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Original Article

EGFR Mutations, ROS1, and ALK Rearrangements in Iranian Non-Small Cell Lung Cancer Patients

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Abstract

Background: Driver mutations, particularly in the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS1 genes, are prevalent in non-small cell lung cancer (NSCLC) and significantly influence patient outcomes. These mutations have become crucial biomarkers for targeted therapy, guiding treatment decisions and improving patient survival. Our study aims to evaluate the prevalence of EGFR mutations, ALK, and ROS1 gene rearrangements in a cohort of Iranian NSCLC patients and to investigate their association with patient characteristics.

Materials and Methods: Tissue samples from patients diagnosed with non-small cell lung cancer (NSCLC) were subjected to molecular analysis. EGFR mutations, ALK, and ROS1 gene rearrangements were assessed. Additionally, the correlation between these genetic alterations and patient demographics, including age and gender, was explored.

Results: Driver mutations or rearrangements were detected in approximately one-third of NSCLC cases. EGFR mutations were the most common, occurring in 22.44% of patients. ALK and ROS1 rearrangements were identified in 8.18% and 2.11% of patients, respectively. The EGFR mutation frequency in patients younger than 36 years was 16%. In contrast, the mutation frequency in older patient cohorts ranged from 11% to 15%. Among EGFR mutations, exon 19 deletions (13.35%) and L858R point mutations (6.81%) were the most prevalent. Notably, exon 19 deletions were more frequent in female patients (27.92%) compared to male patients (9.90%).

Conclusion: EGFR mutations were more prevalent than ALK and ROS1 rearrangements in our cohort. Exon 19 deletions and L858R point mutations were the most common EGFR mutations, with a higher frequency observed in female patients. These mutations are frequently associated with lung adenocarcinoma.

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1. INTRODUCTION

Lung cancer remains a leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) represent the two primary histological subtypes [1]. The past two decades have witnessed a dramatic transformation in the management and prognosis of non-small cell lung cancer (NSCLC), largely driven by the paradigm shift from traditional chemotherapy to molecularly targeted therapies. This evolution has been underpinned by significant advancements in understanding the molecular landscape of NSCLC, particularly the identification and targeting of specific genetic alterations [2]. Notably, mutations in epidermal growth factor receptor (EGFR) [3-4], anaplastic lymphoma kinase (ALK) [5], and tyrosine kinase receptor 1 (ROS1) have emerged as key therapeutic targets [6]. These insights have translated into significant improvements in patient outcomes. Consequently, research aimed at understanding the prevalence of these molecular markers remains crucial for optimizing the diagnosis and treatment of NSCLC patients.

Epidemiological studies have consistently demonstrated a significantly higher prevalence of epidermal growth factor receptor (EGFR) mutations among Asian adenocarcinoma patients, with an estimated frequency of approximately 51.4% [7]. Notably, these patients have exhibited remarkable responses to targeted therapies utilizing tyrosine kinase inhibitors (TKIs), as evidenced by improved overall response rates (ORRs) and progression-free survival (PFS) compared to conventional chemotherapy regimens [8].

Since the approval and widespread adoption of targeted therapies in 2013, a significant decline in population-level mortality from non-small-cell lung cancer (NSCLC) has been observed in the United States, with a 6.3% annual reduction reported between 2013 and 2016 [9]. Concomitantly, patient survival following diagnosis has improved to 35% [10].

The discovery of ALK and ROS1 rearrangements, while less frequent, has significantly impacted the treatment landscape for a subset of NSCLC patients. These genetic alterations have been associated with distinct clinical features and heightened sensitivity to targeted therapies [11].

The development of effective ALK and ROS1 inhibitors, including second- and third-generation tyrosine kinase inhibitors (TKIs) for ALK and crizotinib or lorlatinib for ROS1, has led to substantial improvements in overall survival and disease control, particularly in the metastatic setting [12].

Despite these advancements, challenges persist. Acquired resistance to targeted therapies and the complex interplay of multiple genetic alterations remain significant hurdles. Ongoing research is focused on identifying novel therapeutic targets, developing combination therapies, and exploring next-generation inhibitors to address these challenges and further improve patient outcomes.

This study aims to investigate the prevalence of ALK, ROS1, and EGFR rearrangements in Iranian patients with non-small cell lung cancer. The results of this research are expected to provide insights into optimal patient management, therapeutic approaches, and disease prognosis, as well as guide healthcare resource allocation and future research activities.

2. MATERIALS AND METHODS

2.1. Patient Samples

Patients with histologically confirmed non-small cell lung carcinoma (NSCLC) were enrolled in this study. Tissue samples, including primary tumor biopsies and metastatic lesions, were obtained from formalin-fixed, paraffin-embedded (FFPE) tissue blocks. Slides were screened for tumor content, and FFPE sections with adequate tumor cellularity (>30%) were selected for further analysis.Clinical data, such as age, sex, smoking history, metastatic status, and prior treatment regimens, were collected for each patient. This comprehensive dataset will facilitate the correlation of molecular findings with clinical characteristics, paving the way for personalized therapeutic approaches and advancing our understanding of NSCLC.

2.2. RNA and DNA Extraction

Tumor areas were meticulously identified on hematoxylin-eosin (H&E)-stained slides by a pathologist. Subsequently, two to three 5 µm sections were microdissected from the corresponding regions of the formalin-fixed, paraffin-embedded (FFPE) tissue blocks. To isolate high-quality DNA and RNA, the MagCore Automated Extraction Kit (RBC Bioscience Corp, Taiwan) was utilized. The 401 cartridge was employed for DNA extraction, while the 610 cartridge was used for RNA extraction. The FFPE tissue sections were deparaffinized with xylene and ethanol (100%) and then dried at 37°C. Proteinase K digestion was performed at 56°C overnight to facilitate nucleic acid release. DNA and RNA purity and concentration were assessed using a NanoDrop spectrophotometer. Extracted nucleic acids were stored at -20°C (DNA) and -80°C (RNA) to ensure long-term stability and integrity.

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2.3. cDNA synthesis

mRNA extracted from FFPE tissues was reverse transcribed into cDNA using a reverse transcriptase enzyme at 42°C. Subsequent PCR amplification was performed under optimized conditions: an initial denaturation step at 95°C for 5 minutes, followed by 25-30 cycles of denaturation at 95°C for 25 seconds, annealing at 64°C for 20 seconds, and extension at 72°C for 20 seconds. These stringent conditions ensure the specific amplification of target genes, minimizing the risk of nonspecific product formation.

2.4. Detection of ALK, ROS1 and EGFR Mutations

To detect common EGFR mutations, including exon 18 point mutations (G719X), exon 19 deletions, exon 20 insertions and point mutations (S768I and T790M), and exon 21 point mutations (L858R and L861Q), real-time PCR was performed using the AmoyDx® EGFR 29 Mutation Detection Kit (Amoy Diagnostics Co., Xiamen, China). Additionally, real-time PCR with the AmoyDx® ALK and ROS1 Gene Fusion Detection Kit was employed to assess EML4-ALK and ROS1 gene rearrangements. Positive cases for ALK and ROS1 gene rearrangements were further validated using fluorescence in situ hybridization (FISH) with specific break-apart probes targeting the ALK gene at 2p23.2 and the ROS1 gene at 6q22.

2.5. Statistical analysis

Statistical analyses and graphical representations were performed using GraphPad Prism version 8.0 and Microsoft Excel. The study investigated the prevalence of ALK, EGFR, and ROS1 gene mutations in non-small cell lung cancer (NSCLC) across various patient demographics. the prevalence of these mutations was compared between adenocarcinoma and squamous cell carcinoma, considering patient gender (male and female) and mean age.

The association between patient gender (male and female) and mean age with the presence or absence of ALK, EGFR, and ROS1 mutations was assessed. The prevalence of mutations was analyzed across different age groups: 15-35 years, 36-56 years, 57-77 years, and 78-98 years.

3. RESULTS

This study included 1056 patients with histologically confirmed lung cancer. The cohort comprised 699 males (66.19%) and 357 females (33.80%), with an age range of 15 to 98 years and a mean age of 61.09 years. Histological subtypes included adenocarcinoma in 890 patients (84.3%) and squamous cell carcinoma in 166 patients (15.7%). ALK and ROS1 rearrangements were assessed in 929 and 900 patients, respectively.

Among 1056 patients, 237 (22.44%) exhibited EGFR mutations. The cohort comprised 112 males (10.60%) and 125 females (11.83%), with ages ranging from 15 to 98 years. Notably, EGFR mutations were significantly more prevalent in females (35.01%) compared to males (16.2%). Adenocarcinoma was the predominant histology, observed in 220 (92.82%) of the EGFR-mutated cases. The most frequent mutations were exon 19 deletions (59.49%), followed by L858R (2.53%), exon 20 insertions (7.59%), and exon 21 substitutions (30.37%) (**Table 1**).

ALK rearrangements were observed in 8.18% of cases, with a slightly higher frequency in males (9.57%) compared to females (7.74%), although this difference was not statistically significant ($p > 0.05$). ROS1 fusions were detected in 2.11% of patients, with a slightly higher prevalence observed in females (3.94%) compared to males (1.32%), but this difference did not reach statistical significance ($p > 0.05$) (**Table 1**).

ALK rearrangements were detected by real-time PCR in 76 of 929 patients (8.18%), while ROS1 rearrangements were identified in 19 of 900 patients (2.11%). Among the 76 ALK-positive patients, 97.36% were histologically classified as adenocarcinoma, with the remaining 2.63% diagnosed as squamous cell carcinoma. All 19 ROS1-positive cases were histologically confirmed as adenocarcinoma.

Among patients with EGFR exon 19 deletions (n=141), 63 were male and 78 were female, with an age range of 15 to 98years. Histological analysis revealed that 89.36% (n=126) of these patients were diagnosed with adenocarcinoma, while 10.63% (n=15) were diagnosed with squamous cell carcinoma (**Table 2**). Among patients with exon 19 deletions, one patient (0.70%) harbored the T790M mutation. Of the 72 patients with the L858R mutation, 34 were male and 38 were female, with ages ranging from 15 to 98 years. All patients (100%) with the L858R mutation were diagnosed with adenocarcinoma. Additionally, two patients (2.77%) harbored the T790M mutation in addition to the L858R mutation. Six patients (four males and two females) harbored the G719X mutation, with ages ranging from 57 to 98 years. All six patients (100%) with the G719X mutation were diagnosed with adenocarcinoma.

The exon 20 mutation was identified in 18 patients (11 males and 7 females) with ages ranging from 36 to 98 years. Histological analysis revealed adenocarcinoma in 88.88% (n=16) of these patients and squamous cell carcinoma in 11.11% (n=2) **Table 2**.

EGFR mutations were detected in 237 (22.44%) of patients. ALK rearrangements were present in 76 cases (8.18%), and

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Table 1. Distribution of EGFR Mutations, ALK and ROS1 Rearrangements by gender in the study population.

EGFR mutation (n=1056)	Number (%)	Males n=699 (%)	Median age	Females n=357 (%)	Median age
No mutation	819(77.55)	695(65.81%)	60.73	355 (33.62%)	59.64
G719X	6(.56)	4 (0.38%)	62.75	2 (0.19%)	74
Exon 19	141(13.35)	63 (5.96%)	60.29	78 (7.38%)	59.6
T790M	18(1.70)	11 (1.04%)	66.34	7 (0.66%)	65.57
L858R	72(6.81)	34 (3.22%)	63.37	38 (3.59%)	63.27
ALK rearrangements(n=929)	76(8.18)	54 (5.81%)	60.13	22 (2.36%)	57.5
No mutation	853(91.81)	569(61.25%)	61.11	284 (30.57%)	60.57
ROS1 rearrangements(n=900)	19(2.11)	8 (0.89%)	52.75	11 (1.22%)	46.45
No mutation	881(97.88)	602(66.89%)	61.06	279 (31%)	60.16

Table 2. Histopathology of EGFR-mutated, ALK-rearranged, and ROS1-rearranged Lung Tumors.

Mutation/deletion	Adenocarcinoma n=220	squamous cell carcinoma n=17
No mutation (n=819)	670(81.80%)	149(18.19%)
G719X (n=6)	6(2.53%)	0(0)
Exon 19 (n=141)	126(53.16%)	15(6.32%)
T790M (n=18)	16(6.75%)	2(.84%)
L858R (n=72)	72(30.37%)	0(0)

Table 3. Distribution of ALK and ROS1 rearrangements in the study.

Mutation/EGFR/tumor type and demographic characteristics	ALK positive (number tested)	ROS1 positive (number tested)
No mutation (n=819)	929(76)	900(19)
G719X (n=6)	6(1)	6(0)
Exon 19 (n=141)	131(6)	131(2)
T790M (n=18)	15(0)	15(0)
L858R (n=72)	66(4)	66(0)

Table 4. Distribution of the three driver mutations across various age groups.

Age group in years	Number of patients, n= 1056	EGFR mutation, n= 1056	ALK, n= 929	ROS1, n= 900
15-35	21(1.98)	5(2.10)	2(2.63)	3(15.78)
36-56	330(31.25)	72(30.37)	29(38.15)	12(63.15)
57-77	651(61.64)	139(58.64)	39(51.31)	4(21.05)
78-98	54(5.11)	21(8.86)	6(7.89)	0(0)
Total	1056	237(100)	76(100)	19(100)

ROS1 rearrangements were present in 19 cases (2.11%) (**Table 3**, **Figure 1**).

EGFR mutations exhibited a relatively uniform distribution across age groups, with the exception of the 15- to 35-year age group, which demonstrated a significantly lower prevalence (2.10%). Notably, exon 19 deletions demonstrated a peak prevalence in the 57- to 77-year age group (100%), exhibiting a subsequent decline with advancing age (**Table 4**).

The L858R mutation exhibited a low prevalence in the 15-35 age group, with a subsequent gradual increase across older age cohorts. Notably, G719X and exon 20 mutations were entirely absent in this youngest age group. ALK rearrangements were most frequent in the 57-77-year age group (51.31%), while ROS rearrangements were predominant in the 36-56-year age group (63.15%).

A statistically significant sex disparity was observed in EGFR mutation patterns. Exon 19 deletions were less frequent in males (26.58%) compared to females (32.91%, $P < .005$). Conversely, the absence of EGFR mutations was significantly more prevalent in males (90.98%) than in females (74.4%, $P < .005$). However, no significant sex-based differences were observed in the prevalence of the L858R mutation, with comparable frequencies in males (14.34%) and females (16.3%).

4. DISCUSSION

EGFR activating mutations exhibit significant ethnic and geographic disparities. Studies as early as 2005 [13] demonstrated a higher prevalence of these mutations in Asian female no smokeing. A large, multi-center Asian study reported an EGFR mutation frequency approaching 60% [14], substantially higher than the 25-39% observed in non-Asian populations [15]. Regional variations within Asia are also evident, with exon 18 mutations more common overall, while exon 19 deletions and L858R mutations predominate

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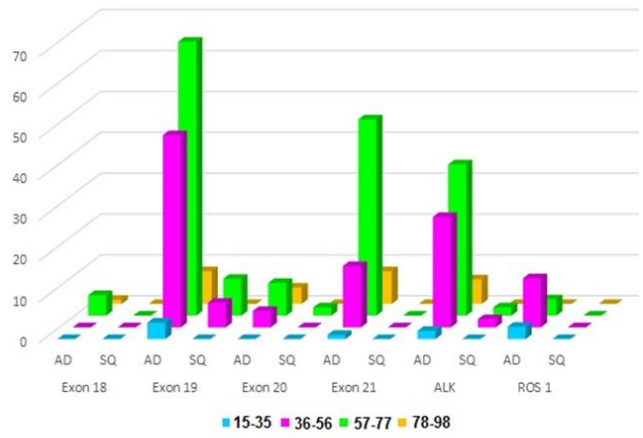

Figure 1. Frequency of EGFR, ALK, and ROS1 mutations in NSCLC by age group.

in Southern Asia and L861Q mutations in Northern Asia [16].

In a European cohort of 552 patients, EGFR mutations were detected in 4.9% [17]. Exon 19 deletions (56%) and exon 21 mutations (30%) were the most prevalent, consistent with established mutation patterns in Caucasian populations. Women exhibited a significantly higher frequency of EGFR mutations (8.5%) compared to men (2.8%). Adenocarcinoma was the predominant histological subtype harboring EGFR mutations (8.5%), while squamous cell carcinomas exhibited a low frequency (1.1%). No significant age difference was observed between patients with EGFR mutations (mean 70.3 years) and those with wild-type EGFR (mean 66.7 years).

A large Spanish study encompassing 2105 non-small cell lung cancer (NSCLC) patients reported an EGFR mutation frequency of 16.6% [18]. Notably, women exhibited a significantly higher prevalence (69.7%), and adenocarcinoma was the predominant histological subtype (80.9%). Age distribution among mutated cases revealed a broad spectrum, with 27.1% aged less than 57 years, 30.1% between 56.7 and 69.1 years, and 42.8% aged over 69 years.

In India, EGFR mutation frequencies vary. Sahoo et al [19]. reported a high prevalence of 51.8% in NSCLC, with exon 19 deletions (52%) and L858R mutations (26%) being the most common. Another Indian study utilizing immunohistochemistry identified EGFR mutations in 26.6% of patients [20]. Furthermore, an analysis of 907 Indian patients revealed an EGFR mutation frequency of 23%, with a female predominance (29.8% vs. 20.4% in males) and adenocarcinoma as the predominant histology (25.9%) [21]. Notably, EGFR mutations were observed in a small proportion (3.8%) of squamous cell carcinomas in this cohort.

Data from Japan and East Asia consistently demonstrate a high prevalence of EGFR mutations in NSCLC, ranging from 27% to 30% [22].

The EGFR mutation frequency observed in our study (22.44%) is comparable to that reported in Japanese and East Asian populations (27-30%) [22] and certain Indian cohorts [20], significantly exceeding the prevalence observed in Spanish (16.6%) [18] and European populations (4.9%)[17]. This disparity in prevalence across different ethnicities has been well-documented in previous literature [23]. Consistent with previous findings in European [17-18] and Indian studies [18, 21], females exhibited a higher prevalence of EGFR mutations (11.83%) compared to males (10.60%). Furthermore, adenocarcinoma remained the predominant histological subtype in our cohort (92.82%), aligning with established observations.

Previous studies have reported conflicting findings regarding the association between age and EGFR mutation status. Some studies have observed an increasing incidence of EGFR mutations with age (36), while others have reported a reduced frequency of EGFR mutations in younger patients (≤50 years) and a higher frequency of uncommon mutations in this younger age group (P = .04) (37). In contrast, our study observed a higher prevalence of uncommon EGFR mutations (G719X, L858R, Exon 20, and Exon 19 deletions) in the older patient population. This discrepancy may be attributable to the older age distribution of our cohort, with 66.76% of patients being over 56 years old. Further investigation is needed to clarify the complex interplay between age and EGFR mutation patterns across diverse patient populations.

The observed frequency of ALK rearrangements in our study (8.18%) aligns with the global prevalence reported in literature (2.7% to 8%) [5, 24-27]. While previous studies have demonstrated a higher incidence of ALK rearrangements in younger patients, with a median age of 51 years [26], our cohort exhibited a slightly older demographic (average age: men 60.13, women 57.5, range: 57-77 years). Despite this, the predominance of adenocarcinoma in ALK-positive cases (92.82%) is consistent with findings from Kwak et al.[26], who reported adenocarcinoma in 96% of ALK-positive lung cancers.

The prevalence of ROS1 rearrangements in our study (2%) is also consistent with previously reported frequencies in the literature [6, 28].

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5. CONCLUSION

This study investigated the prevalence of EGFR mutations, ALK, and ROS1 gene rearrangements in a cohort of Iranian NSCLC patients. EGFR mutations were the most frequent, detected in 22.44% of cases, aligning with higher rates observed in East Asian populations. Exon 19 deletions and L858R point mutations were the most common EGFR mutations, with a higher frequency observed in female patients. ALK rearrangements were found in 8.18% of patients, consistent with global prevalence, and ROS1 rearrangements were identified in 2.11%. Our findings emphasize the clinical significance of these driver mutations in guiding treatment decisions for Iranian NSCLC patients. Further research is warranted to explore the potential impact of age and ethnicity on the mutational landscape of NSCLC in this population.

Acknowledgment

None.

Conflict of interest

The authors declare no conflicts of interest.

Ethical statement

Data were obtained from the hospital information system and anonymized. Informed consent was obtained from all patients prior to sample collection. The study protocol and publication were approved retrospectively by the Institution Ethics Committee (approval number: IR.SBMU.NRITLD.REC.1403.047).

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