Original Article

EGFR Mutation and Neutrophil-Lymphocyte Ratio as Prognostic Biomarkers in Lung Adenocarcinoma: Insights from Western India

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Abstract

Background: Lung adenocarcinoma is a heterogeneous malignancy where epidermal growth factor receptor (EGFR) mutations and systemic inflammation markers like neutrophil-to-lymphocyte ratio (NLR) serve as crucial prognostic tools. Our objective is to analyze the prevalence and types of EGFR mutations, correlation with addiction and histomorphological patterns, and evaluate the prognostic impact of NLR on progression-free survival (PFS) and overall survival (OS).
Methods: This observational study was conducted at a tertiary care center in Gujarat, including 317 cases of lung adenocarcinoma from 2018–2024. EGFR mutation testing was performed on 113 cases using PCR and pyrosequencing. NLR was derived from baseline blood counts and categorized using Youden's index-derived ROC cut-off (2.89). Kaplan–Meier survival analysis and Cox regression were employed to assess outcomes.
Result: EGFR mutations were detected in 36/113 cases (31.8%), more frequently in females (53%) than males (23%). Exon 19 deletions were the most common (66.7%). A significant association was found between EGFR mutation and non-addiction status (p=0.019). Glandular histology predominated among both mutated (58.3%) and wild-type (80.5%) cases. High-NLR status ($\geq$2.89) was significantly associated with shorter PFS (median $\approx$10 vs $\approx$19 months, HR 1.44, p=0.23). OS was shorter in high-NLR cases (median $\approx$11 vs $\approx$24 months, HR 1.51, p=0.18).
Conclusion: EGFR mutations are more prevalent in non-smoking females and are associated with specific histological subtypes. Elevated NLR is a strong predictor of poor PFS, reinforcing its utility as a prognostic biomarker in lung adenocarcinoma. Integrating EGFR and NLR status into diagnostic protocols can enhance individualized management strategies.

Keywords: Lung adenocarcinoma; EGFR mutation; NLR; progression-free survival; histopathology; systemic inflammation.

Introduction

Lung cancer is the most common cause of cancer-related death worldwide. Mutational profiling of lung adenocarcinoma is a routine practice in thoracic oncology. The discovery of activating mutations in the epidermal growth factor receptor (EGFR) of lung adenocarcinoma tumours, and the subsequent recognition that this biomarker predicted high response rates and prolonged progression-free survival after treatment with EGFR tyrosine kinase inhibitors (TKIs), led to a dramatic revolution in the treatment of patients with lung cancer [1, 2, 3, 4]. Molecular markers, such as EGFR mutation and anaplastic lymphoma kinase (ALK) rearrangement, are the best predictors of response to specific TKI treatment agents. Prior to the discussion of the prognostic impact of EGFR mutations and the predictive role of these mutations for responsiveness to cytotoxic agents, the terms "prognostic" and "predictive" should be appropriately defined. Stated simply, a predictive biomarker identifies patients who will or will not respond effectively to a certain drug, while a prognostic biomarker identifies patients who have a favourable or poor prognosis irrespective of treatment [5].

The specific knowledge gap this study addresses for the Gujarat region is the prognostic role of neutrophil lymphocyte ratio in lung adenocarcinoma. Systemic inflammation (SI) plays a central role in the development and progression of cancer by promoting carcinogenesis and angiogenesis; at the same time, oncogenic changes in cancer cells can stimulate SI [6]. SI has also been described as a promoter of the 6 hallmarks of cancer that enable tumour growth and metastatic dissemination [7]. Several laboratory markers of SI have been confirmed as prognostic factors in many types of cancer, including plasma concentration of albumin, C-reactive protein, haemoglobin, platelets, and absolute values of white cells and its components (neutrophils, lymphocytes, monocytes) [8]. The neutrophil to lymphocyte ratio (NLR) is one of the easiest and inexpensive methods to estimate SI, and its value as a prognostic factor has been recognized in a wide variety of tumours, including NSCLC in both early and advanced stages [9, 10, 11, 12, 13].

Histologic features of lung adenocarcinoma may play a role in predicting the outcome in patients with EGFR mutation who are treated with TKIs. Although EGFR mutations are frequently observed in never-smoker females with invasive adenocarcinoma having a predominant lepidic pattern, a significant percentage have also been noted in acinar and papillary variants of adenocarcinoma [14, 15, 16]. Yoshida et al have shown that patients with EGFR mutations with predominant solid pattern of adenocarcinoma have significantly worse overall response to TKIs [17].

Materials and Methods

The current study is a mixed-retrospective and prospective study conducted from January 2018 to December 2024 at Pramukh Swami Medical College & Shree Krishna Hospital, Bhaikaka University, Karamsad, Gujarat. Data will be collected from laboratory information system, electronic health records, patient files and analysed. All the 317 primary bronchoscopic biopsy specimens of lung carcinoma (from 2018 to 2024) came from the Shree Krishna Hospital and were confirmed by histopathology. All the patients had not received preoperative chemotherapy. All the specimens were formalin-fixed paraffin-embedded (FFPE) archival tissue blocks obtained during surgical sampling of the tumours. Exon 18-21 of EGFR were analysed by using polymerase chain reaction (PCR) and Qiagen Pyro Mark 24 sequencer. The overall survival and progression-free survival were estimated on the basis of radiological progression (CT scan) and clinical condition. Of total 317 cases, EGFR mutation analysis was performed in 113 cases considering their affordability. This research study has been approved by IEC (IEC/BU/2023/Ex.29/154/2023) with waiver of consent as patient identity is not revealed.

Statistical Analysis

The χ^2 test and Fisher exact test for independence were used to compare frequencies of clinicopathologic variables. P value < 0.05 was considered statistically significant. We used ROC curves and Youden's Index to classify into two distinct categories of NLR (Cox model). For PFS and OS, the maximal Youden index occurred at NLR$\approx$2.89 using receiver operating characteristic (ROC) curve analysis. In practice we defined "high NLR" as $\geq$2.89 for PFS and OS. For Stratification and survival analysis Patients were split into low-NLR vs high-NLR groups. Statistical analysis was performed with STATA version 19 software.

Results

Total 317 cases were studied, of which EGFR mutation analysis was performed in 113 cases (36%). Of which, 81 cases (71.7%) were male and 32 cases (28.3%) were female.

EGFR Mutation Analysis:

Of total 113 cases evaluated for EGFR mutation analysis, 36 cases (31.8%) results showed EGFR mutation while 77 cases (68.1%) showed wild type EGFR. Of mutated cases most common mutation was of exon 19 (24 cases) and next common mutation was of exon 21 (12 cases). Exon 19 mutations are typically deletions, while exon 21 mutations are point mutations (L858R). Exon 19 deletions are more common than exon 21 L858R mutations.

Of total 81 male patients with adenocarcinoma evaluated for EGFR mutation, 19 cases (23%) were having mutated EGFR while 32 female patients with adenocarcinoma evaluated for EGFR mutation, 17 cases (53%) were having mutated EGFR profile.

EGFR mutation status was significantly associated with addiction history (non-smokers) (p = 0.019) (Table 1). Of total 36 cases with EGFR mutation, 19 cases (53%) did not have any addiction while 11 cases (31%) were smokers, and the rest were having addiction of tobacco 4 cases (11%) and alcohol 2 cases (5%). Of total 77 cases with wild type EGFR, 39 cases (51%) were smokers, 34 cases (44%) with no addiction, 4 cases (5%) with addiction of tobacco chewing. EGFR mutation is more common in nonsmokers.

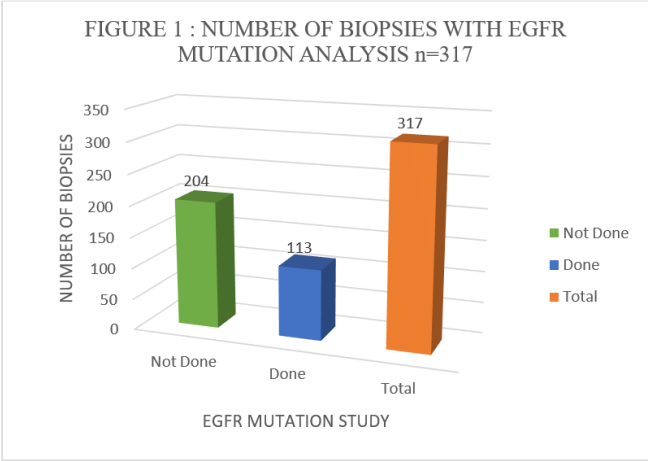

Figure 1: Number of biopsies with EGFR mutation analysis n=317. This figure shows the number of lung adenocarcinoma biopsy specimens analyzed for EGFR mutation (36% of total 317 cases). Among 113 patients, 81 (71.7%) were male and 32 (28.3%) were female.

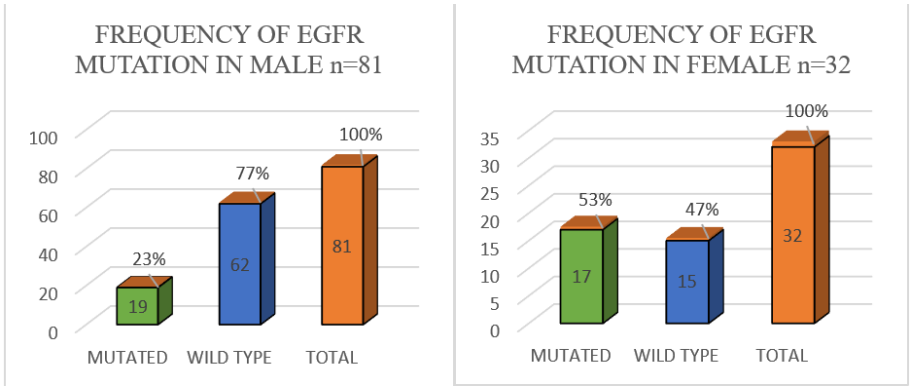

Figure 2: Frequeny of EGFR Mutation in Male n=81 AND Female n=32. This figure illustrates the proportion of EGFR mutations detected among male and female patients. EGFR mutations were found in 19 of 81 males (23%) and 17 of 32 females (53%), demonstrating a higher frequency of mutations in female patients.

Table 1: Distribution of EGFR mutant and wild-type adenocarcinoma cases according to addiction status among 113 patients.

EGFR Status	Addiction	No Addiction	Total
EGFR Mutant Adenocarcinoma	17	19	36
EGFR Wild Type Adenocarcinoma	43	34	77
Total	60	53	113

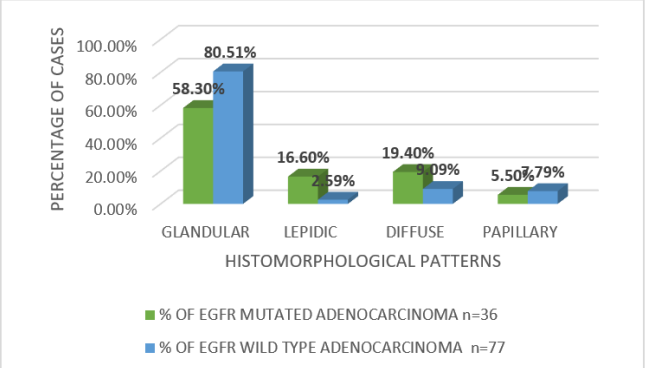

Figure 3: Histopathological pattern of Adenocarcinoma and EGFR Mutation: Figure 3 compares the histological subtypes of adenocarcinoma between EGFR-mutant and wild-type cases. In EGFR-mutant cases (n=36), the most common pattern was glandular (58.3%), followed by diffuse (19.4%), lepidic (16.6%), and papillary (5.5%). In EGFR wild-type cases (n=77), glandular pattern predominated (80.5%), with lower proportions of diffuse (9.1%), papillary (7.8%), and lepidic (2.6%) patterns.

Of total 36 cases with EGFR mutated adenocarcinoma, most common histomorphological pattern is glandular 20 cases (58.30%), second most common is diffuse 7 cases (19.40%), and next most common pattern is lepidic 6 cases (16.60%) followed by papillary 3 cases (5.50%). Of total 77 cases with wild type EGFR adenocarcinoma, most common histomorphological pattern is glandular 62 cases (80.51%), second most common is diffuse 7 cases (9.09%), and next most common pattern is papillary 6 cases (7.79%) followed by lepidic 2 cases (2.59%).

Table 2: Kaplan–Meier survival analysis and univariate Cox regression for overall survival (OS) and progression-free survival (PFS), stratified by neutrophil-to-lymphocyte ratio (NLR) cut-off of 2.89. Median survival values are reported with 95% confidence intervals (CI). Hazard ratios (HR) are derived from univariate Cox regression ($\geq$2.89 vs <2.89).

Endpoint	Group	Cut-off	N	Events, (no. of deaths)	Median (months) [95% CI]	Cox HR ($\geq$ vs <)	Cox p-value
OS	NLR < cut-off	2.89	26	14	24 (0.83-2.72)	1.51	0.18
OS	NLR $\geq$ cut-off	2.89	84	54	11 (0.83-2.72)	1.51	0.18
PFS	NLR < cut-off	2.89	26	14	19 (0.79-2.6)	1.44	0.23
PFS	NLR $\geq$ cut-off	2.89	84	54	10 (0.79-2.6)	1.44	0.23

A total of 110 patients with lung adenocarcinoma were included in the analysis as 3 cases were loss to follow-up. The optimal neutrophil-to-lymphocyte ratio (NLR) cut-off value, derived using receiver operating characteristic (ROC) curve analysis with Youden's index, was 2.89. Patients were stratified into two groups: NLR $<$ 2.89 and NLR $\geq$ 2.89.

Overall Survival (OS)

The median overall survival (OS) was 24 months (95% CI: 0.83–2.72) in the low NLR group and 11 months (95% CI: 0.83–2.72) in the high NLR group. Kaplan–Meier analysis demonstrated inferior OS in patients with NLR $\geq$ 2.89 compared with those with NLR $<$ 2.89 (Figure 4). On univariate Cox proportional hazards regression, high NLR was associated with an increased risk of mortality (HR: 1.51, 95% CI: 0.83–2.72, p = 0.18).

Progression-Free Survival (PFS)

The median progression-free survival (PFS) was 19 months (95% CI: 0.79–2.60) in the low NLR group compared with 10 months (95% CI: 0.79–2.60) in the high NLR group. Kaplan–Meier curves (Figure 4) indicated reduced PFS in patients with NLR $\geq$ 2.89. On univariate Cox regression, high NLR was associated with worse PFS (HR: 1.44, 95% CI: 0.79–2.60, p = 0.23). It should be noted that progression events were not explicitly recorded, and death was considered as the event for PFS estimation.

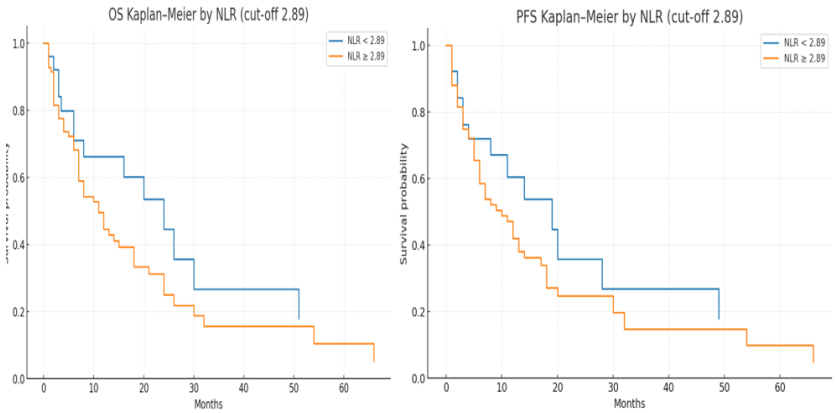

Figure 4: Kaplan-Meier OS and PFS BY NLR cutt-off 2.89. Kaplan–Meier overall survival and progression free survival curves stratified by NLR (cut-off 2.89). Median survival with 95% CI is presented in Table 2.

Discussion

This study investigated various clinicopathological characteristics, EGFR mutation status, and inflammatory markers in a cohort of 317 lung adenocarcinoma cases, with detailed EGFR mutation analysis performed in 113 cases. PFS and OS were analysed in 110 cases as 3 cases were loss to follow-up.

Epidemiological and EGFR Mutation Outlook: The demographic analysis revealed a male preponderance in the overall cohort. This aligns with global trends where lung cancer incidence, including NSCLC, is generally higher in men, potentially

attributable to historical differences in smoking prevalence. Male patients may undergo EGFR mutation analysis more often than female patients due to various factors, including: Higher incidence of lung cancer: Lung cancer is more common in men than women. Smoking prevalence: Smoking rates have been higher in men, increasing their risk of developing lung cancer. NSCLC is more common in men, and EGFR mutations are more frequently found in NSCLC.

Regarding EGFR mutation status, 31.8% (36 out of 113 cases) showed EGFR mutations, while 68.1% (77 cases) were wild type. This mutation rate is comparable to those reported in Asian populations, which tend to have a higher prevalence of EGFR mutations compared to Western populations. Among the mutated cases, exon 19 deletions (24 cases) were more common than exon 21 L858R point mutations (12 cases). This observation is consistent with the observation made by Graham et al which showed that of the treatment-sensitive activating mutations, the most common are exon 19 mutations (7.9% of total cases tested) and the exon 21 L858R mutation (7.6% of total cases tested), and the least common are exon 20 mutations (0.3% of total cases tested) [18]. This may reflect: Structural vulnerability: Exon 19 encodes a critical region of the EGFR protein, making it more susceptible to mutations. Mutational hotspot: Exon 19 contains a mutational hotspot, increasing the likelihood of mutations in this region. Selection pressure: Cancer cells with exon 19 mutations may have a selective growth advantage, contributing to their higher frequency.

Notable finding was the significant female preponderance for EGFR mutations, with 53% of female patients exhibiting mutations compared to 23% of male patients, which is comparable to Pan et al which showed 22 patients with germline EGFR mutations, with the majority harboring an EGFR T790M mutation (95.5%) and an EGFR L858R somatic mutation (50%). Notably, most patients were female (86.4%) [19]. The female preponderance for EGFR mutation is because of: Non-smoking status and Hormonal influences.

Association of EGFR Mutation with Addiction and Histomorphology: Our study established a statistically significant association between EGFR mutation and addiction status (p=0.019). Specifically, 53% of EGFR-mutated adenocarcinoma cases had no history of addiction, compared to 44% of wild-type cases, which is comparable to Pan et al which showed 22 patients with germline EGFR mutations, with the majority cases are non-smokers (81.8%). Conversely, smoking was more prevalent in the wild-type EGFR group (51%) than in the mutated group (31%). This reinforces the understanding that EGFR mutations are more common in non-smokers [19]. This may be attributed to: Different carcinogenic mechanisms: Smoking-related lung cancers may have different molecular mechanisms and mutational profiles compared to non-smoking-related lung cancers. Distinct molecular pathways: EGFR mutations may be more prevalent in lung cancers arising from distinct molecular pathways, which are less common in smokers.

Regarding histomorphological patterns, glandular patterns were most common in both EGFR-mutated (58.3%) and wild-type (80.51%) adenocarcinoma cases. Villa et al reported eight (36%) of 22 minimally invasive adenocarcinomas had EGFR mutations, representing 20% of the lung cancers with EGFR mutant gene as compared to 9% of the lung cancers with wild-type gene. The predominant pattern seen in the EGFR-mutant–positive lung cancer group was lepidic (44%) as compared to patients with wild-type gene, whose tumors exhibited acinar pattern in 69% and lepidic pattern in 15% of cases. While glandular patterns predominated, there were subtle differences in the distribution of other patterns (diffuse, lepidic, papillary) between the two EGFR status groups, suggesting potential morphological correlates of EGFR mutation status that warrant further investigation [20].

Inflammatory Markers and Prognosis: In this study, we evaluated the prognostic value of neutrophil-to-lymphocyte ratio (NLR) in patients with lung adenocarcinoma. Using ROC curve analysis, the optimal NLR cut-off was determined to be 2.89. Patients with high NLR ($\geq$2.89) demonstrated inferior progression-free survival (PFS) and overall survival (OS) compared with those with low NLR. Although the differences did not reach statistical significance on univariate Cox regression, the observed trends support the role of systemic inflammatory markers in predicting outcomes in lung cancer. Aguiar-Bujanda et al reported Median PFS was 10.58 months (95% confidence interval (CI) 6.90–13.05) and median OS was 20.84 months (95% CI 12.72–42.90). Median OS was greater for the low-NLR group, 24.62 months (95% CI 16.24–45.73) compared to 7.43 months (95% CI 1.51–15.32) for the high-NLR group (log-rank test p = 0.0122). A non-significant difference in PFS was observed between patients in both groups: 10.81 months (95% CI 6.90–16.37) in the low-NLR group compared to 7.03 months (95% CI 1.34–13.3) in the high-NLR group (log-rank test p = 0.1502) [21].

Conclusion

To conclude, our study confirms the prevalence of EGFR mutations in lung adenocarcinoma, with a higher frequency of exon 19 deletions and a significant female preponderance. A notable association between EGFR mutation and non-addiction status was also established. Furthermore, our analysis demonstrates that an elevated NLR ($\geq$2.89) is associated with worse survival outcomes in lung adenocarcinoma, reinforcing its utility as a simple, inexpensive, and readily available prognostic biomarker. Larger, prospective, and multicentric studies from India are warranted to validate these findings and to integrate NLR into risk stratification models for routine clinical use.

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Competing Interests: The authors declare that they have no financial or non-financial competing interests that could have influenced the conduct, analysis, or reporting of this study. This work was carried out purely for academic and research purposes, without any involvement or support from pharmaceutical companies, diagnostic industries, or other commercial entities. To the best of our knowledge, this is the first comprehensive study from the Gujarat region that evaluates the interplay between EGFR mutation status, histomorphological patterns, and NLR as a prognostic marker in lung adenocarcinoma. This study thus fills an important gap and contributes novel data from a tertiary care setting in Western India.

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