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Clinical and CT patterns to predict EGFR mutation in patients with non-small cell lung cancer: A systematic literature review and meta-analysis

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HIGHLIGHTS

- GGO, air bronchogram, vascular convergence, pleural retraction, and spiculated margins, are risk factors for EGFR mutation.
- Early disease stage, female gender and non-smoking status are risk factors for EGFR mutation.
- Cavitation is a protective factor for EGFR mutation.

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ABSTRACT

Purpose: This study aims to determine if the presence of specific clinical and computed tomography (CT) patterns are associated with epidermal growth factor receptor (EGFR) mutation in patients with non-small cell lung cancer.

Methods: A systematic literature review and meta-analysis was carried out in 6 databases between January 2002 and July 2021. The relationship between clinical and CT patterns to detect EGFR mutation was measured and pooled using odds ratios (OR). These results were used to build several mathematical models to predict EGFR mutation.

Results: 34 retrospective diagnostic accuracy studies met the inclusion and exclusion criteria. The results showed that ground-glass opacities (GGO) have an OR of 1.86 (95%CI 1.34 −2.57), air bronchogram OR 1.60 (95%CI 1.38 – 1.85), vascular convergence OR 1.39 (95%CI 1.12 – 1.74), pleural retraction OR 1.99 (95%CI 1.72 – 2.31), spiculation OR 1.42 (95%CI 1.19 – 1.70), cavitation OR 0.70 (95%CI 0.57 – 0.86), early disease stage OR 1.58 (95%CI 1.14 – 2.18), non-smoker status OR 2.79 (95%CI 2.34 – 3.31), female gender OR 2.33 (95%CI 1.97 – 2.75). A mathematical model was built, including all clinical and CT patterns assessed, showing an area under the curve (AUC) of 0.81.

Conclusions: GGO, air bronchogram, vascular convergence, pleural retraction, spiculated margins, early disease stage, female gender, and non-smoking status are significant risk factors for EGFR mutation. At the same time, cavitation is a protective factor for EGFR mutation. The mathematical model built acts as a good predictor for EGFR mutation in patients with lung adenocarcinoma.

Abbreviations: NSCLC, non-small cell lung carcinoma; EGFR, epidermal growth factor; KRAS, Kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase mutation; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitors; GGO, Ground glass opacities; OR, Odds ratios; CT, computed tomography; AUC, area under the curve; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis; TP, True Positive; TN, True Negative; FP, False positives; FN, False negatives; ROC, Receiver Operating Characteristics; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2.

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1. Introduction

Lung cancer is a frequent non-hematological malignancy that represents 18% of all neoplasms, affecting mainly men with a median age of 70 years, and representing the leading cause of cancer-related mortality in 2020, with 1.8 million deaths [1,2]. Lung neoplasms are traditionally divided into non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma [3]. Approximately 85% of lung neoplasms are NSCLC, comprising three main subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, which can be affected by mutations in epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), and anaplastic lymphoma kinase mutation (ALK) [3–5]. The detection of EGFR mutation in patients with NSCLC has gained relevance in the last years due to the development of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI), which have shown better outcomes than chemotherapy in selected patients [6–9].

In some scenarios, it is not feasible to acquire adequate tissue for EGFR mutation analysis due to patients' inoperability, small tissue in the biopsy, or sampling artifacts [9]. To deal with this issue, certain predictor factors for EGFR mutation such, as non-smoking status, Asian ethnicity, and female gender, have been proposed; nonetheless, these are not enough to guide the treatment [10,11]. For that reason, the association between chest computed tomography (CT) patterns and EGFR mutation in NSCLC has been a topic of active research in the last years due to its potential to predict the therapeutic efficacy of EGFR TKI in patients whose tissue samples could not be obtained successfully. However, the evidence supporting CT patterns associated with EGFR mutation is contradictory, indicating the presence of a knowledge gap [12–14]. Therefore, this systematic literature review and meta-analysis aims to determine if clinical and chest CT patterns such as ground-glass opacities (GGO), air bronchogram, vascular convergence, pleural retraction, spiculated margins, cavitation, early disease stage, female gender, and non-smoker status are risk factors for EGFR mutation in patients with NSCLC.

2. Material and methods

This systematic literature review and meta-analysis was performed based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) methodology.

2.1. Eligibility criteria

We searched for articles published in journals between January 2002 and July 2021. The lower margin of the search dates was set this way because 2002 was when EGFR mutation was first discovered in a subset of lung cancers [15]; therefore, it is not expected to have articles seeking EFGR mutation in lung cancer before that date.

The inclusion criteria were cross-sectional studies, comparative studies, retrospective studies, randomized and non-randomized clinical trials, articles published in English, Spanish or French, performed in patients all around the world, either hospitalized or ambulatory with a diagnosis of NSCLC presenting a disease progression at any stage, no age or gender predilection were set. The intervention performed must be CT, in which the image patterns had to be characterized and then compared against biopsy or cytology to detect EGFR mutation.

We excluded articles that did not provide information regarding the True Positive (TP), True Negative (TN), False Positives (FP), and False Negatives (FN) of the different clinical and CT patterns to diagnose EGFR mutation, papers with a high risk of bias based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool and articles that assessed patients who received radiotherapy, chemotherapy, biological therapy, or surgery before CT.

2.2. Sources of information

The literature search was performed in several databases, including the Medical Literature Analysis and Retrieval System Online (MEDLINE), the Excerpta Medica database (EMBASE), SCOPUS, The Virtual Health Library (VHL), and the African Index Medicus. These databases were chosen because they summarize the most important publications in different regions worldwide. Also, a search in google scholar was carried out to identify articles not published in major databases. Secondary searching methods were applied, such as the snowballing technique, in which the references of the articles included in the meta-analysis were reviewed to identify more papers. Additionally, we decided to perform a hand search in three major radiology journals (Radiology, European Journal of Radiology, American Journal of Roentgenology); we have agreed to hand search these journals because they were not shown substantially in the database search, and they have a high impact factor in radiology.

2.3. Search

Mesh terms, keywords, and synonyms were used to guarantee that no articles were missed. The search strategy applied was: (((Epidermal growth factor receptor) OR EGFR) OR epidermal growth factor receptor mutation) AND (((((Carcinoma, Non-Small-Cell Lung) OR NSCLC) OR non-small cell lung cancer) OR lung adenocarcinoma) OR lung cancer) OR lung carcinoma) AND (((Tomography, X-Ray Computed) OR Tomography, Spiral Computed) OR computed tomography) OR CT) AND ((Biopsy) OR cytology).

2.4. Study selection

All the articles found through the search strategy were blindly uploaded to Mendeley; subsequently, the duplicates were removed using the Mendeley duplicate detection tool [16]. When the duplicates were removed, the screening process was performed based on title and abstract. The pre-selected articles were assessed for inclusion and exclusion criteria using prespecified questions; then, the articles that met the selection criteria were read completely and subjected to a quality assessment. Two authors carried out the entire process independently, and if disagreements were presented, these were resolved by consensus. If two articles used the same cohort of patients, the authors would only include the study with the largest sample size to avoid enrolling the same individuals twice.

2.5. Data extraction and missing data

All five authors extracted the information from each article, registering it in a qualitative data extraction table which contained the author's names, year of publication, country of publication, study type, number of patients included, the mean age of the participants, the NSCLC histopathological subtype, the disease stage of the participants, the index test (CT), the reference standard used (biopsy or cytology), and the CT patterns described.

Additionally, a quantitative data extraction table was developed to register the TP, FP, FN, and TN of the different clinical and CT patterns when compared to biopsy or cytology to detect EGFR mutation.

When important information was missing in any article selected to be included, the paper's corresponding author was contacted to provide the missing data. Finally, the information was left empty if the corresponding author could not be reached.

Two authors reviewed all the information extracted in the qualitative and quantitative data extraction table to guarantee that no typos or inaccurate data were included. In case of disagreements, these were resolved by consensus.

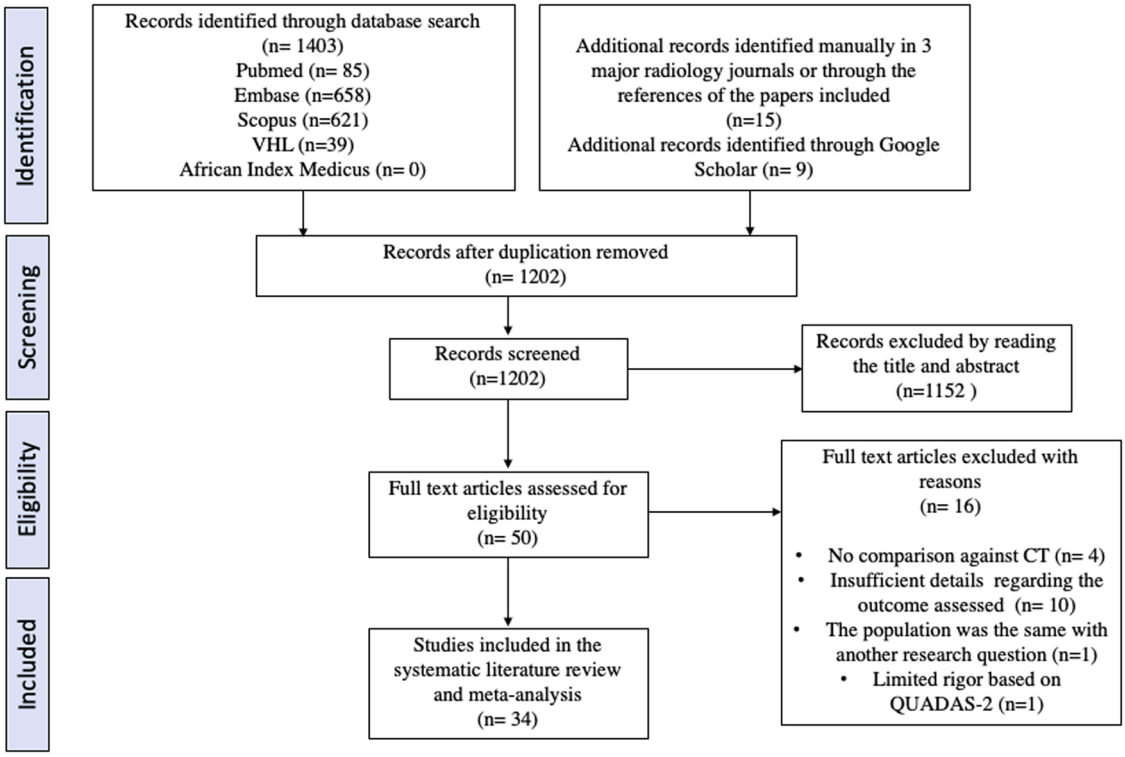

Fig. 1. PRISMA flow diagram, CT: Computed tomography.

2.6. Outcomes

The primary outcome was to evaluate the association of specific clinical characteristics (Non-smoker status, female gender, early disease stage) and chest CT patterns (GGO, air bronchogram, pleural retraction, vascular convergence, spiculation, and cavitation) with EGFR mutation determined by biopsy or cytology in patients with NSCLC.

The secondary outcome was to build several mathematical models, including these CT and clinical patterns, to predict the presence of EGFR mutation in patients with NSCLC.

2.7. Quality assessment

Due to the nature of our research question, all the articles included in the systematic literature review and meta-analysis were of diagnostic accuracy; therefore, the QUADAS-2 tool for diagnostic studies was used (https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/). Only the studies that presented a low or acceptable risk of bias with little concern regarding applicability were considered for inclusion.

The QUADAS-2 tool is a checklist that has four domains, distributed in the following way: 1. "Patient selection," 2. "Index test," 3. "Reference Standard," 4. "Flow and timing." Each domain is evaluated regarding bias, and the first three domains are additionally assessed regarding their applicability. Two independent authors performed the quality assessment of each article, and if disagreements were presented, these were resolved by consensus. The "traffic light" plot for QUADAS-2 was created using the Robvis tool [17].

2.8. Effect measures

Because the primary outcome was categorical, each article's TP, FP, FN, and TN values were used to calculate odds ratios (OR), which would then be pooled in a quantitative synthesis. The secondary outcomes were expressed in relative frequencies.

2.9. Statistical analysis

All statistical analyses were performed using STATA 17 (StataCorp LLC, College Station, TX).

The statistical heterogeneity of the studies included was explored for each clinical and CT pattern using Cochran's Q test and I2 test. If the Cochran's Q test was < 0.05, we considered that the meta-analysis presented a high degree of heterogeneity. If the I2 test value was $<$ 50%, we used a fixed-effect model; nevertheless, we used a random-effect model if the I2 test value was $>$ 50% [18]. If discrepancies between the Cochran's Q test and the I2 tests were presented, a random effect model was chosen.

A forest plot based on OR was performed for each clinical and CT pattern to pool the effects of all the articles. Publication bias was assessed with the egger's test for each forest plot; we considered positive for publication bias if the p-value was < 0.05.

A sensitivity analysis was carried out for each forest plot to evaluate the robustness of the results.

The TP, FP, FN, TN of the CT patterns and clinical characteristics with statistically significant results were used to build several mathematical models using logistic regression. Based on these models, we created multiple Receiver Operating Characteristics (ROC) curves, from which the Area Under the Curve (AUC) was calculated.

3. Results

3.1. Search results

The search provided a total of 1202 non-duplicated citations screened based on title and abstract, from which 1152 did not match the research question. Leaving a total of 50 articles that were read completely, identifying that 4 did not compare EGFR status against CT, 10 provided insufficient details to calculate the OR, 1 used the same population of an already included article but with another research question, and 1 had limited rigor based on QUADAS-2 tool, leaving a total of 34 papers that were included in the systematic literature review

Table 1
Qualitative synthesis of the articles included.

Gender	
Male	4501/10355 patients
Female	4464/10355 patients
Not described	1390/10355 patients
EGFR status	
EGFR positive	5046/10355 patients
EGFR negative	5309/10355 patients
Smoking status	
Smoker	3244/10355 patients
Never smoked	4970/10355 patients
Not described	2141/10355 patients
Country	
China	6254/10355 patients
Korea	2046/10355 patients
Japan	926/10355 patients
Italy	353/10355 patients
Taiwan	311/10355 patients
Germany	282/10355 patients
Canada	119/10355 patients
United States	64/10355 patients
Disease stage	
Stage I	2507/10355 patients
Stage II	562/10355 patients
Stage III	849/10355 patients
Stage IV	1396/10355 patients
Not described	5041/10355 patients
Histological subtype	
Adenocarcinoma	10079/10355 patients
Squamous-cell carcinoma	139/10355 patients
Large-cell carcinoma	2/10355 patients
Not clearly described	135/10355 patients
CT pattern evaluated	
GGO	6893/10355 patients
Air bronchogram	7630/10355 patients
Vascular convergence	1716/10355 patients
Pleural retraction	3471/10355 patients
Spiculation	5871/10355 patients
Cavitation	4891/10355 patients
Sample acquisition method	
Biopsy	10073/10355 patients
Cytology	282/10355 patients
EGFR mutation analysis test	
PCR	8922/10355 patients
FISH	198/10355 patients
Immunohistochemistry	214/10355 patients
Other	850/10355 patients
Not described	171/10355 patients
Interpretation of the images	
Radiologists or clinicians with experience	8246/10355 patients
Machine learning tools	2109/10355 patients

and meta-analysis. These results are better schematized in Fig. 1.

3.2. Summary of studies

A total of 34 retrospective diagnostic accuracy studies were included in the final analysis [9,12,19–50]. These articles assessed 10355 individuals; the sample size fluctuated between 64 and 864 patients per study. The mean age of the individuals ranged between 56 and 68 years. The qualitative synthesis of the articles included is presented in Table 1. If readers would like to access the crude data, this is attached in Appendix A.

3.3. Risk of bias within studies

All the studies included in the analysis showed a low or acceptable risk of bias according to the QUADAS-2 tool. The findings are presented in Fig. 2. If readers want to access the quality assessment of each article, this is attached in Appendix B.

3.4. GGO and EGFR mutation

A total of 6893 patients from 23 different studies were pooled to evaluate the association between GGO and EGFR mutation. The Cochrane Q test p-value was = 0.000, and the I2 value was = 80.3%; based on these results, we considered high heterogeneity in the data; therefore, a random effect model was performed. The overall effect showed an OR of 1.86 (95% CI 1.34 −2.57) (Fig. 3).

3.5. Air bronchogram and EGFR mutation

7630 patients from 27 different studies were pooled to evaluate the association between air bronchogram and EGFR mutation. The Cochrane Q test p-value was = 0.007, and the I2 value was = 44.7%; therefore, we considered a moderate heterogeneity in the data; for which a random effect model was performed. The overall effect showed an OR of 1.60 (95% CI 1.38 – 1.85) (Fig. 4).

3.6. Vascular convergence and EGFR mutation

1716 patients from 6 different studies were pooled to evaluate the association between vascular convergence and EGFR mutation. The Cochrane Q test p-value was = 0.845, and the I2 value was = 0%. Based on these results, we considered low heterogeneity in the data; therefore, a fixed-effect model was carried out. The overall effect showed an OR of 1.39 (95% CI 1.12 – 1.74) (Fig. 5).

3.7. Pleural retraction and EGFR mutation

3471 patients from 11 different studies were pooled to evaluate the association between pleural retraction and EGFR mutation. The Cochrane Q test p-value was= 0.498, and the I2 value was = 0%; therefore, we considered low heterogeneity in the data, for which a fixed-effect model was carried out. The overall effect showed an OR of 1.99 (95% CI 1.72 – 2.31) (Fig. 6).

3.8. Spiculation and EGFR mutation

A total of 5871 patients from 21 different studies were pooled to evaluate the association between spiculated margins and EGFR mutation. The Cochrane Q test p-value was= 0.004, and the I2 value was = 51.2%. Based on these results, we considered moderate-high

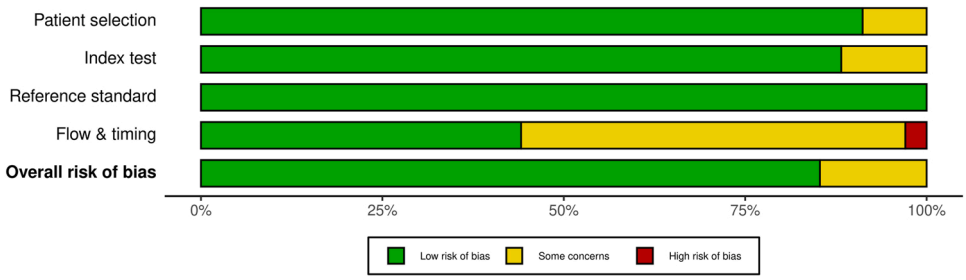

Fig. 2. Quality assessment of all the articles included in the meta-analysis.

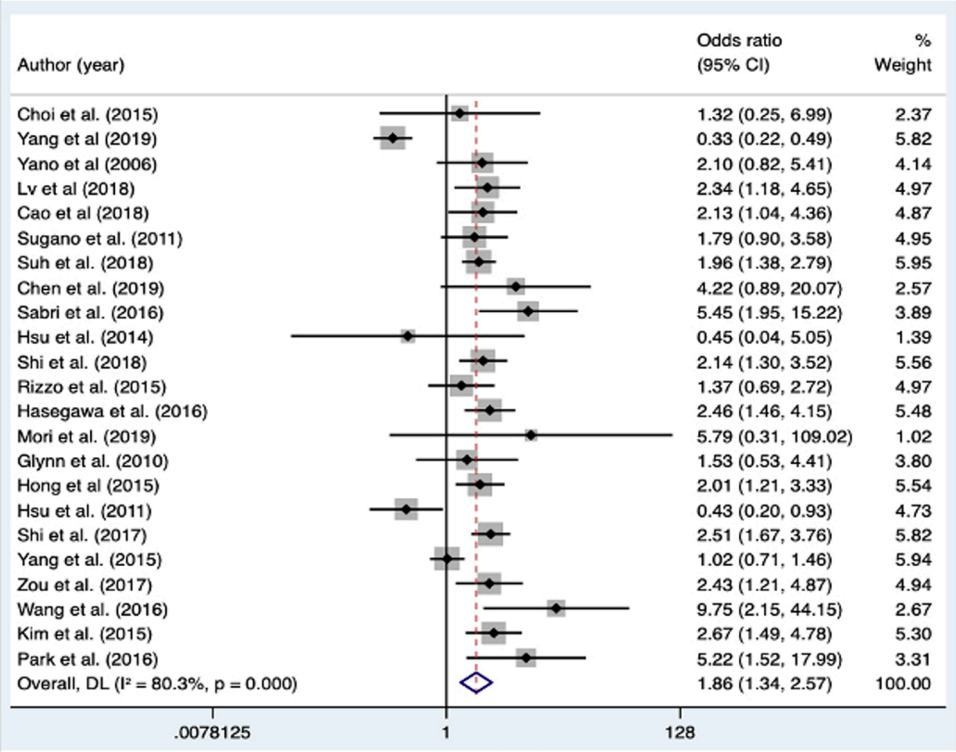

Fig. 3. Forest plot for GGO and EGFR mutation.

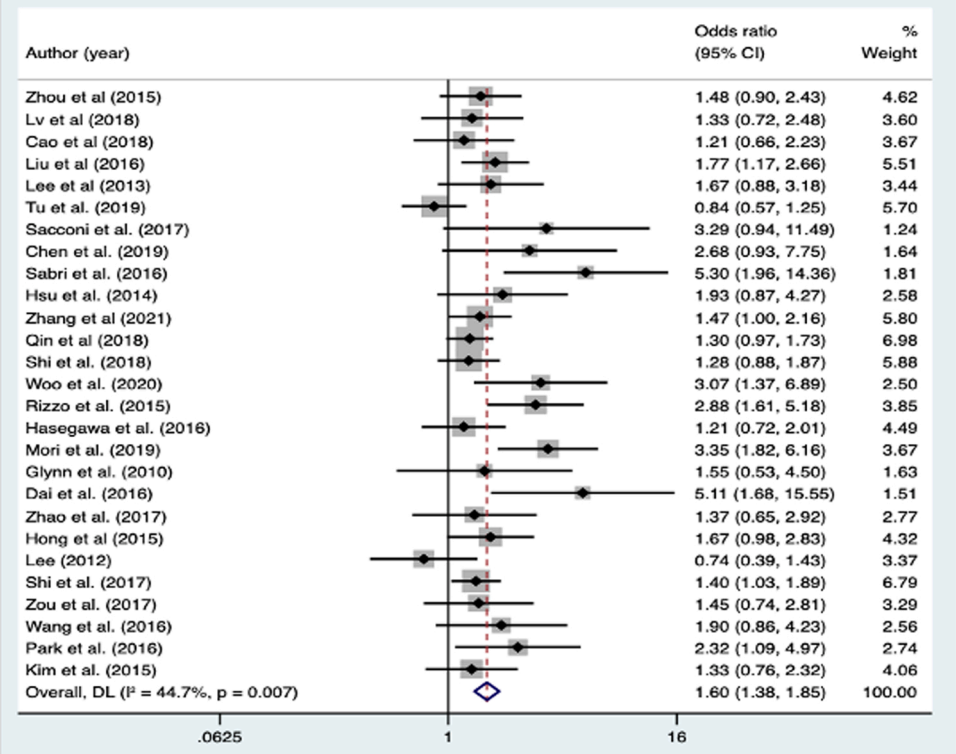

Fig. 4. Forest plot for air bronchogram and EGFR mutation.

heterogeneity in the data; therefore, a random effect model was carried out. The overall effect showed an OR of 1.42 (95% CI 1.19 – 1.70) (Fig. 7).

3.9. Cavitation and EGFR mutation

4891 patients from 15 different studies were pooled to evaluate the association between tumor cavitation and EGFR mutation. The

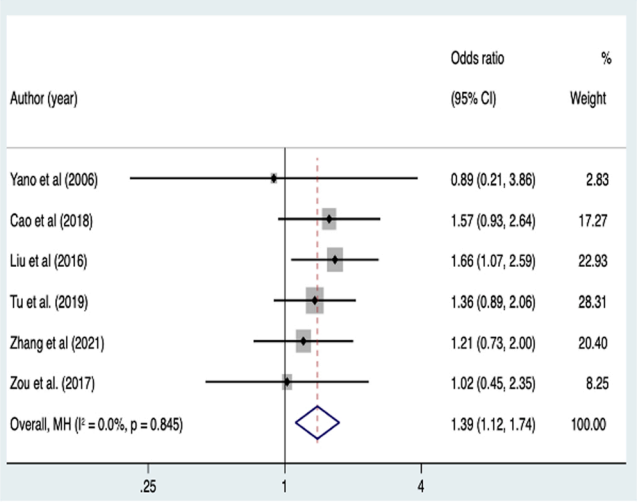

Fig. 5. Forest plot for vascular convergence and EGFR mutation.

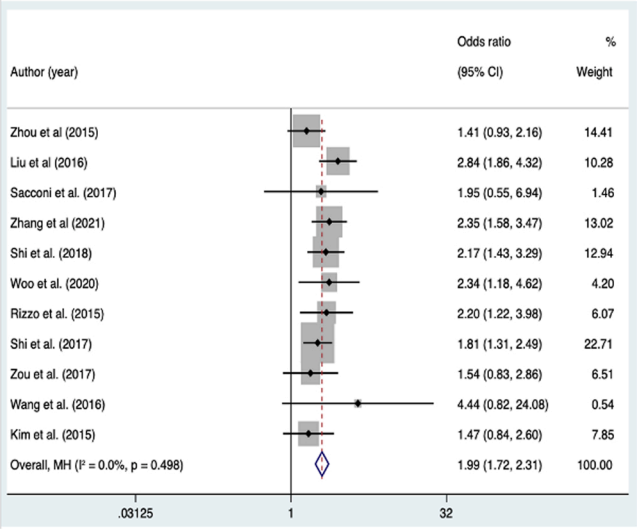

Fig. 6. Forest plot for pleural retraction and EGFR mutation.

Cochrane Q test p-value was= 0.759, and the I2 value was = 0%. Based on these results, we considered low heterogeneity in the data; therefore, a fixed-effect model was carried out. The overall effect showed an OR of 0.70 (95% CI 0.57 – 0.86) (Fig. 8).

3.10. Early disease stage and EGFR mutation

The disease stage was classified categorically as early-stage (I and II) and late-stage (III and IV). We pooled 2494 patients from 10 different studies to evaluate the association between early disease stage and EGFR mutation. The Cochrane Q test p-value was = 0.017 and the I2 value was = 55.2%. Based on these results, we considered moderate-high heterogeneity in the data; therefore, a random effect model was carried out. The overall effect showed an OR of 1.58 (95% CI 1.14 – 2.18) (Fig. 9).

3.11. Non-smoker status and EGFR mutation

8214 patients from 27 different studies were pooled to evaluate the association between non-smoker status and EGFR mutation. The Cochrane Q test p-value was = 0.000 and the I2 value was = 64.6%. Based on these results, we considered moderate-high heterogeneity in the data; therefore, a random effect model was carried out. The overall effect showed an OR of 2.79 (95% CI 2.34 – 3.31) (Fig. 10).

3.12. Female gender and EGFR mutation

8965 patients from 31 different studies were pooled to evaluate the association between female gender and EGFR mutation. The Cochrane Q test p-value was= 0.000 and the I2 value was = 67.7%. Based on these results, we considered moderate-high heterogeneity in the data; therefore, a random effect model was carried out. The overall effect showed an OR of 2.33 (95% CI 1.97 – 2.75) (Fig. 11).

3.13. Sensitivity analysis

Sensitivity analysis was performed for all the forest plots, showing that the overall effect did not cross over the null effect value at any moment, which indicates robustness of all the results. All the sensitivity analysis plots are shown in Appendix C.

3.14. Publication bias

Publication bias was assessed for all forest plots using the egger's test, which showed statistically significant results for the association between air bronchogram and EGFR mutation. Therefore, we considered publication bias, for which a funnel plot was performed, suggesting a lack of small studies with negative effects. The results of the egger's test are better depicted in Table 2.

3.15. Secondary outcomes

All the clinical and CT characteristics assessed in this meta-analysis were used to develop 9 mathematical models to predict EGFR mutation. We performed a model including exclusively clinical factors such as female gender + non-smoker status + early disease stage, which showed an AUC of 0.63; however, when all the clinical and CT patterns assessed were added to the model, the AUC rises to 0.81 (Table 3). The ROC curve prediction for EGFR mutation based on all clinical and CT patterns assessed, is shown in Fig. 12.

4. Discussion

This study aimed to identify the clinical and CT characteristics associated with EGFR mutation in patients with NSCLC, to develop a predictive model. We found that GGO, air bronchogram, vascular convergence, pleural retraction, non-smoker status, and female gender were significant risk factors for EGFR mutation in patients with lung adenocarcinoma, which is supported by previous literature [13]. However, this study showed results that have not been reported previously in other meta-analyses, such as the protective effects of cavitation for EGFR mutation and the association between spiculated margins and early disease stage with EGFR mutation. These discrepancies may be due to a lack of statistical power in previously published studies. This meta-analysis also showed that air bronchogram, spiculated margins, and GGO represents the most frequent CT patterns associated with lung adenocarcinoma.

Mathematical models expressed as ROC curves involving CT and clinical characteristics to detect EGFR mutation have been published previously. Several authors have described models that showed an AUC ranging from 0.87 to 0.68 [9,13,20,25,29,34,42]. Our meta-analysis found an AUC of 0.81 when combining all the clinical and CT patterns assessed, making this model a good predictor for EGFR mutation and subsequently a determinant for EGFR-TKI response. Some studies have shown that radiomic features can be useful to predict EGFR mutation; however, radiomic data combined with morphological characteristics have demonstrated to improve the predictive value just a little; therefore, this area continues to be an active research topic [9,51].

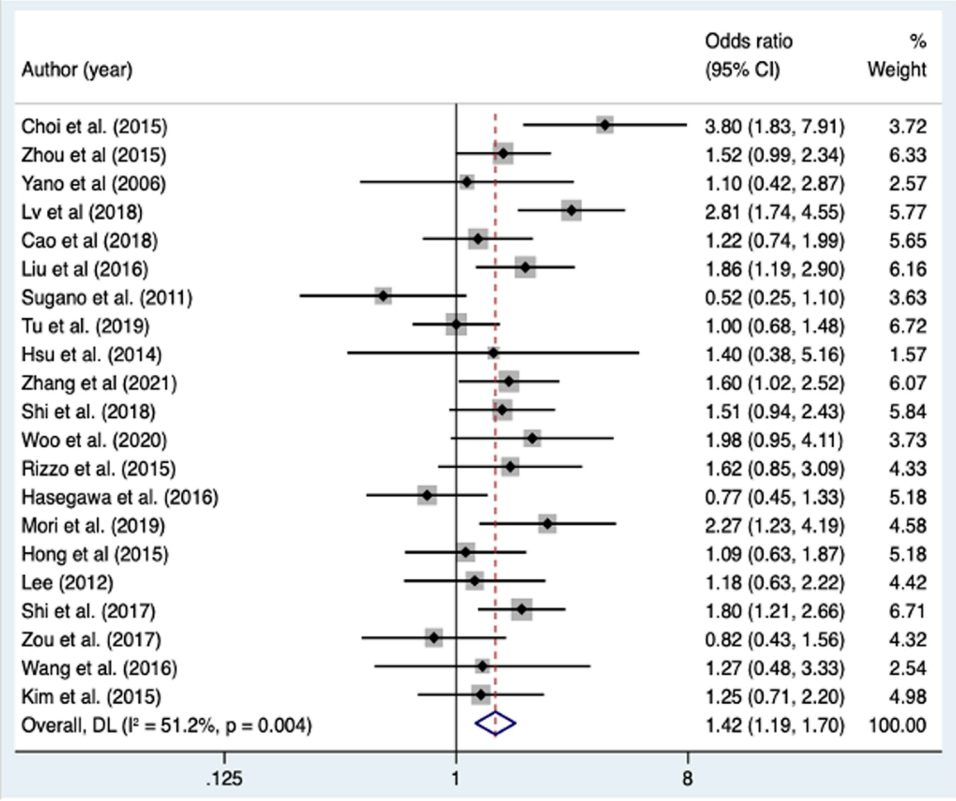

Fig. 7. Forest plot for spiculated margins and EGFR mutation.

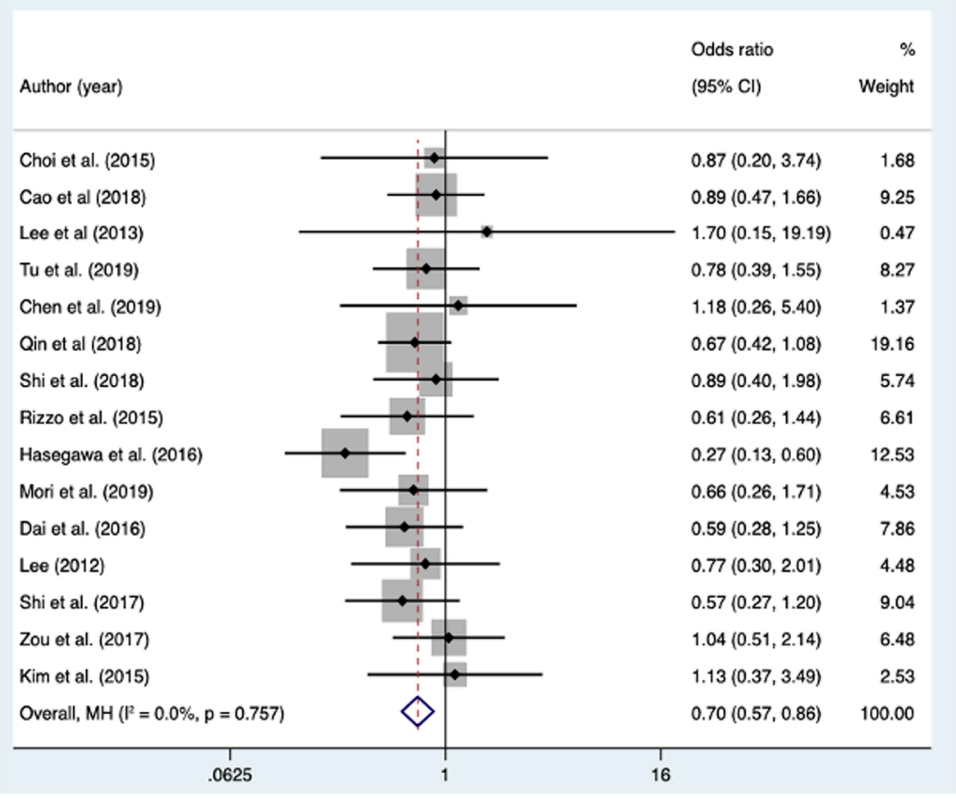

Fig. 8. Forest plot for tumor cavitation and EGFR mutation.

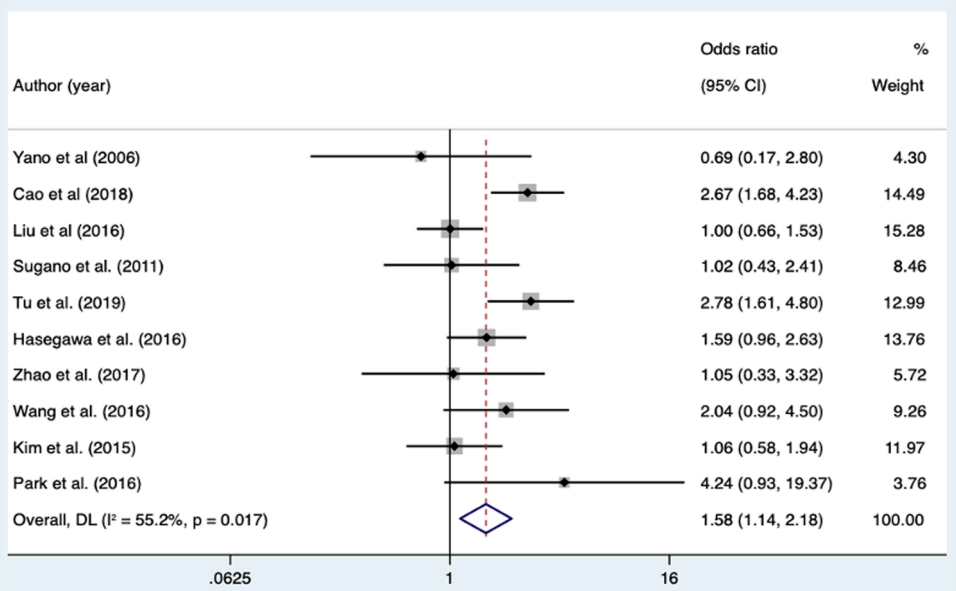

Fig. 9. Forest plot for early disease stage and EGFR mutation.

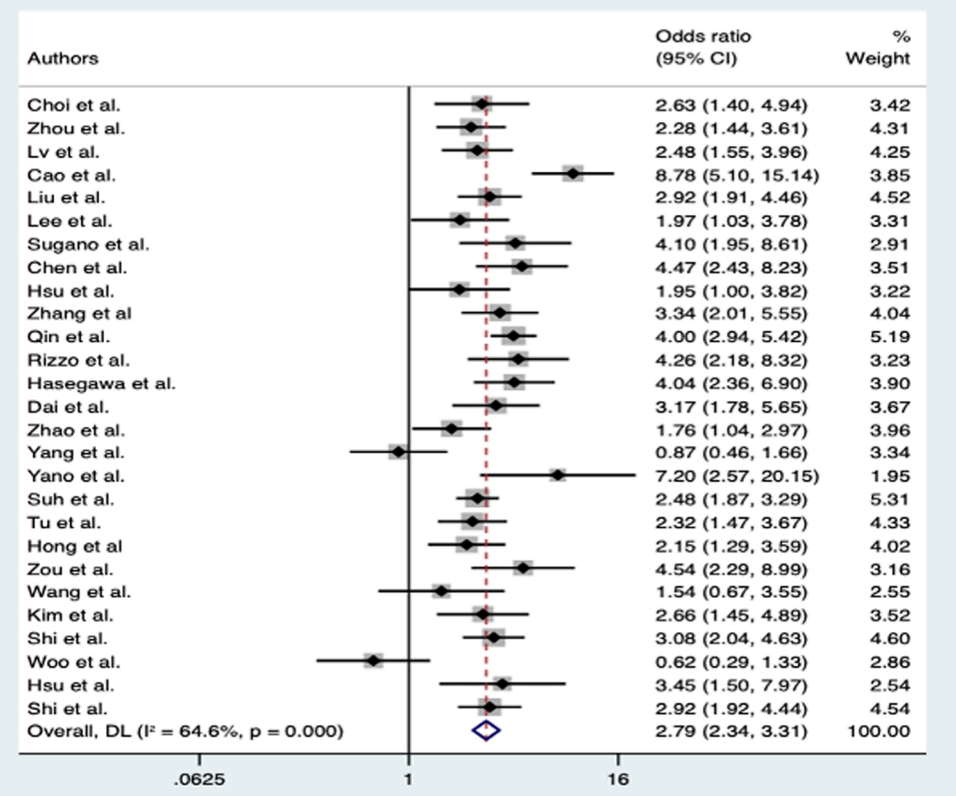

Fig. 10. Forest plot for non-smoker status and EGFR mutation.

The likelihood of having EGFR mutation also varies depending on the histopathological subtype of the NSCLC tumor. For example, Song et al. described that adenocarcinomas with micropapillary or lepidic predominance were more prone to EGFR mutation [52]. Zhang et al. published that the presence of EGFR mutation was correlated with acinar predominant adenocarcinomas [53]. On the other hand, Sun et al. showed that papillary predominant adenocarcinomas were more frequently associated with EGFR mutation [54].

All EGFR mutation subtypes do not show the same radiological and clinical characteristics in patients with adenocarcinoma; for example, it has been described that EGFR mutation in exon 21 is shown more in non-smoker women and tumors with a higher proportion of GGO [33,44,46]. Specifically, L858R mutation in exon 21 is frequently associated with broncho-alveolar adenocarcinoma and non-smoker status [30,55]. On the other hand, EGFR mutation in exon 19 is usually presented more in women, in tumors with a smaller maximum diameter, and pleural retraction [44]. This meta-analysis did not assess the differences between EGFR exon mutations due to the marked heterogeneity in the type

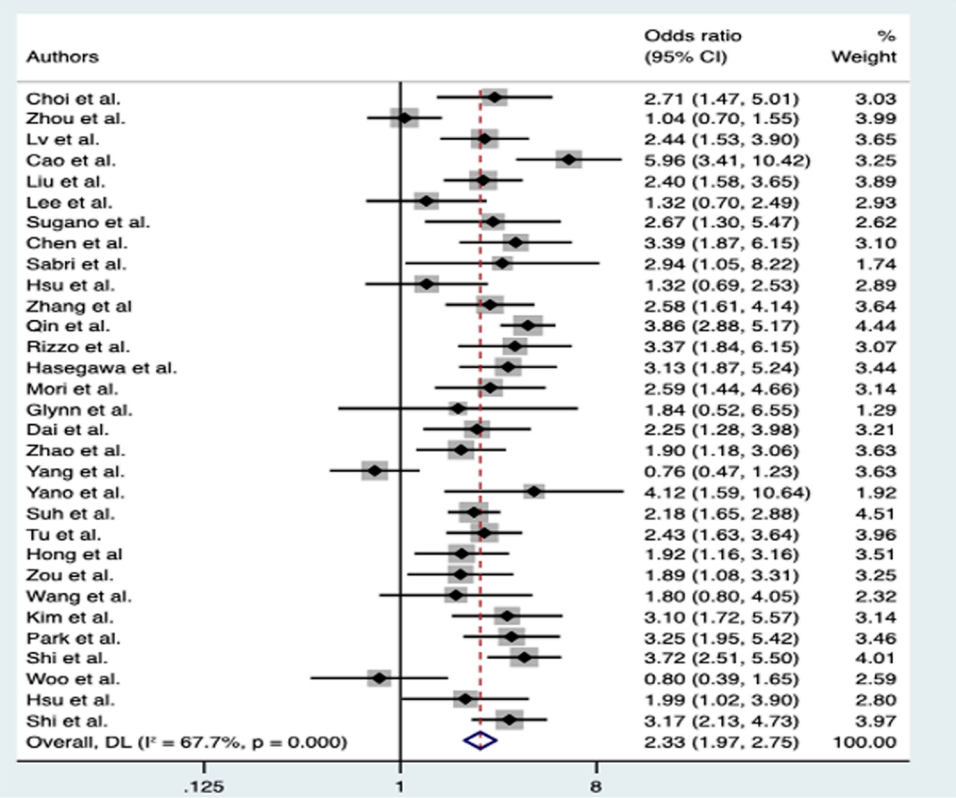

Fig. 11. Forest plot for female gender EGFR mutation.

Table 2
Results of the egger's test to assess publication bias.

Outcome assessed	P-value
GGO and EGFR mutation	0.17
Air bronchogram and EGFR mutation	0.0006
Vascular convergence and EGFR mutation	0.35
Pleural retraction and EGFR mutation	0.66
Spiculation and EGFR mutation	0.50
Cavitation and EGFR mutation	0.40
Early disease stage and EGFR mutation	0.77
Non-smoker status and EGFR mutation	0.80
Female gender and EGFR mutation	0.69

Table 3
Mathematical model to predict EGFR mutation based on radiological and clinical data.

Mathematical model to predict EGFR mutation based on radiological and clinical data	AUC
Female gender + Non-smoker status + GGO + Air bronchogram + Vascular convergence + Cavitation+ Pleural retraction + Spiculation + Early disease stage	0.81
Female gender + Non-smoker status + Spiculation + Pleural retraction	0.78
Female gender + Non-smoker status + Spiculation	0.71
Female gender + Non-smoker status + Vascular convergence	0.67
Female gender + Non-smoker status + Pleural retraction	0.67
Female gender + Non-smoker status + Early disease stage	0.63
Female gender + Non-smoker status + Air bronchogram	0.61
Female gender + Non-smoker status + GGO	0.60
Female gender + Non-smoker status	0.60

of alteration reported in the studies.

The main strengths of our study are that we used a significant sample size of 10355 patients, including only articles with a low or acceptable risk of bias. Also, a sensitivity analysis was performed, providing evidence that all the results presented are robust, and no study is modifying

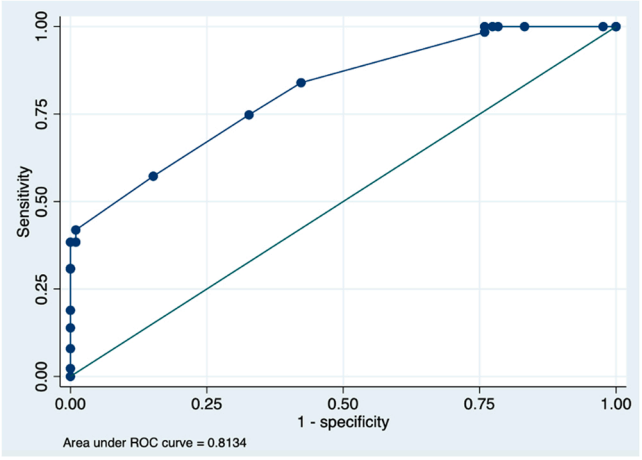

Fig. 12. ROC curve prediction for EGFR mutation based on female gender, non-smoker status, GGO, air bronchogram, vascular convergence, cavitation, pleural retraction, spiculation and early disease stage.

the overall effect by itself. The search strategy was thorough, involving databases worldwide, hand searching, and snowballing methods. Moreover, Publication bias was assessed.

Some of the limitations of this meta-analysis are that all the articles included were retrospective studies which are more prone to selection bias. Also, machine learning tools interpreted 20.3% of all the CT patterns, while human specialists analyzed the other 79.7%; these differences can lead to inconsistencies in the interpretations. Even though 86% of our studies were confirmed using PCR as the gold standard, it remains another 14% in which other methods were used for confirmation (Immunohistochemistry, FISH, etc.) which can lead to a certain degree of verification bias. All these limitations may affect the internal

validity of our study. Nevertheless, these are understandable limitations representing the heterogeneity between studies expected in a meta-analysis. Also, we found publication bias for air bronchogram to detect EGFR mutation, for which a funnel plot was carried out, showing a lack of small studies with negative effects.

A limitation that may affect the external validity of our findings is that 92% of the sample was from Asia. It has been suggested in previous studies that individuals from Asia have an increased prevalence of EGFR mutation in NSCLC [56]. Therefore, our study may overestimate the effect of the clinical and CT patterns when extrapolated to other populations. Due to the high number of Asian patients in our meta-analysis, we did not have enough individuals from different continents to perform subgroup analysis according to location. Another limitation is that 97% of all the patients had adenocarcinoma, limiting our findings' generalizability when extrapolated to other histological subtypes of NSCLC. We consider that the results provided in this study are internally valid but must be extrapolated carefully to the non-Asian population and histological subtypes different than adenocarcinoma.

5. Conclusions

This meta-analysis indicates that there is enough evidence to conclude that GGO, air bronchogram, spiculated margins, vascular convergence, pleural retraction, early disease stage, non-smoker status, and female gender are significantly associated with EGFR mutation. At the same time, cavitation represents a protective factor for the mutation. The model developed in this study, including all the clinical and CT patterns assessed, showed to be a good predictor for EGFR mutation (AUC: 0.81) and subsequently a determinant for EGFR-TKI response. We consider that the results of this model show strong evidence to encourage the development of clinical scores involving radiological and clinical characteristics to predict EGFR mutation, especially useful in populations in which biopsy cannot be achieved. Further studies evaluating these CT patterns to detect EGFR mutation in individuals different to Asiatic are mandatory to assess if the results in other populations (E.g., Latin, North American, European) correlate with those described in this meta-analysis. The predictive value of these CT patterns in histological subtypes other than adenocarcinoma and the clinical-radiological differences between EGFR mutation in exon 21 and exon 19 remains a mystery, making them a potential source of research.

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CRediT authorship contribution statement

Andrés Felipe Herrera: Conceptualization, methodology, Formal analysis, Investigation, writing – original draft, writing review and editing, Visualization, Supervision, Project administration. **Tatiana Cadavid Camacho:** Conceptualization, Supervision, Investigation, Review original draft. **Andrés Francisco Vásquez:** Investigation, Review – original draft. **Valeria del Castillo Herazo:** Investigation, Validation. Review – original draft. **Juan Guillermo Arámbula:** Investigation, Validation, Review – original draft. **María Mónica Yepes:** Investigation, Review – original draft. **Eduard Cadavid Camacho:** Investigation, Conceptualization, Review – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejro.2022.100400.

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