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Prevalence of oncogenic driver mutations in Hispanics/Latin patients with lung cancer. A systematic review and meta-analysis

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ABSTRACT

Introduction: The frequency of actionable mutations varies between races, and Hispanic/Latino (H/L) people are a population with different proportions of ancestry. Our purpose was to establish prevalence of actionable mutations in the H/L population with NSCLC.

Methods: EMBASE, LILACS, MEDLINE, and Virtual Health Library were searched for studies published up to April 2023 that evaluated the prevalence of *ALK, BRAF, EGFR, HER-2, KRAS, MET, NTRK, RET, ROS1* in H/L patients. Meta-analyses were done to determine prevalence using a random effects model.

Results: Fifty-five articles were included. *EGFR* and *KRAS* were the most prevalent genes with high heterogeneity across the countries. The overall mutation frequency for *EGFR* was 22%. The most frequent mutations in the *EGFR* gene were del19 (10%) and L858R (7%). The mean of *KRAS* mutation was a 14% prevalence. KRASG12C was the most frequent mutation with a 7% prevalence in an entire population. The overall frequency of ALK rearrangement was 5%. The mean frequency of ROS-1 rearrangement was 2%, and the frequencies of *HER-2, MET, BRAF, RET, NTRK* molecular alterations were 4%, 3%, 2%, 2%, and 1% respectively. Almost half of the cases were male, and 65.8% had a history of tobacco exposure. The most common clinical stage was IV.

Conclusions: The prevalence of driver mutations such as *EGFR* and *KRAS* in LA populations differs from what is reported in Asians and Europeans. In the present article, countries with a high proportion of Amerindian ancestry show a greater prevalence of *EGFR* in contrast to countries with a high proportion of Caucasians. Lack of information on some countries or studies with a small sample size affects the real prevalence data for the region.

1. Introduction

Lung cancer is the second most commonly diagnosed neoplasm and the number one cause of cancer death worldwide. In Latin America (LA) and the Caribbean, it is the third most common cancer after prostate and breast cancer with 97,601 new cases and the number one cause of cancer death with 86,627 patients per year [1]. Several risk factors have been reported for the development of lung cancer, e.g., smoking, environmental tobacco smoke, chronic obstructive pulmonary disease, family history of lung cancer, infections, and genetic factors [2].

In recent years, the identification of oncogenic driver mutations in non-small cell lung cancer (NSCLC) has led to targeted therapies that have significantly improved outcomes in recent years. Targeted mutations include *ALK* (anaplastic lymphoma receptor tyrosine kinase), *BRAF* (V-raf murine sarcoma oncogene homolog B1), *EGFR* (epidermal growth factor receptor), *HER-2* (human epidermal growth factor receptor), *KRAS* (Kirsten rat sarcoma virus), MET (MET proto-oncogene receptor tyrosine kinase), *NTRK* (neurotrophic tropomyosin receptor kinase), RET (rearranged during transfection), *ROS1* (c-ros oncogene 1), and *NRG1* (neuregulin-1) [3,4]. In addition to targeted therapies, immunotherapy has also improved outcomes in lung cancer patients. Testing for PD-L1 expression is another clinically relevant biomarker and is the only biomarker used in clinical practice to predict response to anti-PD-(L)1 therapies [5]. The latest NCCN Clinical Practice Guidelines

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in Oncology (NCCN guidelines) recommend testing actionable biomarkers and PD-L1 in advanced or metastatic lung cancer [6]. However, molecular testing has also been recommended in early-stage disease [7,8]. The prevalence of driver mutations varies by ethnicity, smoking status, and gender [9].

EGFR mutations occur at a significantly higher frequency in lung adenocarcinoma, women, never smokers, and Asian populations [10]. In a recent study, Shi et al. [9] analyzed the genomic characteristics of 7,023 samples from different ethnicities including Caucasian (84.89%), Asian (8.64%), Black (4.81%), Native American (0.16%), and other (1.50%). While they found different genomic alterations among the races, *EGFR* and *KRAS* were the most aberrant genes in the different racial groups ($P < 0.001$). The L858R mutation in *EGFR* exon 21 was three times more common in Asians than in other races ($P < 0.001$). *ALK* rearrangement was observed more frequently in Asians (4.7%) than in whites (3.1%), and blacks (1.8%). White patients had a higher rate of reported *KRAS*G12C (15.51%) than the others ($P < 0.001$). *RET* rearrangement and *ERBB2* amplification were more common in Asian patients than in the others. *STK11* mutation was seen more frequently in whites (17.2%), blacks (15.1%), and others (15.7%) than in Asians (3.94%) ($P < 0.001$).

In the Latin American region, molecular testing and treatment for NSCLC is limited since there are several challenges to the implementation of diagnostics and therapy [11,12]. Currently, some targeted therapies (*EGFR, ALK, KRAS, ROS1, NTRK*) and checkpoint inhibitors (PD-L1) are approved for NSCLC in LA [12]. The prevalence of driver mutations varies within LA countries. The purpose of this systematic review was to determine the prevalence of targetable mutations in the Hispanic/Latino (H/L) population with NSCLC.

2. Material and methods

This systematic review was reported on the basis of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) checklist [13]. The protocol was submitted to PROSPERO, the International Prospective Register of Systematic Reviews under the number CRD-427244.

2.1. Inclusion criteria

The inclusion criteria for the systematic review were descriptive studies, cohorts, and clinical trials that evaluated the prevalence of actionable genes (*ALK, BRAF, EGFR, HER-2, KRAS, MET, NTRK, RET, ROS1*) and molecular alterations (mutations, rearrangements, amplifications). H/L patients from non-LA countries were included. Articles published up to April 2023 were included. Articles available in all languages were eligible.

2.2. Exclusion criteria

The following exclusion criteria were applied: a) studies that evaluated *EGFR* mutation by immunohistochemistry, b) studies with discrepancies in the text and in the results in the tables, c) in the case of studies with the same population published in different articles, the one with the highest number of cases was selected, d) studies that did not distinguish between from H/L and other ethnicities in regards to molecular alteration information, e) studies that evaluated the prevalence of molecular alteration in patients with a history of other gene mutations.

2.3. Information sources and search strategy

Detailed individual search strategies were followed in each of the following electronic databases: Embase, LILACS, Medline, and Virtual Health Library. Some grey literature was retrieved using Google Scholar. The final search date for all databases was 01 April 2023. In addition to the electronic search, a hand search, and expert consultation were done, and the reference lists of the selected articles were screened. Appropriate truncations and word combinations were used and adjusted for each database search (Table 1S). Terms considered included: Carcinoma, non-small cell lung, lung neoplasms, pulmonary neoplasms, Hispanic or Latino, Spanish origin, Latin America, EGFR, KRAS, ALK, RET, MET, ROS1, HER2, BRAF, NTRK.

2.4. Study selection

Eligibility of the selected articles was assessed in two phases. In phase 1, three authors (JPC, LM, MPV) independently screened the studies by title and abstract. In phase 2, the same authors assessed the abstract and full text of all screened articles and excluded studies that did not meet the inclusion criteria. Disagreements between the authors were resolved by another author (RPM). References from articles that were considered relevant to our review were manually searched. All data included were reviewed by the authors. The final selection was always based on the full text of the publication or the abstract of the conference presentation.

2.5. Data collection process and data extraction

The following data were extracted from each article when possible: author name, country of origin of the patients, year of publication, recruitment time, number of patients, molecular alteration in actionable genes (ALK, BRAF, EGFR, HER-2, KRAS, MET, NTRK, RET, ROS1), non-actionable genes (TP53, STK11, PIK3CA), expression and clinical data (age, smoking status, sex, histological subtype, disease stage, metastasis, and ECOG). Disagreements were resolved by consensus. If the required data were not complete, attempts were made to contact the authors to obtain the missing information.

2.6. Risk of bias and applicability

To assess the methodological quality and applicability of the studies included, a checklist based on the Joanna Bridge Institute Critical Appraisal Checklist for Systematic Reviews and Research Syntheses [14] was applied. Two reviewers (JPC, MPV) answered eight questions for cross-sectional studies and eleven questions for cohort studies. Each question was analyzed as 'yes' (Y), 'no' (N), 'unclear' (U) or 'not applicable' (NA).

2.7. Summary measures

The primary outcome was the prevalence of *ALK, BRAF, EGFR, HER-2, KRAS, MET, NTRK, RET, ROS1*. Prevalence was calculated as patients with mutations divided by all patients tested. Prevalence or incidence of *EGFR* exon (exon 19 to 21) and *KRAS* codon (12 and 13) were also calculated.

2.8. Data synthesis and analysis

All quantitative analyses of studies included were performed in R using the metafor and meta packages. Random effect model and the *meta*-analyses were done to determine the prevalence of *ALK, BRAF, EGFR, HER-2, KRAS, MET, NTRK, RET, ROS1*. Another meta-analysis was done to determine specific genetic alterations of *EGFR* and *KRAS* exons. Heterogeneity was calculated using I^2, and high heterogeneity for values greater than 75% was considered. The significance level was set at 5%. Heterogeneity was assessed by sample size, country, and study design.

3. Results

3.1. Results of the search and screening

We identified 473 original articles in the databases and 30 Latin American manuscripts that were searched using snowball sampling. Of the total, 54 duplicates were identified, and 419 articles, including clinical trials, analytical studies, and descriptive studies, were screened for eligibility. Of these, 297 were rejected based on title and abstract content. Finally, 55 articles met the inclusion and exclusion criteria and were included in the review [15–69]. In the case of 16 articles, data were extracted from the abstract [20,27,34,37,40,42,43,46–51,55,57,61,64,65]. The PRISMA flow diagram that summarized the searches and databases included is shown in Fig. 1. Five multicenter studies in different counties were found. The information was extracted by country [15,38,48,68,69]. Of the total, 16 articles based on a Brazilian population, nine articles based on an Argentine population, seven from Colombia, six from Mexico and Peru, five from Chile, three from

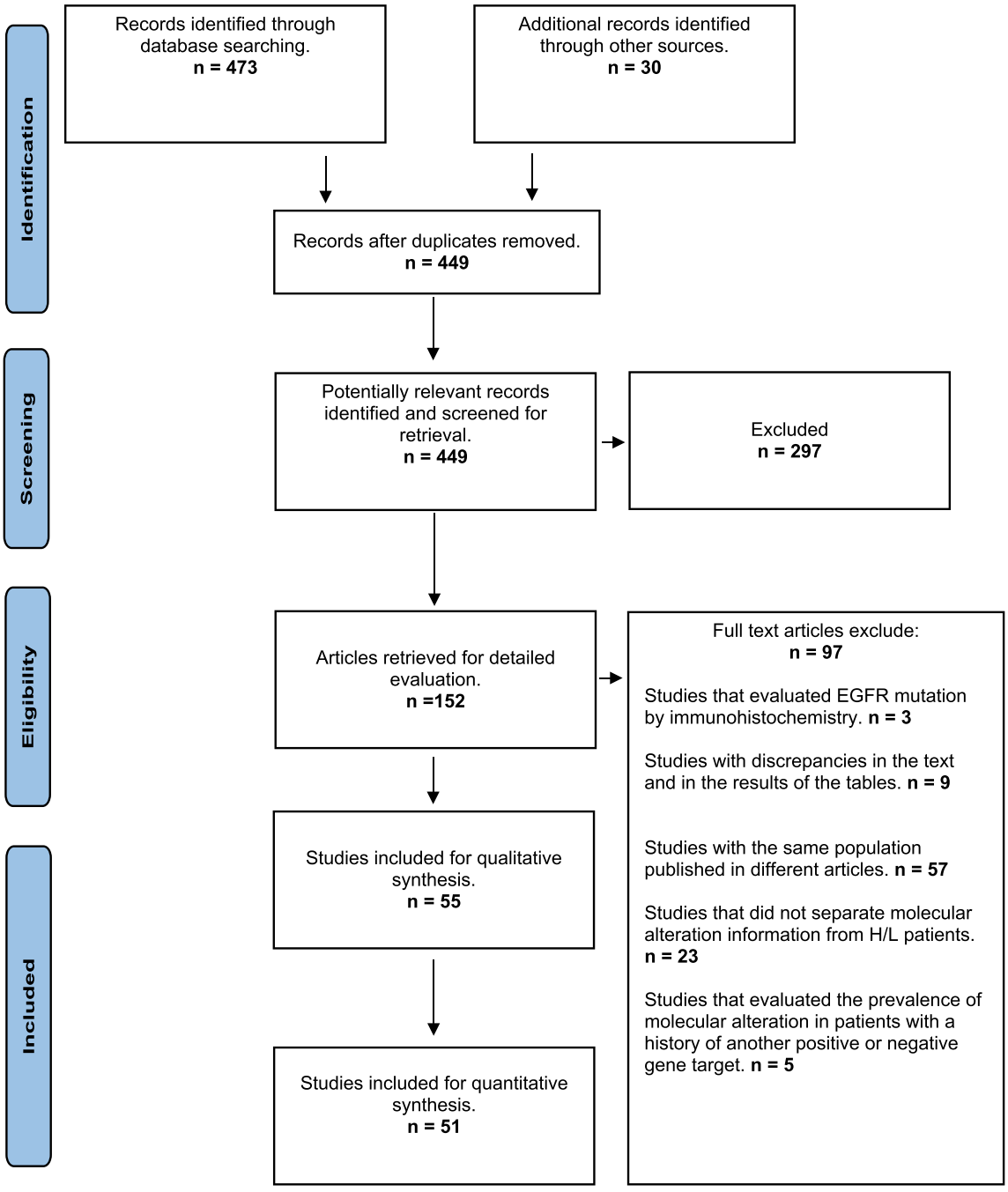


Fig. 1. Flow chart of the systematic literature review.

Ecuador, Uruguay, and Venezuela, two from Costa Rica, Panama, Puerto Rico, and only one article from Bolivia were included. Nine articles included Hispanic patients living in the United States. One abstract analyzed H/L patients from the American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange (GENIE) open-source international genomic data sharing consortium [65] and one article analyzed patients from the Central American and Caribbean region (Dominican Republic, Nicaragua, Panama, Honduras, and Costa Rica) [64]. Detailed information on the total population found in this review is shown in Table 2S.

Even with the emergence of robust research groups at individual centers in LA countries over the last 20 years, the collaborative efforts of cooperating groups have been more effective in bringing together initiatives to improve patient care for those diagnosed with lung cancer. One example is Oncolgroup and CLICaP. The latter is a consortium founded in 2011 that has consistently sought to advance lung cancer research in LA, particularly for the evaluation of patients in clinical trials with subpopulations of patients with specific mutational characteristics [70]. Given the high risk of overestimating mutation frequency in the various published CLICaP studies, two manuscripts that evaluated genetic alterations in *EGFR* and *KRAS* genes separately [15] and analyzed the frequency of rearrangements in ALK were selected [27].

3.2. General clinical information

Clinical information was extracted from 46 articles with data on 22,210 patients in total. In 95.5% (n = 21,216) of the cases, it was possible to extract information related to the sex and age of the patients. The mean age of patients with NSCLC in Latin America was 63.3. The sex of 994 patients could not be determined. Of the remainder, 50.9% (n = 10,798/21,216) of the cases were men, and 49.1% (n = 10,418/21,216) were women. In relation to smoking status, 65.8% (n = 7,444/11,305) were found to have a history of tobacco exposure. There were 18,221 cases with reports of the histopathological subtype; 16,379 of them were adenocarcinomas (89.8%), 910 were squamous cell carcinomas (5%), 910 corresponded to other histopathological patterns or were not specified by the authors (5%), and the remaining 22 cases were adenosquamous carcinomas (0.1%) (Table 1).

Regarding the clinical stage at the time of NSCLC diagnosis, the majority (59.2%) of cases were stage IV disease (n = 1,896/3,202),

Table 1
Clinical characteristics of H/L patients with lung cancer by country.

	Argentina	*Brazil*	*Chile*	*Colombia*	*Costa Rica*	*Ecuador*	*Mexico*	*Panama*	*Peru*	*Puerto Rico*	*Uruguay*	*H/L in US*	*TOTAL*	*%*
Number Of Patients	2739	10,729	2082	2466	102	167	1707	174	475	951	365	253	22,210	
Age														
Median	64	67	65	65,9	65,9	58,9	54,5	63,9	65	69	66	69		
Mean	64,8	62,6	65,7	63,8	65,9	58,9	62,2	63,9	65	69	66	62,2		
Sex														
Female	1128	5069	998	1481	60	80	667	87	131	450	144	123	10,418	49,1
Male	1543	5395	1084	985	42	50	586	87	154	501	221	150	10,798	50,9
Smoking History														
Yes	1484	3212	1331	752	61	43	277	75	31	–	68	110	7444	65,8
No	613	324	89	590	41	110	330	82	51	–	6	99	2335	32,2
Histology Type														
Adenocarcinoma	2451	6708	1646	2201	97	144	1542	165	272	717	319	117	16,379	89,8
Squamous Cell Carcinoma	58	255	135	131	1	4	121	5	–	144	14	9	910	5,0
Adenosquamous Carcinoma	–	–	10	5	–	–	6	–	–	–	–	1	22	0,16
Poorly Differentiated Carcinoma	–	–	–	–	–	–	–	–	–	–	–	–	12	0,09
Carcinoma NOS	22	287	5	105	2	–	30	6	–	–	32	3	492	2,8
Other Histology	2	35	124	24	1	19	8	1	–	90	–	42	346	2,6
Disease Stage														
IA	71	28	42	8	–	–	–	–	–	–	–	10	159	5,23
IB	7	92	8	9	–	–	–	–	–	–	–	3	119	3,91
IIA	1	88	10	8	–	–	–	–	–	–	2	7	116	3,81
IIB	4	124	8	8	–	–	–	–	–	–	–	3	147	4,6
IIIA	10	322	33	22	–	–	–	–	–	–	1	8	396	12,4
IIIB	25	186	28	24	–	–	–	–	–	–	–	2	265	8,3
IIIC	1	–	22	2	–	–	–	–	–	–	3	–	28	0,92
IV	291	505	409	426	–	79	113	–	–	–	70	3	1896	59,2
Not Known	–	–		–	–	–	–	–	–	–	–	15	35	1,15
Metastases														
NOS	–	335	–	–	–	–	–	–	–	–	–	64	399	23,84
Bone	116	5	174	37	–	12	22	–	–	–	31	–	397	19,7
Liver	31	2	77	9	–	14	–	–	–	–	20	3	156	7,7
Brain	53	4	95	17	–	14	17	–	–	–	18	9	227	11,3
Lung	18	–	431	–	–	21	24	–	–	–	–	–	494	24,5
Functional Patient Status														
ECOG 0	76	153	13	71	–	7	76	–	–	–	12	8	416	23,86
ECOG 1	87	374	24	225	–	–	–	–	63	–	17	19	809	46,41
ECOG 2	39	89	6	110	–	67	–	–	12	–	13	1	337	19,33
ECOG 3	10	95	–	50	–	–	–	–	–	–	12	–	167	9,58
ECOG 4	3	–	–	8	–	–	–	–	–	–	3	–	14	0,8
Management														
TKI (1st Gen)	71	–	72	30	–	–	30	–	–	–	33	10	246	80,6
TKI (2nd Gen)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
TKI (3rd Gen)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Immunotherapy	–	–	–	3	–	–	–	–	56	–	–	–	59	19,3

followed by stage IIIA in 12.4% (n = 396/3,202), stage IIIB in 8.3% (n = 265/3,202), and stage IIB in 4.6% (n = 147/3,202). Among patients with metastatic disease, it was possible to obtain information on the anatomical site of metastasis in 2,016 patients. Of these, the most common site was the lung itself in 24.5% (n = 494/2,016) of cases followed by the bone in 19.7% (n = 397/2,016), the central nervous system in 11.3% (n = 227/2,016), and the liver in 7.7% (n = 156/2,016). In 742 cases, metastases were recorded without a clear indication of their location. Finally, functional status information was collected for 1743 patients. Data were included using the ECOG scale with 416 patients ECOG 0 (23.9%), 809 ECOG 1 (46.4%), 337 ECOG 2 (19.3%), 167 ECOG 3 (9.6%), and only 14 patients for ECOG 4 (0.8%) (Table 1).

4. Mutation frequency in Latin America

4.1. Actionable mutations

EGFR. The most commonly tested mutation, *EGFR,* appeared in 41 articles (n = 22,130) with an overall mutation frequency of 22% (CI 95%; 19–25%) in H/L patients including LA countries and H/L in the USA (Figs. 2 and 4). When EGFR mutations are analyzed by country, Peru had the highest mean mutation frequency with 35% (CI 95%; 19–54%) followed by Ecuador with 34% (CI 95%; 21–50%), and Mexico with 33% (CI 95%; 30–36%). In contrast, Argentina and Chile had a frequency of 16% or lower (Fig. 3A).

In addition, *meta*-analyses were done to assess the frequency of mutations within each exon of the *EGFR* gene. Detailed information on the mutated exon of the *EGFR* gene was available for 4,477 patients. The most frequently mutated exons were del19 (10% CI 95%; 8–12%) followed by the L858R mutation (7%; 95% CI; 6-8%). Ins20 was observed in 1% (CI 95%; 1–2%) and T790M in 1% (CI 95%; 1–2%) (Fig. 1S A-D). The results of these and other point mutations in the *EGFR* gene are shown in Fig. 2.

In patients with an *EGFR* gene mutation and reported clinical data (n = 3,168), the median age was 65.4. There was a higher proportion of women in this group of patients (n = 1,601/2,536, 63.1%). The number of non-smoking patients (n = 888/1,394, 63.7%) was higher than the number of patients with a history of tobacco exposure (n = 506/1,394, 36.3%). The proportion of *EGFR*-mutated tumors classified as adenocarcinoma was similar to what was reported in the general population (92.8%, n = 538/580). Data were only available for patients with tumor stages IB (n = 16/146, 11%), IIA (n = 7/146, 4.8%), IIB (n = 11/146, 7.5%), IIIA (n = 31/146, 21.2%), IIIB (n = 57/146, 39%), and IV (n = 8/146, 5.5%) (Table 2).

KRAS. Twenty-six articles (n = 12,914) were found with information related to *KRAS* gene mutations. Regarding the cases with available clinical information and mutated *KRAS*, 1,687 patients were found with a mean age of 65.9, and 872/1,687 were female (51.7%). Of the total, there was information on smoking status in 295 cases and 260 of these (88.1%) were current or former smokers. The majority of cases were classified as adenocarcinomas (n = 303/322, 94.1%), and 63 cases had metastases at diagnosis (Table 2).

The average of *KRAS* mutations in H/L patients was 14% (CI 95%; 11–19%) (Figs. 2 and 5). Brazil was the country with the highest prevalence of *KRAS* mutations with 18% (CI 95%; 12–27%) which was similar to the prevalence seen in the GENIE database (22%, CI 95%; 19–26%). LA countries with a prevalence of<10% were Colombia (6%, CI 95%; 5–7%), Puerto Rico (8%, CI 95%; 7–10%), and Peru (10%, CI 95%; 6–18%) (Fig. 3B). Regarding the proportion of different mutations in the *KRAS* gene, the *meta*-analysis found the G12C mutation was the most common at 7% (95% CI; 6–9%) (Fig. 2 and Fig. 2S A). Other less frequent mutations were G12V (4%, 95% CI; 3–6%), G12D (4%, 95% CI; 3–6%), G12A (1%, 95% CI; 1–2%), and G12S (1%, 95% CI; 1–2%). Codon 13 then had an overall mutation frequency of 1% (1%, 95% CI; 0–1%) and the most representative of these were G13B, G13C, G13D, and G13S mutations (Fig. 2S B). Interestingly, codon 61 mutations were found although at a lower frequency than the above including Q61H (1%, CI 95%; 0–2%) and Q61L (1%, CI 95%; 0–1%) (Fig. 2S C). There were 2% (CI 95%; 1–4%) NOS mutations of the KRAS gene (Fig. 2S D).

ALK. The frequency of *ALK* rearrangement could be determined in 29 articles. A total of 12,046H/L patients with relevant data were found. The overall frequency of *ALK* rearrangement in H/L patients with NSCLC was 5% (CI 95%; 4–6%) (Figs. 2 and 6). The country with the lowest prevalence in LA was Chile with 3% (95% CI; 1–9%) followed by Argentina with 4% (95% CI; 3–6%), and Brazil with 4% (95% CI; 3–6%). Peru was the country with the highest prevalence with only one article that reported *ALK* rearrangement in 11% of 239 patients (Fig. 3C and 6).

Clinical data were collected on 406 patients with reported *ALK* rearrangement. Their mean age was slightly lower than that of the

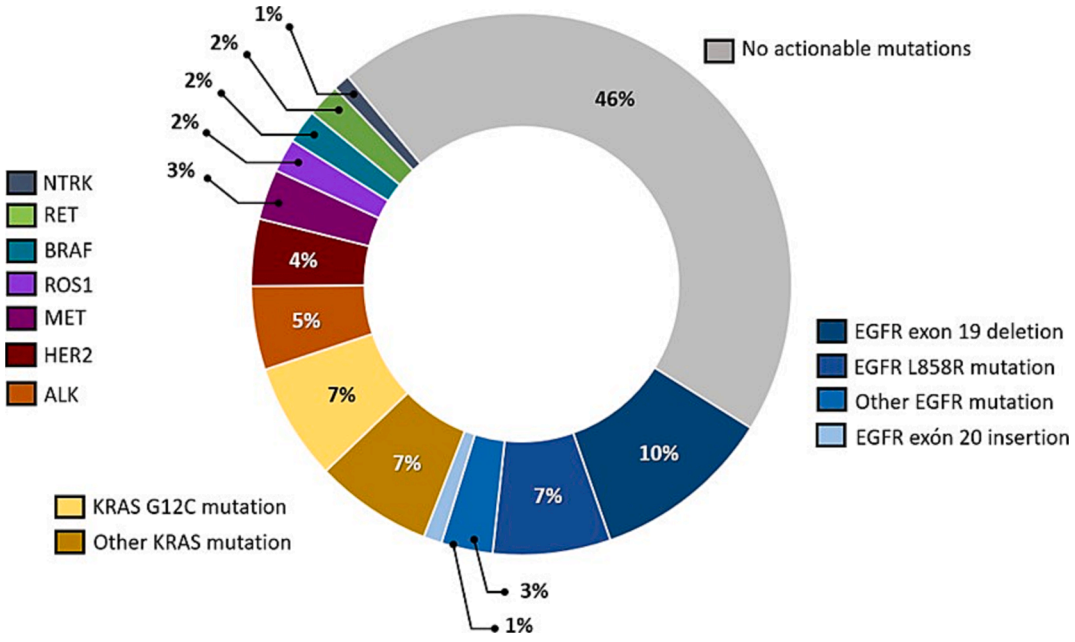


Fig. 2. Detailed frequency of actionable and non-actionable mutations in H/L lung cancer patients.

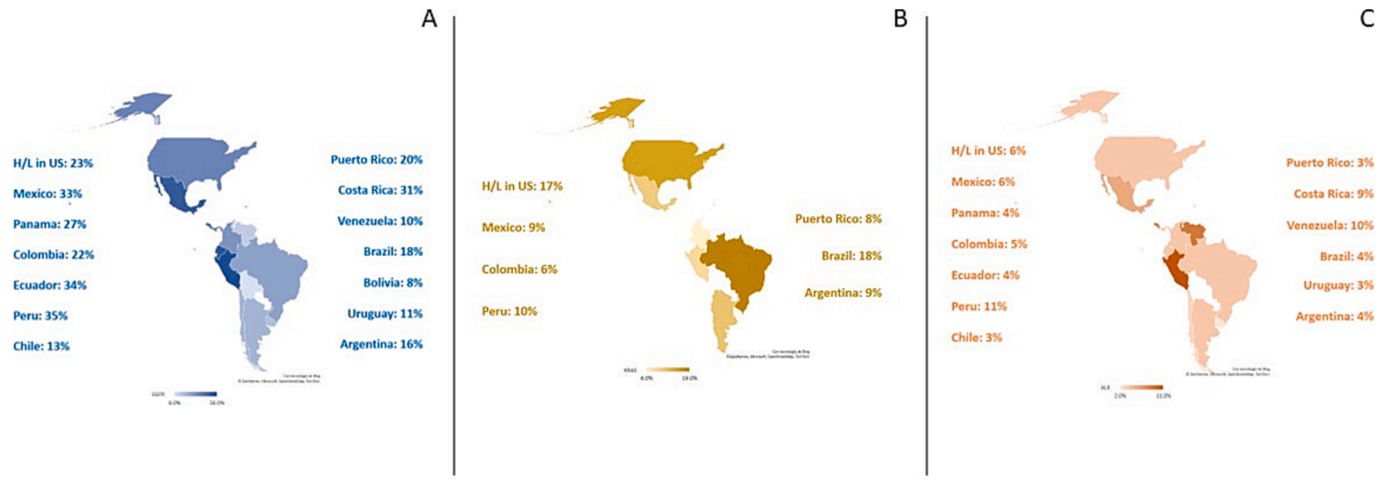


Fig. 3. Prevalence of actionable mutations in lung cancer patients in Latin America and in H/L residents of the USA. A) *EGFR* prevalence mutation, B) *KRAS* prevalence mutation and C) *ALK* prevalence mutation.

previous groups (57.3). Of the total, 55.7% were female (n = 200/359), and 116/227 reported a history of smoking (51.1%). Of the 274 cases with histological information on tumors, 261 (95.3%) were adenocarcinomas. Most cases (n = 28/39, 71.8%) were diagnosed at stage IV with metastases in the bone (n = 11), liver (n = 6) and central nervous system (n = 5) (Table 2).

ROS-1. In 13 articles (n = 2,450), the data reported made it possible to establish the frequency of *ROS-1* rearrangement in the LA population (Table 2). The overall frequency was 2% (CI 95%; 1–2%) (Fig. 3S A)and included patients from Argentina, Brazil, Chile, Mexico, Puerto Rico, H/L in the USA, and Genie consortium (Fig. 2). The highest prevalence was observed in one article from Mexico with 4% (95% CI; 1–7%). In Colombia, Ecuador, and Uruguay no cases of positive *ROS-1* were reported, and in the rest of the countries, no studies have been published with original data that would allow us to establish an accurate rearrangement frequency.

BRAF. Data related to the frequency of *BRAF* mutations were found in nine articles (n = 2,876), including data from Brazil, Argentina, Mexico, Puerto Rico, and H/L in the USA. Likewise, data from the GENIE consortium were recorded. The countries with the highest number of articles and the highest number of patients were H/L in USA and Brazil with a prevalence of 5% (CI 95%; 2–14%) and 2% (CI 95%; 1–5%) respectively. The prevalence of mutations found in the GENIE consortium data was 6% (CI 95%; 5–9%). Considering all registries and countries with BRAF reporting, a mutational prevalence of 2% (CI 95%; 1–4%) was found in LA patients (Fig. 2 and Fig. 3S B). From a clinical perspective, clinical information was found in two articles that included 65 patients with the presence of the *BRAF* gene mutation. The mean age of the patients was 67, with 30 female and 35 male patients**.** According to the research done by Andreis et al. [23] and Mascarenhas et al. [29], the prevalence of the V600E mutation compared to other *BRAF* mutations was found to vary between 50% and 68.4%. This mutation accounted for the majority of genetic mutations found in the H/L population (Table 2).

HER-2. Five articles were found (n = 1,418) that had information from Brazil, Mexico, Puerto Rico, H/L in the USA, and the GENIE consortium. The overall prevalence was found to be 4% (CI 95%; 1–10%) (Fig. 2 and Fig. 3S C). In the Mexican population, Hérnandez-Pedro et al. [45], found 11.1% *HER2* mutations. I655V (exon 17) was detected at a high frequency. Follow by GENIE database, 6.4% [65], H/L patients from California, 5.6% [59]; Puerto Rico, 5.8% [52], and Brazil, 4.9% [29].

RET. Regarding RET gene rearrangements, four articles were found (n = 1,406) that had information from Brazil, H/L in the USA, and the GENIE consortium. The overall prevalence was found to be 2% (CI 95%; 1–3%) (Fig. 2 and Fig. 3S D). All reports came from the use of NGS as a molecular detection technique. In the study by Velazquez et al. [65] RET fusions were reported in ten patients, 6 of whom were women.

MET. When the *MET* gene was analyzed, seven articles (n = 1,355) were found from Argentina, Brazil, Chile, Colombia, Mexico, Puerto Rico, Uruguay, and H/L in the USA. An overall prevalence of 3% (CI 95%; 1–7%) was recorded (Fig. 2 and Fig. 3S E).). Most of the cases came from Mexican patients (20%, CI 95%; 12–30%) followed by patients from Brazil and H/L in the USA. Clinical information could only be gathered from one article [52] about Puerto Rican patients that reported the mutation in 18 patients with a mean age of 66, 11 of whom were women. Martin et al. [68] discovered the presence of *MET* mutations in 1.4% of patients from Argentina, Colombia, Chile, and Uruguay (Table 2).

NTRK. Only three articles (n = 867) were found where the authors recorded the prevalence of the NTRK gene rearrangements [29,40,59] Mejia et al. detected *NTRK* in 0.8% of Colombian patients using IHC and RNA-seq [40]. Mascarenhas et al. [29] found *NTRK* rearrangements in 0.6% and Hsu et al. [59] 1.1 % (1/90) of H/L patients in California. In our analysis, the prevalence observed was 1% (CI 95%; 0–1%) (Fig. 2 and Fig. 3S F).

Non-actionable mutations. Among the non-actionable mutations included in the study, the most frequently reported in LA was TP53 with a prevalence of 30% (CI 95%; 13–56%) followed by a mutation of PIK3CA in 4% (CI 95%; 1–14%) and STK11 in 4% (CI 95%; 2–9%) (Fig. 4 A-C).

Co-mutations. Although infrequent, we found some registries of patients with multiple mutations of actionable and non-actionable mutations in LATAM patients. In the *EGFR* gene, 239/3840 (6.2%) patients were found to have multiple mutations with other genes. Among these, multiple *EGFR* mutations with *KRAS* were found in 35% (n = 84/239), *TP53* in 33% (78/239), *ALK* in 12% (n = 31/239), *MET* in 8% (n = 19/239), *PIK3CA* in 3% (n = 7/239), *RET* 2% (n = 4 %239), *ROS1* in 3% (n = 7/239) and with *BRAF* in only 2% of the cases (n = 6/239). In the *ALK* gene, 108 co-mutations were found in L/H patients, being EML4 the most prevalent gene involved in co-mutations, with 50% (n = 54/108), followed by *ROS1* in 21% (n = 23/108), *TP53 IN 8% (n* = 9/108), *STK11* in 12% (n = 13/108), PIK3CA in 2% (n = 2/108), *CDK4* in 1% (n = 1/108), *MET* in 2% (n = 2/108), *KRAS* in 1% (n = 1/108), *NTRK* in 1% (n = 1/108), and *RET* cases in 1% (n = 1/108). Regarding KRAS co-mutations, we found 97 patients. TP53 was found in 66% of them (n = 64/97), followed just by STK11 with 32% (n = 31/97).

Among co-mutations in the *EGFR* gene, 70 simultaneous multiple mutations were found. The most frequent were dual mutations of exon 21 of which at least one was L858R (n = 18, 25.7%), followed by

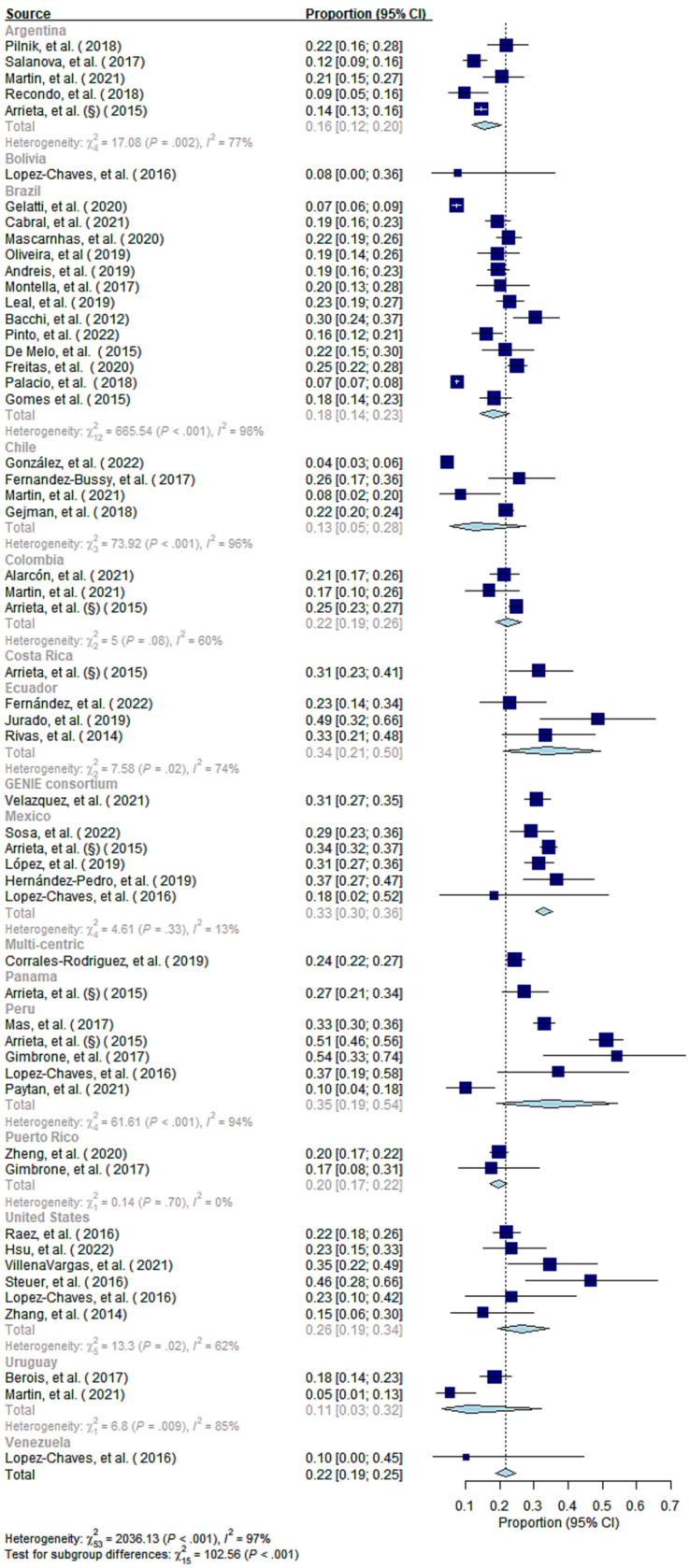


Fig. 4. Meta-analysis of *EGFR* frequency mutations.

Table 2
Clinical characteristics of H/L patients with lung cancer and reported mutations.

	EGFR +	*KRAS* +	*ALK* +	*KRAS* +/ *EGFR* +	*ERRB2* +	*BRAF* +	*ROS 1* +	*MET* +	*RET* +	*TOTAL*	*%*
Number Of Patients	3168	1687	406	121	69	65	23	18	10	4124	
Age											
Median	63	69	66,5	–	66	67	–	66	–		
Mean	65,5	65,6	57,3	–	66	67	–	66	–		
Sex											
Female	1601	872	200	36	40	30	15	11	6	2811	58,6
Male	841	815	156	85	29	35	8	7	4	1980	41,3
Smoking History											
Yes	506	260	116	0	–	–	5	–	–	887	43,9
No	888	14	110	121	–	–	5	–	–	1133	56,08
Histology Type											
Adenocarcinoma	538	303	261	–	–	–	–	–	–	1102	95,6
Squamous Cell Carcinoma	21	–	1	–	–	–	–	–	–	22	1,9
Adenosquamous Carcinoma	3	–	1	–	–	–	–	–	–	4	0,3
Poorly Differentiated Carcinoma	–	–	4	–	–	–	–	–	–	4	0,3
Carcinoma NOS	11	–	1	–	–	–	–	–	–	12	1,04
Other Histology	2	–	6	–	–	–	–	–	–	8	0,69
Disease Stage											
IA	–	–	2	–	–	–	–	–	–	2	0,54
IB	16	–	–	–	–	–	–	–	–	26	7,14
IIA	7	–	–	7	–	–	–	–	–	17	4,67
IIB	11	–	1	14	–	–	–	–	–	43	11,81
IIIA	31	–	–	27	–	–	–	–	–	97	26,64
IIIB	57	–	8	32	–	–	–	–	–	97	26,64
IIIC	–	–	–	–	–	–	–	–	–	–	–
IV	8	–	25	41	–	–	–	–	–	74	18,13
Not Known	16	–	–	–	–	–	–	–	–	16	4,39
Metastases											
NOS	14	48	13	–	–	–	–	–	–	75	77,3
Bone	–	–	11	–	–	–	–	–	–	11	11,34
Liver	–	–	6	–	–	–	–	–	–	6	6,18
Brain	–	–	5	–	–	–	–	–	–	5	5,15
Lung	–	–	–	–	–	–	–	–	–	–	–
Functional Patient Status											
ECOG 0	23	–	–	–	–	–	–	–	–	46	43,8
ECOG 1	15	–	–	–	–	–	–	63	–	49	46,66
ECOG 2	4	–	–	–	–	–	–	12	–	10	9,52
ECOG 3	–	–	–	–	–	–	–	–	–	–	–
ECOG 4	–	–	–	–	–	–	–	–	–	–	–
Management											
TKI (1st Gen)	45	–	15	–	–	–	–	–	–	60	76,92
TKI (2nd Gen)	–	–	1	–	–	–	–	–	–	1	1,28
TKI (3rd Gen)	–	–	–	–	–	–	–	–	–	–	–
Immunotherapy	–	17	–	–	–	–	–	56	–	17	21,79

multiple simultaneous mutations of exon 19 and exon 20 (n = 14, 20%) and of exon 20 and 21 (n = 10, 14.3%). Other multiple mutations were represented at lower frequencies. Only four cases of triple mutations were reported, two cases reported by Mascarenhas et al. [29] and two other cases reported by Berois et al. [62]. There were only 6 cases of multiple mutations within the *KRAS* gene, and 3 of these were the G12V + G12A mutation. Multiple mutations within each of the genes included in this review are detailed in supplementary material (Table 3S).

4.2. Quality assessment

The quality of 36 studies was assessed, and the results are shown in the supplementary material (Table 4S). Most of the studies meet JBI criteria. In the cross-sectional studies, Cabral et al. 2016, Gimbrone et al. 2013, and Alarcon et al. 2021, there was a lack of description of the measurement of outcomes and no explanation of the statistical analysis. Mascarenhas et al. 2021, Perez et al. 2016, and Ruiz-Patiño et al. 2022 did not describe the study subjects included in detail. In the cohort study, Steuer et al. 2016 and Martin et al. 2021 did not detail laboratory techniques used to run the genetics test. Hernandez-Pedro et al. 2019 did not describe the measurement of outcomes and gave no explanation of the statistical analysis nor did they give details on follow-up time. Cavagna et al. 2021 did not describe the characteristics of the study subjects in detail.

5. Discussion

In the present study, the prevalence of driver mutations in NSCLC in H/L patients were determined. The most common genes studied were these genes with therapy target approved in LA, e.g., *EGFR, KRAS, ALK,* and *ROS1* [12,71]. One of the most important results seen was the difference in the prevalence compared to other races and among the LA countries (Fig. 3). The LA population has a heterogeneous mix of Amerindian, African, and Caucasian ancestries with different proportions in different regions. Countries such as Mexico, Perú, and Bolivia have a higher proportion of Amerindian ancestries while regions in Argentina, Brazil, Colombia, Costa Rica, Uruguay, and Venezuela have a higher proportion of Caucasian [72]. This mixed ancestry in the H/L population together with environmental factors may explain the diversity of oncogenic driver mutation prevalence. Different studies have revealed that ancestry is related to the presence of biomark*er* mutations in H/L patients. Carrot-Zhang et al. found that there was a relationship between Native American ancestry and specific driver mutations in *EGFR, KRAS*, and *STK11* and tumor mutational burden (TMB) in 1153 lung cancer patients from Mexico and Colombia [73]. In a further analysis of these data, Cardona et al., found that the Native American

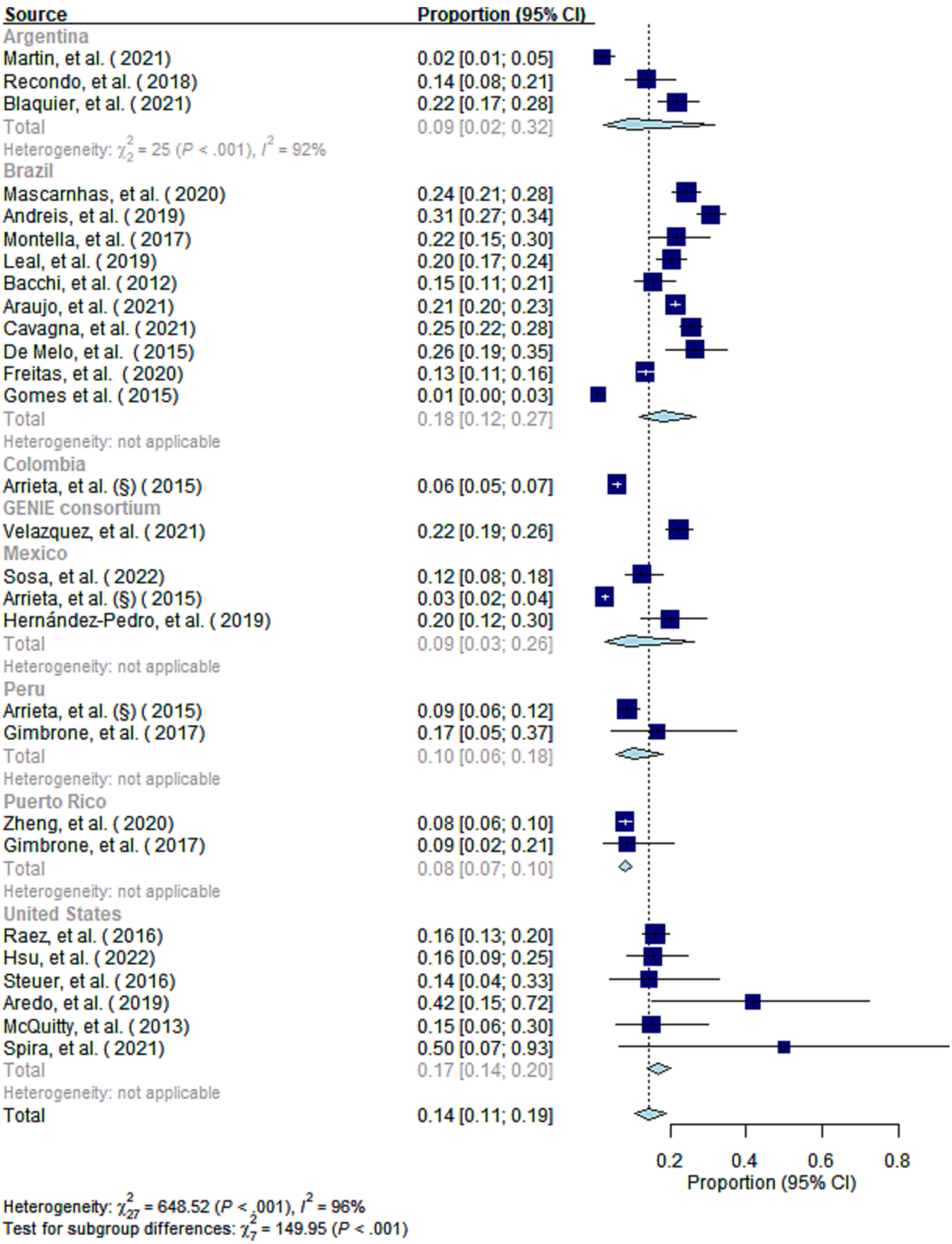


Fig. 5. Meta-analysis of *KRAS* frequency mutations.

ancestry was associated with *EGFR* mutations (L858R, del19, and other activating mutations) [74]. Gimbrone et al., detected that ancestry influenced the rate of *TP53* mutations (p 0.009) and may have influenced the rate *of EGFR, KRAS,* and *STK11* mutations in 120H/L patients [48].

EGFR mutation is one of the most frequent oncogenic drivers evaluated in NSCLC patients. The interest in this mutation is due to its prevalence and the clinical prognosis [75]. In the LA population a higher frequency of lung adenocarcinomas was found in women and never smokers with an average age of 65.4. The prevalence observed in H/L patients in this study was 23% (CI 95%; 20% – 26%). A recent *meta*-analysis estimated the prevalence of *EGFR* to be 49.1% in Asia and

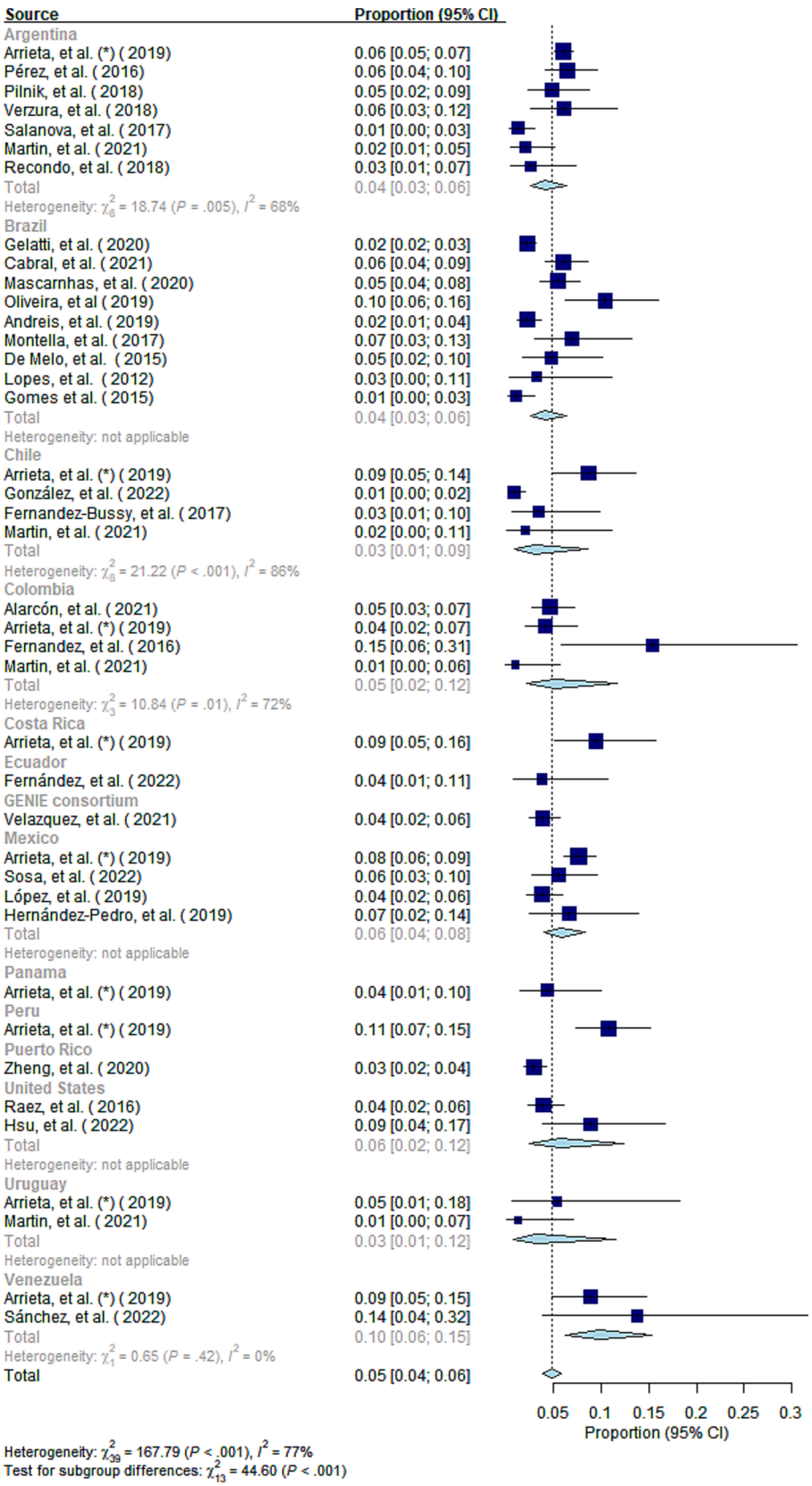


Fig. 6. Meta-analysis of *ALK* frequency mutations.

12.8% in Europe [76]. Another *meta*-analysis demonstrated a prevalence of 38.8%, 17.4%, and 17.2%, in Asian, White, and Black patients respectively [77]. A recent *meta*-analysis reported a 6% prevalence of *EGFR* in Black patients [78]. Lower *EGFR* prevalence was seen in countries with a higher proportion of Caucasians in contrast to countries with a higher proportion of Amerindian ancestries such as Mexico and Peru. Notably, the prevalence in LA changes from one country to another. (Figs. 2-3). Peru as a country has a unique genetic profile due to a high proportion of Amerindian ancestries but it also has a slightly higher Asian ancestry than other LA countries [79].

Identification of *EGFR* mutations has implications for the treatment and prognosis of NSCLC patients. Types of mutations have been divided into five categories: common mutations, uncommon or atypical mutations, EGFR exon 20 insertion, compound mutations, and resistance mutations [4]. Common mutations include the deletion of exon 19 (amino acid residues 747–750) and L858R point mutations of exon 21. These represent 80% to 90% of all *EGFR* mutations. The prevalence of common mutations also changes from race to race. In the Asian population, Exon 19 deletions are present in 49.2% of patients with lung cancer, and exon 21 L858R substitution in 41.1% while, in European patients, these are present in 48.4% and 29.9% respectively (72). In the present study, the most frequent *EGFR* gene mutations were found to be del19 and L858R. Uncommon or atypical mutations included all mutations except L858R, deletion of exon 19, and T790M mutations. The most frequently reported are G719X in exon 18 (0.9–4.8% of all EGFR mutations), exon 20 insertions (0.8–4.2%), L861X (0.5–3.5%) in exon 21, and S768I in exon 20 (0.5–2.5%) [80]. In our results, the prevalence of Exon 20 insertions was found in 1% of lung cancer patients which was consistent with other reports that also found less favorable outcomes than were found with other uncommon mutations [80]. Compound mutations have also been referred to as double, complex, or multiple in the same sample. In a recent systematic review, multiple mutations in the *EGFR* gene were identified in<1% [81]. The response rate (ORR) and the progression-free survival are different in patients with dual common and uncommon mutations treated with first-generation or second-generation TKIs [82]. Interestingly, only 70 cases with simultaneous multiple mutations were found. The most frequent multiple mutations identified were in exon 21, specifically, dual mutations in 18 cases (25.7%). Other common mutation sites included the region between exon 19 and exon 20 (14 cases, 20%) and the region between exon 20 and exon 21 (10 cases, 14.3%).

KRAS is another oncogenic driver with a different prevalence based on race. Our data shows that, in LA countries, the prevalence is 15% (CI 95%; 12–18%). This contrasts with the distribution in other races, e.g., Whites (33.38%), Blacks (27.33%), and Asians (11.75%) [9]. More than 97% of *KRAS*-mutant cases affect specifically codon 12, 13, 61, and 146 located in exon 2 and 3 [83]. In the present study, Glycine (G) to Cysteine (C) substitution at codon 12 (*KRAS* p.(G12C) was the most frequent codon variant for *KRAS* (7%). *KRAS* G12C became the first mutation to have a FDA-approved therapy directly targeting it [84]. This mutation seems to be more frequent in women and younger patients. It has been associated with poor prognosis compared to that of patients with other KRAS mutations or KRAS wild types [85]. *KRAS* G12C is more common in Whites (15.51%) than Blacks (10.31%) and Asians (3.39%) [9]. Hsu et al., reported a lower prevalence of *KRAS* G12C mutations in Asians (14.3%) versus Hispanics (42.9%) [59]. This mutation was seen in 7% of all lung cancer patients. Other studies have shown that the most commonly observed mutation in KRAS genes was G12C in former/current smokers (45%) while G12D was predominant in never smokers (46%). However, there were no significant differences in survival based on *KRAS* status, G12C mutation status, specific KRAS mutation subtypes, or other mutation preferences for downstream pathways (relate to survival) [86].

The most commonly tested fusion genes are *ALK* and *ROS1*. *ALK* was the first oncogenic driver with FDA approval (2011) in the first-line setting for patients with advanced NSCLC [4]. The most frequent fusion gene partner is EML4 in 95% of the cases. At least 90 different novel fusion gene partners have been identified in the last few years due to the increase in Next Generation Sequencing (NGS) testing [87]. *ALK* fusions are commonly found in never smoker or light smokers, younger patients, and patients with advanced-stage disease [88]. *ALK* rearrangements are typically detected in lung adenocarcinomas with acinar and solid pattern, or with cellular features of signet-ring cell carcinoma [88,89]. *ALK* prevalence found in our review was 5%, which is similar to results presented by Fan et al. in a systematic review and *meta*-analysis that saw 5% (1,178 ALK rearranged cases/ 2,0541 NSCLC patients) in different races [90]. However, in a recent article published in the United States observed a prevalence of 2.8% among 36,691 patients tested [91].

ROS 1, in turn, is a fusion gene with several partner genes. The most frequent are CD74 (38–54%), EZR (13%–24%), SDC4 (9–13%), and SLC34A2 (5–10%) [92]. *ROS1* rearrangement is more prevalent in female patients and, like ALK rearrangements, is found more frequently in patients without a history of smoking, those at more advanced stages [93], and those with adenocarcinoma that has mainly solid architecture often including cribriform features, psammoma-rich stroma, and signet-ring tumor cells [94]. A 2% prevalence of *ROS1* rearrangement was found in patients from LA. Similarly, some authors reported a prevalence of 2% with a higher prevalence in Asian patients: 2.2% (95% CI = 0.016—0.029) compared to non-Asian patients: 1.9% (95% CI: 0.012—0.027). However, no statistically significant differences were found. They also reported a lower mean age (54.5) in Asian patients compared to non-Asian patients (59). The authors suggest that women, Asians, and non-smoking patients with advanced clinical stage IV NSCLC may be at an increased risk of developing *ROS1*-positive NSCLC [95].

Comprehensive genomic profiling by NGS has made it possible to find genomic alterations in actionable and non-actionable driver mutations, co-occurring genomic alterations, and TMB calculation. Co-occurring genomic mutations with potential prognostic and predictive implications have been described in patients treated with TKIs [96,97], and TMB is associated with immune cell infiltration and response to immunotherapy [98]. In LA, a few studies using NGS in NSCLC were included. These could be explained by challenges to the implementation of molecular testing [11,12]. These studies have shown the most common genomic alterations of less tested actionable driver mutations e.g., *TP53, BRAF, MET, RET, NTRK,* and *HER-2*. Mascarenhas, et al. [29] identified single nucleotide variations (SNVs) (81.0%) as the most common genomic alterations in tissue and plasma in 513 Brazilian NSCLC patients. This was followed by copy number variations (CNVs) (49.7%), frameshift mutations (31.4%), indels (19.3%), splice site mutations (19.1%), and rearrangements/ fusions (12.5%). TP53 was the most mutated (53.6%) and co-mutated gene with EGFR (51.6%). Low TMB (<5 mutations/Mb) was found in 42.7%, intermediate TMB (5–9 mutations/Mb) in 32.4%, and high TMB was found in 5.5% of the samples (≥10 mutations/Mb). High TMB was especially frequent among *TP53, STK11, PIK3CA,* and *NTRK* mutant samples while low TMB was associated with *ALK* and *ROS1*. Hernandez-Pedro et al. [45] also noted that there was a high prevalence of *TP53* mutations (47.8%) in 90 Mexican patients and were frequently co-mutated with *EGFR, MET, KRAS*, and *PDGFRA genes* but not with *HNF1, APC,* and *HER2*. In a recent study published by Heredia et al. [99], co-occurring genomic alterations were detected by NGS in 111 patients from Mexico, Colombia, and Peru with advanced NSCLC *EGFR*-mutant. In the results, they found that the most frequent co-occurring genomic alterations were *TP53* mutations (64.9 %), *CDKN2AB* alterations (13.6 %), *BRCA2* (13.6 %), and *PTEN* (12.7 %) mutations. Patients with a *TP53* mutation and ≥ 3 concurrent genomic alterations had worse outcomes.

Mutations, deletions, fusions, and amplifications that have been seen in NSCLC are molecular alterations observed in *BRAF* gene [4]. The prevalence accounts for 3–4% of lung adenocarcinoma, and occurs most frequently in women, never-smokers, and aggressive histological types including a micropapillary pattern [100]. BRAF mutation is divided into *BRAF* V600 mutation and *BRAF* non-V600 mutated cases. Current

approved targeted drugs were specifically designed around the structure of *BRAF* V600E [100]. In our results, the frequency of the V600E mutation among all *BRAF* mutations was found to range from 50 to 68.4% and represented the majority of mutations in this gene in the L/H population [23,29].

Different molecular dysregulation can occur in the *MET* gene, e.g., gene amplification, point mutations, fusions, exon 14 skipping mutations, or protein overexpression. *MET* exon 14 skipping mutation (METex14) is the first subtype of *MET* alterations approved as targeted therapy [101]. Increases in *MET* copy number are also another molecular alteration used in target therapy [102]. METex14 mutations are found in females with a median age at diagnosis of 72.5, smoking history, and adenosquamous cell carcinoma or pleomorphic carcinoma [101]. The frequency of METex14 in a Caucasian population is 3 to 4% while in an Asian one it is 0.9% [103,104]. In an H/L population, the presence of *MET* alterations has been reported in seven studies with a prevalence of 3% (CI 95%; 1–7%) of *MET* alterations. However, the frequency of METex14 is unknown. *MET* alterations and mutations were studied in different patient populations across multiple regions. Hernandez-Pedro et al. [45] detected MET alterations in 20% of Mexican patients associated with factors such as female gender, pulmonary effusion, and TP53 mutations. Zheng et al. [52] observed MET amplification in 10.5% of Puerto Rican patients. Mascarenhas et al. [29] found MET alterations in 4.7% of 513 Brazilian patients tested using NGS. Martin et al. [68] discovered MET mutations in 1.4% of patients from Argentina, Colombia, Chile, and Uruguay. Among H/L in the United States, three studies focused on testing *MET*. Raez et al. [55] reported a 27% prevalence of c-MET in H/L patients from Florida. Hsu et al. [59] identified MET mutations in 1.1% (1 out of 90) of H/L patients from California. McQuitty et al. [53] did not find any MET mutations among a population of 40H/L patients in Texas.

Three *HER2* activating mechanisms that have been described in NSCLC are gene mutation (1%-4%), gene amplification (2%-5%), and protein overexpression (2%-30%) [105]. *HER2* mutations and amplifications have been associated with female sex, Asian ethnicity, non-smoking status, and moderately to poorly differentiated adenocarcinoma. *HER2* mutation and number increases are the molecular alterations with target therapy [102]. The exon 20 insertion is the most common mutation (96%) [105]. In the Mexican population, Hérnandez-Pedro et al. [45], found 11.1% *HER2* mutations. I655V (exon 17) was detected at a high frequency. In Brazil, 4.9% was seen [29]; in Puerto Rico, 5.8% [52]; in H/L patients from California, 5.6%; and in GENIE database, 6.4% [65].

RET and *NTRK* are gene fusions with fewer target therapies. Different *RET* molecular alterations e.g., mutations (39%), fusions (31%), and amplifications (25%) have been seen in different tumors [106]. *RET* fusions are present in 1% to 2% of lung adenocarcinoma patients that are mainly $\leq$ 60 years of age, never smokers and whose disease is advanced [107]. In LA, two studies from Brazil found RET alterations in 2.4 to 3% (43,91). In the GENIE database, *RET* fusion was detected in 1.5% of H/L patients [65]. Raez et al. [55] did not detect *RET* in 122H/L patients from Florida. NTRK, in turn, is present in about 0.1 to 0.3 % of NSCLC [108]. *NTRK* fusions have mostly been described in middle-aged non-smokers or never-smokers [109]. Mejia et al., detected *NTRK* in 0.8% of Colombians using IHC and RNA-seq [40]. Mascarenhas, et al. [29] found *NTRK* rearrangements in 0.6% and Hsu et al. [59] found them in 1.1 % (1/90) of H/L patients from California.

The presence of molecular alterations in actionable genes may also present an acquired resistance mechanism to TKI therapy. Three acquired resistance mechanisms have been described: target gene modification, alternative pathway activation, and histological or phenotypic transformation [110]. Molecular alterations in targetable genes after TKI therapy have been identified in the LA population [111–113] After 34H/L patients progressed to Erlotinib as first- line treatment, they were re-biopsied and the molecular profile showed *EGFR* T790M mutation in 47.1% of these patients, PI3K mutations in 14.7%, *EGFR* amplification in 14.7%, *KRAS* mutation in 5.9%, *MET* amplification in 8.8%, HER2 alterations in 5.8% (deletions/insertions in exon 20), and small cell lung cancer transformation in 2.9% [111]. In another study, 94H/L patients progressed to Osimertinib as first- line treatment. The NGS were evaluated in liquid biopsy or tissue biopsy of a progressive tumor lesion. They found alterations in actionable and non-actionable genes. The most common genomic alterations were in *EGFR* (35.4%) (T90M loss 15.4%, mutations 11.6%, amplifications 8.4%), *TP53* mutations (29.2%), *HER-2* amplifications (6.2%), *KRAS* mutation (4.8%), *BRAF* alteration (4.8%) (mutation 3.4% and fusion 1.4%), *PIK3CA* mutation (3.4%), *MET* alteration (3.3%) (mutations 2.7% and amplifications 0.6%), and *RET* fusion (2.7%). They also found that patients with three or more mutations on actionable genes at the time of progression had a significantly improved median post-progression survival compared with those with a low number of co-mutations [112]. Recently, co-mutations have been more frequently found in Colombian patients including *TP53, RAS*, and *RB1* in the cohort of patients with intrinsic resistance to first-line Osimertinib plus high levels AXL mRNA, and low levels of BIM mRNA, T790M de novo, *EGFR* p.L858R presence, and a high TMB [113].

Our study has several limitations. First, the clinical information on patients with oncogenic driver mutations could not be collected in a large percentage of studies. Second, LA countries without information or countries with few studies and small sample sizes may have underestimated or overestimated the prevalence. Third, it was noted that many authors belonged to different LA network consortiums that shared the same patient database for different publications. Therefore, in this case an effort was made to identify the most recent article with the highest number of patients and amount of information to prevent a possible bias. In addition, different publications reported higher numbers of patients from certain populations, and this may have biased the true prevalence in countries with lower numbers of patients analyzed and thus skewed the true frequencies. For example, overall prevalence in H/L may have a bias due to the fact that the Latino population in some regions in the USA is more representative of Mexico and Central America. Finally, a few studies have been using NGS in NSCLC. Therefore, the prevalence of less frequently actionable mutations (*MET, RET, NTRK,* and *HER-2*) may have caused a bias in the present study.

6. Conclusions

In general, the prevalence of driver mutations in H/L patients e.g., EGFR and KRAS, differs from what has been reported in Asians and Europeans. Countries with a high proportion of Amerindian ancestries show a higher prevalence of EGFR in contrast to countries with a high proportion of Caucasians. Lack of information on some countries or studies with small sample sizes affect the real prevalence data for the region. Countries in LA have several challenges with respect to the implementation of and access to molecular testing in NSCLC. This is particularly true in the case of testing the less frequently actionable mutations. Therefore, testing LA patients with NGS at different stages and enrollment of H/L patients in clinical trials will provide a real prevalence of actionable driver mutations and with their specific molecular alteration. In addition, it is important design more studies in H/L patients that assess the ancestry and studies with specify the molecular alteration and gene location due to their impact on the treatment and prognosis.

CRediT authorship contribution statement

Rafael Parra-Medina: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Juan Pablo Castañeda-González:** Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. **Luisa Montoya:** Data curation, Formal

analysis, Investigation, Methodology. **María Paula Gómez-Gómez:** Data curation, Formal analysis, Investigation, Methodology. **Daniel Clavijo Cabezas:** Data curation, Formal analysis, Investigation, Methodology. **Merideidy Plazas Vargas:** Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Validation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Rafael Parra-Medina reports writing assistance was provided by University Foundation of Health Sciences. Rafael Parra-Medina reports a relationship with University Foundation of Health Sciences that includes: employment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.107378.

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