*Review*

# Prevalence and Patterns of EGFR Mutations in Non-small Cell Lung Cancer in the Middle East and North Africa

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**Youssra Boustany[1,2], Abdelilah Laraqui[1], Hicham El Rhaffouli[1], Tahar Bajjou[1], Bouchra El Mchichi[1], Hicham El Anaz[1], Idriss Lahlou Amine[1], Hafsa Chahdi[1], Mohammed Oukabli[1], Hicham Souhi[1], Hanane Elouazzani[1], Ismail Abderrahmani Rhorfi[1], Ahmed Abid[1], Tarik Mahfoud[1], Rachid Tanz[1], Mohammed Ichou[1], Khaled Ennibi[1], Bouchra Belkadi[2], and Yassine Sekhsokh[1]**

## Abstract

**Objectives:** This study aims to analyze the prevalence and spectrum of epidermal growth factor receptor (EGFR) mutations within the Middle East and North Africa region, compare the findings to other parts of the world, and explore the geographic disparities of EGFR mutations across the region.

**Methods:** We conducted a literature search using the terms "[EGFR] AND [mutation] AND [Non-Small Cell Lung Cancer] AND [Middle East OR North Africa]", using PubMed, Science Direct, Web of science, Embase, Scopus, and Google scholar.

**Results:** A total of 15 eligible studies were included and 6122 patients with non-small cell lung cancer (NSCLC) were analyzed. Male patients were predominant in all of the considered studies, accounting for 70.4%. Of the included patients, 65.6% were smokers and 88.3% had been diagnosed with adenocarcinoma. Overall, EGFR mutations prevalence was 17.2%. In the Middle East, the reported frequency was 16.5%, ranging from 11.3% in Lebanon to 29.7% in the Gulf region. In North Africa, the prevalence of EGFR mutations was 18%, ranging from 17.5% in Egypt to 21.5% in Morocco. The most prevalent mutations were the exon 19 deletions (46.7%) followed by exon 21 substitutions (31.1%). Exon 20 alterations were detected in 10.8% of the analyzed cases, whereas exon 18 mutations were reported in 3.4% of the EGFR-mutated patients. There was 1.1% of patients that had concurrent EGFR mutations. Overall, EGFR mutation prevalence was higher in females [females vs males: 29.7% vs 5.9%, P<.001], non-smokers [non-smokers vs smokers: 31.3% vs 9.6%, P<.001], and patients with adenocarcinoma [adenocarcinoma vs non-adenocarcinoma: 18.8% vs 6.5%, P<.001].

**Conclusion:** EGFR mutation prevalence among the Middle East and North Africa populations is slightly higher than that seen in NSCLC patients of Caucasian ethnicity but is lower than that identified in Asian NSCLC patients. The distribution of these mutations varies considerably throughout the region.

## Keywords

Non-small cell lung cancer, EGFR mutations, Middle East and North Africa

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[1]Mohamed V Military Teaching Hospital, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, Morocco
[2]Microbiology and Molecular Biology Team, Faculty of Sciences, Mohammed V University in Rabat, Morocco

**Corresponding Author:**
Youssra Boustany, Mohamed V Military Teaching Hospital, Faculty of Medicine and Pharmacy, Mohammed V University in Rabat, Morocco, Microbiology and Molecular Biology Team, Faculty of Sciences, Mohammed V University in Rabat, Morocco.
Email: youssra.boustany@um5s.net.ma

## Introduction

Lung cancer remains a major public health issue, being the leading cause of cancer-related mortality worldwide. In 2020, the death toll from lung cancer reached 1.8 million deaths globally. In terms of incidence rates, lung cancer is the second most prevalent malignancy with 2,2 million new diagnosed cases worldwide.[1] In the Middle East and North Africa region, while lower incidence and mortality rates are estimated, a gradual increase in these figures is witnessed.[2,3] Lung cancer incidence rates increases are more eminent among older age groups.[4]

Lung carcinomas are categorized by the size and appearance of the malignant cells and are divided into 2 broad categories of small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC). NSCLC is a highly heterogeneous disease and is mainly divided into 3 major histological subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[5,6] NSCLC has been regarded as a distinct biological subset, characterized with molecular alterations that are targets to available or promising personalized therapies.[7] The ever changing landscape of NSCLC treatment have been revolutionized by the discovery of epidermal growth factor receptor (EGFR) mutations.[8]

EGFR is a transmembrane glycoprotein receptor endowed with a tyrosine kinase activity, being a member of the ErbB receptor tyrosine kinase (TK) family.[9] The activation of EGFR with its specific ligands induces receptor dimerization and tyrosine autophosphorylation, leading to cell survival, proliferation, migration, and metastasis.[10] Sensitizing EGFR mutations lead to constitutive activation of the receptor, independently of the presence of the ligand, promoting oncogenic phenotypes including, heightened cell division and invasion.[11] In NSCLC, these alterations play a role in sensitizing the receptor to tyrosine kinase inhibitors (TKIs), as EGFR-mutated patients show a 70% to 80% response rate to TKIs, and act as predictive markers for the response to TKIs.[12] EGFR mutations in exons 18 to 21 are more common in patients with adenocarcinomas, in women, and in non-smokers.[13]

Previous studies have reported that EGFR mutation rates are influenced by ethnicity. The highest frequencies were seen among Asian patients (40%-50%), whereas the lowest were found in Caucasian patients (10%).[14] In the MENA countries, reports on the prevalence of EGFR mutations lack dramatically, as EGFR molecular characterization is not standard of care in most countries. This calls for a surge in EGFR mutation testing in the region, in order to have an accurate depiction of EGFR mutation prevalence and spectrum.

In this study, we conducted a systematic review of the literature in order to determine the prevalence and patterns of EGFR mutations in NSCLC patients of the region, to position the findings in the international context, and to highlight the correlation between these alterations' rates and patients' clinicopathological characteristics.

## Methods

We conducted a systematic review of literature published on *EGFR* mutation prevalence and its association with geographic region/country and clinic-pathological features in NSCLC patients in the Middle East and North Africa. We carried out a literature search of original articles published in 6 databases (PubMed, Science Direct, Web of science, Embase, Scopus, and Google scholar) from the time of inception until February 2022. Included articles have been published in English in peer-reviewed journals. Search terms included lung cancer, or lung tumor, or lung adenocarcinoma, or NSCLC, or *EGFR*, or *EGFR* mutation, or *EGFR* oncogene mutations, or *EGFR* oncogenic driver mutation, or *EGFR* activating mutation, or *EGFR* prevalence, or *EGFR* rate, or *EGFR* incidence or *EGFR* frequency. An additional literature search was also conducted using Middle East, Middle Eastern, North Africa, North African and specific country names belonging to the considered region and any other variant names for any of the MENA countries (ex: Maghreb, Levant, Gulf, Arab). We manually checked reference lists of the included studies and relevant review articles to identify additional records. We also searched relevant abstracts reported in the most important multi-disciplinary societies of medical oncology such as the American Society of Clinical Oncology (ASCO) to identify unpublished studies.

The included studies had to meet the following criteria: the study must relate to the role of the *EGFR* gene in NSCLC, analyze mutations in exon 18, 19, 20, and 21 or select exons of the *EGFR* gene, provide sufficient information on the clinic-pathological characteristics of the included NSCLC patients, and include at least 100 NSCLC patients analyzed for EGFR mutations.

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyse (PRISMA) guidelines.[15]

### Statistical Analysis

The potential correlations between EGFR mutation status and patients' clinicopathological characteristics were analyzed using $\chi 2$ statistics. A $P$ value less than .05 was considered statistically significant. All analyses were performed using SPSS (version 28.0.1.1; SPSS Inc., Chicago, IL).

## Results

### Literature Research

The initial literature search in the queried databases yielded 29 publications. An additional study that was identified through article references. Of the 30 publications, 24 studies were selected after the elimination of redundancies.

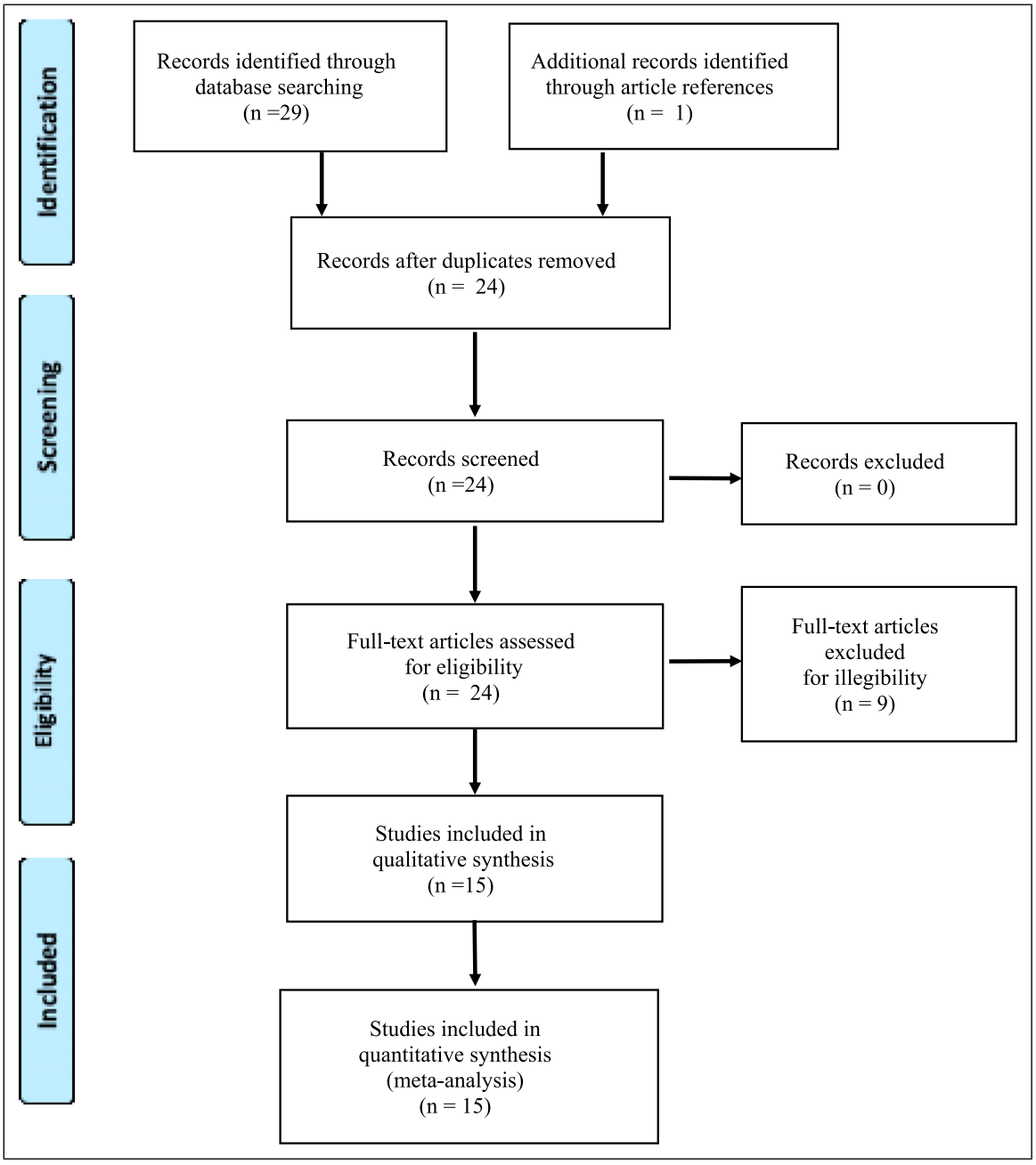


**Figure 1.** Flow chart of the studies identified and included in this review.

These articles were assessed for eligibility and 15 studies were selected for this review: 11 (73.3%) from the Middle East[16-26] and 4 (26.6%) in North Africa.[27-30] Original articles were identified from Jordan,[16] Iran,[17] Turkey,[18-20] Iraq,[22] Lebanon,[23-25] Morocco,[27-29] and Egypt.[30] A multicenter prospective study from the Levant (Lebanone, Syria, Palestine, Jordan, Iraq, and Egypt)[26] and a multisite retrospective study from the Gulf (Saudi Arabia, the United Arab Emirates and Qatar) were also identified and will be part of our analysis.[21] (Figure 1).

## *Description of Sample Sizes and Included Regions*

We identified 15 eligible studies: 11 (73.3%) in the Middle East[16-26] and 4 (26.6%) in North Africa.[27-30] EGFR exons 18 through 21 mutations were assessed in 14 out of the 15 considered studies, in 88.5% (5419/6122) of the analyzed patients: Jordan (1 study, 166 patients),[19] Iran (1 study, 103 patients),[17] Turkey (2 studies, 1368 patients),[18,19] the Gulf Region (1 study, 230 patients),[21] Iraq (1 study, 138 patients),[22] Lebanon (3 studies, 477 patients),[23-25] the Levant region

(1 study, 210 patients),[26] Morocco (3 studies, 710 patients),[27-29] and Egypt (1 study, 2017 patients).[30] One study from Turkey (703 patients), did not specify EGFR exons genotyped.[20]

## Specimens and Methods used in the EGFR Mutation Analysis

In most studies, specimens were formalin-fixed paraffin-embedded (FFPE) tissues, and included small biopsies such as trans-bronchial biopsy or tru-cut biopsy and also resection materials. DNA extraction was applied on tissue samples using kits that extracted DNA from paraffin blocks. Mutations in exon 18 (codon 719), exon 19 deletions, exon 20 (codons 768 and 790), and exon 21 (codons 858 and 861) were assessed in 93.3% (14/15) of the studies. One study from Turkey (703 patients) did not mention specific exons genotyped.[20] A wide variety of detection methods were used to identify mutations of the *EGFR* kinase domain. Direct sequencing was broadly used, as it was used in 7 of the included studies.[16,17,20,25-28] qPCR-based assays were also widely used, as they were used in 7 studies.[19,22-25,29,30] The INFINITI system using BioFilmChip-based microarray assay was used in 1 study from Turkey.[18] Details of the study methods and population characteristics are summarized in Table 1.

## Patients' Clinicopathological Characteristics

Overall, *EGFR* mutations were analyzed in 6122 patients with NSCLC [3395 (55.45%) in the ME and 2727 (44.54%) in NA]. The median age was 62 years old, with a range of 22 to

**Table 1.** Characteristics of the Included Studies.

| Country/ Region | Author [Reference] | Year of Publication | Cases | Age (years) | Male/ Female n (%) | Smokers/ Non Smokers n (%) | ADK/ NADK n (%) | Detection Gene site (Exon) | Test Type |
|---|---|---|---|---|---|---|---|---|---|
| Jordan | Obeidat et al[16] | 2016 | 166 | 59 ± 12.6 | 116 (70)/ 50 (30) | 129 (77)/37 (23) | 166 (100)/0 (0) | 18, 19, 20, and 21 | PCR/Sequencing |
| Iran | Basi et al[17] | 2018 | 103 | 67 | 51 (49.5)/ 52 (50.5) | 37 (36)/66 (64) | 103 (100)/0 (0) | 18, 19, 20, and 21 | PCR/Sequencing |
| Turkey | Calibasi et al[18] | 2020 | 409 | 60 | 299 (73.1)/ 110 (26.9) | 246 (60.1)/ 163 (35.9) | 409 (100)/0 (0) | 18, 19, 20, and 21 | INFINITI method |
| | Tezel et al[19] | 2017 | 959 | 60 | 700 (73)/ 259 (27) | 1 (10)/25 (2.6) | 698 (72.8)/ 261(27.2) | 18, 19, 20, and 21 | RT-PCR |
| | Ozcelik et al[20] | 2019 | 703 | 63.3±12.5 | 545 (77.6)/ 158 (22.3) | 546 (83.5)/ 154 (16.5) | 613 (87)/90 (13) | - | PCR/Sequencing |
| Gulf region | Jazieh et al[21] | 2015 | 230 | 61 | 162 (70.4)/ 68 (29.5) | 96 (41.7)/ 134 (58.2) | 191 (83.4)/ 39 (16.6) | 18, 19, 20, and 21 | PCR |
| Iraq | Ramadhan et al[22] | 2021 | 138 | 60.1± 12.4 | 79 (57.2)/ 59 (42.8) | — | — | 18, 19, 20, and 21 | RT-PCR/PCR |
| Lebanon | Naderia et al[23] | 2015 | 201 | 65.2± 10.4 | 123 (61.2)/ 78 (38.8) | 157 (78.1)/ 44 (21.9) | 182 (90.5)/ 19 (9.5) | 18, 19, 20, and 21 | Scorpion-ARMS technology |
| | Kattan et al[24] | 2015 | 170 | 65.2 | 102 (59.8)/ 68 (40.2) | 131 (76.8)/ 39 (23.9) | 157 (92.1)/ 13 (7.9) | 18, 19, 20, and 21 | Scorpion-ARMS technology |
| | Fakhruddin et al[25] | 2014 | 106 | 62.1±10.4 | 72 (67.9)/ 34 (32.1) | 59 (55.7)/18 (17) | 106 (100)/0 (0) | 18, 19, 20, and 21 | Scorpion-ARMS technology |
| Levant region | Tfayli et al[26] | 2017 | 210 | 63.4 ± 10.8 | 139 (66.2)/ 71 (33.8) | 152 (72.4)/ 49 (23.3) | 210 (100)/0 (0) | 18, 19, 20, and 21 | PCR |
| Morocco | Errihani et al[27] | 2013 | 137 | 59 | 91 (66)/46 (44) | 79 (58)/58 (42) | 137 (100)/0 (0) | 18, 19, 20, and 21 | Sequencing |
| | Sow et al[28] | 2020 | 334 | 62 | 242 (72.5)/ 92 (27.5) | 178 (53)/135 (40) | 314 (94)/20 (6) | 18, 19, 20, and 21 | PCR/Sequencing |
| | Kaanane et al[29] | 2019 | 239 | 61.4 ± 8.9 | 169 (70.7)/ 70 (29.3) | 139 (58.2)/ 100 (41.8) | 218 (91.2)/ 21 (8.8) | 18, 19, 20, and 21 | ARMS technology and the Idylla™ system |
| Egypt | Ibrahim et al[30] | 2019 | 2017 | — | — | — | — | 18, 19, 20, and 21 | PCR |

89 years old. Male patients were predominant in all of the considered studies, accounting for 70.4% (2890/4105). One study from Egypt[30] did not include information about the male/female ratio. There were more smokers than non-smokers, as 65.6% (1950/2972) self-reported a history of smoking; they were either former or current smokers. Two of the considered studies did not report data regarding patient smoking history.[22,30] The histological subtype was defined in 13 of the included studies.[16-21,23-29] Predominately, 88.3% (3504/3967) of the analyzed patients presented with adenocarcinoma. Specimens were obtained from FFPE blocks in 19 studies.[16-19,22,23,25-30] Three of the considered studies failed to report the type of specimens used.[20,21,24] Baseline characteristics of enrolled studies are summarized in Table 1.

## EGFR Mutation Prevalence

The prevalence of *EGFR* mutations among the analyzed NSCLC patients in the MENA region was 17.2% (1054/6122). In the ME, the reported frequency was 16.5% (561/3395) and varied throughout the region. *EGFR* mutations were least common in Lebanon, accounting for 11.3% (56/477)[23-25] and most frequent in the Gulf region with 28.7% (66/230).[21] In NA, *EGFR* mutations were found in 18% (493/2727) of NSCLC patient. In Morocco, *EGFR* mutation prevalences ranged from 15.9% to 26.8%.[27-29] Details of *EGFR* mutation prevalences in the MENA region are summarized in Table 2.

## EGFR Mutation Spectrum

Overall, the most frequently encountered *EGFR* mutations were the exon 19 deletions (46.7%, 487/1041) and exon 21 substitutions (31.1%, 324/1041). Exon 20 alterations were detected in (10.8%, 97/896) including the T790 M substitution (5.7%, 51/896). Exon 18 mutations were reported in 3.4% (31/896) of the *EGFR*-mutated patients. In the ME, we report that 43% (241/561) of NSCLC patients were positive for exon 19 deletions vs 49.9% (246/493) in NA. Exon 21 mutations were slightly more commonly detected in the ME (32.2%, 181/561) compared with NA (29%, 143/493). Exon 20 mutations were less prevalent in the ME (7.6%, 31/403) relevant to NA (13.3%, 66/493), the opposite was seen regarding exon 18 mutations, as these alterations were more frequent in the ME (6%, 22/365) than in NA (1,8%, 9/493) (Table 2).

Concurrent mutations were found in 1.1% (12/1054) of the included patients. A total of 10 Turkish patients had multiple exon mutations.[18,19] A single Turkish study reported that 8 patients harbored concurrent mutations: 1 patient had mutations in exon 18 and exon 19, 3 patients had mutations in exon 18 and exon 21, 1 patient had mutations in exon 19 and exon 21, and 3 patients had mutations in exon 20 and exon 21.[18] In 2 Turkish cases, exon 19 deletions and exon 20 T790 M point mutation were detected together in a single patient, and exon 21 L858 R mutation and exon 18 G718X point mutation were found together in another patient.[19] A single Jordanian patient carried 4 concurrent mutations: A735 T, D770_N771 insY, G719 A, L861Q, and L858P.[16] One *EGFR*-positive Lebanese patient harbored a double mutation; an exon 19 deletion and an exon 20 T790 M substitution.[23]

## Association Between EGFR Mutations and Patients' Clinicopathological Characteristics

Patients' clinicopathological characteristics (gender, smoking history, and histology) had a significant influence on *EGFR* mutation prevalences. A total of 13 studies highlighted the correlation between the *EGFR* mutational status and gender. Overall, *EGFR* mutation prevalence was higher in females [females vs males: 29.7% (294/989) vs 5.9% (248/4200), $P < .001$]. The association between the *EGFR* mutational

**Table 2.** Correlation Between Clinicopathological Features Of Included Patients and the EGFR Mutational status.

| Country/Region | Author [Reference] | Frequency of EGFR Mutation n (%) | Exon 18 n (%) | Exon 19 n (%) | Exon 20 n (%) | Exon 21 n (%) |
|---|---|---|---|---|---|---|
| Jordan | Obeidat et al[16] | 24 (14.7) | 2 (8.3) | 9 (37.5) | 1 (4.2) | 12 (50) |
| Iran | Basi et al[17] | 25 (24.3) | — | 10 (40) | - | 15 (60) |
| Turkey | Calibasi et al[18] | 68 (16.6) | 5 (1.2) | 26 (38.2) | 15 (22) | 30 (44.1) |
| | Tezel et al[19] | 160 (16.7) | 9 (5.6) | 78 (48.8) | 9 (5.6) | 61 (38.1) |
| | Ozcelik et al[20] | 92 (13) | | | — | |
| Gulf region | Jazieh et al[21] | 66 (28.7) | 4 (6) | 36 (54.5) | 1 (.01) | 26 (39.4) |
| Iraq | Ramadhan et al[22] | 38 (27.5) | — | 26 (65.8) | 2 (5.3) | 10 (26.3) |
| Lebanon | Naderia et al[23] | 25 (12.4) | 1 (4) | 12 (48) | 2 (8) | 10 (40) |
| | Kattan et al[24] | 22 (12.7) | 1 (4.2) | 11 (50) | 1 (4.2) | 9 (41.6) |
| | Fakhruddin et al[25] | 9 (8.8) | — | 8 (88.9) | — | 1 (11.1) |
| Levant region | Tfayli et al[26] | 32 (15.6) | — | 25 (78.1) | — | 7 (21.9) |
| Morocco | Errihani et al[27] | 29 (26.8) | 2 (7) | 20 (69) | 1 (3) | 6 (21) |
| | Sow et al[28] | 73 (21.9) | 5 (6.8) | 48 (65.8) | 3 (4.1) | 17 (23.3) |
| | Kaanane et al[29] | 38 (15.9) | 2 (5.2) | 27 (71) | 3 (7.8) | 6 (15.7) |
| Egypt | Ibrahim et al[30] | 353 (17.5) | 0 (0) | 151 (42.8) | 59 (16.7) | 114 (32.2) |

**Table 3.** Distribution of EGFR Mutations among Included Patients by Mutation Type.

| Country/Region | Author [Reference] | Male EGFR+/Female EGFR+ n (%) | EGFR+ADK/EGFR+NADK n (%) | EGFR+ Smokers/EGFR+ Nonsmokers n (%) |
|---|---|---|---|---|
| Jordan | Obeidat et al[16] | 13 (11.2)/11 (22) | 24 (100)/0 (0) | 9 (37.5)/15 (62.5) |
| Iran | Basi et al[17] | 14 (27.4)/11 (21.1) | 25 (100)/0 (0) | 8 (12.1)/17 (46) |
| Turkey | Calibasi et al[18] | 42 (14)/26 (23.6) | 68 (100)/0 (0) | 32 (13)/36 (22) |
| | Tezel et al[19] | 64 (9.1)/96 (37.1) | 142 (20.3)/18 (6.8) | 2 (20)/10 (40) |
| | Ozcelik et al[20] | | — | |
| Gulf region | Jazieh et al[21] | — | 62 (32.4)/4 (10.2) | — |
| Iraq | Ramadhan et al[22] | 22 (27.8)/16 (27.1) | | — |
| Lebanon | Naderia et al[23] | 8 (6.5)/16 (20.5) | 25 (13.7)/0 (0) | 8 (5)/16 (36.3) |
| | Kattan et al[24] | 8 (7.8)/14 (20.5) | — | 8 (6.1)/14 (35.8) |
| | Fakhruddin et al[25] | 2 (2.7)/7 (20.5) | 9 (8.4)/0 (0) | 1 (1.6)/5 (27.7) |
| Levant region | Tfayli et al[26] | 12 (9.6)/20 (40.8) | 32 (15.2)/0 (0) | 14 (10.4)/16 (50) |
| Morocco | Errihani et al[27] | 7 (7.6)/22 (47.8) | 29 (21.1)/0 (0) | 5 (6.3)/24 (41.3) |
| | Sow et al[28] | 35 (14.5)/38 (41.3) | — | 23 (13)/47 (35) |
| | Kaanane et al[29] | 21 (12.4)/17 (24.2) | 38 (17.4)/0 (0) | 16 (11.5)/22 (22) |
| Egypt | Ibrahim et al[30] | | — | |

status and patients smoking history was underlined in 11 studies.[16-19,23-29] The prevalence of *EGFR* mutations was higher in non-smokers [non-smokers vs current smokers: 31.3% (222/709) vs 9.6% (126/1308), $P < .001$]. NSCLC patients with adenocarcinoma were far more likely to carry *EGFR* mutations [adenocarcinoma vs non-adenocarcinoma: 18.8% (454/2420) vs 6.5% (22/340), $P < .001$] in overall cases from studies that reported tumor histological subtypes (Table 3).

## Discussion

In the present report, we provide updated data about EGFR mutations in the Middle East and North Africa, offering a better insight into EGFR mutation prevalence and spectrum in different subgroups of NSCLC patients of the region. This information is particularly useful in informing policy makers of patients' subgroups who are more likely to benefit from TKI treatment. Since the occurrence of the dramatic shift in treatment, from the all-encompassing chemotherapy approach to the personalized therapeutic strategies, NSCLC patients genotyping for EGFR mutations has become an absolute necessity for lung cancer management. While EGFR molecular epidemiology varies depending on, inter alia, ethnicity, very little is known about EGFR mutational status of NSCLC patients in the region.

This systematic review revealed that EGFR mutation prevalence among the Middle East and North Africa populations is higher than that seen in NSCLC patients of Caucasian ethnicity but is lower than that identified in Asian NSCLC patients. Furthermore, it was found that the distribution of these mutations varies considerably throughout the MENA region, an expected outcome since mutation rates are known to vary depending on geographic locations and racial/ethnic backgrounds of the demographically heterogenous populations of the region.

Overall, the EGFR mutation rate was 17.2%, as 1054 of 6122 patients harbored mutations in at least 1 of the considered exons. Exon 19 deletions were the most frequently encountered mutations (46.7%). EGFR exon 19 deletions accounted for 49.9% in NA and 43% in ME. These figures corroborate data from the literature reporting an average frequency of 40% regarding exon 19 deletions.[31] Exon 21 made up 31.1% of the identified mutations (29% in NA and 32.2% in ME). Exon 20 mutations accounted for 10.8% of the detected alterations (13.3% in NA and 7.6% in the ME), of which the T790 M tyrosine kinase inhibitors (TKIs) resistant mutation was the most prevalent (5.7%). Data regarding patients' treatment lacked from the considered studies, therefore, little is known about whether the T790 M mutations were detected in TKI-naïve patients at diagnosis or in patients whose disease progressed on first- or second-generation TKI therapies. Also, the use of highly sensitive techniques (eg qPCR-based assays) in a wide range of the considered studies might have contributed to the high prevalence of an otherwise uncommon EGFR mutation. The least prevalent EGFR alterations were exon 18 mutations, making up 3.4% (1.8% in NA and 6% in the ME).

The EGFR mutation status was associated with the female gender [females vs males: 29.7% (294/989) vs 5.9% (248/4200), $P < .001$], the adenocarcinoma subtype [adenocarcinoma vs non-adenocarcinoma:18.8% (454/2420) vs 6.5% (22/340), $P < .001$], and non-smoking status [non-smokers vs current smokers: 31.3% (222/709) vs 9.6% (126/1308), $P < .001$]. These findings are in concordance with established data in the literature.[32] Although typically seen in the absence of a smoking history, a significant minority (9.6%) of former and current smokers harbored EGFR-mutated tumors, arguing

against excluding smokers from EGFR testing. Highlighting the influence of patients clinicopathological features on the EGFR mutational status could be helpful in targeting patients who would respond favorably to EGFR-TKIs.

Deletions in exon 19 and alterations in exon 21 are the most common EGFR mutations, together, they account for 90% of all *EGFR* mutations in NSCLC.[33] These mutations confer sensitivity to *EGFR*-TKIs and are prominent predictive markers of clinical response to TKIs.[34] Exons 18 and 20 insertion mutations are less common and represent the remaining 10% of *EGFR* mutants in NSCLC. They are predictive of treatment resistance to first- and second-generation *EGFR* TKI therapies.[35] Our results showed a combined frequency of exon 19 deletions and exon 21 mutations of 77.8% among all detected mutations. This difference in rates (77.8% vs 90%) is likely due to the heterogeneity in screening methods, potentially inducing inaccuracies in the incidence rates of otherwise very common *EGFR* mutations.

These results corroborate those obtained by Benbrahim et al on the frequency of EGFR mutations in the MENA region. They found that EGFR mutations are more frequent in the Middle East and North African populations than in Caucasian populations but still lower than frequencies reported among Asian populations. Also, they reported that the most frequent EGFR alterations detected were exon 19 deletions. The EGFR mutation status was found to correlate with both female sex and non-smoking status, but not with the histological subtype.[36]

In concordance with previous reports, Rondell et al, reported a frequency of 16.1% of EGFR-mutated cases among African and Middle Eastern NSCLC patients, in a large scale study involving 23 757 patients from different parts of the world: Northern Asia, Southern Asia, Europe, Africa (including the Middle East), South America, and North America. Among the studied cases, Taiwan had the highest rate of EGFR-activating mutations [55% (2802/5103)], followed by China [37% (1009/2702)], then Japan [29% (9644/32 935)] and lastly India with a rate of 29% (605/2077). While The highest rates were recorded in Asia, the lowest were in South America with 7,9% (114/1439). In Europe, the frequency of EGFR mutations was 13.4% (138/1030). In North America, where the largest studied population was (86 654 patients), 9,2% carried EFGR mutations.[37]

A major strength of this systematic review is the inclusion of available studies from a wide range of MENA countries and covering the diverse populations of the region, without compromising the statistical power of the study, in order to have an accurate depiction of EGFR mutation prevalence and spectrum in the area.

Although results from this study were consistent with findings from previous reports, they should be considered cautiously due to some limitations. Firstly, the types of specimens and genotyping methods used in the included studies lacked homogeneity; in some studies, the mutations were confirmed by sequencing whereas in others they were not. Secondly, the restricted access of patients to EGFR molecular testing in some countries of the region could induce a disproportion in study population size to NSCLC patients in the country, potentially creating some bias in the study. Finally, the demographically non-homogeneous nature of the populations of the region could potentially contribute to the heterogeneity of the study.

## Conclusion

EGFR mutation prevalence among MENA populations is slightly higher than that seen among NSCLC patients of Caucasian ethnicity but is lower than that identified in Asian NSCLC patients. The distribution of these mutations varies considerably throughout the MENA region. These estimates can serve as a reference for the future research or policy making. While EGFR molecular epidemiology varies depending on, inter alia, ethnicity, very little is known about EGFR mutational status of NSCLC patients in the region. This entails the introduction of EGFR mutation analysis as standard of care for NSCLC patients in the region.

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### Authors' Contributions

YB and AL have conceived the study, exploited data, coordinated and drafted the paper. TB, BElM, HElA, and HC participated in the study design. HS, HE, IAR and, TM were involved in data analyses. YS, BB, KE, IL-A, MI, RT, AA, and MO critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

### Declaration of Conflicting Interests

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### Availability of Data and Materials

The data that support the findings of this study are available from original articles that have been included in this study. Data are available from the authors upon reasonable request from the corresponding author.

### ORCID iD

Youssra Boustany https://orcid.org/0000-0002-1253-7636

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