Scientific Research Publishing

Advances in Lung Cancer, 2024, 13, 1-21
https://www.scirp.org/journal/alc
ISSN Online: 2169-2726
ISSN Print: 2169-2718

Epidemiology of EGFR Mutation in Adenocarcinoma NSCLC Patients in India: A Systematic Review and Meta-Analysis

Ankita Jain[1*], Kumar Prabhash[2], Venkatraman Radhakrishnan[3], Shashank Srinivasan[1]

[1]Pfizer Products India Private Limited, Mumbai, India
[2]Tata Memorial Hospital, Mumbai, India
[3]Cancer Institute (W.I.A.), Chennai, India
Email: *ankita.jain@pfizer.com, kprabhash1@gmail.com, venkymd@gmail.com, shashank.srinivasan@pfizer.com

How to cite this paper: Jain, A., Prabhash, K., Radhakrishnan, V. and Srinivasan, S. (2024) Epidemiology of EGFR Mutation in Adenocarcinoma NSCLC Patients in India: A Systematic Review and Meta-Analysis. *Advances in Lung Cancer*, **13**, 1-21.
https://doi.org/10.4236/alc.2024.131001

Received: December 11, 2023
Accepted: March 11, 2024
Published: March 14, 2024

Abstract

Studies reporting the Indian prevalence of Epidermal Growth Factor Receptor (EGFR) mutation are mostly single centers with small sample sizes. This systematic review and meta-analysis summarized the available evidence of EGFR mutation epidemiology in Indian patients with adenocarcinoma (ADC) Non-Small Cell Lung Cancer (NSCLC). We conducted a structured literature search in PubMed, and EMBASE databases from January 2004 through October 2019. The primary outcome of interest was prevalence of EGFR mutation by gender, smoking status, and mutation subtype. The review included 34 studies. EGFR mutation prevalence was 39.5% in patients with ADC, and significantly higher in females, non-smokers, and patients with exon 19 deletions. The EGFR mutation frequency in Indian patients with ADC was higher than reported in Caucasians but at a lower range of that reported in East Asians. These findings support the use of EGFR mutation testing to guide choice of treatment.

Keywords

Epidemiology, Epidermal Growth Factor Receptor, Adenocarcinoma, Non-Small Cell Lung Cancer, India

1. Introduction

Lung cancer is the predominant cause of the global cancer burden. As per GLOBOCAN 2020, lung cancer is the leading cause of cancer-related death in men, with an incidence rate of 14.3% (1.4 million new cases) and a mortality

rate of 21.5% (1.2 million deaths). In women, lung cancer is the third most common cancer, with an incidence rate of 8.4% (0.7 million new cases) and a mortality rate of 13.7% (0.6 million deaths) [1]. In the Indian scenario, the National Cancer Registry Program report published in 2020 predicted that 1 in 68 males in India would develop lung cancer during their lifetime. Further, lung cancer was projected to be among the 5 most common cancers in both sexes in 2020. Most lung cancer cases present in advanced stages in both sexes with 44% and 47.6% cases in males and females respectively being metastatic at presentation [2].

Lung cancer is broadly categorized as Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) based on histology. Despite various advances in treatment strategies, lung cancer still has a poor prognosis, with a relatively low 5-year survival rate [3].

Non-small cell lung cancer is further classified as Adenocarcinoma (ADC), squamous, and large cell carcinoma. Adenocarcinoma begins in the glandular tissue that forms the alveolar lining of the lung [4].

Tobacco consumption is one of the most important risk factors for NSCLC [5]. However, ADC was a more common subtype among women and never smokers [6]. Molecular profiling of patients with NSCLC has revealed the presence of oncogenic driver mutations, which may drive carcinogenesis in more than 80% of the ADC cases, including Epidermal Growth Factor Receptor (EGFR) mutations [7]. Therefore, a better understanding of these oncogenic driver mutations, particularly EGFR mutations, will change the treatment landscape for NSCLC patients [8]. Epidermal growth factor, a cell surface receptor, regulates cell proliferation, apoptosis, angiogenesis, adhesion, and motility through intracellular signaling and controls tumor progression [8]. Sensitizing EGFR mutations are the most common actionable driver mutations that may induce Tyrosine Kinase (TK) activation and phosphorylation of downstream pathways, resulting in aggravating cancer [9] [10]. In-frame deletions in exon 19 and point mutations in exon 21 (L858R) are the most common EGFR mutations [8]. Tyrosine Kinase Inhibitors (TKIs) are an important new class of molecularly targeted anti-cancer agents that block corresponding kinases from phosphorylating tyrosine residues of their substrates and then inhibit the activation of downstream signaling pathways involved in cancer proliferation, invasion, metastasis, and angiogenesis [11]. Use of TKIs against these EGFR-sensitizing mutations in advanced NSCLC patients as the first line of treatment can improve survival and quality of life [12]. Therefore, EGFR tumor genotyping acts as an essential guide in making treatment decisions regarding the use of EGFR TKIs in NSCLC patients. Mutation testing empowers patients with EGFR mutation-positive NSCLC of ADC histology to undergo personalized treatment with EGFR TKIs. Based on the tumor's molecular characteristics, these TKIs directly act on EGFR oncogenes, resulting in improved treatment outcomes [7].

Various epidemiological factors, such as race, sex, and age, affect the inci-

dence of an oncogenic driver mutation. EGFR gene mutations are predominantly observed in women and non-smokers of East Asian ethnicity [13]. Further, the frequency of EGFR mutation was higher in East Asians (40% - 55%) compared to Caucasians (5% - 15%) [14]. These considerable variations in the prevalence and pathology of the disease at the global level indicate the need for regional research for a detailed appreciation of molecular epidemiology and clinical management. Therefore, genetic testing might be beneficial for countries like India, where genetic variability is common [15]. Few Indian studies have reported data regarding EGFR mutation in ADC NSCLC patients [7] [16]-[21]. However, information that would be helpful to policymakers and service providers is scarce. Therefore, this systematic review and meta-analysis is aimed to assess the EGFR mutations epidemiology in ADC NSCLC patients in India and compare it with Caucasian and East Asian data.

2. Methodology

2.1. Data Sources and Selection

A structured literature search was conducted in PubMed and EMBASE databases from January 2004 through October 2019 for articles reporting data on EGFR mutations in ADC NSCLC patients in India. Appropriate keywords and database-specific subject terms related to "epidemiology, non-small cell lung cancer, adenocarcinoma, epidermal growth factor receptor positivity, Indian population" were employed, along with suitable Boolean operators for the search. The literature search was restricted to only human studies. Further, relevant conference abstracts and papers, articles in the press, short surveys, and errata were also searched to identify the grey literature not captured by the formal searches.

2.2. Study Selection

We included studies on EGFR mutations in ADC NSCLC patients from India, published in English from January 2004 to October 2019 for evidence synthesis. Studies with the non-Indian population, other cancer types, not specifying the type of NSCLC or not including ADC patients, reviews, meta-analyses, and studies not in scope (such as guidelines and *in-vitro* studies) were excluded. Duplicate publications were checked, and the validity of the article titles was verified. Abstracts and full texts were reviewed in-depth in the following phase. Two reviewers handled the study selection independently.

2.3. Data Extraction

The data collected from each study included the following details: study title, the first author, journal, publication year, study design, study location, number of NSCLC patients (sample size), number of patients with an EGFR mutation, age, study period, diagnostic method, the prevalence of EGFR positivity in NSCLC and ADC, and different mutation subtypes (such as exon 19 deletions, exon 21

substitutions, exon 20, and exon 18 mutations). Two reviewers handled the data extraction independently, and any disagreements were resolved by a third reviewer to reach a consensus.

2.4. Outcome Measure and Subgroup Variables

The primary outcome of interest in the review is the EGFR mutation and its prevalence determined using mutation testing by gender (male or female), smoking status (never or ever-smokers, according to the definitions of the original studies), and mutation subtype (exon 19 deletions or exon 21 substitutions).

2.5. Data Analysis

Rev Man 5 software by Cochrane Collaboration was used to perform the random-effects meta-analysis using the Inverse variance method with a dichotomous data type to calculate the Odds Ratio (OR) with 95% confidence intervals. Furthermore, subgroup analysis was performed according to gender (males/females), smoking status (smokers/non-smokers), and exon subtype (exon 19 deletion/exon 21 substitution). The random-effects model was used to consider the diversity and heterogeneity in the studies included in the review. The Cochran's Q-test and the I^2 statistic were applied to evaluate the statistical heterogeneity among the studies and were considered significant at a p value ≤ 0.10 for the Cochran's Q-test or an $I^2 \geq 50\%$ for study heterogeneity [22].

3. Results

A structured search from PubMed resulted in 268 articles; likewise, EMBASE search yielded 1326 articles. Supplementary search resulted in four articles resulting in a total of 1598 articles. After removing 176 duplicates, title, and abstract screening were performed on 1422 articles. After excluding 1367 records [country other than India (13), not in scope studies (1291), reviews/meta-analyses (14), and other cancer types (4)], 55 records met the criteria for full-text review. Among these 55 articles, 27 full text articles (lacking complete information regarding NSCLC, ADC) were excluded. Finally, 34 eligible studies were included in the qualitative and quantitative synthesis to understand the role of NGS-guided precision oncology in improving overall patient outcomes in advanced cancer. A PRISMA flow chart explaining the procedure to select the study is explained in **Figure 1**.

The general characteristics of the studies reporting EGFR positivity in ADC NSCLC patientsare summarized in **Table 1**. All the studies were observational, mostly retrospective (70.6%) and cross-sectional (14.7%) study designs. The median number of patients included in these studies was found to be 123, which ranged from 35 [23] to 3351 [24].

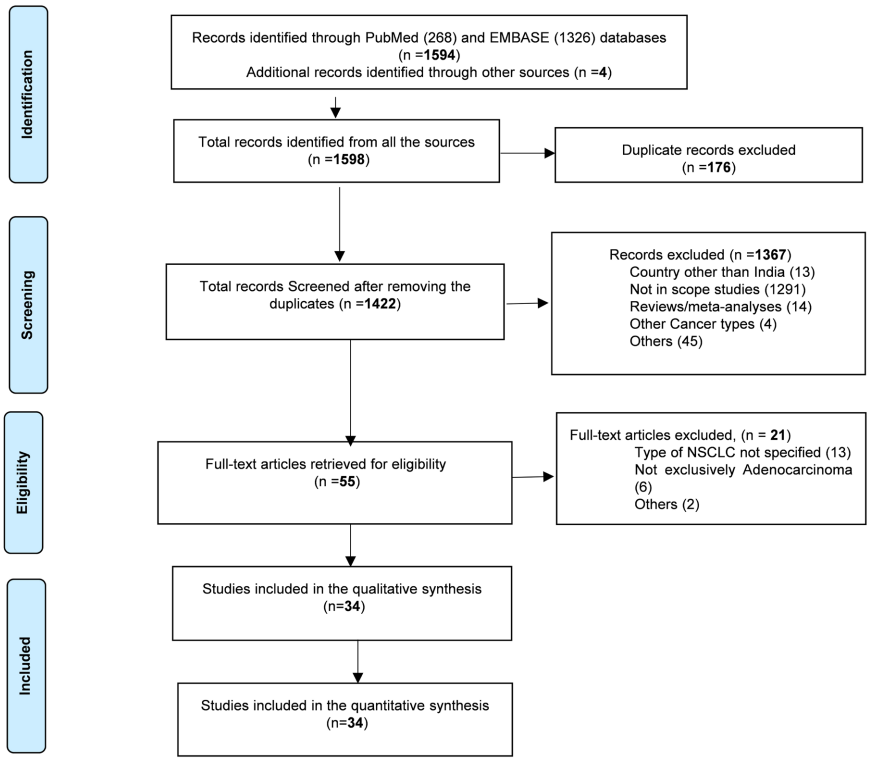

Figure 1. Flow diagram of studies included in the systematic review and meta-analysis.

Most of the studies were from the Northern part of India (35%), followed by studies from the South (20.6%) and Central India (20.6 %). The remaining studies were either from the East (5.8%), west (3%) or without regional details (14.7%). Six percent of the studies were multi-centric, while most (94%) were single-center studies.

3.1. Biases and Confounding Patient Characteristics

Information on age was available for 94% (32 out of 34) of studies and was primarily reported as medians (67.6%) and means (17.6%), while the rest was presented as the age range (8.8%) (**Table 1**). Gender-related information was available for 94% (32 out of 34) of studies (**Table 2**). Among these studies, females were 33%, and males constituted 67% of the study population. Smoking-related information was available for 79% of studies. Heterogeneous distribution of smoking patterns was observed amongst the studies, with the percentage of smokers varying from 14% [25] to 81% [21] and non-smokers varying from 15% [21] to 81% [26]. Among the 27 studies with information on smoking, 41% were smokers, and 54% were non-smokers (**Table 3**). Information regarding exon subtypes was available for 67.6% of studies. Among these studies, exon 19 deletion was predominant, varying from 45% [27] to 81% [28] [29], followed by exon 21 substitution, varying from 15% [29] to 46% [16] among the EGFR-positive patients. The homogeneity of studies included in the review was assessed based on the detection methods of the EGFR mutation. Information on the techniques

used for detecting the EGFR mutation was available for 97% of the studies, in which most of the studies used Real-Time Polymerase Chain Reaction (RT-PCR) (44%) and PCR (35.3%), followed by immunohistochemistry (14.7%) and fluorescence *in situ* hybridization (2.9%) (Table 1).

The screening of the studies followed by data extraction was performed by two reviewers independently, and a third reviewer was consulted to resolve the discrepancies to avoid selection bias.

Table 1. Basic Characteristics of the included studies.

S. No.	First Author	Year of Study	Study Design	Region	Diagnostic Method	Median Age, Range (in Years)	Total No. of Subjects, n	NSCLC, n (%)	ADC Cases in NSCLC, n (%)	EGFR Positive Cases in ADC, n (%)
1	Samdariya *et al.* [49]	2016	Retrospective study	Jodhpur, India	NR	13 - 80	133	122 (92)	37 (30)	20 (54)
2	Rana *et al.* [50]	2017	Clinical and epidemiological study	Pune, India	PCR and gene sequencing	57.5 (25 - 86)	152	152 (100)	135 (88.8)	48 (35.5)
3	Bal *et al.* [28]	2016	Retrospective study	Chandigarh, India	RT-PCR	61.8 (mean)	240	240 (100)	240 (100)	37 (15.4)
4	Verma *et al.* [21]	2017	Retrospective and prospective study	Lucknow, India	IHC	55.3 (Mean)	69	69 (100)	18 (26.1)	14 (77.8)
5	Doval *et al.* [30]	2015	Retrospective study	Indian multi-centric (6 centres)	FISH	58	500	500 (100)	500 (100)	164 (32.8)
6	Doval *et al.* [51]	2017	Retrospective study	New Delhi, India	PCR	60 (24 - 90)	401	322 (80.3)	196 (60.9)	33* (22.8)
7	Bhatt *et al.* [52]	2013	Retrospective study	Vellore, India	PCR	55	154	106 (55)	76 (72)	42 (55.2)
8	Shankar *et al.* [53]	2014	Retrospective study	Chennai, India	IHC	<40 to >80	90	84 (93)	46 (55)	41 (89)
9	Singh *et al.* [20]	2017	Retrospective study	New Delhi, India	RT-PCR	62	421	388 (92.2)	223 (57.5)	24** (20)
10	Ashutosh *et al.* [36]	2016	Cross-sectional	New Delhi, India	PCR	56.2 (Mean)	102	102 (100)	102 (100)	21 (20.6)
11	Sahoo *et al.* [54]	2011	Retrospective study	Bangalore, India	RT-PCR	59	220	220 (100)	176 (80)	114 (64.7)
12	Bala *et al.* [29]	2016	Retrospective study	Hyderabad, India	RT-PCR	58	353	353 (100)	250 (70.8)	47# (35)
13	Jain *et al.* [25]	2017	Retrospective study	New Delhi, India	Sanger sequencing and RT-PCR	58	116	116 (100)	84 (72.4)	17 (20.2)
14	Sharma *et al.* [19]	2018	Retrospective study	Chandigarh, India	PCR	61 - 80	61	61 (100)	48 (79)	19 (39.6)
15	Udupa *et al.* [35]	2015	Cross-sectional	Chennai, India	RT-PCR	55	85	85 (100)	85 (100)	34 (40)

Continued

16	Chatterjee *et al.* [17]	2016	Cross-sectional	Kolkata, India	PCR followed by bidirectional Sanger's sequencing	58	224	224 (100)	214 (96)	68 (31.7)
17	Vaid *et al.* [27]	2013	Retrospective study	North India	PCR	61.5 (27 - 87)	105	105 (100)	80 (76.2)	22 (27.5)
18	Chatterjee *et al.* [16]	2017	Retrospective study	Kolkata, India	RT-PCR	56 (42 - 72)	108	106 (98)	106 (100)	35 (33)
19	Ansari *et al.* [55]	2017	Case control study	North India	RT-PCR	54.5 ± 11.5 (Mean ± SD)	111	111 (100)	61 (55)	14 (22.9)
20	Kota *et al.* [56]	2015	Retrospective study	Hyderabad, India	RT-PCR	56 (30 - 80)	147	111 (75.5)	95 (85.6)	34 (35.8)
21	Singh *et al.* [34]	2018	Retrospective study	North India	RT-PCR	58	125	125 (100)	125 (100)	31 (24.8)
22	Gupta *et al.* [57]	2019	Prospective study	Hyderabad, India	PCR	58.2	64	64 (100)	51 (80)	23 (45.1)
23	Noronha *et al.* [33]	2017	Retrospective study	Mumbai, India	RT-PCR	56 (49 - 62)	580	580 (100)	580 (100)	227 (39.1)
24	Kasana *et al.* [32]	2018	Cross-sectional	Jammu and Kashmir, India	PCR	56.9 (Mean)	57	57 (100)	57 (100)	20 (35.1)
25	Choughule *et al.* [18]	2013	Retrospective study	Mumbai, India	PCR	NA	1018	1018 (100)	255 (25)	255 (100)
26	Bharadwaj *et al.* [58]	2016	Retrospective study	New Delhi, India	IHC	62.7 (42 - 79) (Mean)	60	60	20 (33.3)	18 (90)
27	Poonamalle *et al.* [23]	2013	Retrospective study	India	IHC	> 50	35	35 (100)	26 (74.3)	21 (80.7)
28	Dutt *et al.* [24]	2014	Cohort study	India	PCR	57.9 (25 - 90)	3351	3079 (92)	3079 (100)	748## (28.2)
29	Prabhash *et al.* [42]	2017	Retrospective study	Indian multicentric	RT-PCR	57	301	252 (84)	213 (84.5)	59 (27.7)
30	Doval *et al.* [31]	2013	Retrospective study	New Delhi, India	PCR	60	166	166 (100)	166 (100)	43 (25.9)
31	Dang *et al.* [59]	2013	Retrospective study	India	IHC	NA	149	149 (100)	63 (42)	38*# (90)
32	Chougule *et al.* [41]	2013	Retrospective study	Mumbai, India	RT-PCR	Males 57, females 54	907	907 (100)	780 (86)	210 (26.9)
33	Noronha *et al.* [26]	2013	Retrospective study	Mumbai, India	RT-PCR	55	NA	111	107 (96.4)	39 (36.4)
34	Kumari *et al.* [60]	2019	Cross-sectional	Lucknow, India	RT-PCR	60 (26 - 87)	530	226 (90)	169 (74.8)	79 (46.7)

NSCLC: Non-Small Cell Lung Cancer; ADC: Adenocarcinoma; EGFR: Epidermal Growth Factor Receptor; NR: Not Reported; PCR: Polymerase Chain Reaction; RT-PCR: Real-Time Polymerase Chain Reaction; IHC: Immunohisto Chemistry; FISH: Fluorescence *in Situ* Hybridization. *EGFR positive/EGFR mutated, 33/145 (23%); **EGFR positive/EGFR mutated, 24/120 (24%); #EGFR positive/EGFR mutated, 47/134 (35%); ##EGFR positive/EGFR mutated, 748/2653 (28.2%); *#EGFR positive/EGFR mutated, 38/42 (90%).

Table 2. Male-female distribution of lung cancer patients.

S. No.	First Author	Total No. of Subjects		EGFR-positive Subjects	
		Females, n (%)	Males, n (%)	Females, n (%)	Males, n (%)
1	Samdariya *et al.* [49]	41 (31)	92 (69)	NA	NA
2	Rana *et al.* [50]	60 (39.5)	92 (60.5)	23 (48)	25 (52)
3	Bal *et al.* [28]	NA	NA	18 (48.6)	19 (51.4)
4	Verma *et al.* [21]	17 (24.64)	52 (75.36)	5 (35.7)	9 (64.3)
5	Doval *et al.* [30]	163 (32.6)	337 (67.4)	68 (41.5)	96 (59)
6	Doval *et al.* [51]	64 (19.9)	258 (80.1)	NA	NA
7	Bhatt *et al.* [52]	33 (31.2)	73 (68.8)	15 (35.7)	27 (64.3)
8	Shankar *et al.* [53]	31 (37)	53 (63)	NA	NA
9	Singh *et al.* [20]	90 (23.2)	298 (76.8)	18 (75)	6 (25)
10	Ashutosh *et al.* [36]	40 (39)	62 (61)	NA	NA
11	Sahoo *et al.* [54]	97 (44)	123 (56)	56 (49.1)	58 (50.9)
12	Bala *et al.* [29]	100 (28.3)	253 (71.7)	NA	NA
13	Jain *et al.* [25]	30(36)	54 (64)	NA	NA
14	Sharma *et al.* [19]	17 (35.4)	31 (64.6)	11 (57.9)	8 (42.1)
15	Udupa *et al.* [35]	20 (24)	65 (76)	NA	NA
16	Chatterjee *et al.* [17]	54 (26)	153 (74)	36 (53.7)	32 (46.3)
17	Vaid *et al.* [27]	22 (27.5)	58 (72.5)	NA	NA
18	Chatterjee *et al.* [16]	41 (38.6)	65 (61.3)	19 (54.3)	16 (45.7)
19	Ansari *et al.* [55]	19 (31.2)	42 (68.8)	NA	NA
20	Kota *et al.* [56]	50 (45)	61 (55)	22 (64.7)	12 (35.3)
21	Singh *et al.* [34]	35 (28)	90 (72)	10 (32.3)	21 (67.7)
22	Gupta *et al.* [57]	13 (27.5)	35 (72.5)	6 (26.1)	17 (73.9)
23	Noronha *et al.* [33]	205 (35.3)	375 (64.7)	86 (37.9)	141 (62.9)
24	Kasana *et al.* [32]	26 (46)	31 (57)	14 (70)	6 (30)
25	Choughule *et al.* [18]	318 (31.2)	700 (68.8)	109 (44.5)	146 (57.3)
26	Bharadwaj *et al.* [58]	16 (26.7)	44 (73)	10 (55.6)	8 (44.4)
27	Poonamalle *et al.* [23]	9 (25.7)	26 (74.3)	NA	NA
28	Dutt *et al.* [24]	1205 (36)	2146 (64)	NA	NA
29	Prabhash *et al.* [42]	83 (32.9)	169 (67.1)	27 (45.8)	32 (54.2)
30	Doval *et al.* [31]	55 (33.1)	111 (66.9)	18 (41.9)	25 (58.1)
31	Dang *et al.* [59]	NA	NA	NA	NA
32	Chougule *et al.* [41]	265 (29.8)	642 (70.8)	79 (37.6)	131 (62.4)
33	Noronha *et al.* [26]	53 (47.7)	58 (52.3)	27 (69.2)	12 (30.8)
34	Kumari *et al.* [60]	75 (30)	175 (70)	30 (37.9)	49 (62.1)

EGFR: Epidermal Growth Factor Receptor; NA: Not Available.

Table 3. Distribution of NSCLC patients by smoking habits.

S. No.	First Author	Total No. of Subjects			EGFR-positive Subjects		
		Smokers, n (%)	Non-smokers, n (%)	Others (Reformed, Former, Unknown)	Smokers, n (%)	Non-smokers, n (%)	Others (Reformed, Former, Unknown,)
1	Samdariya *et al.* [49]	81 (61)	52 (39)	NA	NA	NA	NA
2	Rana *et al.* [50]	NA	NA	NA	NA	NA	NA
3	Bal *et al.* [28]	NA	NA	NA	NA	NA	NA
4	Verma *et al.* [21]	56 (81.2)	13 (18.8)	NA	NA	NA	NA
5	Doval *et al.* [30]	164 (32.8)	250 (50)	Unknown 86 (17.2)	29 (17.7)	108 (43.2)	27 (31.4)
6	Doval *et al.* [51]	167 (51.9)	138 (42.9)	NA	NA	NA	NA
7	Bhatt *et al.* [52]	35 (33.0)	71 (67)	NA	7 (16.7)	35 (83.3)	NA
8	Shankar *et al.* [53]	NA	NA	NA	NA	NA	NA
9	Singh *et al.* [20]	NA	NA	NA	NA	NA	NA
10	Ashutosh *et al.* [36]	32 (31)	40 (39)	Reformed 31 (30)	NA	NA	NA
11	Sahoo *et al.* [54]	104 (47)	116 (53)	NA	64 (56.1)	50 (43.9)	NA
12	Bala *et al.* [29]	177 (50.1)	176 (49.9)	NA	NA	NA	NA
13	Jain *et al.* [25]	12* (48)	13* (52)	NA	NA	NA	NA
14	Sharma *et al.* [19]	24 (50)	21 (44)	NA	4 (21.1)	15 (78.9)	NA
15	Udupa *et al.* [35]	39 (46)	46 (54)	NA	NA	NA	NA
16	Chatterjee *et al.* [17]	NA	NA	NA	NA	NA	NA
17	Vaid *et al.* [27]	37 (46)	43 (54)	NA	9 (41)	13 (59)	NA
18	Chatterjee *et al.* [16]	28 (26.4)	78 (73.6)	NA	5 (14.3)	30 (85.7)	NA
19	Ansari *et al.* [55]	23 (38)	38 (62)	NA	NA	NA	NA
20	Kota *et al.* [56]	41 (37)	70 (63)	NA	5 (14.7)	29 (85.3)	NA
21	Singh *et al.* [34]	86 (68.8)	39 (31.2)	NA	19 (61.2)	12 (38.7)	NA
22	Gupta *et al.* [57]	NA	NA	NA	NA	NA	NA
23	Noronha *et al.* [33]	231 (39.9)	349 (60.1)	NA	59 (26)	168 (74)	NA
24	Kasana *et al.* [32]	32 (56.1)	25 (43.9)	NA	7 (35)	13 (65)	NA
25	Choughule *et al.* [18]	382 (37.5)	597 (58.6)	Unknown 6 (15)	61 (25)	188 (77)	NA
26	Bharadwaj *et al.* [58]	48 (80)	12 (20)	Former 7 (11.7)	7 (38.9)	8 (44.4)	3 (16.6)
27	Poonamalle *et al.* [23]	21 (60)	14 (40)	NA	NA	NA	NA
28	Dutt *et al.* [24]	NA	NA	NA	NA	NA	NA
29	Prabhash *et al.* [42]	88 (35)	147 (58)	Former Smoker 69 (29.4)	5 (9.3)	45 (83.3)	4 (7.4)
30	Doval *et al.* [31]	71 (43)	95 (57)	Former Smoker 28 (16.9)	4 (9.3)	6 (21.4)	33 (34.7)
31	Dang *et al.* [59]	NA	NA	NA	NA	NA	NA
32	Chougule *et al.* [41]	360 (39.6)	516 (56.8)	Unknown 31 (3.4)	55 (26.2)	152 (72.4)	3 (1.4)
33	Noronha *et al.* [26]	23 (21)	88 (79.2)	NA	4 (10.3)	35 (89.7)	NA
34	Kumari *et al.* [60]	115 (46)	135 (54)	NA	29 (36.8)	50 (63)	NA

EGFR: Epidermal Growth Factor Receptor; NA: Not Available. *Smoking data were available for 25 patients only.

Table 4. Distribution of EGFR mutations in ADC NSCLC patients by mutation types.

S. No.	First Author	Exon 19, n (%)	Exon 21, n (%)	Exon 18, n (%)	Exon 20, n (%)	Combination, n (%)
1	Samdariya *et al.* [49]	NA	NA	NA	NA	NA
2	Rana *et al.* [50]	34 (70.8)	10 (20.8)	2 (4.2)	2 (4.2)	NA
3	Bal *et al.* [28]	30 (81)	6 (16)	NA	1 (3)	NA
4	Verma *et al.* [21]	NA	NA	NA	NA	NA
5	Doval *et al.* [30]	NA	NA	NA	NA	NA
6	Doval *et al.* [51]	NA	NA	NA	NA	NA
7	Bhatt *et al.* [52]	32 (76.2)	7 (16.6)	1 (2.4)	2 (4.8)	NA
8	Shankar *et al.* [53]	NA	NA	NA	NA	NA
9	Singh *et al.* [20]	NA	NA	NA	NA	NA
10	Ashutosh *et al.* [36]	14 (67)	5 (24)	1 (4.7)	1 (4.7)	NA
11	Sahoo *et al.* [54]	59 (52)	32 (28)	9 (7.9)	3 (3)	NA
12	Bala *et al.* [29]	38 (80.9)	7 (14.9)	NA	2 (4.2)	NA
13	Jain *et al.* [25]	10 (58.8)	6 (35.3)	NA	1 (6)	NA
14	Sharma *et al.* [19]	12 (63.2)	6 (31.6)	NA	1 (5.3)	NA
15	Udupa *et al.* [35]	23 (68)	6 (17.6)	1(2.9)	2 (6)	2 (5.9)
16	Chatterjee *et al.* [17]	42 (61.8)	19 (27.9)	NA	NA	NA
17	Vaid *et al.* [27]	10 (47)	8 (36)	NA	NA	NA
18	Chatterjee *et al.* [16]	18 (51.4)	16 (45.7)	NA	2 (5.7)	NA
19	Ansari *et al.* [55]	9 (64.4)	4 (28.6)	NA	NA	NA
20	Kota *et al.* [56]	24 (71)	9 (26)	1 (3)	NA	NA
21	Singh *et al.* [34]	21 (68)	6 (19)	1 (3)	6 (19)	NA
22	Gupta *et al.* [57]	NA	NA	NA	NA	NA
23	Noronha *et al.* [33]	143 (63)	72 (31.7)	12 (5.2)	NA	NA
24	Kasana *et al.* [32]	11 (55)	6 (30)	NA	3 (15)	NA
25	Choughule *et al.* [18]	135 (52.9)	97 (38)	15 (5.8)	6 (2)	2 (0.8)
26	Bharadwaj *et al.* [58]	11 (61.1)	5 (27.7)	2 (11.1)	NA	NA
27	Poonamalle *et al.* [23]	NA	NA	NA	NA	NA
28	Dutt *et al.* [24]	NA	NA	NA	NA	NA
29	Prabhash *et al.* [42]	33 (55.9)	23 (39)	1 (1.7)	NA	NA
30	Doval *et al.* [31]	22 (51.2)	15 (34.9)	1 (2.3)	2 (4.7)	3 (7)
31	Dang *et al.* [59]	NA	NA	NA	NA	NA
32	Chougule *et al.* [41]	105 (50)	86 (40.9)	15 (7.1)	4 (1.9)	NA
33	Noronha *et al.* [26]	29 (74.3)	9 (23.1)	1 (2.6)	NA	NA
34	Kumari *et al.* [60]	NA	NA	NA	NA	NA

ADC: Adenocarcinoma; EGFR: Epidermal Growth Factor Receptor; NSCLC: Non-Small Cell Lung Cancer.

3.2. EGFR Mutation Frequency

The 34 studies included in the systematic review had 10,342 NSCLC patients, of which ADC was reported in 8463 patients. Adenocarcinoma in NSCLC patients

ranged from 25% [18] to 100% in ten studies [16] [24] [28] [30]-[36]. Among the ADC patients, EGFR mutation prevalence was reported to be 39.5%, which varied from 10.8% [20] to 100% [18] among the studies. Moreover, information regarding the mutation subtype was available for 1416 subjects. The major mutation subtypes of ADC were exon 19 deletion (60.3%), which was followed by exon 21 substitution (32.5%), exon 18 mutation (4.4%), and exon 20 mutation (2.7%) (**Table 4**).

3.3. Subgroup Analysis of EGFR Mutation

In this review, the influence of gender, smoking patterns, and exon subtype on EGFR mutation prevalencein ADC NSCLC patients was assessed using meta-analysis. EGFR mutation prevalence was higher in femalescompared to males (OR, 2.27; 95% CI, 1.79 - 2.87). The results indicated a significant effect of gender on EGFR mutation ($p < 0.00001$). High heterogeneity ($I^2 = 64\%$, $p < 0.0001$) was indicated by the test results (**Figure 2**). Likewise, non-smokers had a significantly higher EGFR mutation prevalencethan smokers (OR, 2.58; 95% CI, 1.91 - 3.49), which emphasizes the positive association between non-smokers and EGFR mutations ($p < 0.00001$). Substantial variation ($I^2 = 71\%$, $p < 0{\cdot}00001$) was observed in the studies included in the analysis (**Figure 3**).

In the case of exon subtypes, the prevalence of exon 19deletions was significantly higher than exon 21 substitutions (OR, 4.20; 95% CI, 2.98 - 5.92), which emphasizes the positive association between exon 19 deletions and EGFR mutations ($p < 0.00001$). Moreover, substantial variation ($I^2 = 75\%$, $p < 0{\cdot}00001$) was observed in the studies included in the analysis (**Figure 4**).

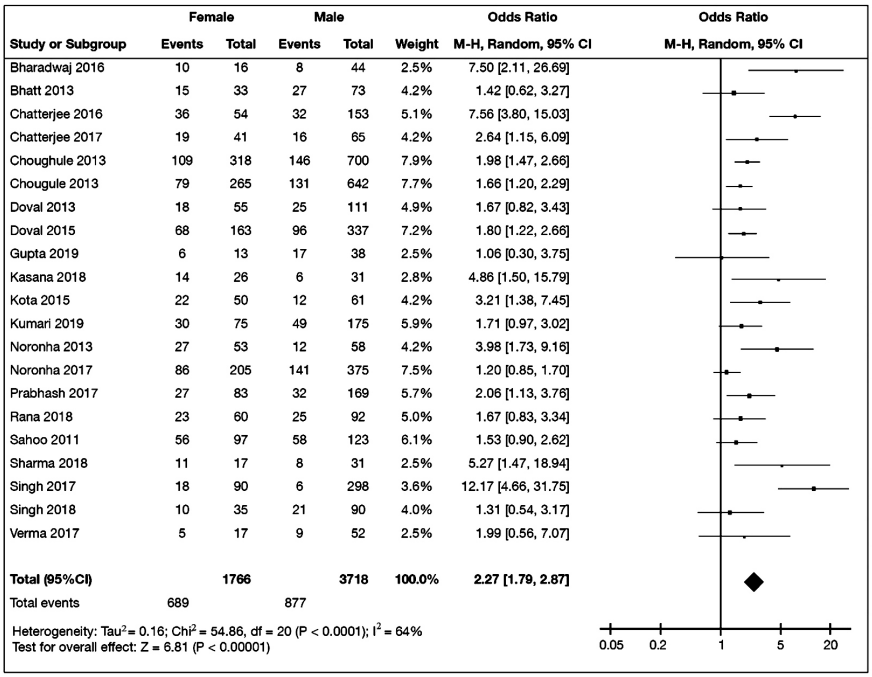

Figure 2. Odds ratio for prevalence of EGFR mutation by gender.

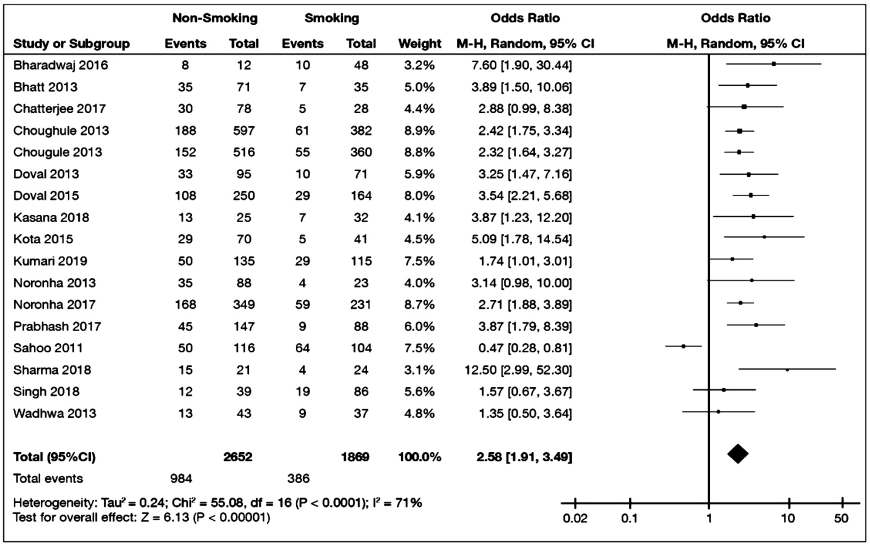

Figure 3. Odds ratio for prevalence of EGFR mutation by smoking pattern.

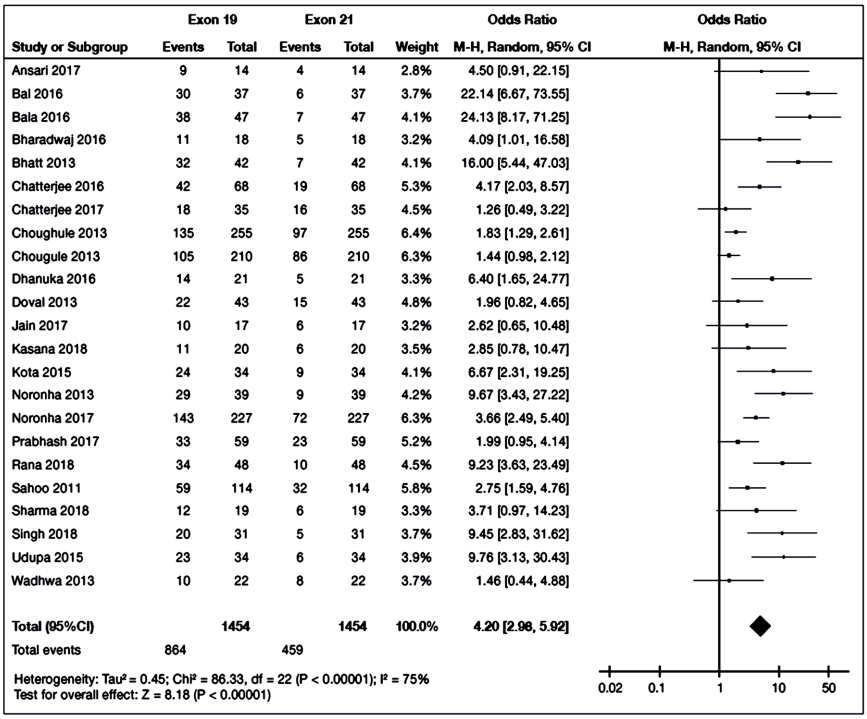

Figure 4. Odds ratio for prevalence of EGFR mutation by mutation subtype.

4. Discussion

Globally, lung cancer is the commonest cause of cancer-related deaths in both genders [1], with NSCLC constituting most cases. Moreover, advanced NSCLC has a poor prognosis with a low survival rate [12] [22] [37] [38]. However, research in the past two decades on oncogenic driver mutations, such as EGFR in ADC NSCLC patients, led to novel molecular targeted therapies, resulting in revolutionizing treatment strategies with improved efficacy and survival rate [39].

Apart from smoking, other risk factors for lung cancers include passive smoke inhalation, household radon, occupational exposures, infection, and genetic variability, which increases the burden on minorities and socioeconomically challenged population [40]. Hence, in developing countries with substantial genetic variability like India, genetic testing of lung cancer can be considered beneficial in the treatment and management of lung cancer. However, most of the studies conducted in India to estimate EGFR mutations in ADC NSCLC are single-centered and might not estimate the true prevalence. Further, the small sample sizes and patients' clinical selection result in overestimating the incidence rate [41]. Therefore, a systematic review and meta-analysis were conducted to assess epidemiology and estimate EGFR mutations in ADC NSCLC patients in the Indian scenario. Further, the influence of gender, smoking pattern, and exon subtype was assessed, which can be major players in influencing the epidemiology of ADC NSCLC.

The current systematic review and meta-analysis included 34 Indian studies with 10,342 NSCLC patients, of which 8643 patients with ADC had 2659 EGFR-positive patients. Based on information available for gender, 3347 patients were found to be females and 6827 were males. According to smoking status, there were 2508 smokers and 3128 non-smokers. The overall prevalence of EGFR positivity was 25.9% (95% CI, 22.7 - 29.3) in NSCLC patients while it was 39.5% (95% CI, 32.1 - 47.1) in ADC patients. In the current study, the EGFR mutation prevalence in ADC NSCLC patients was variable based on gender, smoking pattern, and mutation subtype. Overall, EGFR positivity was significantly higher in females (females vs. males: 42.8 vs. 24.3%; OR, 2.27; 95% CI, 1.79 - 2.87), non-smokers (non-smokers vs. smokers: 39.8 vs. 21.3%; OR, 2.58; 95% CI, 1.91 - 3.49), and patients with exon 19 deletions subtype (exon 19 deletions vs. exon 21 substitutions (61.9 vs. 29.2%; OR, 4.20; 95% CI, 2.98 - 5.92) (Table 5).

Table 5. Prevalence of EGFR positivity.

Group Variables	No. of Studies	Prevalence of EGFR Positivity % (95% CI)	Tests of Heterogeneity		
			Q	p-value	I^2 (%)
Overall NSCLC	34	25.9 (22.7 to 29.3)	430.6	<0.0001	92.3
		Gender			
Male	21	24.3 (19.3 to 29.7)	252.5	<0.0001	92.1
Female	21	42.8 (36.9 to 46.9)	82.3	<0.0001	75.7
		Smoking Status			
Smokers	17	21.2 (16.3 to 26.6)	106.4	<0.0001	85.0
Non-smokers	17	39.8 (35.5 to 44.3)	71.6	<0.0001	77.6
		Histology			
ADC	34	39.5 (32.1 to 47.1)	1442.2	<0.0001	97.7
		Exon Subtype			
Exon 19	23	61.9 (57.6 to 66.2)	53.8	0.0002	59.1
Exon 21	23	29.2 (25.5 to 33.1)	47.1	0.0015	53.2

In this review, the EGFR positivity was reported to be 39.5% in ADC NSCLC cases, which was found to be in line with the findings of an Indian multi-centric study that reported the EGFR mutation prevalence to be 33% in the ADC NSCLC patients [30]. EGFR mutation prevalence was reported as 23% by Choughule *et al.* [18] Another Indian multi-centric study reported a varied prevalence of EGFR mutations in these patients ranging from 22% to 51.8% [42]. A prospective study by Shi *et al.* reported EGFR mutation frequency of 22% in Indian patients with advanced lung adenocarcinoma compared to 51.4% in other Asian populations [43].

Geographical location, ethnicity, and many other factors influence the mutation rate. The EGFR mutation rate among the Spanish NSCLC patients, consisting majorly Caucasians, was 11.6% [44]. Another study conducted in an unselected Caucasian population reported this rate to be 5% [45]. Melosky *et al.* in their meta-analysis, estimated EGFR mutation prevalence in NSCLC patients in Caucasians as 12.8% and 49.1% in East Asians [46]. A study by Kohno *et al.* also presented similar results where this rate was reported as 5% - 15% in Caucasians and 40% - 55% in East Asians [14]. A study conducted by Chougule *et al.* reported EGFR mutation incidencein NSCLC patients of Indian ethnicity o be intermediate (23%) compared to Caucasians (10% - 15%) and East Asians (27% - 62%) [41]. The current systematic review, however, indicates that the prevalence of EGFR mutations in India is 39.5%, which is higher than previously reported and is at the low range of the prevalence reported in East Asian ethnicity. Further, the variations in the EGFR prevalence among Asian countries highlight the genetic heterogeneity among Asians.

In the current review, females and non-smokers were found to have a higher EGFR mutation prevalence. A study with Moroccan patients has reported that women and never smokers had a considerably higher EGFR mutation rate [47]. Research also indicated that indoor air pollution and occupational exposures might have a larger influence on female lung cancer in the Asian sub-continent [40]. Other studies have reported similar findings of a significantly higher EGFR mutatiorateste in non-smokers as compared to smokers or ex-smokers [48]. The current review also reported a higher frequency of EGFR mutations in the exon 19 deletion subtype compared to exon 21 substitution. A similar finding was reported by a study where a higher frequency of EGFR mutations was detected in exon 19 deletions (69%) compared to exon 21 substitutions (21%) in the Moroccan patients [47].

The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend screening for EGFR mutations in all patients with non-squamous cell carcinoma that is advanced or metastatic NSCLC [22]. The limitations with standard chemotherapy encourage the testing of EGFR mutations, which may improve the overall prognosis by allowing patients to receive first-line EGFR-TKI treatment sooner.

This review has extensively screened studies to estimate EGFR mutations in ADC NSCLC patients in India. The meta-analysis used for subgroups revealed

the risk associated with females, non-smokers, and exon 19 deletions subtype. Further, the review emphasized the need for regular genetic screening for EGFR mutations in ADC NSCLC patients. The findings of this review may provide first-hand information to researchers and policymakers regarding the accurate estimate of EGFR mutation prevalence in ADC NSCLC patients in India. However, considering the shortcomings, the findings of this systematic analysis should be interpreted with caution. Firstly, the small sample size observed in a few studies would reduce the detection power to estimate the true prevalence. Secondly, the limited data on gender, smoking status, age, and differences in the study settings may result in heterogeneity. Thirdly, most of the included studies are retrospective and cross-sectional. Despite the limitations, this systematic review enhances our knowledge of the prevalence of EGFR mutations in ADC NSCLC patients in India. It provides a comparative analysis of the Asian and Caucasian populations [14] [46]. This review further highlights the need for information on EGFR mutation that may be immensely useful for treating Indian ADC NSCLC patients.

5. Conclusions

This systematic review provides a precise estimate of the epidemiology of EGFR mutations in ADC NSCLC patients in India. Further, the frequency of EGFR mutations in the Indian population was found to be higher than in Caucasians but at a lower range of that reported in East Asians, emphasizing the genetic heterogeneity among Asians. The meta-analysis in the subgroup highlighted the association of female gender, non-smoking population, and exon 19 deletions with the higher incidence of EGFR mutations. These findings encourage the implementation of extensive regular testing in the advanced setting to enhance therapeutic outcomes for these individuals.

The results of this review should be taken into consideration while noting the limitations. More extensive studies or cooperative group registries are required to understand EGFR positivity rate, the patient profile of EGFR-positive patients, and its treatment outcome in Indian ADC NSCLC patients.

6. Summary Points

1) Evidence concerning the epidemiology of Epidermal Growth Factor Receptor (EGFR) mutations is beneficial in managing lung cancer. However, most studies reporting the prevalence of EGFR mutations in India are single-center studies with small sample sizes.

2) We conducted a systematic review and meta-analysis to summarize the available evidence of the epidemiology of EGFR mutation in Indian patients with Adenocarcinoma (ADC) Non-Small Cell Lung Cancer (NSCLC).

3) Out of 1598 studies, 34 were included for evidence synthesis. All the studies were observational, mostly retrospective (70.6%) and cross-sectional (14.7%) study designs.

4) The 34 studies included in the review consisted of 10,342 NSCLC patients, of which 8643 patients with ADC had 2659 EGFR-positive patients. The overall prevalence of EGFR-positive mutations was 25.9% in NSCLC patients and 39.5% in ADC patients.

5) The prevalence of EGFR-positive mutations in ADC NSCLC patients was found to vary based on gender, smoking pattern, and exon subtype. Overall, the prevalence of EGFR mutation was reported to be higher in females (females vs. males: 42.8 vs. 24.3%; OR, 2.27, 95% CI, 1.79 - 2.87), non-smokers (non-smokers vs. smokers: 39.8 vs. 21.3%; OR, 2.58, 95% CI, 1.91 - 3.49), and exon 19 deletions (exon 19 deletions vs. exon 21 substitutions: 61.9 vs. 29.2%; OR, 4.20, 95% CI, 2.98 - 5.92).

6) The prevalence of EGFR mutations in ADC NSCLC patients in India (39.5%) was found to be higher than in Caucasians and at a lower range of that reported in East Asians (40% - 55%), highlighting the genetic heterogeneity among Asians.

7) Conclusions drawn from this systematic analysis should be interpreted with caution. All the included studies are observational; few had a small sample size. Limited data on gender, smoking status, age, and differences in the study settings might have resulted in heterogeneity.

8) This systematic review enhances our knowledge of the prevalence of EGFR mutations in ADC NSCLC patients in India despite the limitations. It provides a comparative analysis of the Asian and Caucasian populations.

9) This review further highlights the need for information on EGFR mutation that may be of immense use for treating Indian ADC NSCLC patients.

Acknowledgements

Medical writing and editorial support were provided by Dr. Sivaprasad Mudili and Ruchira Das at Turacoz Healthcare Solutions (https://www.turacoz.com/) and was funded by Pfizer. Kumar Prabhash: Grants from Alkem Laboratories, Roche India Pvt Ltd, and Cadilla Pharma (all grants received towards research have gone to the employer). All authors have contributed to the manuscript in significant ways and have reviewed and agreed upon the contents of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Mathur, P., Sathishkumar, K., Chaturvedi, M., Das, P., Sudarshan, K.L., Santhappan, S., Nallasamy, V., *et al.* (2020) Cancer Statistics, 2020: Report from National Cancer

Registry Programme, India. *JCO Global Oncology*, **6**, 1063-1075. https://doi.org/10.1200/GO.20.00122

[3] Lu, T., Yang, X., Huang, Y., Zhao, M., Li, M., Ma, K., Yin, J., Zhan, C. and Wang, Q. (2019) Trends in the Incidence, Treatment, and Survival of Patients with Lung Cancer in the Last Four Decades. *Cancer Management and Research*, **11**, 943-953. https://doi.org/10.2147/CMAR.S187317

[4] Zappa, C. and Mousa, S.A. (2016) Non-Small Cell Lung Cancer: Current Treatment and Future Advances. *Translational Lung Cancer Research*, **5**, 288-300. https://doi.org/10.21037/tlcr.2016.06.07

[5] Rahal, Z., El Nemr, S., Sinjab, A., Chami, H., Tfayli, A. and Kadara, H. (2017) Smoking and Lung Cancer: A Geo-Regional Perspective. *Frontiers in Oncology*, **7**, Article 194. https://doi.org/10.3389/fonc.2017.00194

[6] Pesch, B., Kendzia, B., Gustavsson, P., Jöckel, K.-H., Johnen, G., Pohlabeln, H., Olsson, A., *et al.* (2012) Cigarette Smoking and Lung Cancer—Relative Risk Estimates for the Major Histological Types from a Pooled Analysis of Case-Control Studies. *International Journal of Cancer*, **131**, 1210-1219. https://doi.org/10.1002/ijc.27339

[7] Midha, A., Dearden, S. and McCormack, R. (2015) EGFR Mutation Incidence in Non-Small-Cell Lung Cancer of Adenocarcinoma Histology: A Systematic Review and Global Map by Ethnicity (MutMapII). *American Journal of Cancer Research*, **5**, 2892-2911.

[8] Rajendra, A., Noronha, V., Joshi, A., Patil, V.M., Menon, N. and Prabhash, K. (2019) Epidermal Growth Factor Receptor-Mutated Non-Small-Cell Lung Cancer: A Primer on Contemporary Management. *Cancer Research, Statistics, and Treatment*, **2**, 36-53. https://doi.org/10.4103/CRST.CRST_51_19

[9] Soon, Y.Y., Vellayappan, B., Chee Seong Tey, J., Leong, C.N., Koh, W.Y. and Keong Tham, I.W. (2017) Impact of Epidermal Growth Factor Receptor Sensitizing Mutations on Outcomes of Patients with Non-Small Cell Lung Cancer Treated with Definitive Thoracic Radiation Therapy: A Systematic Review and Meta-Analysis. *Oncotarget*, **8**, 109712-109722. https://doi.org/10.18632/oncotarget.21019

[10] Castellanos, E., Feld, E. and Horn, L. (2017) Driven by Mutations: The Predictive Value of Mutation Subtype in EGFR-Mutated Non-Small Cell Lung Cancer. *Journal of Thoracic Oncology*, **12**, 612-623. https://doi.org/10.1016/j.jtho.2016.12.014

[11] Huang, L.L., Jiang, S.Y. and Shi, Y.K. (2020) Tyrosine Kinase Inhibitors for Solid Tumors in the Past 20 Years (2001-2020). *Journal of Hematology & Oncology*, **13**, Article No. 143. https://doi.org/10.1186/s13045-020-00977-0

[12] Da Cunha Santos, C., Shepherd, F.A. and Tsao, M.S. (2011) EGFR Mutations and Lung Cancer. *Annual Review of Pathology: Mechanisms of Disease*, **6**, 49-69. https://doi.org/10.1146/annurev-pathol-011110-130206

[13] Mitsudomi, T. (2014) Molecular Epidemiology of Lung Cancer and Geographic Variations with Special Reference to EGFR Mutations. *Translational Lung Cancer Research*, **3**, 205-211.

[14] Kohno, T., Nakaoku, T., Tsuta, K., Tsuchihara, K., Matsumoto, S., Yoh, K. and Goto, K. (2015) Beyond ALK-RET, ROS1 and Other Oncogene Fusions in Lung Cancer. *Translational Lung Cancer Research*, **4**, 156-164.

[15] Malik, P.S., Jain, D. and Kumar. L. (2016) Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Advanced Non-Small Cell Lung Cancer. *Oncology*, **91**, 26-34. https://doi.org/10.1159/000447578

[16] Chatterjee, K., Ray, A. and Chattopadhyay, B. (2017) Incidence and Characteristics of Epidermal Growth Factor Receptor (EGFR) Mutation in Non-Small-Cell Lung

Cancer (Adenocarcinoma Histology): A Report of 106 Patients from Kolkata. *Indian Journal of Cancer*, **54**, 305-307. https://doi.org/10.4103/ijc.IJC_239_17

[17] Chatterjee, S., Arora, N., Parihar, M., *et al.* (2016) 9 EGFR and EML4-Alk Testing for Non-Small Cell Lung Cancer Patients—A Single Centre Experience. 14*th Annual British Thoracic Oncology Group Conference* 2016, Vol. 91, Dublin, 27-29 January 2016, S4. https://doi.org/10.1016/S0169-5002(16)30026-5

[18] Choughule, A., Noronha, V., Joshi, A., Desai, S., Jambhekar, N., Utture, S., Thavamanni, A., Prabhash, K. and Dutt, A. (2013) Epidermal Growth Factor Receptor Mutation Subtypes and Geographical Distribution among Indian Non-Small Cell Lung Cancer Patients. *Indian Journal of Cancer*, **50**, 107-111. https://doi.org/10.4103/0019-509X.117023

[19] Sharma, S., Gupta, N., Singh, N., Chaturvedi, R., Behera, D. and Rajwanshi, A. (2018) Cytomorphological Features as Predictors of Epidermal Growth Factor Receptor Mutation Status in Lung Adenocarcinoma. *CytoJournal*, **15**, Article 11. https://doi.org/10.4103/cytojournal.cytojournal_45_17

[20] Singh, R. and Rohtagi, N. (2017) Clinicopathological and Molecular Epidemiological Study of Lung Cancer Patients Seen at a Tertiary Care Hospital in Northern India. *South Asian Journal of Cancer*, **6**, 171-175. https://doi.org/10.4103/sajc.sajc_63_17

[21] Verma, S., Kumar, M., Kumari, M., Mehrotra, R., Kushwaha, R.A.S., Goel, M., Kumar, A. and Kant, S. (2017) An Immunohistochemical Study of Anaplastic Lymphoma Kinase and Epidermal Growth Factor Receptor Mutation in Non-Small Cell Lung Carcinoma. *Journal of Clinical and Diagnostic Research*, **11**, EC22-EC25. https://doi.org/10.7860/JCDR/2017/27941.10279

[22] Zhang, Y.L., Yuan, J.Q., Wang, K.F., Fu, X.H., Han, X.R. Threapleton, D., Yang, Z.Y., Mao, C. and Tang, J.L. (2016) The Prevalence of EGFR Mutation in Patients with Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. *Oncotarget*, **7**, 78985-78993. https://doi.org/10.18632/oncotarget.12587

[23] Poonamalle, B., Shivakumar, S., Meganathan, P., Srinarahari, V. and Nagaraj, P.C. (2013) Immuno-Histochemistry (IHC) Typing of Molecular Markers, Its Correlation with Clinical Parameters and Response to Chemotherapy in Non Small Cell Lung Cancer (NSCLC)—A Pilot Study. 15*th World Conference on Lung Cancer*, Vol. 8, Sydney, 27-31 October 2013, S1312.

[24] Dutt, S., Advani, S.H., Dhabhar, B.N., Dattatreya, P.S., Patil, S., Chatterjee, S., Srinivasan, S., *et al.* (2014) Experience of Alk Mutation Testing in 3351 Indian Patients of Nsclc. *Annals of Oncology*, **25**, iv58-iv84. https://doi.org/10.1093/annonc/mdu326.25

[25] Jain, D., Ramachandrappa, V.S., Singh, V., Malik, P.S., Madan, K., Faruq, M. and Guleria, R. (2017) Use of Exfoliative Specimens and Fine-Needle Aspiration Smears for Mutation Testing in Lung Adenocarcinoma. *Acta Cytologica*, **61**, 455-461. https://doi.org/10.1159/000479217

[26] Noronha, V., Prabhash, K., Thavamani, A., Chougule, A., Purandare, N., Joshi, A., Sharma, R., *et al.* (2013) EGFR Mutations in Indian Lung Cancer Patients: Clinical Correlation and Outcome to EGFR Targeted Therapy. *PLOS ONE*, **8**, e61561. https://doi.org/10.1371/journal.pone.0061561

[27] Vaid, A.K., Wadhwa, J., Sharma, D., *et al.* (2013) EGFR Mutational Status in Adenocarcinoma Lung: A Single Centre Experience from India. 15*th World Conference*, Sydney, 27-30 October 2013.

[28] Bal, A., Singh, N., Agarwal, P., Das, A. and Behera, D. (2016) *ALK* Gene Rearranged

Lung Adenocarcinomas: Molecular Genetics and Morphology in Cohort of Patients from North India. *APMIS*: *Acta Pathologica*, *Microbiologica*, *et Immunologica Scandinavica*, **124**, 832-838. https://doi.org/10.1111/apm.12581

[29] Bala, S., Gundeti, S., Linga, G.V., Maddali, L.S., Digumarti, R.R. and Uppin, S.G. (2016) Clinicopathological Features and Outcomes in Advanced Nonsmall Cell Lung Cancer with Tailored Therapy. *Indian Journal of Medical and Paediatric Oncology*, **37**, 242-250. https://doi.org/10.4103/0971-5851.195735

[30] Doval, D., Prabhash, K., Patil, S., Chaturvedi, H., Goswami, C., Vaid, A., Desai, S., *et al*. (2015) Clinical and Epidemiological Study of EGFR Mutations and EML4-ALK Fusion Genes among Indian Patients with Adenocarcinoma of the Lung. *OncoTargets and Therapy*, **8**, 117-123. https://doi.org/10.2147/OTT.S74820

[31] Doval, C.D., Azam, S., Batra, U., Choudhury, K.D., Talwar, V., Gupta, S.K. and Mehta, A. (2013) Epidermal Growth Factor Receptor Mutation in Lung Adenocarcinoma in India: A Single Center Study. *Journal of Carcinogenesis*, **12**, Article 12. https://doi.org/10.4103/1477-3163.114970

[32] Kasana, B.A., Dar, W.R., Aziz, S.A., Lone, A.R., Sofi, N.U., Dar, I.A., Latief, M., Arshad, F., Hussain, M. and Hussain, M. (2016) Epidermal Growth Factor Receptor Mutation in Adenocarcinoma Lung in a North Indian Population: Prevalence and Relation with Different Clinical Variables. *Indian Journal of Medical and Paediatric Oncology*, **37**, 189-195. https://doi.org/10.4103/0971-5851.190356

[33] Noronha, V., Choughule, A., Patil, V.M., Joshi, A., Kumar, R., Susan Joy Philip, D., Banavali, S., Dutt, A. and Prabhash, K. (2017) Epidermal Growth Factor Receptor Exon 20 Mutation in Lung Cancer: Types, Incidence, Clinical Features and Impact on Treatment. *OncoTargets and Therapy*, **10**, 2903-2908. https://doi.org/10.2147/OTT.S133245

[34] Singh, V., Guleria, P., Malik, P.S., Mohan, A., Thulkar, S., Pandey, R.M., Luthra, K., Arava, S., Ray, R. and Jain, D. (2019) Epidermal Growth Factor Receptor (EGFR), KRAS, and BRAF Mutations in Lung Adenocarcinomas: A Study from India. *Current Problems in Cancer*, **43**, 391-401. https://doi.org/10.1016/j.currproblcancer.2018.12.003

[35] Udupa, K.S., Rajendranath, R., Sagar, T.G., Sundersingh, S. and Joseph, T. (2015) Dual Surrogate Markers for Rapid Prediction of Epidermal Growth Factor Receptor Mutation Status in Advanced Adenocarcinoma of the Lung: A Novel Approach in Resource-Limited Setting. *Indian Journal of Cancer*, **52**, 266-268. https://doi.org/10.4103/0019-509X.176693

[36] Ashutosh, D., Anant, M., Randeep, G., *et al*. (2016) Prevalence of Tissue EGFR Mutation in Patients of Adenocarcinoma Lung and Its Ability to Predict Response to Tyrosine Kinase Inhibitors. *CHEST Annual Meeting*, Vol. 150, Los Angeles, 22-26 October 2016, 724A.

[37] Non-Small Cell Lung Cancer Collaborative Group (2010) Chemotherapy and Supportive Care versus Supportive Care Alone for Advanced Non-Small Cell Lung Cancer. *The Cochrane Database of Systematic Reviews*, No. 5, Article No. CD007309.

[38] Cataldo, V.D., Gibbons, D.L., Pérez-Soler, R. and Quintás-Cardama, A. (2011) Treatment of Non-Small-Cell Lung Cancer with Erlotinib or Gefitinib. *The New England Journal of Medicine*, **364**, 947-955. https://doi.org/10.1056/NEJMct0807960

[39] Lee, V.H.F., Mok, T.S.K., Goto, Y., Hsue, V.C.C., Yang, L., Jiang, Y., Leung, D.K.C., Lau, K.S. and Tse, P.Y. (2020) Differences Between the East and the West in Managing Advanced-Stage Non-Small Cell Lung Cancer. *Clinical Oncology* (*Royal College of Radiologists* (*Great Britain*)), **32**, e1-e9. https://doi.org/10.1016/j.clon.2019.07.014

[40] De Groot, P.M., Wu, C.C., Carter, B.W. and Munden, R.F. (2018) The Epidemiology of Lung Cancer. *Translational Lung Cancer Research*, **7**, 220-233. https://doi.org/10.21037/tlcr.2018.05.06

[41] Chougule, A., Prabhash, K., Noronha, V., Joshi, A., Thavamani, A., Chandrani, P., Upadhyay, P., *et al.* (2013) Frequency of *EGFR* Mutations in 907 Lung Adenocarcioma Patients of Indian Ethnicity. *PLOS ONE*, **8**, e76164. https://doi.org/10.1371/journal.pone.0076164

[42] Prabhash, K., Rauthan, A., Rajappa, S., Desai, C., Mistry, R., Dutt, A., Chougule, A., *et al.* (2017) Feasibility of Molecular Testing in a Multicenter Study with Geographical Variation in India: Epidermal Growth Factor Receptor Mutation as a Model Molecular Test. *Asian Journal of Oncology*, **3**, 39-44. https://doi.org/10.4103/ASJO.ASJO_104_16

[43] Shi, Y.K., Siu-Kie Au, J., Thongprasert, S., Srinivasan, S., Tsai, C.-M., Khoa, M.T., Heeroma, K., Itoh, Y., Cornelio, G. and Yang, P.-C. (2014) A Prospective, Molecular Epidemiology Study of EGFR Mutations in Asian Patients with Advanced Non-Small-Cell Lung Cancer of Adenocarcinoma Histology (PIONEER). *Journal of Thoracic Oncology*, **9**, 154-162. https://doi.org/10.1097/JTO.0000000000000033

[44] Esteban, E., Majem, M., Martinez Aguillo, M., Martinez Banaclocha, N., Dómine, M., Gómez Aldaravi, L., Juan, O., Cajal, R., Gonzalez Arenas, M.C. and Provencio, M. (2015) Prevalence of EGFR Mutations in Newly Diagnosed Locally Advanced or Metastatic Non-Small Cell Lung Cancer Spanish Patients and Its Association with Histological Subtypes and Clinical Features: The Spanish REASON Study. *Cancer Epidemiology*, **39**, 291-297. https://doi.org/10.1016/j.canep.2015.02.003

[45] Skov, B.G., Høgdall, E., Clementsen, P., Krasnik, M., Larsen, K.R., Sørensen, J.B., Skov, T. and Mellemgaard, A. (2015) The Prevalence of EGFR Mutations in Non-Small Cell Lung Cancer in an Unselected Caucasian Population. *APMIS*: *Acta Pathologica*, *Microbiologica*, *et Immunologica Scandinavica*, **123**, 108-115. https://doi.org/10.1111/apm.12328

[46] Melosky, B., Kambartel, K., Häntschel, M., Bennetts, M., Nickens, D.J., Brinkmann, J., Kayser, A., Moran, M. and Cappuzzo, F. (2022) Worldwide Prevalence of Epidermal Growth Factor Receptor Mutations in Non-Small Cell Lung Cancer: A Meta-Analysis. *Molecular Diagnosis & Therapy*, **26**, 7-18. https://doi.org/10.1007/s40291-021-00563-1

[47] Errihani, H., Inrhaoun, H., Boukir, A., Kettani, F., Gamra, L., Mestari, A., Jabri, L., Bensouda, Y., Mrabti, H. and Elghissassi, I. (2013) Frequency and Type of Epidermal Growth Factor Receptor Mutations in Moroccan Patients with Lung Adenocarcinoma. *Journal of Thoracic Oncology*, **8**, 1212-1214. https://doi.org/10.1097/JTO.0b013e31829f6b4a

[48] Gahr, S., Stoehr, R., Geissinger, E., Ficker, J.H., Brueckl, W.M., Gschwendtner, A., Gattenloehner, S., *et al.* (2013) EGFR Mutational Status in a Large Series of Caucasian European NSCLC Patients: Data from Daily Practice. *British Journal of Cancer*, **109**, 1821-1828. https://doi.org/10.1038/bjc.2013.511

[49] Samdariya, S., Bagri, P., Pareek, P. and Kumawat, R. (2016) 39P A Tertiary Care Hospital Based Retrospective Study Evaluating Epidemiology of Lung Cancers in a Western State of India. *Journal of Thoracic Oncology*, **11**, S71. https://doi.org/10.1016/S1556-0864(16)30153-8

[50] Rana, V., Ranjan, P., Jagani, R., Rathi, K.R., Kumar, D. and Khera, A. (2018) A Study of Therapy Targeted EGFR/ALK Mutations in Indian Patients with Lung Adenocarcinoma: A Clinical and Epidemiological Study. *Medical Journal Armed Forces India*, **74**, 148-153. https://doi.org/10.1016/j.mjafi.2017.09.005

[51] Doval, D.C., Sinha, R., Batra, U., Choudhury, K.D., Azam, S. and Mehta, A. (2017) Clinical Profile of Nonsmall Cell Lung Carcinoma Patients Treated in a Single Unit at a Tertiary Cancer Care Center. *Indian Journal of Cancer*, **54**, 193-196. https://doi.org/10.4103/0019-509X.219591

[52] Bhatt, A.D., Pai, R., Rebekah, G., Nehru, G.A., Dhananjayan, S., Samuel, A., Singh, A., Joel, A., Korula, A. and Chacko, R.T. (2013) Clinicopathologic Features of Non-Small Cell Lung Cancer in India and Correlation with Epidermal Growth Factor Receptor Mutational Status. *Indian Journal of Cancer*, **50**, 94-101. https://doi.org/10.4103/0019-509X.117016

[53] Shankar, S., Thanasekaran, V., Dhanasekar, T. and Duvooru, P. (2014) Clinicopathological and Immunohistochemical Profile of Non-Small Cell Lung Carcinoma in a Tertiary Care Medical Centre in South India. *Lung India*, **31**, 23-28. https://doi.org/10.4103/0970-2113.125889

[54] Sahoo, R., Vidya Harini, V., Chitti Babu, V., Patil Okaly, G.V., Rao, S., Nargund, A., Venkataswamy, E., Rao, R. and Ajai Kumar. B.S. (2011) Screening for EGFR Mutations in Lung Cancer, a Report from India. *Lung Cancer*, **73**, 316-319. https://doi.org/10.1016/j.lungcan.2011.01.004

[55] Ansari, A., Mohan, A., Masroor, M., Saxena, A., Luthra, K., Madan, K., Hadda, V., Khilnani, G. and Guleria, R. (2017) P1.02-038 Over-Expression of Epidermal Growth Factor Receptor 1 (EGFR1) Gene in Serum of Adenocarcinoma Lung at a Tertiary Level Centre in North India. *Journal of Thoracic Oncology*, **12**, S510-S511. https://doi.org/10.1016/j.jtho.2016.11.621

[56] Kota, R., Gundeti, S., Gullipalli, M., Linga, V.G., Maddali, L.S. and Raghunadharao, D. (2015) Prevalence and Outcome of Epidermal Growth Factor Receptor Mutations in Non-Squamous Non-Small Cell Lung Cancer Patients. *Lung India*, **32**, 561-565. https://doi.org/10.4103/0970-2113.168099

[57] Gupta, P., Gowrishankar, S. and Swain, M. (2019) Epidermal Growth Factor Receptor and Anaplastic Lymphoma Kinase Mutation in Adenocarcinoma Lung: Their Incidence and Correlation with Histologic Patterns. *The Indian Journal of Pathology & Microbiology*, **62**, 24-30. https://doi.org/10.4103/IJPM.IJPM_516_16

[58] Bharadwaj, R., Dewan, K. and Mann, N. (2016) Genetic Analysis of EGFR Mutations in Non-Small Cell Lung Carcinoma: A Tertiary Care Center Experience. *Journal of Medical Society*, **30**, 44-49. https://doi.org/10.4103/0972-4958.175851

[59] Dang, K., *et al.* (2013) Expression of Epidermal Growth Factor Receptor and Anaplastic Lymphoma Kinase Protein in Primary Adenocarcinoma of Lung. Presented as Abstract in a Local Conference.

[60] Kumari, N., Singh, S., Haloi, D., Mishra, S.K., Krishnani, N., Nath, A. and Neyaz, Z. (2019) Epidermal Growth Factor Receptor Mutation Frequency in Squamous Cell Carcinoma and Its Diagnostic Performance in Cytological Samples: A Molecular and Immunohistochemical Study. *World Journal of Oncology*, **10**, 142-150. https://doi.org/10.14740/wjon1204