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Original Research Article

Immunoprofiling in poorly differentiated non-small cell lung cancer, analysis of data in a tertiary care center

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ABSTRACT

Background: Lung cancer is a leading cause of cancer-related deaths worldwide, including India, where it accounts for 5.9% of cancer cases and 8.1% of cancer-related mortality. Differentiating between major histologic subtypes of non-small cell lung carcinoma (NSCLC)-adenocarcinoma (ACA) and squamous cell carcinoma (SCC) is crucial due to significant differences in treatment response. Our study addresses the IHC profile of NSCLC in a tertiary care centre in South India. We have also deliberated whether a 2 panel IHC markers would be sufficient for the final diagnosis in a resource poor setting as compared to the traditional 4 IHC panel.
Methods: A hospital-based cross-sectional study (2018-2022) analysed 319 histologically confirmed poorly differentiated NSCLC cases. IHC markers (TTF-1, Napsin A, p63 and p40) were used for subtyping per WHO classification. Staining patterns were semi-quantitatively scored against controls. Sensitivity, specificity, PPV, NPV, and overall accuracy were calculated. Data analysis was performed using SPSS v23.
Results: Of the 319 cases, ACA was the most common (65.2%), followed by SCC (31.03%). Males accounted for 81.2% of cases, with the peak incidence in the 62-66 age group. For ACA, TTF-1 had higher sensitivity (97.17%) compared to Napsin A (83.49%), while Napsin A showed better specificity (96.04%). For SCC, p63 demonstrated higher sensitivity (93.07%) than p40 (78.22%), while p40 had better specificity (89.62%).
Conclusions: The study highlights the need for tailoring the IHC panel to suit the histopathological specimen in order to clinch the final diagnosis. In finance effectiveness, two marker panel can also be used.

Keywords: Immunohistochemistry, p63, TTF-1, Napsin-A, Squamous cell carcinoma, Adenocarcinoma

INTRODUCTION

In India, lung cancer ranks among the prominent cancer sites, comprising 5.9% of total cancer cases and 8.1% of all cancer related deaths. Kerala exhibits a concerning surge in lung cancers in both males and females with lung cancer ranking in the top 5 cancers in both sexes (male-20.8% and female-4%).[1]

Recent strides in NSCLC treatment and molecular diagnosis underscore the necessity to differentiate between major histologic subtypes-ACA and SCC. Disparities in their response to chemotherapy highlight the importance of accurate subtyping. Notably, certain drugs, such as bevacizumab, pose risks for SCC patients due to fatal hemorrhage observed in these patients.[2] Gefitinib and erlotinib demonstrate greater effectiveness in treating ACA compared to SCC in NSCLC.[3] Conversely, Pemetrexed, an antifolate agent, exhibits enhanced efficacy in non-SCC cases.[4] These distinctions in drug response underscore the importance of necessitating tailored treatment strategies.

The clinical application of targeted therapies in NSCLC is heavily reliant on accurate histological subclassification.

This is especially crucial for patients with advanced-stage disease (stage III and IV) and metastatic NSCLC, where surgical resection is often not an option. About 70% of lung cancer cases are diagnosed when the disease has already reached an advanced stage and is deemed unresectable.[5] In these cases, Tru-cut needle biopsy is commonly utilized to obtain tumor tissue for diagnostic purposes, including histologic and molecular testing. Most NSCLC cases can be subclassified through histomorphologic examination using hematoxylin and eosin stained slides, which remains a fundamental approach in clinical practice.[6,7] However there remains a subset of carcinomas which are poorly differentiated and which require IHC for their final diagnosis.

Retrospective studies done in USA showed that a 2-marker panel of TTF-1/p63 is sufficient for subtyping the majority of ACA and SCC, and addition of Napsin A is useful in only subset of cases. Whereas performing expanded 4-marker panel (TTF-1, Napsin A, p63, p40) upfront is time-efficient option for specimens with sufficient cellularity.[8]

Recent studies have explored the potential of combining multiple IHC markers to improve the subclassification of NSCLC. These investigations have shown promising results, particularly with dual markers. For instance, a combination of TTF-1 and Napsin A demonstrated 74% sensitivity and 87-96% specificity in identifying lung ACA using fine-needle aspiration material. Similarly, the dual marker of p63 and CK5 achieved 100% sensitivity and specificity for identifying lung SCC with FNA samples. Additionally, lung tumor tissue microarray data revealed that a combination of TTF1 and p40 provided 93% sensitivity and 92% specificity for diagnosing SCC. These findings suggest that dual or triple IHC markers can offer comparable sensitivity and specificity to individual markers while also minimizing the amount of tumor tissue required for accurate histological subclassification.[9-12]

Research encompassing a broad age range and a substantial patient cohort, particularly focused on small biopsy specimens, is limited in India.[13] Consequently, our study aims to fill this gap by investigating the immunoprofiling of poorly differentiated lung carcinoma using markers such as TTF1, Napsin, P63, and P40.

Our objective is to evaluate the practicality of IHC markers in subtyping poorly differentiated NSCLCs based on biopsy specimens. This comprehensive approach seeks to enhance our understanding of the IHC characteristics of poorly differentiated NSCLCs, particularly in the context of diverse patient demographics and the challenges posed by small biopsy samples in the Indian population.

METHODS

The research adopted a hospital-based cross-sectional design conducted over a 4-year period (2020-2024) at Amala institute of medical sciences, Kerala, India, focusing on 319 histologically confirmed cases of lung carcinomas. The sample size was calculated using statistical methods ($n=Z^21-\alpha/2pq/d^2$).[14] The study exclusively involved small biopsy specimens from patients with poorly differentiated NSCLCs, subjected to immunohistochemical analysis using four markers: TTF-1, Napsin, p63, and p40. Exclusions comprised biopsy specimens for non-malignant lung pathology, large resection specimens, and lung biopsies with prior neoadjuvant chemotherapy or radiotherapy. The formalin-fixed endobronchial biopsy from all cases underwent processing and paraffin embedding. Multiple 3-5 mm sections were stained with hematoxylin and eosin (H and E), and subtyping of lung carcinomas was performed based on WHO classification of lung tumors.[15] Immunohistochemical examination employed a soluble complex method. Four-micrometer-thick sections were prepared on poly lysine-coated slides, subjected to overnight incubation at 37°C and one hour at 60°C, followed by dewaxing in xylene. Hydration, antigen retrieval, and staining procedures ensued.

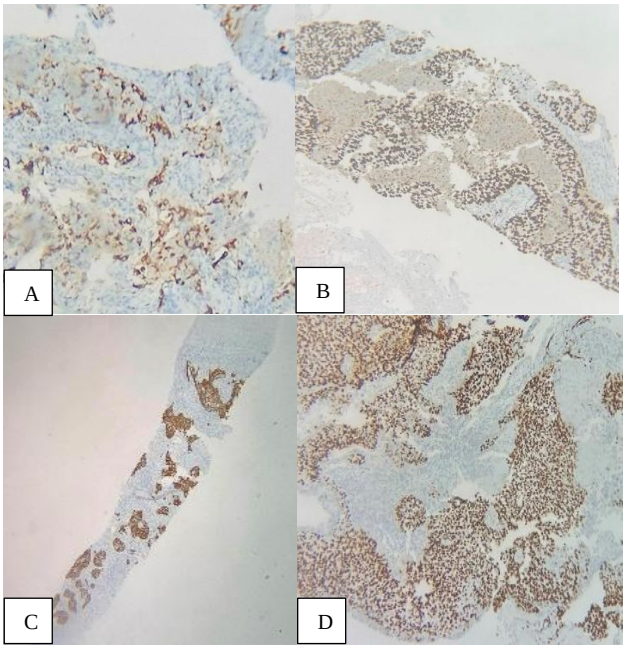

Figure 1 (A-D): A-Napsin A staining of lung biopsy specimens diagnosed as ACA. B-TTF-1 staining of lung biopsy specimens diagnosed as ACA. C-p-63 staining of lung biopsy specimens diagnosed as SCC. D-p-40 staining of lung biopsy specimens diagnosed as SCC.

A-Granular cytoplasmic staining of lung biopsy specimens that were diagnosed as ACA. Rabbit monoclonal antibody Napsin-A was used for immunohistochemical staining. B-Nuclear staining of lung biopsy specimens that were diagnosed as ACA. Rabbit monoclonal antibody TTF-1 was used for immunohistochemical staining. C-This figure shows the nuclear staining of tumor cells in lung biopsy specimens that were diagnosed as SCC. Rabbit monoclonal antibody p-63 was used for immunohistochemical staining. D-Nuclear staining of squamous cells in lung biopsy specimens that were diagnosed as SCC Rabbit monoclonal antibody p-40 was used for immunohistochemical staining.

The employed antibodies for immunohistochemistry were as follows: Rabbit monoclonal antibody p40, mouse monoclonal antibody p63, rabbit monoclonal antibody TTF-1 and rabbit monoclonal antibody Napsin-A.

Cytoplasmic staining indicated positivity for Napsin-A, while nuclear staining indicated positivity for TTF-1, p40, and p63. (Figure 1 A-D) Immunoreactivity was semi-quantitatively scored based on the percentage of reactive tumor cells, with pneumocytes and bronchial basal cells serving as internal controls.

Subsequent analysis, conducted using SPSS version 23, focused on immunoprofiling and its correlation with various subtypes of poorly differentiated NSCLC in terms of sensitivity and specificity. This approach aimed to identify an effective and efficient panel of two immunohistochemistry markers out of four (TTF1, Napsin-A, p63 and p40) in aiding the categorization of poorly differentiated NSCLCs.

RESULTS

The 319 cases of poorly differentiated NSCLC were diagnosed during the 4-year period from 2020 to 2024. Of these, ACA accounts for 65.2% (208 cases) followed by SCC 31.03% (99 cases), adenosquamous 1.2% (4 cases), not otherwise specified 0.6% (2 cases) (Figure 2).

Out of 319 cases of NSCLC 267 (83.6%) occurred in males and 52 (16.4%) in females. Incidence of NSCLC peaked among patients aged 55-69 years (Figure 3 and Table 1).

Subtyping of NSCLC was based on the algorithm followed by the IATC/ATS/ERS international multidisciplinary team.

We started off, with the hypothesis that p63 and p40 are positive in cases of SCC s whereas TTF-1 and Napsin-A are positive in ACA.

Statistical analysis showed that: In the case of ACA (Table 2), TTF-1 is the more sensitive marker with a sensitivity of 97.17% as compared to Napsin-A (83.49%) and Napsin-A is the more specific marker with a specificity of 96.04% as compared toTTF-1 (92.08%).

In case of SCC (Table 3) p63 is the more sensitive marker with a sensitivity of 93.07% as compared to p40 (78.22%) and p40 is more specific marker with a specificity of 89.62% as compared to p63 (80%), (Figure 4).

Co-expression profiles of TTF-1 and Napsin showed double positivity in 168 cases (80.7%). Co-expression profiles of p63 and p40 showed double positivity in 74 cases (74.7%).

In the case of adenosquamous carcinoma both TTF-1 and p63 were seen to be positive in the 3 cases. One case of adenosquamous carcinoma showed positivity for Napsin-a TTF-1 and p63.

In the specimens of NSCLC NOS (not otherwise specified), a clear algorithm could not be decoded with positivity being highly variable in the 2 cases.

Table 1: Age at the time of diagnosis and sex of the patient during the 4-year study period in patients with poorly differentiated NSCLC, (n)=319.

Lung cancer cases	2019	2020	2021	2022	Total	Percent (%)
Age group (in years)						
0-54	13	27	19	7	66	21
55-69	28	46	53	35	162	51
≥70	18	35	20	18	91	28
Sex						
Male	52	89	76	50	267	83.60
Female	7	20	16	10	52	16.40

Table 2: Statistical parameters of immunohistochemical markers Napsin-A and TTF-1.

Statistical parameter	TTF-1	NAPSIN-A
Sensitivity	97.17%	83.49%
Specificity	92.08%	96.04%
Positive likelihood ratio	12.27	21.08
Negative likelihood ratio	0.03	0.17
Positive predictive value	96.26%	97.79%
Negative predictive value	93.94%	73.48%
Accuracy	95.53%	87.54%

Napsin-A and TTF-1 used for staining lung biopsy specimens diagnosed as ACA via histopathological parameters. SPSS version 23 was used for statistical analysis.

Table 3: Statistical parameters of immunohistochemical markers P63 and P40.

Statistical parameter	P63	P40
Sensitivity	93.07%	78.22%
Specificity	80.66%	89.62%
Positive likelihood ratio	26.86	7.54
Negative likelihood ratio	0.07	0.24
Positive predictive value	93.07%	78.22%
Negative predictive value	96.53%	89.62%
Accuracy	95.38%	85.94%

P-63 and p-40 used for staining lung biopsy specimens diagnosed as SCC via histopathological parameters. SPSS version 23 was used for statistical analysis.

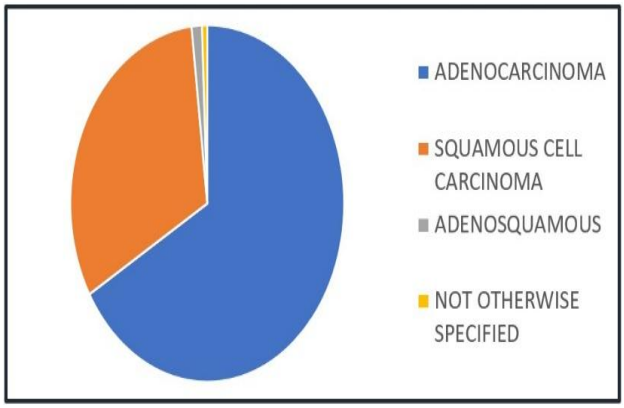

Figure 2: Final diagnoses of the patients in the study group.

This chart shows the relative prevalence of the different non-small cell lung cancer subtypes based on histopathology which was taken as our gold standard-ACA: (65.20%), SCC: (31.03%), adenosquamous: (1.20%), not otherwise specified: (0.60%)-(not otherwise specified refer to the samples which show an uncertain histopathology as a consequence of small sample sizes and highly heterogeneous tumors, which limit the consistency and accuracy of subtyping using bronchoscopic biopsies.

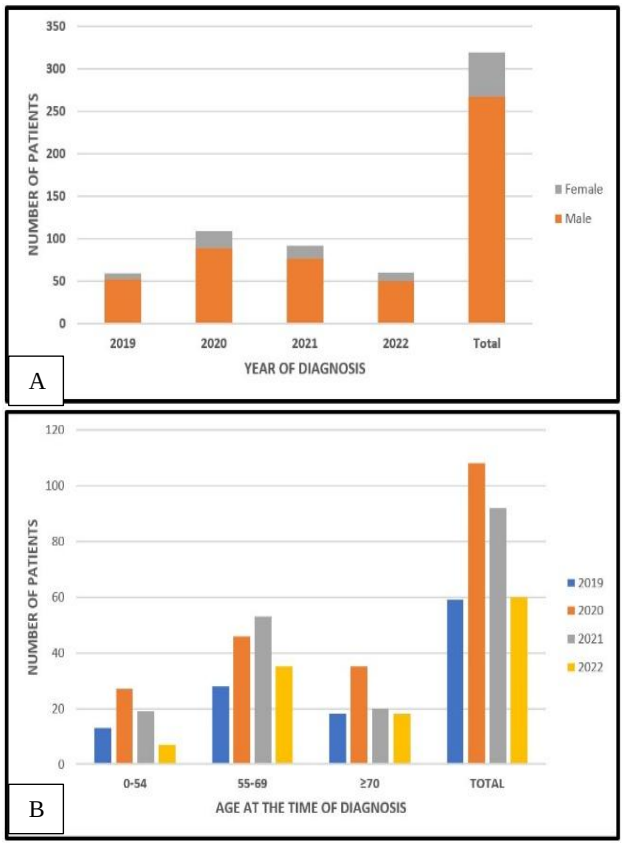

Figure 3 (A and B): A-Gender distribution and year of diagnosis of patients with poorly differentiated NSCLC. B-Age at the time of diagnosis during the 4-year study period in patients with poorly differentiated NSCLC.

A-The graph shows an 83.6% prevalence in males and 16.4% in females. B-The incidence of NSCLC peaked among patients aged 55 to 69 years.

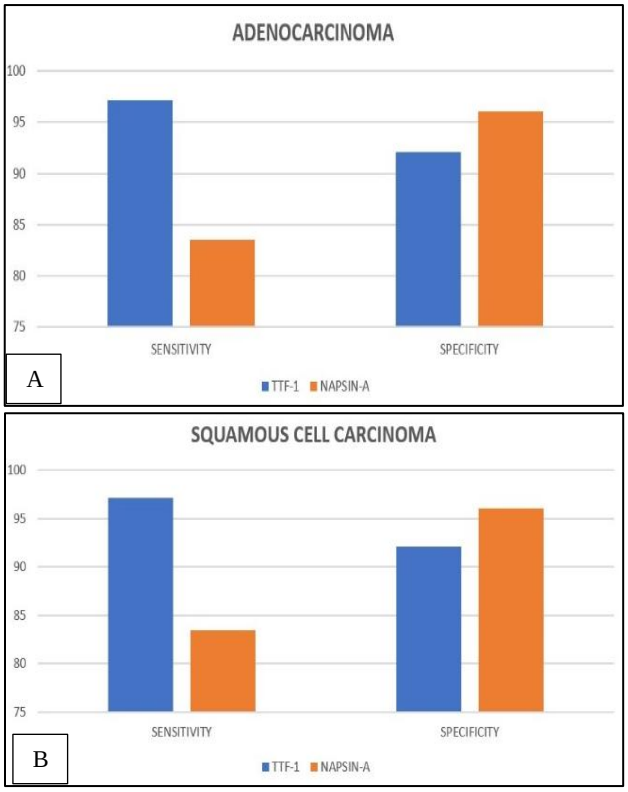

Figure 4 (A and B): Sensitivity and specificity of immunohistochemical markers Napsin-A and TTF-1. B- Sensitivity and specificity of immunohistochemical markers p-63 and p-40.

Used for staining lung biopsy specimens diagnosed as ACA via histopathological parameters. SPSS version 23 was used for statistical analysis. In the case of ACA, TTF-1 is seen to be the more sensitive marker whereas Napsin-A is the more specific marker. Used for staining lung biopsy specimens diagnosed as SCC via histopathological parameters. SPSS version 23 was used for statistical analysis. In the case of SCC, p-63 is seen to be the more sensitive marker whereas p-40 is the more specific marker.

DISCUSSION

Lung cancer is the leading cause of adult cancer-related deaths in most countries, and non-small-cell carcinomas comprise about 80% of these cases.[16] The global lifetime risk of developing lung cancer is estimated to be 1 in 13 for men and 1 in 16 for women, with smokers facing a markedly higher risk compared to non-smokers. Despite significant advancements in therapeutic strategies over the past few decades, the prognosis for lung cancer patients remains dismal, with a 5-year overall survival rate stagnant at around 15%. This underscores the urgency for continued research and innovation in early detection, prevention, and treatment modalities to improve patient outcomes.[15,17]

This 4-year analysis represents one of the largest single-center studies in India, focusing on a substantial sample size of non-small cell lung cancer cases and uncovers several notable trends. The average age of our patients was 60 years, which is similar to that reported in previous studies conducted on Indian cohorts.[18,19] Our study showed

a peak in incidence among patients aged between 55-69 years. While the risk of developing lung cancer rises significantly after the age of 70, our study included fewer patients in this age group, likely due to mortality from other causes and comorbidities before a lung cancer diagnosis could be made.

Our study population showed a male predominance across the 4 years which is in accordance with Indian studies which reported similar findings.[18,19] No change in this trend was noted during the study period.

Of the 319 cases of poorly differentiated NSCLC ACA accounts for 65.2% followed by SCC 31.03%. This is similar to the studies of Thai et al and Travis et al which showed 50-60% of ACA cases and 20-30% of SCC cases in their respective study populations.[20,21]

Since the 2004 WHO classification, therapeutic advances for NSCLC have been closely linked to precise histologic classification. Morphologic diagnosis forms the basis of diagnosis of NSCLC and is further supplemented by a panel of immunohistochemical markers. Tumor cells in ACA are positive for TTF-1, Napsin and cytokeratin-7. SCCs are positive for p-63, cytokeratin-5/6 and NTRK-1 and NTRK-2.[15] These developments have underscored the importance of distinguishing between subtypes of NSCLC, as treatment responses vary significantly. For example, patients with ACA or NSCLC-NOS have shown greater responsiveness to pemetrexed compared to those with SCC.[22] Additionally, the use of bevacizumab in lung cancer treatment has raised concerns, as it has been associated with life-threatening hemorrhage in patients with SCC, leading to its contraindication in this subgroup.[23] These findings emphasize the critical role of accurate histologic classification in guiding treatment decisions and improving patient outcomes.

TTF-1 has long been the predominant IHC marker for identifying lung ACA, with a reported sensitivity of 75% to 80%. However, TTF-1 is not entirely specific to lung tissue, as it can also stain other tissues and tumors, including thyroid tissue, metastatic breast carcinoma, and neuroendocrine tumors like small cell lung carcinoma and carcinoid. TTF-1 is a nuclear protein, that regulates the transcription of lung-specific genes for surfactant and Clara cell secretory proteins. Additionally, TTF-1 expression decreases with tumor dedifferentiation, making poorly differentiated ACAs less likely to express this marker.[24]

Bishop et al observed that 69 of 95 (73%) ACA s to be positive for TTF-1, whereas Folpe et al and Kaufmann et al also observed TTF-1 expression in 90-100% of small cell lung carcinomas.[24-26] Studies by Balakrishnan et al also observed 100% sensitivity and specificity for TTF-1 in diagnosing ACA.[14]

Recently, Napsin-A has emerged as a novel marker for lung ACA, particularly for well to moderately differentiated tumors. Napsin is also a promising marker and has been detected in the cytoplasm of type 2 pneumocytes and alveolar macrophages.[27] Studies have shown that Napsin-A performs comparably or even better than TTF-1 in determining lung origin in these cases. Napsin A has been evaluated on surgically resected lung cancers and has been found to be positive in a recent study in 79 of 95 (83%) of lung ACA s and negative in all 46 lung SCC in the study by Bishop et al.[24] Napsin A is moderately sensitive (79-85%) and highly specific (100%) for ACA.[15]

However, in our study, TTF-1 demonstrated a higher overall sensitivity (97.17%) compared to Napsin (83.49%). Napsin-A expression is also noted in the cytoplasm of normal lung cells and kidney cells, as well as in renal cell carcinomas, which must be considered when interpreting results.[8,26,27]

Our findings are consistent with previously reported studies, which demonstrate the usefulness of TTF-1+ Napsin A dual color immunostaining in distinguishing lung AD C versus SCC.[28,29] Stoll et al have also reported that combined application of Napsin A and TTF-1 immunomarkers may be necessary to improve diagnostic accuracy in lung ACA.[30]

The human ‘p63’ gene, located on chromosome 3q27-29, produces two types of proteins through two promoters: the full-length TAp63, containing the N-terminal transactivation domain, and the truncated ΔNp63, which lacks this domain. The ΔNp63 isoform can be specifically identified by the p40 antibody, while the full-length TAp63 is detected using the p63 antibody (4A4). p63 is expressed in the normal respiratory epithelium of the central air conducting system and does not carry any prognostic implications in NSCLC patients.[31]

Recent studies have demonstrated that p40 exhibits exceptional performance in identifying SCC, with reported sensitivity and specificity of 100% and 98-100%, respectively. Antibody p40, identifies ΔNp63, its use for distinction of lung SCC and ACA was only recently studied. p40 is consistently predominant isoform expressed in SCC.[23] Studies by Bishop et al and Nonaka showed that p40 has 100% sensitivity and specificity in lung SCC.[25,33] Another study by Tacha et al reported an 85% sensitivity and 98% specificity.[34]

The sensitivity of p-63 ranges from 75% to more than 95%, whereas the specificity for SCC is between 70% and 100%.[15] Immunostaining for p63 has been described as the single best marker to separate ACA from SCC, with a sensitivity of 84%, and specificity of 85% for SCC.[35]

In our study, p63 was observed to be the more sensitive marker, with a sensitivity of 93.07%, compared to p40's 78.22%. Conversely, p40 showed greater specificity at 89.62%, compared to p63, which had a specificity of 80%. These findings suggest that p63 and p40 offer

complementary roles in SCC diagnosis, with p63 providing higher sensitivity and p40 offering greater specificity.

The co-expression analysis of TTF-1 and Napsin-A revealed that both markers were positive in 168 cases (80.7%), highlighting their strong association with ACA phenotypes. In the study conducted by Fatima et al showed that dual TTF-1/Napsin A has a sensitivity of 74% and specificity of 87% for diagnosing ACA and, hence, is useful in differentiating ACA from SCC.[9]

Similarly, co-expression of p63 and p40 showed dual positivity in 74 cases (74.7%), affirming their relevance in SCC diagnosis. Notably, in the three cases of adenosquamous carcinoma, TTF-1 and p63 were both positive, indicating the mixed histologic nature of these tumors.

Analysis of co-expression profiles showed that co-expression of p63 and CK5/6 irrespective of TTF1 and co-expression of p63 and CK5/6 in TTF-1 negative tumor both were 100% sensitive and specific for SCC s in a similar study conducted in an Indian cohort.[14] Further it was also observed that TTF-1 positive and p63 negative co-expression profile showed 100% specificity in diagnosing ACAs.[14]

Interestingly, one case of adenosquamous carcinoma demonstrated triple positivity for Napsin A, TTF-1, and p63, further supporting the dual differentiation of these tumors. However, in the specimens of NSCLC-NOS, a consistent immunohistochemical algorithm could not be established due to the highly variable expression patterns observed in the two cases, underscoring the diagnostic challenges in this heterogeneous group.

This study provides valuable insights into the immunohistochemical characterization of poorly differentiated NSCLCs, yet several limitations must be acknowledged to contextualize the findings. The research was confined to a single tertiary care center, which may introduce institutional bias and restrict the broader applicability of the results. Inclusion of multiple centers with diverse patient populations would strengthen generalizability.

Molecular profiling was not incorporated into the study design. The addition of targeted mutation analysis, such as EGFR, ALK, or ROS1, could have enhanced diagnostic precision and aligned the findings with current trends in precision oncology. Another constraint lies in the lack of clinical follow-up. Without longitudinal data on treatment response or survival outcomes, the prognostic relevance of the immunohistochemical profiles remains uncertain. This limitation was further compounded by challenges during the COVID-19 pandemic, which likely introduced follow-up bias due to delayed investigations and missed visits, affecting long-term data collection.

The use of semi-quantitative scoring to assess immunoreactivity introduces potential interobserver variability. Employing digital image analysis or blinded assessments may improve reliability and reproducibility. While the study utilized a well-established panel of four markers-TTF-1, Napsin-A, p63, and p40-this focused approach may limit diagnostic accuracy in morphologically ambiguous cases. Expanding the panel to include additional markers such as CK5/6 or CK7 could enhance subtype differentiation. Overall, the study underscores the diagnostic utility of immunohistochemistry in poorly differentiated NSCLCs. Nonetheless, broader multicentric validation and integration with molecular and clinical data are essential for improving diagnostic fidelity and clinical applicability.

CONCLUSION

A two-marker IHC panel consisting of TTF-1 and p63 shows 91.13% accuracy, 90.39% sensitivity, and 75.83% specificity, making it a cost-effective alternative in resource-limited settings. However, lower specificity suggests some cases may require additional markers such as Napsin A, p40 for definitive subtyping, ensuring greater diagnostic confidence where needed.

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