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Comparative analysis of artificial intelligence–assisted and manual assessment of the Ki-67 proliferation index in pulmonary neuroendocrine tumors

Gizem Teoman, Zeynep Türkmen Usta, Zeynep Sağnak Yılmaz, Şafak Ersöz

ORCID:
Gizem Teoman: 0000-0001-5767-5007
Zeynep Türkmen Usta: 0000-0002-0757-3077
Zeynep Sağnak Yılmaz: 0000-0002-3225-2486
Şafak Ersöz: 0000-0001-5521-7133

Department of Medical Pathology, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye

Address for correspondence:
Dr. Gizem Teoman, Department of Medical Pathology, Karadeniz Technical University Faculty of Medicine, Trabzon, Türkiye.
E-mail: dr.gizemcivelek@gmail.com

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Abstract:

BACKGROUND AND AIM: The Ki-67 proliferation index is widely used for diagnostic classification and prognostic assessment of pulmonary neuroendocrine tumors. Manual evaluation of Ki-67 immunohistochemistry is subject to interobserver variability, particularly in hot-spot selection and cell counting, which can affect diagnostic reliability. This study aimed to directly compare manual pathologist assessments with an artificial intelligence (AI)–based digital analysis algorithm and to evaluate the reproducibility and reliability of AI-assisted measurements.

METHODS: Fifty-four pulmonary neuroendocrine tumor cases diagnosed between 2020 and 2024 were included: 27 typical carcinoids (TC), 6 atypical carcinoids (AC), and 21 large cell neuroendocrine carcinomas (LCNEC). Ki-67–stained slides were digitized using a high-resolution scanner. Four pathologists independently evaluated hot-spot regions and manually calculated the Ki-67 index (approximately 2,000 tumor cells per hot spot), while the AI algorithm automatically identified hot spots and quantified Ki-67-positive cells (500–2000 tumor cells per case). Interobserver agreement among pathologists was assessed using the intraclass correlation coefficient (ICC), and concordance between manual and AI-based measurements was analyzed using Spearman's correlation coefficient (r).

RESULTS: Very high agreement was observed among pathologists (ICC=0.999, 95% confidence interval: 0.998–1.000). AI-derived Ki-67 indices strongly correlated with the mean pathologist-derived values (Spearman's r=0.972, p<0.001). Consistency was maintained across both carcinoid subtypes and large cell neuroendocrine carcinomas, demonstrating that AI provides reproducible and reliable results comparable to manual assessment.

CONCLUSIONS: AI-assisted digital analysis is a robust, reproducible, and time-efficient alternative to manual Ki-67 counting in pulmonary neuroendocrine tumors. Incorporating AI tools into routine pathology practice can reduce interobserver variability, standardize proliferation marker evaluation, and enhance diagnostic accuracy. This study highlights the potential of AI as a complementary method to manual assessment, rather than a replacement, in clinical pathology.

Keywords:

Artificial intelligence, digital pathology, Ki-67, lung, neuroendocrine tumors

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Introduction

Pulmonary neuroendocrine tumors (NETs) represent a heterogeneous group of neoplasms, including typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC).[1] Accurate classification and prognostic assessment of these tumors are essential for guiding clinical management and predicting patient outcomes. The Ki-67 proliferation index, a well-established marker of cell proliferation, is widely used in both diagnostic and prognostic evaluation of pulmonary NETs. Specifically, Ki-67 helps differentiate between tumor subtypes and provides important information regarding tumor aggressiveness and clinical behavior.[2]

Manual evaluation of Ki-67 immunohistochemical staining, however, is prone to interobserver variability, particularly in the selection of "hot spot" regions and in counting positive tumor cells. Such variability may compromise the reproducibility and reliability of proliferation assessments, potentially affecting clinical decision-making.[3]

Recent advances in digital pathology and artificial intelligence (AI)–based image analysis have enabled more standardized, rapid, and reproducible quantification of Ki-67. AI algorithms can objectively identify Ki-67–positive cells in hot spot regions and calculate proliferation indices with minimal observer bias. While AI-assisted Ki-67 analysis has been explored extensively in gastrointestinal and pancreatic NETs, studies focusing on pulmonary NETs remain limited. Notably, prior work has demonstrated that deep learning–based algorithms can achieve high concordance with manual pathologist assessments, improving consistency and potentially supporting clinical workflows.[4,5]

Given the clinical importance of Ki-67 and the potential of AI to enhance its evaluation, this study was designed as a comparative analysis of manual pathologist assessments versus a digital pathology–integrated AI algorithm for Ki-67 quantification in pulmonary NETs. By assessing concordance, reliability, and reproducibility, we aimed to determine whether AI-assisted analysis can serve as a complementary tool to manual assessment in routine diagnostic practice.

Materials and Methods

Ethics statement

This study was conducted in accordance with the ethical standards of the responsible institutional Ethics Committee and the World Medical Association Declaration of Helsinki for studies involving human participants. Ethical approval was obtained from the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (Approval Number: 24237859-630, Date: 24.09.2025). Additionally, permission to use archived pathology materials was granted by the Hospital Directorate. As this was a retrospective study, informed consent was waived; however, all patient data were anonymized, and confidentiality was strictly maintained. No identifiable information, such as names, initials, or hospital numbers, was used in the analysis or illustrative material.

Case selection

This retrospective study included 54 pulmonary neuroendocrine tumor cases diagnosed between 2020 and 2024 in the Department of Medical Pathology, Karadeniz Technical University Faculty of Medicine. The cohort comprised 27 typical carcinoids, 6 atypical carcinoids, and 21 large cell neuroendocrine carcinomas. Only cases with available paraffin-embedded tissue blocks derived from excisional biopsies or surgical resections were eligible for inclusion; consultation cases and small biopsy specimens were excluded. Small cell carcinoma cases were also excluded, as the diagnoses were established exclusively on small needle biopsies without subsequent surgical resection, precluding adequate material for further analysis.

Given the relatively low number of atypical carcinoid cases (n=6), the statistical power for subgroup analyses is limited. Therefore, this study is considered exploratory, aimed at providing preliminary insights into AI-assisted Ki-67 quantification in pulmonary neuroendocrine tumors. A formal power analysis was not feasible due to the rarity of these tumors.

Ki-67 assessment and blinding procedures

Ki-67 immunohistochemical staining had been performed for routine diagnostic purposes. Slides were retrieved from the pathology archive for analysis. Four experienced pathologists independently evaluated the Ki-67 index using the hot-spot method, which identifies regions with the highest density of Ki-67–positive tumor cells. Pathologists were blinded to the AI algorithm re-

sults, to each other's scores, and to clinical information, and prior pathology reports. This blinding approach minimized observer bias and ensured objective evaluation.

For manual Ki-67 assessment, approximately 2,000 tumor cells per hot-spot region were counted, and the percentage of positively stained nuclei was calculated to determine the Ki-67 proliferation index.[6]

Slides were digitized using the VENTANA DP® 200 high-resolution scanner (Roche, Germany). Digital images were analyzed using the uPath Ki-67 image analysis algorithm (version 1.0.0.5; Roche Diagnostics). This commercially validated system employs a convolutional neural network (CNN)–based nuclear detection and segmentation model, trained on a large multicenter dataset that includes Ki-67–stained neuroendocrine and non-neuroendocrine tumor samples.

The algorithm automatically identifies tumor regions, detects hot-spot areas based on the highest density of Ki-67–positive nuclei, and classifies each nucleus as positive or negative using predefined optical density and chromogen intensity thresholds. For each case, the algorithm calculated the Ki-67 labeling index by evaluating a minimum of 500 and a maximum of 2,000 tumor cells, in accordance with international recommendations for neuroendocrine neoplasms.[7]

Potential factors that may influence AI performance—such as image quality, focus, tissue thickness, background staining, and chromogen variability—were examined prior to analysis. All slides were processed in a single laboratory using the same staining protocol and were scanned under identical technical conditions to minimize pre-analytic variability. The final Ki-67 index for each case was automatically computed as the percentage of tumor nuclei classified as Ki-67–positive by the algorithm.[8]

Statistical analysis

All obtained data were entered into the SPSS database (IBM SPSS Statistics, version 27.0; IBM Corp., Armonk, NY, USA). Interobserver agreement among pathologists was assessed using the intraclass correlation coefficient (ICC), and concordance between manual assessments and the AI algorithm was evaluated using Spearman's correlation coefficient (r). To evaluate potential differences in Ki-67 indices across tumor subtypes, a Kruskal-Wallis test was performed. Statistical significance was set at $p<0.05$.

No artificial intelligence-assisted technologies, including large language models (LLMs), chatbots, or image generators, were used in the preparation of this manuscript.

Results

Interobserver agreement among pathologists

The Ki-67 proliferation index was independently assessed by four experienced pathologists using the hot-spot method. Very high agreement was observed among the pathologists, with an intraclass correlation coefficient of 0.999 (95% confidence interval [CI]: 0.998–1.000), indicating excellent reproducibility of manual evaluations.

Descriptive statistics of Ki-67 indices

Ki-67 proliferation indices for each tumor subtype, as assessed by manual pathologist evaluation and AI analysis, are summarized in Table 1. For typical carcinoids (n=27), median Ki-67 values were 2% (range: 0.1–7.7%) for pathologists and 1.9% (range: 0.6–23.3%) for AI. For atypical carcinoids (n=6), median values were 14.8% (range: 13–20.2%) and 23.1% (range: 14.9–27.5%), respectively. For large cell neuroendocrine carcinomas (n=21), median values were 63.7% (range: 35.2–85%) and 60.1% (range: 23.4–82.6%), respectively. These descriptive statistics provide a clear overview of proliferation indices across different tumor subtypes.

Concordance between manual and AI-based assessments

Comparison of the mean Ki-67 indices calculated by the pathologists with the values obtained from the AI algorithm revealed a strong positive correlation (Spearman's $r=0.972$, $p<0.001$), demonstrating that the AI algorithm reliably reproduces manual assessments. Scatter plot analyses [Fig. 1] further illustrate the concordance between AI-derived and pathologist-derived Ki-67 indices, while highlighting minor interobserver variability among pathologists. Regression trendlines indicate that Pathologists 1 (blue) and 2 (green) exhibited the closest agreement with AI, followed by Pathologists 3 (orange) and 4 (purple).

Comparative analysis across tumor subtypes

A comprehensive comparative evaluation of Ki-67 proliferation indices revealed highly significant differences among the three tumor subtypes across both manual pathologist assessments and AI-derived hotspot quantification ($p<0.001$). The proliferation profiles exhibited

Table 1: Ki-67 proliferation index values of pulmonary neuroendocrine tumors determined by four pathologists and an AI algorithm

Case	Pathologist 1	Pathologist 2	Pathologist 3	Pathologist 4	AI Ki-67
1	15	10	14	13	27.5
2	4	4	3	4	4.9
3	3	3	3	3	5
4	8	7	7	9	12.4
5	72	80	75	75	70.3
6	15	15	15	15	15
7	5	5	4	5	4.9
8	21	20	20	20	23.8
9	15	14	15	15	22.5
10	2	2	2	2	3.2
11	2	2	2	2	1.9
12	55	58	55	55	53.6
13	45	50	50	42	57.1
14	60	65	65	60	60.1
15	55	60	60	60	47.3
16	6	5	5	5	8.6
17	52	55	55	55	47.7
18	2	2	2	2	2.1
19	2	2	2	2	23.3
20	2	1	1	2	1.6
21	80	85	85	85	78.4
22	85	85	85	85	77.7
23	75	80	80	80	65.9
24	1	2	1	2	0.9
25	75	75	80	80	68.1
26	2	2	2	2	2.9
27	2	2	2	3	1.6
28	2	2	2	2	1.6
29	45	45	45	50	33.6
30	22	15	20	20	24
31	1	1	1	1	2.4
32	1	1	1	1	1.3
33	1	1	1	1	5.3
34	1	1	1	2	1.4
35	1.5	1.2	1	2	1.7
36	0.1	0.1	0.1	0.1	0.9
37	0.1	0.1	0.1	1	0.6
38	67	70	70	70	67.7
39	4	4	4	5	13
40	35	36	35	35	34.8
41	75	75	75	75	69.8
42	50	50	50	50	47.4
43	2	2	2	2	2.6
44	48	45	45	45	23.4
45	65	60	60	65	37.8
46	85	85	85	85	82.6
47	70	65	65	70	34.4
48	0.1	0.1	0.1	0.1	0.7
49	0.1	0.1	0.1	0.1	1.2
50	0.1	0.1	0.1	0.1	0.8
51	13	13	15	12	14.9
52	65	65	65	60	64.2
53	71	70	70	70	71.4
54	0.1	0.1	0.1	0.1	0.8

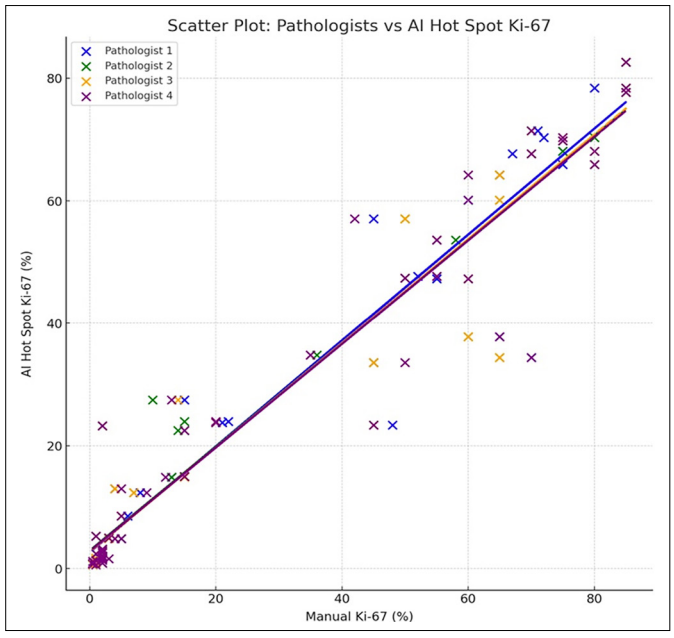

Figure 1: Scatter plot of the Ki-67 labeling index (%) for all 54 cases assessed by four pathologists (Pathologist 1–4; blue, green, orange, and purple) and by the artificial intelligence (AI) hot-spot method. Solid lines represent trendlines for each pathologist, illustrating the degree of concordance and variability between manual and AI-based evaluations

a clear and biologically coherent stratification: typical carcinoids demonstrated minimal proliferative activity, atypical carcinoids displayed intermediate levels, and large cell neuroendocrine carcinomas showed markedly elevated proliferation indices.

This gradient mirrors the known histopathological progression within pulmonary neuroendocrine neoplasms and reinforces the established correlation between tumor grade and proliferative behavior. The consistency of this pattern across manual and AI-based evaluations underscores the robustness of the findings and supports the diagnostic utility of both approaches.

Post hoc pairwise comparisons provided further statistical confirmation of these differences. LCNEC exhibited significantly higher Ki-67 indices than both TC and AC in all analytic frameworks, highlighting its distinct biological aggressiveness and aligning with its well-recognized high-grade clinical course. Conversely, the proliferative distinction between TC and AC, although present, was comparatively modest, consistent with their placement within the low- to intermediate-grade spectrum.

Taken together, these results emphasize that Ki-67 accurately reflects the biological continuum of neuroendocrine tumor behavior and demonstrate the value of integrating AI-assisted quantification into routine analysis to enhance reproducibility. The detailed distribution of these proliferation indices is presented in Figure 2.

Hot spot analysis and AI quantification

AI-based Ki-67 immunohistochemical analysis enabled precise identification and quantification of proliferative

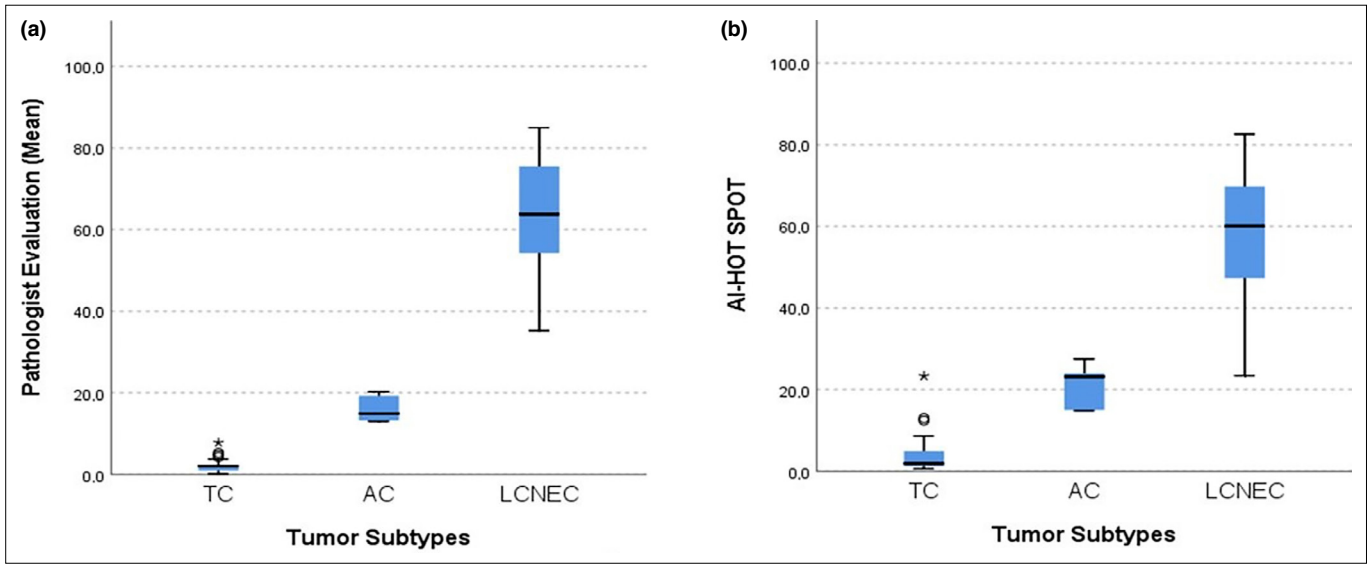

Figure 2: Comparative Ki-67 proliferation indices across pulmonary neuroendocrine tumor subtypes. Box-and-whisker plots depict Ki-67 labeling indices for typical carcinoid (TC), atypical carcinoid (AC), and large cell neuroendocrine carcinoma (LCNEC) as determined by manual pathologist assessment and artificial intelligence (AI)-assisted hot-spot quantification. The data demonstrate a clear gradation in proliferative activity, with TC showing the lowest, AC intermediate, and LCNEC the highest Ki-67 indices. Statistical significance was assessed using post hoc pairwise comparisons ($p<0.001$), highlighting marked differences between LCNEC and the other subtypes, while the distinction between TC and AC was more modest

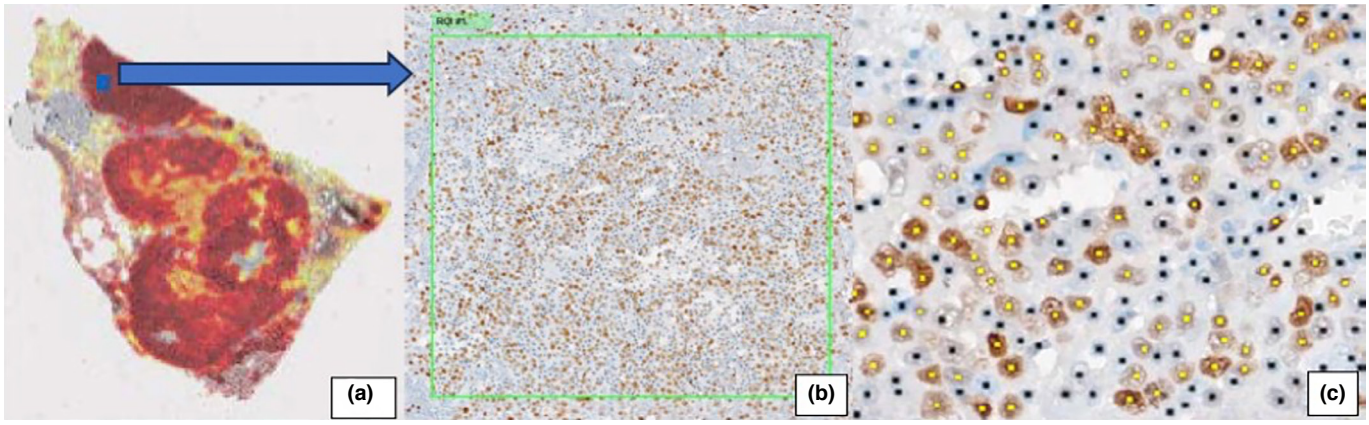

Figure 3: Example of artificial intelligence–based analysis of Ki-67 immunohistochemical staining. (a) A "hot spot" area with high proliferative activity is identified within the tumor tissue. (b) Tumor cell nuclei within the selected square region of interest (ROI) are enlarged and evaluated. (c) At higher magnification, Ki-67–positive nuclei (yellow markings) and Ki-67–negative nuclei (black markings) are automatically distinguished and quantified by the algorithm

tumor regions. Within each tumor, the single area with the highest Ki-67 labeling, referred to as the "top hot spot," was identified [Fig. 3a]. A square region of interest (ROI) was selected from this area, and tumor cell nuclei were segmented and evaluated at higher magnification [Fig. 3b]. The algorithm automatically classified nuclei as Ki-67–positive (yellow) or Ki-67–negative (black), providing accurate measurements of proliferative activity within the selected hot spot [Fig. 3c]. Across all cases, AI-derived indices demonstrated consistent and reproducible results comparable to manual assessment.

Discussion

The Ki-67 proliferation index is a central biomarker for evaluating tumor growth dynamics, offering valuable prognostic and therapeutic insights in neuroendocrine tumors.[1] However, manual evaluation of the Ki-67 index is inherently prone to variability due to differences in hot-spot selection, counting methodology, and interpretation among observers.[3] This study evaluated interobserver agreement among four experienced pathologists and compared manual Ki-67 assessments with AI-assisted measurements in pulmonary neuroendocrine tumors. To our knowledge, this is one of the first studies specifically focusing on AI-assisted Ki-67 quantification in pulmonary neuroendocrine tumors, highlighting the originality and clinical relevance of this work.

Our analysis revealed excellent concordance among pathologists, with an ICC of 0.999 (95% CI: 0.998–1.000), demonstrating highly reproducible manual evaluations under standardized conditions. Similar findings have been reported by Zehra et al.,[4] who observed 98% interobserver agreement. In contrast, Satturwar et al.[9] documented a lower concordance rate (84%) for manual hot-spot evaluation, indicating that reproducibility may vary depending on tumor heterogeneity and methodological consistency. These discrepancies underscore a key limitation of manual Ki-67 assessment—namely, its sensitivity to subjective interpretation, especially in borderline or heterogeneous lesions.

A strong positive correlation was identified between manual Ki-67 indices and AI-generated values, supporting the reliability and reproducibility of AI-assisted quantification. These observations are in agreement with those of Tang et al.,[10] who demonstrated strong concordance between digital image analysis and manual counting (ICC=0.98) and substantial agreement with mean eyeball estimations. The lower intra-observer consistency in manual counts (ICC=0.39±0.26) in our data further illustrates the inherent limitations of manual assessment and highlights the potential utility of AI tools in reducing subjective variability. Together, these results support the growing role of AI-assisted image analysis in enhancing standardization and diagnostic accuracy in pathology.

AI-assisted quantification may complement traditional pathology practice by providing more objective and reproducible metrics, reducing evaluation time, and improving workflow efficiency. In routine laboratory settings, integration of AI requires consideration of cost, software accessibility, personnel training, and compatibility with existing digital pathology infrastructure. Moreover, variability in immunohistochemical staining intensity across institutions—stemming from different fixation protocols, antibody clones, and staining platforms—may

still influence Ki-67 quantification, even when AI is used. Standardizing staining protocols remains essential for maximizing the reliability of AI-based analyses.[11]

This study has several limitations that should be acknowledged to contextualize the findings. First, the dataset was relatively small (n=54), which is expected given the rarity of pulmonary NETs; however, subgroup sizes—particularly for atypical carcinoids—were limited and may constrain statistical power. Second, the study was conducted at a single center, which may limit generalizability to broader patient populations. Third, the research relied on a retrospective design, introducing potential selection bias and limiting control over pre-analytical variables such as fixation and staining protocols. Fourth, only one AI tool was used, and its performance may not represent that of other commercially available or open-source systems. Fifth, the study did not include small cell lung carcinoma cases, restricting the tumor spectrum assessed. Finally, blinding constraints in the evaluation process may have introduced methodological bias. Recognizing these limitations provides transparency and supports appropriate interpretation of the study results.

Conclusion

In summary, our findings demonstrate excellent interobserver agreement among pathologists and strong concordance between manual and AI-assisted Ki-67 assessments in pulmonary neuroendocrine tumors. The results support the potential role of AI as an adjunct tool to enhance the accuracy, reproducibility, and efficiency of Ki-67 evaluation in clinical practice. Moreover, this study contributes original evidence to an emerging field, representing one of the earliest efforts to apply AI-supported Ki-67 quantification specifically to pulmonary NETs.

Future directions

Future research should explore the integration of AI-assisted Ki-67 quantification in multicenter studies and larger cohorts, including diverse pulmonary neuroendocrine tumor subtypes such as small cell lung carcinoma. Further development of AI algorithms, including deep learning and machine learning approaches, may improve detection accuracy, hot-spot selection, and reproducibility. Additionally, prospective studies evaluating the impact of AI-assisted pathology on clinical decision-making, patient outcomes, and workflow efficiency will be essential to fully realize the potential of digital pathology in routine practice.

Ethics Committee Approval

The study was approved by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee (No: 24237859-630, Date: 24/09/2025).

Informed Consent

Written informed consent was waived.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance

No use of AI-assisted technologies was declared by the authors.

Author Contributions

Concept – G.T., Ş.E.; Design – G.T., Ş.E.; Supervision – G.T., Ş.E.; Resource – G.T., Ş.E.; Materials – G.T., Ş.E.; Data Collection and/or Processing - G.T., Z.T.U., Z.S.Y., Ş.E.; Analysis and/or Interpretation - G.T., Z.T.U., Z.S.Y., Ş.E.; Literature Review – G.T., Ş.E.; Writing – G.T.; Critical Review – G.T., Z.T.U.

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