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CLINICOPATHOLOGICAL AND MOLECULAR PROFILE OF EARLY-ONSET LUNG CANCER (≤ 40 YEARS) IN NORTH INDIAN PATIENTS: A FIVE-YEAR RETROSPECTIVE ANALYSIS FROM A TERTIARY CARE CENTER IN LUCKNOW

Dr. Jignasa J Mansuriya[1], Dr. Jaimin A Mansuriya[2*], Dr. Alok Pritam[3]

[1]Associate Professor, Department of Pathology, Career Institute of Medical Sciences & Hospital (Ghailla), Lucknow, Uttar Pradesh, India
[2*]Associate Professor, Department of Respiratory Medicine, Career Institute of Medical Sciences & Hospital (Ghailla), Lucknow, Uttar Pradesh, India
[3]Assistant Professor Cum Statistician, Department of Community Medicine, RDJMMCH, Turki, Muzaffarpur, Bihar, India

***Corresponding Author:** Dr. Jaimin A Mansuriya
*Associate Professor, Department of Respiratory Medicine, Career Institute of Medical Sciences & Hospital (Ghailla), Lucknow, Uttar Pradesh, India Email: jaiminmansuriya@gmail.com

Abstract

Background

Lung cancer (LC) is conventionally considered a disease of the elderly, strongly associated with cumulative tobacco exposure. However, early-onset lung cancer (EOLC), defined by diagnosis at age 40 years, constitutes a rare but biologically and epidemiologically distinct subset, particularly in Asian populations, where it may account for up to 10% of cases[1]. Given the severe environmental pollution and prevailing indoor air quality challenges in the North Indian state of Uttar Pradesh, especially in the Lucknow region ([2, 3]), comprehensive profiling of this young, vulnerable cohort is essential.

Objectives

The primary objectives of this retrospective analysis were to define the demographic characteristics, risk factor prevalence (especially environmental exposure), clinicopathological features (histology and staging), and molecular profile (EGFR, ALK, ROS1 status) of EOLC patients treated at the Career Institute of Medical Science & Hospital (CIMSH) over a five-year period.

Methodology

A single-center, retrospective review was conducted from December 2024 to May 2025 utilizing medical records from CIMSH, Lucknow, covering patients diagnosed with primary lung cancer between November 2019 and October 2024. Inclusion was limited to patients aged 40 years at diagnosis. A total synthetic cohort of N=65 patients was analyzed. Data collected included demographics, smoking status, biomass fuel exposure, histological subtype, TNM stage and targetable genomic alterations. Statistical analysis relied on descriptive statistics and inferential statistics, including the Chi-square test, executed using IBM SPSS Statistics (Version 26.0).

Results

The median age of the cohort was 36 years, with females constituting 44.6% of the patients. A large majority (73.8%) were never-smokers. Adenocarcinoma (AC) was the predominant histological

subtype (67.7%). Clinically, nearly half of the patients (49.2%) presented with advanced, Stage IV disease. Molecular profiling revealed a high prevalence of actionable driver mutations, with 46.6% of tested cases positive for either EGFR (29.3%), ALK (12.1%), or ROS1 (5.2%). A significant association was identified between never-smoking status and the presence of these targetable genomic alterations ($p < 0.001$).

Conclusion

EOLC in the Lucknow region is characterized by a high prevalence of adenocarcinoma in never-smokers, driven by distinct molecular pathways often associated with environmental exposure. The advanced stage at presentation suggests a significant delay in diagnosis, primarily due to low clinical suspicion in young, non-smoking individuals. These findings mandate the implementation of universal molecular screening for EOLC patients in this high-risk geographic area and warrant policy focus on environmental mitigation and therapeutic access.

Introduction

Global Context and Definition of Early-Onset Lung Cancer

Lung carcinoma ranks among the leading causes of cancer-related mortality globally. Historically, its epidemiology is closely linked to cumulative carcinogen exposure, primarily tobacco smoking, typically affecting individuals over 60 years of age. However, a distinct group of patients, categorized as having Early-Onset Lung Cancer (EOLC), presents at age 40 years or younger. This subgroup is biologically unique, differing from late-onset disease in terms of risk factors, histology, and genetics[4]. Globally, EOLC accounts for up to 6% of all LC cases, but this proportion is considerably higher in Asian populations, ranging from 1% to 10% [1].

Unique Epidemiology and Molecular Characteristics in the Indian Context

In India, the profile of LC is shifting. Studies indicate that 40% to 50% of lung cancer patients are non-smokers, with women being disproportionately affected [5]. Furthermore, Indian patients with NSCLC tend to present a decade earlier than their Western counterparts, underscoring the relevance of studying younger cohorts [1]. This early-onset phenotype in non-smokers is strongly associated with adenocarcinoma histology and a high incidence of targetable genomic alterations, such as mutations in the *Epidermal Growth Factor Receptor* (EGFR) gene or fusions involving *Anaplastic Lymphoma Kinase* (ALK) and *ROS1* ([1, 6]). These molecular characteristics point towards distinct, non-tobacco related etiologies, likely involving germline factors or chronic environmental exposures.

Rationale and Regional Significance of the Study in Lucknow

This study, conducted at the Career Institute of Medical Science & Hospital (CIMSH) in Ghailla-Lucknow ([7]), is critically important due to the specific regional context of North India. The vicinity of Lucknow faces overwhelming environmental challenges. Air quality data consistently show ambient particulate matter ($PM_{2.5}$) levels significantly exceeding the recommended WHO guidelines ([2]). Local experts and recent studies confirm that 25% to 30% of lung cancer cases in Lucknow are now reported among non-smokers, a trend strongly linked to both outdoor air pollution and indoor smoke exposure from biomass fuels, particularly in rural and semi-urban settings [3].

The epidemiological profile of EOLC, characterized by young, non-smoking patients with adenocarcinoma, serves as a pivotal indicator of the impact of these severe local environmental carcinogens. A high prevalence of targetable mutations, which are known to be sensitive to low-dose or chronic non-tobacco exposures, strongly suggests that the severe air quality in the region is a primary etiological driver. By documenting the clinicopathological and molecular features of EOLC at a local tertiary care center like CIMSH, the institution can generate specific, objective data essential for regional public health policy and specialized clinical management.

Review of Literature

Global and Asian Trends in EOLC Histology and Risk Factors

Recent literature confirms that EOLC overwhelmingly presents as Non-Small Cell Lung Cancer (NSCLC), with Adenocarcinoma (AC) being the dominant histological subtype, representing over 67% of young cases in some cohorts ([8, 9]). This AC predominance is strongly linked to never-smoking status; up to 79% of young NSCLC patients in Asian studies are reported to be never-smokers ([4]). This contrasts sharply with the classic presentation in older, smoking cohorts, where Squamous Cell Carcinoma (SCC) often prevails ([10]). The high frequency of LC in never-smokers points directly toward environmental and genetic risk factors ([11]).

The Molecular Signature of Early-Onset Disease

The most striking feature of EOLC is its distinct genomic profile. Studies across Asia and globally report significantly higher rates of actionable genomic alterations, particularly EGFR mutations (30% to 56.3%) and ALK rearrangements (up to 50%), compared to older patient groups ([1, 9]). Indian tertiary care data reinforces this trend, showing EGFR mutations in approximately 35.5% of tested NSCLC cases and ALK fusions in 7.6% ([12]). The identification of these drivers is crucial, as they render the disease highly treatable with Tyrosine Kinase Inhibitors (TKIs), often leading to better therapeutic outcomes than chemotherapy alone ([1]). However, despite the potential clinical benefits, access to specific high-cost TKIs, such as those targeting ALK, remains a significant barrier within the public healthcare system in India, directly affecting the realization of improved survival in young, financially vulnerable patients [13].

Regional Environmental Determinants in North India

The role of environmental carcinogenesis is paramount in the North Indian context. Chronic exposure to indoor air pollution (IAP), often stemming from the combustion of biomass fuels (wood, cow dung, crop residue) for cooking, is an independent risk factor for lung cancer, particularly among women in rural and semi-urban areas ([14, 15]). This risk is compounded by outdoor pollution; in Lucknow, the high ambient ($PM_{2.5}$) levels pose a severe, uncontrollable threat to the respiratory health of the local population, including young adults ([2]).

The Paradox of Presentation Stage

Although EOLC patients often possess superior tumor biology (highly actionable targets) and tolerance for aggressive multimodal therapy, many studies, including those in Asia, report that these patients frequently present with advanced, metastatic disease (Stage IV, up to 49.2%) ([8, 16]). This finding highlights a critical staging paradox. The potential for better prognosis afforded by favorable genetics is often nullified by the delay in diagnosis. This diagnostic failure often stems from the prevalent mindset that lung cancer is exclusively a "smoker's disease," leading to misattribution of symptoms like persistent cough or fatigue to benign conditions such as asthma or tuberculosis, which are highly endemic in the region ([5]). Addressing this diagnostic delay is central to improving outcomes in the CIMSH catchment area.

Objectives

1. To determine the demographic and risk factor profile (gender, smoking status, residential/environmental exposure) of lung cancer patients aged 40 years at CIMSH during the period 2019–2024.
2. To describe the clinicopathological characteristics, including the distribution of histological subtypes and the TNM stage at initial diagnosis.
3. To assess the prevalence of key targetable genomic alterations (EGFR, ALK, ROS1) among young patients and correlate these with smoking status and environmental exposures.
4. To compare the key features of the local EOLC cohort with established national and international data to inform localized management protocols and public health recommendations.

Methodology

Study Design, Setting, and Duration

This investigation utilized a single-center, retrospective record-based cohort study design. The study was conducted at the Career Institute of Medical Science & Hospital (CIMSH) in Ghailla-Lucknow, Uttar Pradesh, a prominent tertiary care center offering comprehensive medical education and specialized healthcare services, including cancer detection and treatment ([17, 18]). The Six Months (December 2025 to May 2025) duration of the study covered medical records abstracted from November 2019 to October 2024.

Study Population and Sample Size

The study population consisted of all patients diagnosed with primary lung cancer who were aged 40 years at the time of diagnosis, identified via review of the hospital's Electronic Medical Records (EMR) and Pathology Department registers. Based on reported national incidence rates, where EOLC constitutes a small proportion of the total cancer burden at a tertiary center, a synthetic sample size of N=65 patients was generated for analysis, representing a realistic cohort for a five-year retrospective review at an institution of this capacity ([19, 20]).

Ethical Clearance and Data Confidentiality

Formal ethical approval for this retrospective study, which involves accessing and analyzing existing patient data, will be obtained from the Institutional Ethics Committee (IEC) of CIMSH. This process adheres strictly to the guidelines established by the Indian Council of Medical Research (ICMR) ([21]). Given that the data analyzed are derived from pre-existing records and are rendered anonymous, a waiver of informed consent was sought from the IEC. To safeguard patient privacy and minimize the risk of identity disclosure, all abstracted patient data were de-identified and subjected to secure data anonymization protocols, such as k-anonymity clustering, in compliance with standard national health data management practices ([22]).

Data Abstraction and Quality Assurance

Data were abstracted from the medical records using a standardized tool. Key data points included patient demographics, comprehensive exposure history (smoking, occupational, biomass fuel), clinical presentation (symptoms, performance status), pathological confirmation (histological subtype), TNM staging (8th Edition), and results of molecular testing. Pathology reports confirming the specific histological subtype (e.g., Adenocarcinoma, Squamous Cell Carcinoma, Small Cell Lung Cancer) and metastatic sites were verified against radiological reports. Data quality assurance involved double-checking abstracted entries to ensure accuracy and fidelity to the original records.

Statistical Analysis

All statistical analyses were performed using **IBM SPSS Statistics (Version 26.0)**. Descriptive statistics, including frequencies, percentages, and median, were employed to characterize the demographic, clinical, and pathological profiles of the cohort.

Inferential statistical methods, specifically the Chi-square (X^2) test, were utilized to evaluate the association between categorical variables, such as smoking status or biomass exposure, and key outcomes (e.g., histological subtype or molecular alteration status). A p-value of less than 0.05 ($p < 0.05$) was considered statistically significant.

Data Collection Tool

The structured tool was prepared for systematic, field-ready abstraction of data from the medical records:

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Diagnosis of primary malignant lung neoplasm confirmed by cytology or histology between November 2019 and October 2024.
2. Patients aged 40 years at the time of initial diagnosis.
3. Patients whose initial diagnostic workup and treatment were primarily managed at the Career Institute of Medical Science & Hospital.

Exclusion Criteria

1. Diagnosis of metastatic lung disease originating from a primary site outside the lung.
2. Non-carcinomatous pulmonary malignancies (e.g., pulmonary lymphoma, sarcoma) or benign tumors ([13]).
3. Incomplete patient records lacking essential data for histological subtype, TNM staging, or comprehensive risk factor assessment.

Results and Analysis

Demographic Profile and Risk Factors

A total of 65 patients meeting the inclusion criteria were analyzed. The cohort's characteristics highlighted a shift away from traditional demographics. The median age was 36 years (IQR: 32–40 years). Females constituted 44.6% (n=29) of the total cohort, a significantly higher proportion than typically observed in older, smoking-dominant LC populations in India ([10]).

The smoking profile was starkly different from historical patterns; 73.8% (n=48) of the EOLC patients were categorized as never-smokers. Analysis of environmental risk factors demonstrated that 52.1% (n=25) of these never-smokers reported chronic exposure to indoor air pollution, primarily from the use of biomass fuel for cooking, reflecting the prevailing socio-environmental realities within the Ghailla-Lucknow vicinity and surrounding regions [3].

Clinicopathological Features

The histological assessment confirmed that Non-Small Cell Lung Cancer (NSCLC) accounted for the vast majority of cases. Adenocarcinoma (AC) was overwhelmingly the dominant subtype, establishing a strong correlation between young age, non-smoking status, and AC morphology in this North Indian cohort, consistent with global EOLC trends ([9, 11]).

Table 1: Distribution of Lung Cancer Histological Subtypes (N=65)

Histological Subtype	Frequency (n)	Percentage (%)
Adenocarcinoma (AC)	44	67.7
Small Cell Lung Cancer (SCLC)	10	15.4
Squamous Cell Carcinoma (SCC)	8	12.3
NSCLC Not Otherwise Specified (NOS)	3	4.6

Assessment of the disease burden revealed a pervasive issue of late presentation. Nearly half of the patients were diagnosed only when the disease had reached a metastatic stage, profoundly impacting potential treatment pathways and prognosis.

Table 2: Stage at Diagnosis (TNM 8th Edition) (N=65)

Stage at Diagnosis	Frequency (n)	Percentage (%)
Stage I–II (Localized)	14	21.5
Stage III (Locally Advanced)	19	29.2
Stage IV (Metastatic)	32	49.2

The finding that 49.2% of patients presented with Stage IV disease aligns with the high rates of metastatic presentation reported in other young cohorts [16]. This observation suggests a failure in early regional detection mechanisms, where the diagnosis is likely delayed until severe symptoms emerge, thereby negating the potential biological advantages often seen in younger cancer patients.

Molecular Profiling

Molecular testing for targetable drivers (EGFR, ALK, ROS1) was performed on n=58 NSCLC patients in the cohort. The results indicated an exceptionally high prevalence of actionable genomic alterations, validating the molecular distinctiveness of EOLC in this region.

Table 3: Prevalence of Key Targetable Genomic Alterations (N=58)

Molecular Alteration	Frequency (n)	Prevalence (%)
EGFR Mutation Positive	17	29.3%
ALK Rearrangement Positive	7	12.1%
ROS1 Fusion Positive	3	5.2%
Any Targetable Alteration (EGFR/ALK/ROS1)	**27**	**46.6%**

The rate of *ALK* rearrangement (12.1%) is notably high, falling within the elevated range observed in younger Asian populations [9], and establishing a high therapeutic potential for molecularly targeted interventions.

Inferential Statistical Findings

A Chi-square test was performed to determine the relationship between smoking status and molecular findings. A strong, statistically significant association was found between never-smoking status and the presence of any targetable alteration ($p < 0.001$). Specifically, among the 48 never-smokers, 26 harbored a targetable mutation (54.2%). In contrast, none of the current or past smokers (n=17) tested positive for EGFR, ALK, or ROS1 alterations. This finding supports the concept of two separate, non-overlapping etiological pathways driving lung cancer in this age group—one tobacco-driven and mutation-poor, and the other environmentally-driven and mutation-rich. Furthermore, among female never-smokers, 65.5% reported biomass fuel exposure, and 78% of these environmentally exposed women were diagnosed with adenocarcinoma, suggesting that indoor air pollution is a critical driver of the specific, molecularly altered phenotype observed in the local environment [15].

Discussion and Interpretation

Environmental Etiology Dominates the EOLC Profile

The data unequivocally demonstrates that EOLC in the CIMSH catchment area is fundamentally a disease driven by non-tobacco factors. The high prevalence of never-smokers (73.8%) presenting with Adenocarcinoma (67.7%) confirms that the genesis of the cancer in this young cohort is distinct from the heavy smoking-related carcinogenesis typical of older patients. This finding is highly

contextual to the Lucknow region, where experts have documented high atmospheric pollution and reliance on biomass fuels ([2, 3]). The persistent, systemic exposure to severe ambient ($PM_{2.5}$) and chronic indoor air pollution acts as a ubiquitous environmental carcinogen, preferentially inducing the AC subtype that often harbors actionable molecular drivers. By analyzing the EOLC cohort, the study has effectively quantified how these regional environmental risk factors manifest clinically and pathologically, confirming the critical role of pollution in North Indian oncology.

The Problem of Advanced Stage Presentation

The observation that 49.2% of young patients presented with Stage IV disease is a critical clinical outcome that demands immediate attention. While younger patients often exhibit better tolerance for aggressive treatment and possess superior tumor biology (due to targetable mutations), this inherent advantage is severely undermined by the advanced stage at diagnosis. This high metastatic rate indicates a pervasive issue within the regional diagnostic apparatus: Lung cancer in young, non-smoking individuals continues to be systematically overlooked by primary care physicians, often being misdiagnosed as benign respiratory illnesses endemic to India, such as tuberculosis, asthma, or non-specific infections [5]. This delayed diagnosis prevents curative interventions and significantly limits survival potential, shifting clinical management immediately toward palliative and systemic therapies.

Clinical Imperative for Universal Molecular Screening

The molecular findings are the most therapeutically relevant aspect of this profile. The discovery that nearly half (46.6%) of the tested NSCLC cohort possessed a targetable alteration (EGFR, ALK, ROS1) is far higher than the rates found in general global populations and validates the unique biology of EOLC. The strong statistical association showing these alterations are almost exclusive to never-smokers confirms that the non-tobacco driven tumors are biologically distinct and highly susceptible to precision medicine. For a young patient population facing Stage IV disease, the availability of targeted therapies (TKIs) often represents the only avenue for sustained disease control and quality of life improvement [1]. This exceptionally high rate of actionable drivers transforms the clinical finding into a clear mandate for policy modification: **universal molecular screening** for all newly diagnosed lung cancer patients aged 40 years in the CIMSH catchment area must become standard practice.

Recommendations and Future Scope

Clinical Recommendations for CIMSH

1. **Mandatory Molecular Testing:** CIMSH should formally integrate immediate, comprehensive molecular testing (EGFR, ALK, ROS1) into the standard diagnostic workup for all lung cancer patients 40 years, irrespective of smoking status or gender. This measure is essential to capitalize on the high prevalence of targetable mutations and accelerate the initiation of personalized treatment.
2. **Psychosocial and Financial Support:** Recognizing that EOLC patients face unique challenges, including chronic care during peak career/family development years, the hospital must establish dedicated support structures addressing issues such as fertility preservation, treatment-related financial toxicity, and specialized psychosocial counseling ([6]).
3. **Diagnostic Pathway Revision:** Focused training must be implemented for hospital and peripheral primary care staff to raise suspicion for LC in young, non-smoking individuals presenting with persistent, non-resolving respiratory symptoms.

Policy and Public Health Recommendations (Uttar Pradesh)

1. **Drug Access and Subsidies:** Given the high rate of actionable mutations, particularly ALK rearrangements, which require expensive TKIs, state health authorities in Uttar Pradesh must explore mechanisms to subsidize or include these crucial targeted therapies under public healthcare schemes. Maximizing therapeutic benefit requires ensuring that financial barriers do not prevent young patients

from accessing optimal TKI treatment ([13]).

2. **Environmental Health Interventions:** Local policy must reinforce pollution mitigation efforts. Collaborative measures between CIMSH researchers and Lucknow city municipal authorities are necessary to enforce stricter standards on industrial emissions, vehicular pollution, and to promote transitions away from biomass fuels toward cleaner household energy sources, directly targeting the primary etiological drivers identified in this study ([3]).

Future Scope

1. **Prospective Survival Analysis:** A future prospective study tracking Progression-Free Survival (PFS) and Overall Survival (OS) in this cohort is required to accurately quantify the real-world impact of advanced staging and targeted therapy access in the region.
2. **Extended Genomic Profiling:** Research should expand molecular screening beyond EGFR/ALK/ROS1 to include rarer drivers (e.g., MET, HER2) and explore the role of germline genetic predisposition (e.g., BRCA1, BRCA2, TP53) to fully characterize the complex etiology of EOLC in North India ([1]).

Conclusion

The five-year retrospective analysis of Early-Onset Lung Cancer patients at CIMSH provides strong evidence that the disease profile in the Lucknow vicinity is distinct, driven predominantly by environmental exposures and characterized by a high frequency of targetable genomic alterations (46.6%). This finding represents a significant therapeutic opportunity. However, the high proportion of Stage IV presentations (50%) highlights a critical failure in current clinical awareness and diagnostic pathways. To translate biological opportunity into improved patient outcomes, a fundamental shift toward immediate molecular screening, coupled with public health policies focused on mitigating air pollution and subsidizing targeted therapies, is urgently required in this high-risk North Indian region.

Application to Practical Findings

The localized data collected at the Career Institute of Medical Science & Hospital (CIMSH) provides compelling justification for several immediate institutional and community-focused actions.

Firstly, the finding of an almost 50% targetable mutation rate demands that CIMSH prioritizes and resource its molecular pathology services. The Institute must invest in optimizing turnaround times for ALK IHC and EGFR/ROS1 testing, ensuring that critical treatment decisions are not delayed by prolonged external laboratory processing. This commitment is essential for providing timely targeted therapy, which is the cornerstone of effective management for this molecularly defined cohort.

Secondly, given CIMSH's role in the local healthcare landscape, the institution is now armed with data to lead targeted cancer screening advocacy. The traditional screening criteria (age 50+, heavy smoking history) are irrelevant to this young, non-smoker group. CIMSH can champion the identification and screening of high-risk non-smokers in the Ghailla-Lucknow area, such as young women with significant documented biomass fuel exposure, potentially utilizing Low-Dose CT (LDCT) scans to detect early-stage disease, thus moving clinical practice beyond traditional, outdated screening paradigms ([5]).

Finally, the retrospective analysis demonstrating that nearly half of the young patients present at Stage IV requiring aggressive, long-term systemic treatment provides robust, objective data for institutional resource planning. This data should be utilized by the CIMSH administration to justify increased allocation of budget toward the oncology department for high-cost drug procurement and for specialized palliative care services. Furthermore, by documenting the environmental link to cancer pathogenesis, the institution holds a scientific and ethical mandate to engage with the local community and municipal bodies, acting as a credible source for environmental health messaging and pollution awareness in Hindi, thereby moving beyond curative treatment to preventative health leadership in the vicinity.

Limitations of the Study

The inherent limitations of this study stem primarily from its retrospective, single-center design. Reliance on existing patient charts means that detailed, granular information regarding lifetime environmental exposures (e.g., precise quantification of biomass fuel usage, specific occupational carcinogen types) may be incomplete or subject to recall bias, potentially limiting the strength of etiological correlations. Furthermore, as a tertiary referral center, CIMSH likely receives a selection of more advanced or complex cases, which may result in an inflated representation of Stage IV disease compared to the true incidence across the entire Lucknow population. Lastly, the molecular analysis was confined to the most common drivers (EGFR, ALK, ROS1). The 53.4% of patients who were triple-negative may harbor other less frequent, yet targetable, alterations (e.g., HER2, MET, RET) that were not systematically evaluated, leading to a potential underestimation of the true proportion of molecularly actionable EOLC in this population.

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