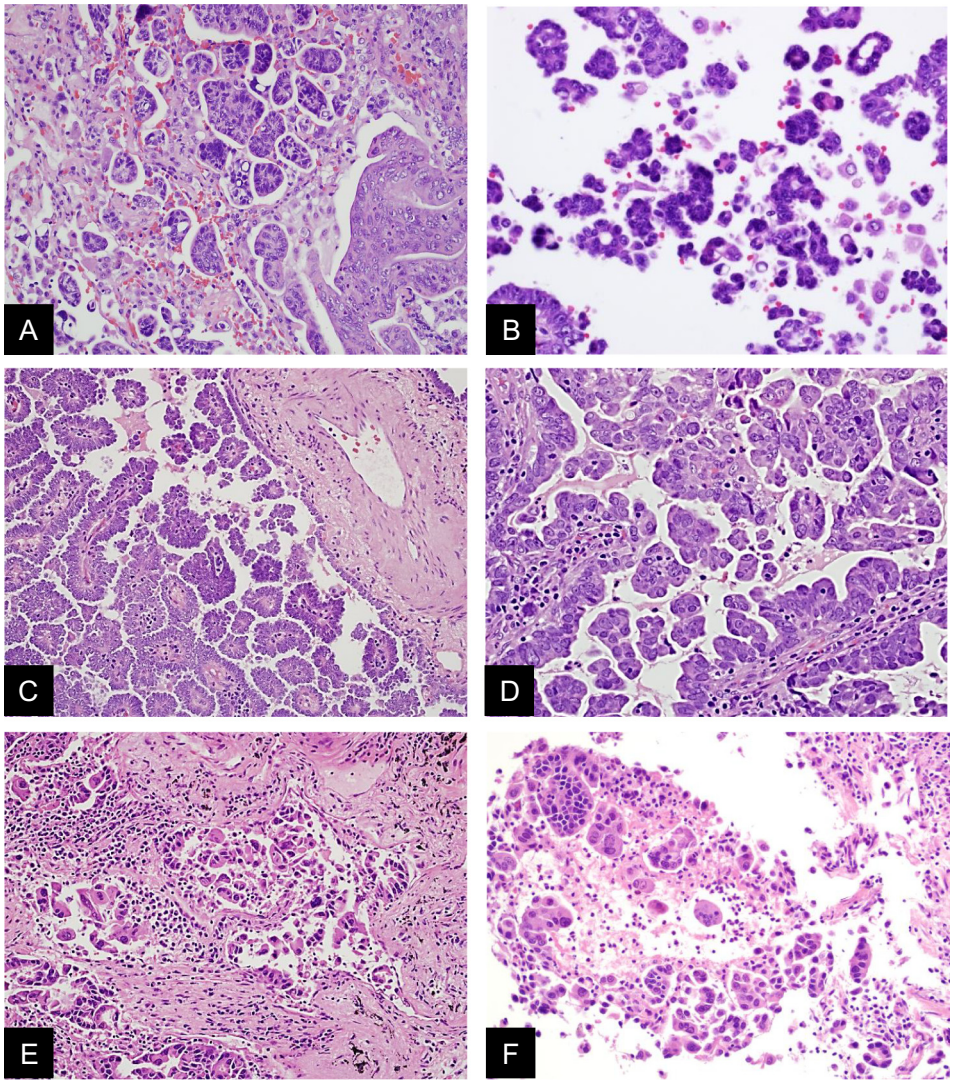


Fig. 1. Digital images of representative tumors chosen for the study are shown in A-F. Cases with unequivocal areas of micropapillary morphology were selected (A-B). Cases with admixed morphologies, such as papillary and micropapillary, were also selected (C-D). Additionally, tumors with challenging areas "suspicious for micropapillary" were selected for the study (E–F).

the subgroups (MPC0, MPC1, MPC2) for the 17 morphological features (addressed in the third question of the survey; Table 2). We further selected the morphological criteria with reported averages that were significantly different between at least two hierarchical subgroups ($n = 8$), and we eliminated those that overlapped in all three ($n = 9$) (Table 3). Our results showed that the percentage of MPC gradually increased in the hierarchical subgroups (MPC2 > MPC1 > MPC0), and 4 morphological criteria gradually increased within the same subgroups: "intracytoplasmic vacuolization", "multiple nests in same lacunar/alveolar space", "small tumor nest size (< 4 cells)", and "medium tumor nest size (< 12 cells)" (the former 3 were seen in MPC1 and MPC2 in ≥50% of the cases; $p = 0.048$, 0.005, 0.001, 0.004, respectively; Fig. 3A-D). In addition, the only criterion that was present almost exclusively within the MPC2 subgroup (predominantly MPC), in > 50% of the cases, was "epithelial nest anastomosis/confluence" (Fig. 3E).

We further evaluated the frequency of morphological criteria in groups with MPC histology (MPC1 and 2) as compared to MPC0 (small to no MPC component). Our results showed that "peripherally oriented nuclei" and "epithelial signet ring-like forms" were more commonly seen in MPC1 and MPC2, and were low to absent in the MPC0 subgroup ($p = 0.002$, 0.047, respectively). The detected percentage for both criteria did not differ significantly within the MPC1 and MPC2 groups (Tables 2 and 3). On a separate note, we identified that "central fibrovascular core" was present almost exclusively in the MCP subgroup (30% in MPC1, vs. 0–10% in MPC0 and MPC2, $p \leq 0.001$) (Table 2). Furthermore, cluster analysis, using the 8 morphological criteria, with significant mean differences between sub-groups in Table 2 yielded a dendrogram that also separated our 30 cases into 3 sub-groups (Fig. 4). The subgroups reported by the clustering analysis of diagnostic impression (Fig. 2A*)* and morphological criteria (Table 3) were in substantial agreement with each other (Kappa = 0.631, [CI, 0.420–0.843]).

Finally, we arbitrarily divided our reviewers into 2 groups based on their years of experience in the field. The groups were designated as "less than 15 years" vs. "15 years or more". We then assessed their diagnostic impressions among the tumor cases (Fig. 5). Statistical analysis showed that the overall percent of agreement reached within the pathologists of each group was significantly high and similar among the pathologists with less vs. > 15 years of experience: 50.5% vs. 41.3% (CI, 48.8–52.4; CI, 40.0–42.8, respectively).

Table 1
Survey design and questions (examined diagnostic criteria).

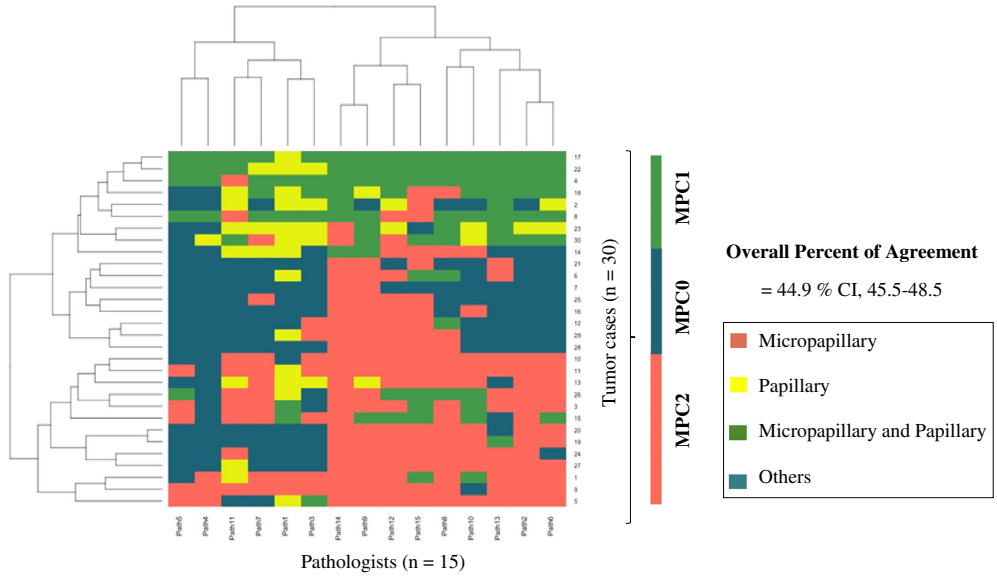
Survey questions per case	Answer options
1. What is the diagnosis?	a- Invasive micropapillary adenocarcinoma (MPC) of Lung b- Papillary Lung Adenocarcinoma c- MPC and Papillary Lung Adenocarcinoma d- Others
2. If present, what is the percentage of MPC seen in the case evaluated?	Write in the percentage in the blank provided
3. Of the morphologic criteria listed, indicate which are present (even if just focally) in the case evaluated:	Write an X in the column corresponding to those criteria identified (present) in the case evaluated:
• Columnar cells	__
• Elongate slender cell nests	__
• Extensive stromal retraction	__
• Lumen formation with internal epithelial tufting	__
• Epithelial signet ring-like forms	__
• Intracytoplasmic vacuolization	__
• Multiple nests in same alveolar space	__
• Back-to-back lacunar spaces	__
• Epithelial nest anastomosis	__
• Marked pleomorphism	__
• Peripherally oriented nuclei	__
• Randomly distributed nuclei	__
• Small tumor nest size	__
• Medium tumor nest size	__
• Large tumor nest size	__
• Fibrovascular core	__
• Spread through air-spaces (STAS)	__

4. Discussion

In this study, we investigated the objective morphological criteria used by pulmonary pathologists to diagnose MPC of the lung. The pathologists evaluated and provided their diagnostic interpretation for 30 tumor cases. The overall percent of agreement reached in their interpretation of the cases (MPC0, MPC1, and MPC2) was moderate (45.0%). We further evaluated the overall percent of agreement among the three hierarchical subgroups individually. Our results showed that the MPC0 subgroup had the lowest overall percent of agreement (11.3%); nonetheless, the percentage increased significantly in MPC1 (47.9%) and even more in MPC2 (57.5%). Coincidentally, the median percentage of MPC reported in each subgroup followed the same pattern; it was lowest in MPC0, and increased in the MPC1 and MPC2 groups. The higher percent of agreement among the cases, including at least one component of MPC (MPC1 and 2), indicates that the selected morphological features can be successfully applied in MPC pattern identification.

We subsequently focused on identifying morphological criteria that are useful to diagnose MPC of the lung. Thus, we did not further analyze the features that did not show significant differences between diagnostic subgroups (columnar cells, elongated slender cell nests, extensive stromal retraction, lumen formation with internal epithelial tufting, back-to-back lacunar spaces, marked nuclear pleomorphism, randomly distributed nuclei, large tumor nest size, and STAS). We drew several conclusions after considering the remaining 8 morphological criteria (see Table 3). The following 5 specific criteria were encountered more frequently in the categorized subgroups with MPC histology: intracytoplasmic vacuolization, epithelial cell anastomosis/confluence,

A



B

Hierarchical Subgroup:	Designation:	Overall Percent of Agreement
Others	MPC0	11.3% CI (10.6-11.9)
Micropapillary and papillary	MPC1	47.9% CI (47.3-48.6)
Micropapillary	MPC2	57.5% CI (56.8-58.2)

C

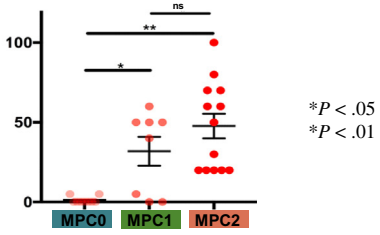
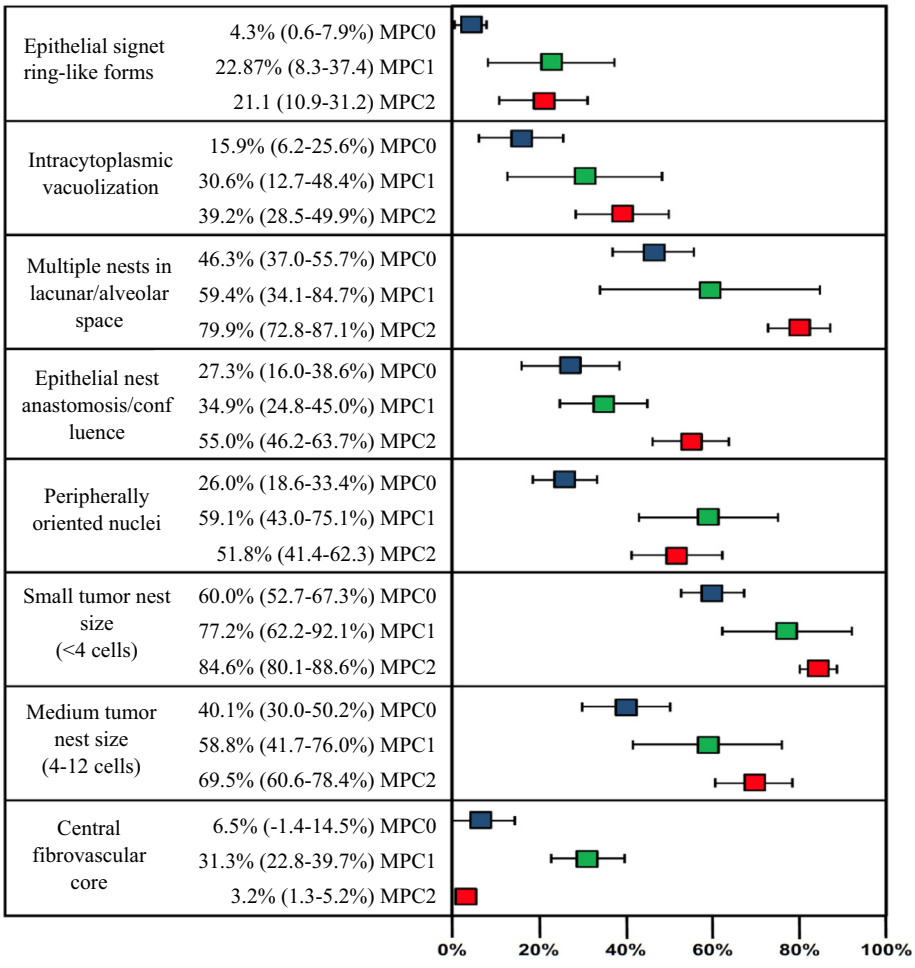


Fig. 2. Hierarchical clustering analysis of the diagnostic interpretations among pulmonary pathologists (addressed in the first question of the survey) resulted in three subgroups with different predominant diagnoses: others, mixed papillary with micropapillary, and invasive micropapillary adenocarcinoma (MPC) of lung, designated as MPC0, MPC1, and MPC2, respectively (A). Based on hierarchical subgroups, the overall percent of agreement among reviewers was higher in the order MPC2 > MPC1 > MPC0 (B). The median percentage of micropapillary component, identified among cases in each subgroup, correlated with the diagnostic impressions initially recorded (C).

Table 2
Mean percentage of morphological features reported by pathologists as present per hierarchical subgroups. Values in parenthesis highlight the confidence intervals of the averages.

Morphologic criteria	MPC0 (n = 9)	MPC1 (n = 8)	MPC2 (*n* = 13)
Columnar cells	36.5% (26.3–46.9%)	38.0% (32.1–43.9%)	26.5% (21.0–32.0%)
Elongated slender cell nests processes	32.3% (23.2–41.3%)	42.2% (30.8–53.5%)	38.0% (32.0–44.0%)
Extensive stromal retraction	3.4% (0.8–5.9%)	7.1% (1.4–12.8%)	16.8% (5.8%–27.8%)
Lumen formation with internal epithelial tufting	26.2% (18.0–34.4%)	43.5% (22.9–64.2%)	36.8% (28.0–45.7%)
Epithelial signet ring-like forms	4.3% (0.6–7.9%)	22.8% (8.3–37.4%)	21.1% (10.9–31.2%)
Intracytoplasmic vacuolization	15.9% (6.2–25.6%)	30.6% (12.7–48.4%)	39.2% (28.5–49.9%)
Multiple nests in same space	46.3% (37.0–55.7%)	59.4% (34.1–84.7%)	79.9% (72.8–87.1%)
Back-to-back lacunar spaces	9.7% (6.3–13.0%)	24.0% (8.7–39.3%)	29.4% (13.1–45.8%)
Epithelial nest anastomosis/confluence	27.3% (16.0–38.6%)	34.9% (24.8–45.0%)	55.0% (46.2–63.78%)
Marked nuclear pleomorphism	31.4% (19.4–43.4%)	33.0% (23.5–42.5%)	35.0% (27.4–42.5%)
Peripherally oriented nuclei	26.0% (18.6–33.4%)	59.1% (43.0–75.1%)	51.8% (41.4–62.3%)
Randomly distributed nuclei	57.8% (48.9–66.7%)	43.2% (27.0–59.4%)	68.7% (62.0–75.3%)
Small tumor nest size	60.0% (52.7–67.3%)	77.2% (62.2–92.1%)	84.6% (80.1–88.6%)
Medium tumor nest size (4–12 cells)	40.1% (30.0–50.2%)	58.8% (41.7–76.0%)	69.5% (60.6–78.4%)
Large tumor nest size (> 12 cells)	9.6% (0–19.3%)	21.7% (11.9–31.6%)	29.6% (18.9–40.3%)
Nest cells central fibrovascular core	6.5% (−1.4–14.5%)	31.3% (22.8%–39.7%)	3.2% (1.3%–5.2%)
STAS (spread through airspaces)	49.9% (37.6–62.1%)	51.9% (44.4–59.3%)	43.4% (34.1–52.8%)

Table 3
Mean percentage of the 8 morphologic criteria with significant differences among the hierarchical subgroups.



multiple nests in same lacunar/alveolar space, small tumor nest size, and medium tumor nest size. In particular, the last 4 criteria were seen in ≥30% of the cases within the MPC1 subgroup, and ≥ 55% of the cases within the MPC2 subgroup, suggesting that their presence within an adenocarcinoma of the lung is associated or linked to MPC histology. The cases with MPC histology were also associated with intracytoplasmic vacuolization; however, this occurred less frequently (approximately 30% in MPC1 and 40% in MPC2). Epithelial nest anastomosis/confluence seemed to be the least reliable criterion to distinguish between tumors with admixed histological patterns, including MPC and papillary (MPC1 subgroup), and tumors without an MPC component (MPC0, referred to as “others” in our study).

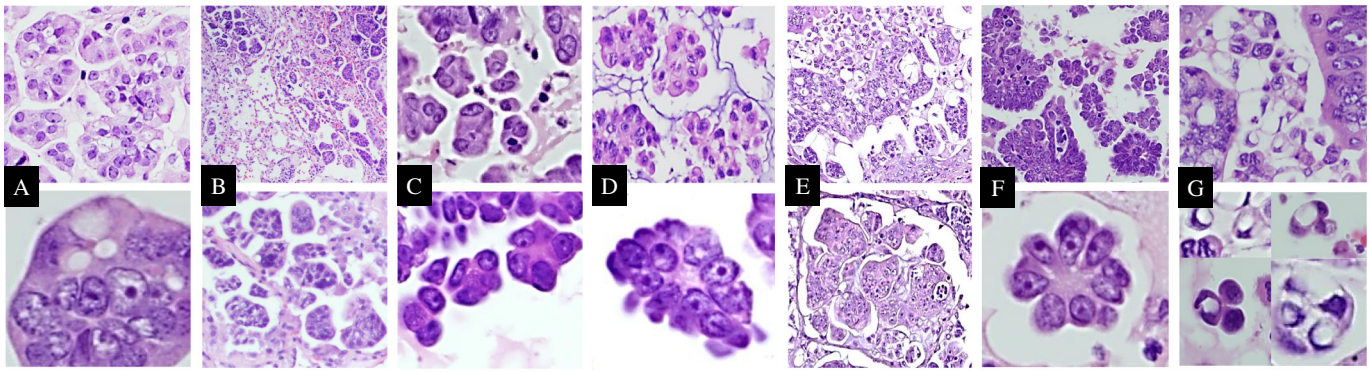


Fig. 3. The most commonly identified morphological criteria associated with diagnosis of MPC (both MPC1 and MPC2) were: intracytoplasmic vacuolization (A), multiple nests in same lacunar/alveolar space (B), small tumor nest size (< 4 cells) (C), medium tumor nest size (< 12 cells) (D), epithelial nest anastomosis/confluence (E), peripherally oriented nuclei (F), and epithelial signet ring-like forms (G).

On another note, the criteria "peripherally oriented nuclei" and "epithelial signet ring-like forms" were encountered almost equally in the MPC1-2 subgroups (percentages were not significantly different), and were nearly absent in MPC0. However, the former criterion was identified more frequently in the MPC1–2 groups (≥ 50%) compared to MPC0 (20–25%). This suggests that the presence of "peripherally oriented nuclei" is a slightly more reliable criterion to diagnose a tumor with a component of MPC of lung and/or with MPC as a unique histological pattern. Additionally, our results showed that the presence of a central fibrovascular core favors diagnosis of a tumor with papillary morphology (a feature considered to be characteristic of this histological variant) but is not helpful to distinguish micropapillary from other adenocarcinoma types.

The internal validity of our results is supported by a strong agreement of diagnostic sub-groups, predicted by two different cluster analyses based on two independent criteria: morphological and diagnostic interpretation. These results were independent of the years of experience that each individual pathologist had in the field.

Our study had certain limiting factors that could have caused significant bias, for example, the fact that the reviewers knew that the study aimed to improve diagnosis of MPC of lung. Also, the reproducibility of our results could have been impacted because an exact definition or illustrative image for each criterion was not provided. Additionally, we were unable to determine the sensitivity/specificity of our criteria (which have been assessed in similar studies in the past) [5]. This limitation is attributed to the fact that currently, neither a gold standard nor an objective assessment to determine whether a case has or does not have MPC histology can be found in the literature (hence the importance of this study).

Other constraints of our study include the limited heterogeneity observed between the dataset among raters. This did not allow us to reliably trust the Fleiss' kappa function in most of our statistical analyses (executed with the "kappa.fleiss" in R). Low heterogeneity can influence the formula to calculate Fleiss' kappa, creating a paradoxical result that does not correlate with the real agreement [15]. Homogeneity of the data increases the probability of responses arising by chance when applying this statistical tool (this topic has been extensively studied in the past, and further details are beyond the scope of this manuscript) [38-39]. Thus, in our cases, we decided to report OPA to show the high concordance that was truly seen between raters.

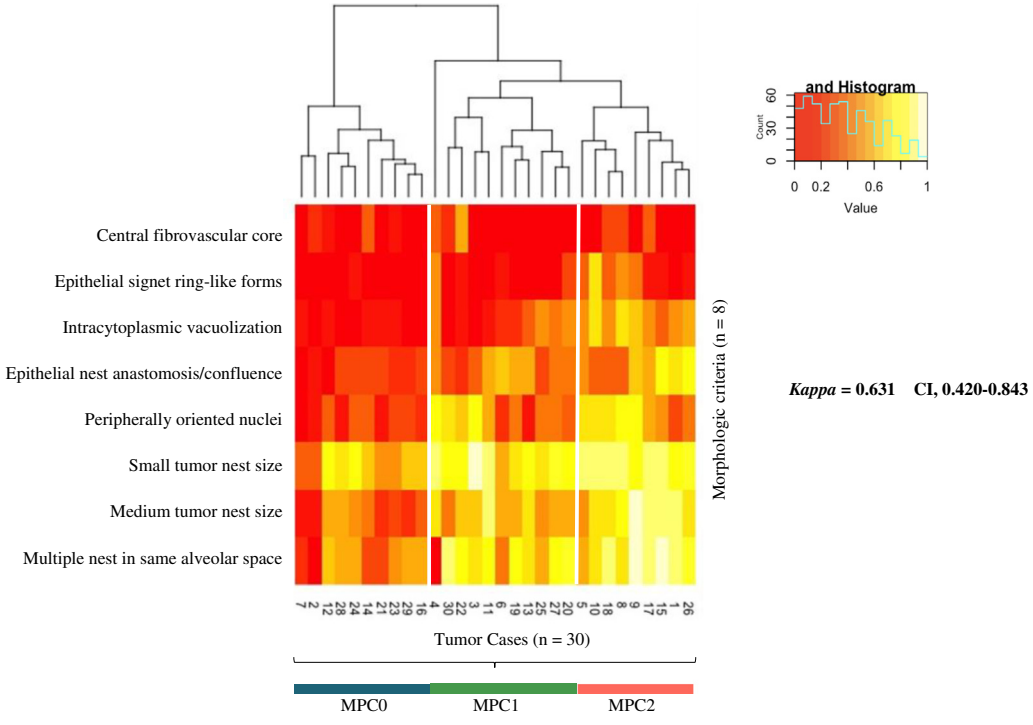


Fig. 4. A total of 8/17 morphological criteria demonstrated significant differences among hierarchical subgroups. These criteria were compared with the diagnostic interpretations of the pathologists through hierarchical clustering analysis. Results from the dendrogram demonstrated strong agreement among the subgroups from the hierarchical cluster based on both diagnostic impression and the reported morphological criteria (Kappa = 0.631 CI, 0.420–0.843).

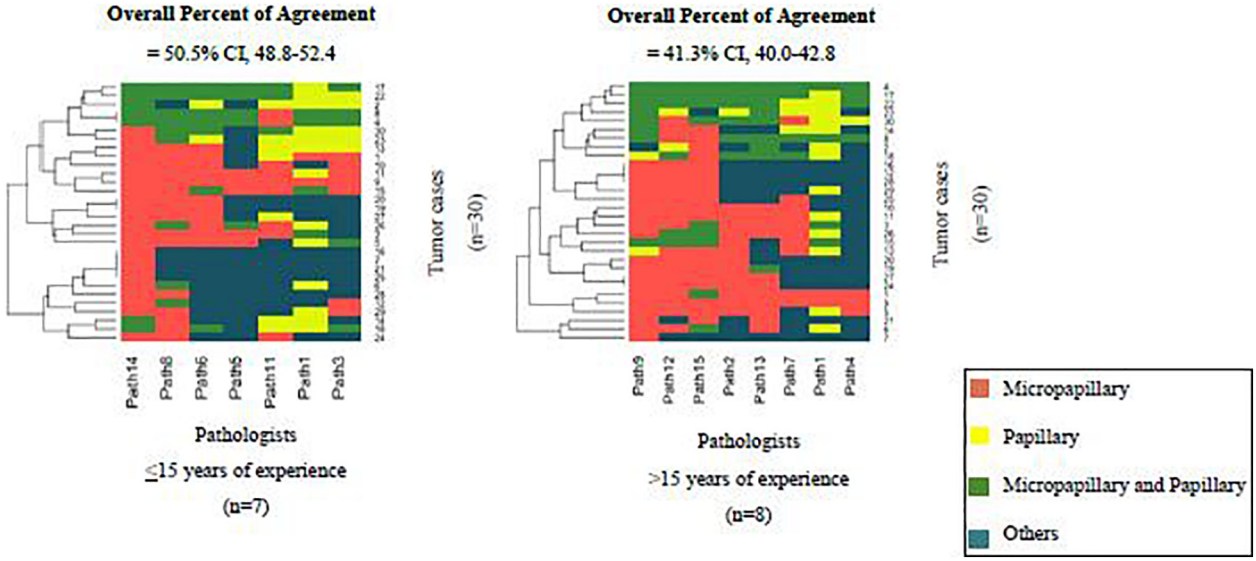


Fig. 5. Hierarchical clustering analysis of the diagnostic interpretations of pulmonary pathologists with 15 years of experience or less (50.5%) vs. pathologists with > 15 years of experience in the field (41.3%) showed that no significant differences existed between the groups.

Another example showing the absence of higher heterogeneity in our study was the use of narrow/limited options for diagnostic interpretations. Our design preset the answer to our first question to four specific variants: MPC, papillary, mixed papillary and MPC, or others. More so, the pathologists were provided with two picutres of representative areas selected of each slide. This could have biased the pathologists towards a particular diagnosis, and could have influenced the number of cases diagnosed with MPC and papillary components. By not providing additional options for mixed histological patterns (other than papillary mixed with MPC), we could have not taken into account MPC cases exhibiting mixed patterns with non-papillary variants such as acinar, lepidic or solid. This is evidenced by the rare cases within the MPC0 group, for which a percentage of MPC was provided in the second question of the survey, even though diagnosis of "others" had been selected.

Importantly, we had to take into consideration in the interpretation of our results the fact that the static digital images used in the study showed a limited area of tumor; and that we decided to also include pictures of particular areas that may have not been classic of the main tumor diagnosis. Our goal was not to assess consistent reproducibility of the correct diagnosis for the cases included in the study (whole slide imaging would have been a more sensitive technique to achieve this). Moreover, we aimed to address the opinion of experts regarding particular tumor areas including some where the diagnosis could have been. These areas spanned a morphological spectrum that included MPC of lung mimics, MPC of lung mixed with papillary, and areas with more "classic" MPC.

Despite these potential limitations, our study provides an unprecedented, strong, multi-institutional, detailed diagnostic approach among experts in the field; we believe that this study will assist the identification of MPC of the lung. Given that currently there is no gold standard to diagnose this entity in the lung, our study aimed to address the morphological criteria encountered in MPC of lung cases in which pulmonary pathologists agreed on the diagnoses.

Several interesting issues remain to be addressed in future studies, notwithstanding the fact that they are beyond the scope of this study. For example, intra-observer variability amongst pathologists who diagnosed the same cases over time. This parameter would objectively test consistency, precision, and internal reproducibility more thoroughly. More so, it would have been interesting to determine the association of clinicopathological associations and overall prognosis to individual morphological features observed in MPC of lung. Additionally, it would be interesting to assess the interpretation of cases and compare the reproducibility and overall percent of agreement among pathologists, after proper training sessions regarding diagnostic morphological features have been evaluated in the study. Also, it is notable that papillary lung adenocarcinoma showed a tendency to cluster with MPC; this illustrates the challenge to separate the two entities in cases with limited tissue sampling. Finally, considering the genotypic correlation and examining driver mutations and lineage markers in tumors with micropapillary morphology among lung adenocarcinomas has relevant research potential. Further studies are necessary to address this.

In summary, our study showed that the significant features for MPC diagnosis are: "multiple nests in same lacuna or alveolar space", "small to medium tumor nest size", and "epithelial nests anastomosis/confluence". In addition, "intracytoplasmic vacuolization" could also be useful; however, it was not identified in a significant number of the cases in this study, and thus we did not consider it as important as the other criteria. Also, "peripherally oriented nuclei" and "epithelial signet ring-like forms" can be useful in cases with admixed tumor types. Finally, as it has been previously described, our study showed that the presence of fibrovascular cores corresponds to diagnosis of papillary adenocarcinoma and not MPC. However, it is possible that this feature can be a confounding factor favoring sole papillary adenocarcinoma diagnosis in cases with mixed papillary and MPC histology. In these cases, we suggest searching for additional features such as "peripherally oriented nuclei" and "epithelial signet ring-like forms". These two additional features were commonly seen in the MPC1 (mixed papillary and MPC) subgroup of our study, and could prove to be useful.

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Disclosure

The authors of this manuscript have no disclosures.

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