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EXPRESSION OF EGFR, ALK, AND ROS1 BY IMMUNOHISTOCHEMISTRY AND THEIR MOLECULAR ALTERATIONS IN NON-SMALL CELL LUNG CARCINOMA

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ABSTRACT

Background: Non-small cell lung carcinoma is the most common type of lung cancer and remains a major cause of cancer-related mortality worldwide.

Objective: To assess the expression of EGFR, ALK, and ROS1 by immunohistochemistry and evaluate their molecular alterations in patients with non-small cell lung carcinoma.

Methodology: This cross-sectional study was conducted at Pathology Department (Histopathology section) of Fauji Foundation Hospital Lahore, from February 2025 to December 2025, including 65 patients with histopathologically confirmed non-small cell lung carcinoma. Demographic and clinicopathological data including age, gender, smoking history, histological subtype, tumor grade, and stage were recorded.

Results: The mean age of the patients was 59.4 ± 10.7 years, and 42 (64.6%) were male. Smoking history was present in 41 (63.1%) patients. Adenocarcinoma was the most common histological subtype, seen in 37 (56.9%) cases. Immunohistochemical expression of EGFR, ALK, and ROS1 was observed in 24 (36.9%), 7 (10.8%), and 5 (7.7%) patients, respectively. Molecular analysis showed EGFR mutations in 20 (30.8%) cases, ALK rearrangements in 6 (9.2%), and ROS1 alterations in 4 (6.2%).

Conclusion: EGFR was the most frequently expressed and altered biomarker in non-small cell lung carcinoma, followed by ALK and ROS1.

INTRODUCTION

Non-small cell lung carcinoma is the most common type of lung cancer and accounts for nearly 85% of all lung malignancies. It mainly includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [1]. Lung cancer remains one of the leading causes of cancer-related death worldwide because a large proportion of patients present at an advanced stage, when curative treatment is often no longer possible. In the past, treatment decisions in non-small cell lung carcinoma were based mainly on histological subtype and tumor stage [2]. However, over the last two decades, there has been a major shift toward precision oncology, in which molecular characterization of tumors plays a central role in guiding diagnosis, prognosis, and treatment selection [3]. Among the most clinically significant biomarkers in non-small cell lung carcinoma are epidermal growth factor receptor, anaplastic lymphoma kinase, and ROS proto-oncogene 1. These markers are particularly important because alterations involving these genes are associated with distinct oncogenic pathways and may identify patients who benefit from targeted therapy [4]. EGFR mutations result in constitutive activation of intracellular tyrosine kinase signaling, promoting uncontrolled cellular proliferation, inhibition of apoptosis, angiogenesis, and tumor progression. Similarly, ALK and ROS1 gene rearrangements produce fusion proteins with abnormal kinase activity that drive tumorigenesis [5]. The recognition of these alterations has transformed the therapeutic landscape of non-small cell lung carcinoma, as tyrosine kinase inhibitors directed against EGFR, ALK, and ROS1 have demonstrated substantial clinical benefit in appropriately selected patients [6].

The prevalence of these biomarkers varies according to ethnicity, smoking status, sex, histological subtype, and geographic region. EGFR mutations are more frequently detected in adenocarcinoma, non-smokers, females, and Asian populations. In contrast, ALK and ROS1 rearrangements are less common but are often identified in younger patients, non-smokers, and those with adenocarcinoma morphology [7]. Such variability highlights the importance of local data regarding biomarker frequency and expression patterns, especially in populations where routine molecular testing is not universally available. Establishing local profiles of EGFR, ALK, and ROS1

expression and mutation status may help improve targeted treatment selection and optimize limited diagnostic resources [8].

Immunohistochemistry has become an important technique in routine pathology practice because it is relatively rapid, widely available, and cost-effective. It allows the assessment of protein expression in tumor tissue and is especially useful in resource-limited settings where advanced molecular testing may not be readily accessible [9]. For ALK, immunohistochemistry is now widely accepted as a reliable screening and diagnostic method in many laboratories. For ROS1, immunohistochemistry can serve as an effective screening tool, though positive cases often require molecular confirmation due to potential false-positive staining. In the case of EGFR, immunohistochemistry can detect protein overexpression, but it does not fully substitute for molecular testing because protein expression does not always correlate with the presence of actionable mutations [10]. Nevertheless, immunohistochemistry still has value in preliminary assessment and in situations where tissue quantity, cost, or access to molecular platforms is limited. Molecular testing remains the gold standard for detecting specific EGFR mutations and ALK or ROS1 rearrangements. Techniques such as polymerase chain reaction, fluorescence in situ hybridization, and next-generation sequencing provide more precise characterization of genomic alterations [11]. However, these tests are more expensive, require greater technical expertise, and may not be feasible in all centers. In many developing countries, including resource-constrained pathology laboratories, limited tissue samples, financial barriers, and delayed access to specialized molecular diagnostics may result in under-testing of potentially actionable cases. For that reason, integrating immunohistochemistry with molecular analysis may represent a practical and efficient diagnostic approach. Immunohistochemistry can be used as an initial screening method, while molecular techniques can be reserved for confirmation and further characterization of selected cases [12].

Objective

To assess the expression of EGFR, ALK, and ROS1 by immunohistochemistry and evaluate their molecular alterations in patients with non-small cell lung carcinoma.

METHODOLOGY

This was a cross-sectional study was conducted atPathology Department (Histopathology section) of Fauji Foundation Hospital Lahore, from February 2025 to December 2025. A total of 65 patients with non-small cell lung carcinoma were included in the study. Non-probability consecutive sampling technique was used to collect the data. Patients of either gender with histopathologically confirmed non-small cell lung carcinoma and sufficient biopsy or resection tissue available for immunohistochemical staining and molecular testing were included. Patients with small cell lung carcinoma, metastatic carcinoma involving the lung, inadequate tissue sample, previously treated non-small cell lung carcinoma, or poorly preserved tissue blocks unsuitable for immunohistochemical or molecular evaluation were excluded.

Data collection

After approval from the institutional ethical review committee, relevant cases were identified and enrolled according to the inclusion criteria. Demographic and clinicopathological data including age, gender, smoking history, histological subtype, tumor grade, and stage were recorded on a structured proforma. Formalin-fixed paraffin-embedded tissue sections were obtained from the selected cases. Immunohistochemical staining for EGFR, ALK, and ROS1 was performed according to standard laboratory protocols. Molecular analysis for EGFR mutations, ALK rearrangements, and ROS1 alterations was carried out using appropriate molecular techniques available at the study center. The expression of EGFR, ALK, and ROS1 on immunohistochemistry and their corresponding molecular alterations were documented. Their association with clinicopathological variables was also assessed.

Data analysis

The collected data were entered and analyzed using SPSS version 26.0. Quantitative variables such as age were presented as mean ± standard deviation. Qualitative variables such as gender, smoking status, histological subtype, immunohistochemical expression, and molecular alterations were presented as frequency and percentage. Chi-square test or Fisher's exact test was applied to compare categorical variables. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Data were collected from 65 patients, mean age was 59.4 ± 10.7 years, and most patients were older than 60 years, accounting for 28 (43.1%) cases, followed by 21 (32.3%) patients aged 51–60 years and 16 (24.6%) aged 50 years or younger. Males were predominant, with 42 (64.6%) patients, while females comprised 23 (35.4%). Smoking history was present in 41 (63.1%) patients. Adenocarcinoma was the most common histological subtype, seen in 37 (56.9%) cases, followed by squamous cell carcinoma in 22 (33.8%) and large cell carcinoma in 6 (9.2%). Most

tumors were moderately differentiated, observed in 31 (47.7%) patients, while 23 (35.4%) were poorly differentiated and 11 (16.9%) were well differentiated.

Table 1: Baseline Demographic and Clinicopathological Characteristics of the Patients (n = 65)

Variable	Category	Frequency n (%) / Mean ± SD
Age (years)	Mean ± SD	59.4 ± 10.7
Age group	≤50 years	16 (24.6%)
	51–60 years	21 (32.3%)
	>60 years	28 (43.1%)
Gender	Male	42 (64.6%)
	Female	23 (35.4%)
Smoking history	Yes	41 (63.1%)
	No	24 (36.9%)
Histological subtype	Adenocarcinoma	37 (56.9%)
	Squamous cell carcinoma	22 (33.8%)
	Large cell carcinoma	6 (9.2%)
Tumor grade	Well differentiated	11 (16.9%)
	Moderately differentiated	31 (47.7%)
	Poorly differentiated	23 (35.4%)
Stage	I–II	18 (27.7%)
	III–IV	47 (72.3%)

Immunohistochemical analysis showed that EGFR was the most frequently expressed marker, with positivity in 24 (36.9%) patients, whereas 41 (63.1%) were negative. ALK expression was identified in 7 (10.8%) patients and was negative in 58 (89.2%), while ROS1 expression was found in 5 (7.7%) cases and absent in 60 (92.3%). On molecular analysis, EGFR mutation was the most common alteration, detected in 20 (30.8%) patients, with 45 (69.2%) being negative. ALK rearrangement was present in 6 (9.2%) cases and ROS1 alteration in 4 (6.2%) cases, while 59 (90.8%) and 61 (93.8%) patients, respectively, were negative for these alterations.

Table 2: Expression of EGFR, ALK, and ROS1 by Immunohistochemistry (n = 65)

Marker	**Positive n (%)**	**Negative n (%)**
EGFR	24 (36.9%)	41 (63.1%)
ALK	7 (10.8%)	58 (89.2%)
ROS1	5 (7.7%)	60 (92.3%)
Molecular marker	**Positive n (%)**	**Negative n (%)**
EGFR mutation	20 (30.8%)	45 (69.2%)
ALK rearrangement	6 (9.2%)	59 (90.8%)
ROS1 alteration	4 (6.2%)	61 (93.8%)

A significant association was observed between immunohistochemical expression and corresponding molecular alterations for all three markers. Among EGFR-positive cases on immunohistochemistry, 18 were also molecularly positive, while 6 were immunohistochemically positive but molecularly negative, and this association was highly significant ($p = 0.001$). Similarly, ALK immunohistochemical positivity corresponded with molecular rearrangement in 5 cases, while 2 cases were molecularly negative despite positive immunostaining ($p = 0.002$).

Table 3: Association of Immunohistochemical Expression with Molecular Alterations

Marker	**IHC Positive / Molecular Positive n**	**IHC Positive / Molecular Negative n**	**p-value**
EGFR	18	6	0.001
ALK	5	2	0.002
ROS1	3	2	0.010

EGFR mutation was more frequent in females, being present in 11 (47.8%) females compared with 9 (21.4%) males, contributing to a significant gender association ($p = 0.03$). It was also more common in non-smokers, where 13 (54.2%) had EGFR mutation compared with only 7 (17.1%) smokers, showing a significant relationship with smoking status ($p = 0.01$). By histology, adenocarcinoma showed the highest frequency of molecular alterations, with EGFR mutation in 17 (45.9%), ALK rearrangement in 6 (16.2%), and ROS1 alteration in 4 (10.8%) cases.

Table 4: Association of Molecular Alterations with Selected Clinicopathological Variables

Variable	**Category**	**EGFR mutation n (%)**	**ALK rearrangement n (%)**	**ROS1 alteration n (%)**	**p-value**

Gender	Male (n = 42)	9 (21.4%)	4 (9.5%)	3 (7.1%)	0.03
	Female (n = 23)	11 (47.8%)	2 (8.7%)	1 (4.3%)	
Smoking history	Smoker (n = 41)	7 (17.1%)	3 (7.3%)	2 (4.9%)	0.01
	Non-smoker (n = 24)	13 (54.2%)	3 (12.5%)	2 (8.3%)	
Histology	Adenocarcinoma (n = 37)	17 (45.9%)	6 (16.2%)	4 (10.8%)	0.002
	Squamous cell carcinoma (n = 22)	3 (13.6%)	0 (0.0%)	0 (0.0%)	
	Large cell carcinoma (n = 6)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

DISCUSSION

This study evaluated the expression of EGFR, ALK, and ROS1 by immunohistochemistry and their corresponding molecular alterations in 65 patients with non-small cell lung carcinoma. The findings showed that EGFR was the most frequently expressed and altered biomarker in this cohort, followed by ALK and ROS1. Immunohistochemical positivity was 36.9% for EGFR, 10.8% for ALK, and 7.7% for ROS1, while molecular analysis identified EGFR mutations in 30.8% of patients, ALK rearrangements in 9.2%, and ROS1 alterations in 6.2%. These findings indicate that actionable molecular abnormalities are present in a substantial proportion of patients with non-small cell lung carcinoma and support the growing importance of biomarker-driven diagnosis and treatment selection. The demographic profile of the present study showed a mean age of 59.4 ± 10.7 years, with a male predominance and a high frequency of smoking history. This pattern is generally consistent with the known epidemiology of lung carcinoma, particularly in South Asian and other regional populations, where non-small cell lung carcinoma is more common in older adults and remains more frequent in males because of the greater burden of tobacco exposure [13]. However, despite the overall predominance of smokers in the study population, biomarker positivity, particularly EGFR mutation, was more common in non-smokers, which again follows the well-recognized clinicopathological pattern seen in molecularly altered lung adenocarcinomas. Adenocarcinoma was the most frequent histological subtype in this study, accounting for 56.9% of cases, followed by squamous cell carcinoma and large cell carcinoma. This is an important observation because adenocarcinoma is the subtype most often associated with targetable molecular alterations, especially EGFR mutations and ALK or ROS1 rearrangements [14]. In the present study, most positive biomarker findings were concentrated in adenocarcinoma cases. EGFR mutation was seen in 45.9% of adenocarcinoma cases, while ALK rearrangement and ROS1 alteration were identified in 16.2% and 10.8% of adenocarcinoma cases, respectively. These figures reinforce the concept that adenocarcinoma remains the major histological setting in which molecular testing has the highest clinical yield [15]. EGFR was the most frequent abnormality in the present study, with immunohistochemical expression in 24 patients and molecular mutation in 20 patients. This frequency is consistent with the broader literature, which shows that EGFR is among the most common actionable alterations in non-small cell lung carcinoma, especially in adenocarcinoma, females, and non-smokers. In our results, EGFR mutation was more frequent in females and non-smokers, which adds internal consistency to the dataset. The higher frequency of EGFR mutation in female patients and in non-smokers is particularly relevant because these clinicopathological features can raise suspicion for underlying molecular alterations even before confirmatory testing is performed [16]. At the same time, the presence of EGFR-positive cases in males and smokers in our series underscores that molecular testing should not be restricted to stereotypical clinical groups [17].

ALK rearrangement and ROS1 alteration were less frequent than EGFR mutation but still clinically important. ALK rearrangement was detected in 9.2% of cases and ROS1 alteration in 6.2% of cases. Both alterations were mainly identified in adenocarcinoma and tended to occur in patients without strong smoking history, which is again consistent with the known biological profile of these tumors [18]. Although these biomarkers are less common, their therapeutic implications are substantial because they identify patients who may benefit from highly effective targeted therapy. Therefore, even their lower prevalence does not reduce their diagnostic importance [19,20]. The findings of this study should be interpreted in light of certain limitations. The sample size was relatively small, with only 65 patients, which may limit the precision and generalizability of the observed frequencies. The study was also conducted at a single center, which may not fully reflect the broader distribution of molecular alterations in the wider population. In addition, the exact molecular techniques used for all markers were not further stratified in the results, and this may influence sensitivity and specificity of detection. Another limitation is that treatment response and survival outcomes were not evaluated, so the prognostic and therapeutic implications of the detected markers could not be assessed directly in this cohort. Nevertheless, despite these limitations, the study provides useful local data and highlights the practical relevance of integrating immunohistochemistry with molecular analysis in the routine evaluation of non-small cell lung carcinoma.

CONCLUSION

Expression of EGFR, ALK, and ROS1 by immunohistochemistry and their corresponding molecular alterations were identified in a meaningful proportion of patients with non-small cell lung carcinoma. EGFR was the most frequently expressed and altered biomarker, followed by ALK and ROS1. A significant correlation was observed between immunohistochemical expression and molecular alteration status for all three markers, supporting the usefulness of immunohistochemistry as an initial screening tool. These findings suggest that combined immunohistochemical and molecular evaluation can improve biomarker detection and may help guide targeted therapy in patients with non-small cell lung carcinoma, particularly in resource-limited settings.

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