EGFR-plasma mutations in prognosis for non-small cell lung cancer treated with EGFR TKIs: A meta-analysis

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Abstract

**Background:** The plasma-based epidermal growth factor receptor (EGFR) mutation testing is approved recently to use in clinical practice. However, it has not been used as a prognostic marker yet because of contradictory results.

**Aim:** This meta-analysis aims to clarify the role of the EGFR-plasma test in prognosis for non-small cell lung cancer (NSCLC) who have mutant tumors and receive EGFR tyrosine kinase inhibitors (TKIs).

**Methods and Results:** The PubMed/MEDLINE, Web of Science, Cochrane Library, and Google Scholar databases were searched for relevant studies by April 10, 2021. The hazard ratio (HR) from reports was extracted and used to assess the correlation of EGFR-plasma status with progression-free survival (PFS) and overall survival (OS).

A total of 35 eligible studies with 4106 patients were enrolled in the final analysis. Patients with concurrent EGFR mutations in pretreatment plasma have shorter PFS (HR = 2.00, 95% confidence interval [CI]: 1.73–2.31, p < .001) and OS time (HR = 2.31, 95% CI: 1.89–2.83, p < .001) compared to the tumor-only mutation cases. Besides, the persistence of EGFR-activating mutations in post-treatment plasma is associated with worse PFS (HR = 3.84, 95% CI: 2.96–4.99, p < .001) and OS outcome (HR = 3.22, 95% CI: 2.35–4.42, p < .001) compared to others. Notably, the prognostic value of the EGFR-plasma test is also validated in treatment with third-generation EGFR TKI and significance regardless of different detection methods.

**Conclusion:** The presence of EGFR-plasma mutations at pretreatment and after EGFR TKI initiation is the worse prognostic factor for PFS and OS in NSCLC.

**KEYWORDS**

ctDNA, EGFR, NSCLC, prognosis

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1 | BACKGROUND

EGFR TKIs have been recommended as the first-line agents in treatment for NSCLC patients for many years. Accordingly, biopsy procedures must be done to get tumor tissues, then tested for the drug sensitivity mutations as EGFR\textsuperscript{E19del} (exon 19 deletions) and EGFR\textsuperscript{L858R} (Leucine-to-Arginine point mutation in exon 21). Unfortunately, not all patients are eligible for biopsy procedures, while the failure rate of biopsy might be high as 20%, accompanied by dangerous complications. In such cases, EGFR mutation testing in plasma samples is an alternative method that assists the initial diagnosis and also helps in treatment monitoring. Although the EGFR-plasma test is approved to use in clinical practice recently, it has not been used as a prognostic marker yet because of contradictory results. In meta-analyses of Mao C and Fan G, authors concluded that patients with EGFR mutations in the blood are associated with improved PFS and OS outcomes, which are different from the evidence of recent clinical trials. These analyses were conducted on studies that included both EGFR-positive and EGFR-negative patients. Currently, EGFR-negative patients are not introduced to treatment with EGFR TKIs, and therefore should not include them in such analyses. Our meta-analysis aims to clarify the prognostic role of the EGFR-plasma test in mutant tumor NSCLC treated with EGFR TKIs.

2 | MATERIALS AND METHODS

This meta-analysis was conducted according to the guideline of preferred reporting items for systematic reviews and meta-analyses (PRISMA).

2.1 | Database searching and selection of study

The electronic database as PubMed/MEDLINE, Web of Science, and Cochrane Library were searched for relevant studies. The keywords used in searching include “EGFR,” “ctDNA or circulating tumor DNA,” “cfDNA or circulating free DNA,” “plasma or peripheral blood,” “NSCLC or non-small cell lung cancer,” “lung cancer,” “lung carcinoma,” “survival,” “outcome,” “PFS,” and “OS.” Besides the above databases, Google Scholar was used for study searching. Moreover, the citation reports of potential studies were also reviewed for finding additional articles. The cut-off date of database searching is April 10, 2021 (the start date was not applied). After searching, all relevant studies were exported into the EndNote list (4432 records) and removed duplicates (1687 records, Figure 1).

By screening titles and abstracts, 2588 records were excluded from the study, while 157 remained articles were assessed in detail for eligibility. Studies included in the meta-analysis which are clinical trials meet criteria: (1) dealt with non-small cell lung cancer who have EGFR-activating mutations (EGFR\textsuperscript{E19del} and EGFR\textsuperscript{L858R} \pm EGFR\textsuperscript{T790M}) in tumor tissue and treated with EGFR TKIs as gefitinib, erlotinib, icotinib, afatinib, and osimertinib (first-line and second-line); (2) analyzed the association of EGFR status in paired tumor tissue and plasma/serum (T \(+\): EGFR+ in both tumor tissue and plasma/serum; T \(+\) \(+\): EGFR+ in tumor tissue but not in plasma/serum) with survival (PFS, OS); (3) have at least five patients in each comparison arms; and (4) have enough information to determine HR directly or indirectly. For the non-trial studies, besides these criteria, the adjusted HR values must be available. Finally, 35 studies were included in this meta-analysis (27 clinical trials and 8 non-trial studies).

2.2 | Quality assessment and data extraction

The Newcastle-Ottawa Scale (NOS), which comprises three aspects equivalent to a maximum score of 9 points (selection: 4 points; comparability: 2 points; and outcome: 3 points), was used to assess the included studies. In the comparability aspect, studies were scored 2 points if (1) comparable of treatment agents, and (2) comparable of patient’s characteristics (age, gender, histology, clinical stage, and metastasis status) between two arms (T \(+\) \(+\) and T \(+\) \(-\)).

We extracted data from articles including author’s name, publication year, country, study design, the number of patients in each arm, patient’s age, clinical stage, sample type, sampling time-point, the technique used to detect EGFR mutations, treatment agent, length of follow-up, outcome (PFS, OS), HR value, method of survival analysis (univariate/multivariate), and NOS score. In cases of not availability, HR values were calculated indirectly according to the recommendations of Tierney JF.

2.3 | Statistical analysis

Data analyses were done with the guidance of Harrrer, performed with R statistical software v.4.0.5 (R foundation, 1020 Vienna, Austria).
FIGURE 2  Forest plots of HR for the impact of prior-EGFR on PFS (A) and OS (B). HR, hazard ratio; OS, overall survival; PFS, progression-free survival

FIGURE 3  Funnel plots for publication bias in analyses with prior-EGFR for PFS (A) and OS (B). OS, overall survival; PFS, progression-free survival
### Table 1: Subgroup meta-analyses of prior-EGFR for PFS

| Variable            | No. of study | No. of patient | HR (95% CI)    | p-Value*   | Heterogeneity | p-Value** | p-Value*** |
|---------------------|--------------|----------------|----------------|------------|---------------|-----------|-----------|
| Ethnicity           |              |                |                |            | p², %         |           |           |
| Asian               | 9            | 1001           | 2.02 (1.72–2.39)| <0.001     | 0             | 0.472     | 0.371     |
| Caucasian           | 5            | 543            | 2.21 (1.45–3.38)| <0.001     | 67            | 0.018     |           |
| Mixed               | 4            | 642            | 1.69 (1.35–2.12)| <0.001     | 3             | 0.379     |           |
| Treatment           |              |                |                |            | p-Value***    |           |           |
| 1st/2nd-gen TKI     | 14           | 1693           | 1.88 (1.65–2.13)| <0.001     | 0             | 0.559     | 0.349     |
| Osimertinib         | 4            | 493            | 2.49 (1.40–4.43)| 0.002      | 72            | 0.014     |           |
| Technique           |              |                |                |            | I², %         |           |           |
| asPCR               | 7            | 1044           | 1.83 (1.56–2.15)| <0.001     | 0             | 0.520     | 0.143     |
| dPCR                | 4            | 285            | 2.94 (1.86–4.63)| <0.001     | 39            | 0.176     |           |
| PCR clamping        | 3            | 470            | 1.65 (1.27–2.14)| <0.001     | 0             | 0.393     |           |
| Other a             | 4            | 387            | 2.14 (1.59–2.89)| <0.001     | 6             | 0.364     |           |
| HR extraction method|              |                |                |            | p-Value**     |           |           |
| Direct              | 7            | 748            | 2.40 (1.79–3.21)| <0.001     | 52            | 0.053     | 0.086     |
| Indirect            | 11           | 1438           | 1.80 (1.56–2.07)| <0.001     | 0             | 0.566     |           |
| Survival analysis   |              |                |                |            | I², %         |           |           |
| Multivariate        | 5            | 522            | 2.53 (1.65–3.86)| <0.001     | 62            | 0.031     | 0.167     |
| Univariate          | 13           | 1664           | 1.85 (1.62–2.10)| <0.001     | 0             | 0.550     |           |
| Clinical trial      |              |                |                |            | p-Value***    |           |           |
| No                  | 4            | 431            | 2.59 (1.49–4.50)| <0.001     | 72            | 0.014     | 0.262     |
| Yes                 | 14           | 1755           | 1.87 (1.65–2.12)| <0.001     | 0             | 0.578     |           |

Note: *Significance within groups; **significance of heterogeneity; ***significance between groups.

Abbreviations: HR, hazard ratio; NGS, next-generation sequencing; OS, overall survival; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.

### Table 2: Subgroup meta-analyses of prior-EGFR for OS

| Variable            | No. of study | No. of patient | HR (95% CI)    | p-Value*   | Heterogeneity | p-Value** | p-Value*** |
|---------------------|--------------|----------------|----------------|------------|---------------|-----------|-----------|
| Ethnicity           |              |                |                |            | p², %         |           |           |
| Asian               | 7            | 710            | 2.50 (1.85–3.38)| <0.001     | 26            | 0.233     | 0.372     |
| Caucasian           | 5            | 629            | 2.40 (1.56–3.69)| <0.001     | 56            | 0.061     |           |
| Mixed               | 2            | 295            | 1.86 (1.36–2.54)| <0.001     | 0             | 0.509     |           |
| Treatment           |              |                |                |            | p-Value***    |           |           |
| 1st/2nd-gen TKI     | 12           | 1488           | 2.24 (1.81–2.78)| <0.001     | 36            | 0.103     | 0.195     |
| Osimertinib         | 2            | 146            | 3.13 (1.83–5.38)| <0.001     | 0             | 0.490     |           |
| Technique           |              |                |                |            | I², %         |           |           |
| ARMS                | 1            | 33             | 3.65 (1.04–12.84)| 0.044      | -             | -         | 0.056     |
| asPCR               | 6            | 801            | 2.01 (1.56–2.58)| <0.001     | 33            | 0.192     |           |
| dPCR                | 3            | 323            | 3.58 (2.37–5.41)| <0.001     | 0             | 0.592     |           |
| PCR clamping        | 1            | 164            | 1.50 (0.82–2.74)| 0.188      | -             | -         |           |
| Other a             | 3            | 313            | 2.60 (1.73–3.92)| <0.001     | 0             | 0.437     |           |
| HR extraction method|              |                |                |            | p-Value**     |           |           |
| Direct              | 6            | 726            | 2.49 (1.70–3.64)| <0.001     | 47            | 0.090     | 0.577     |
| Indirect            | 8            | 908            | 2.21 (1.74–2.81)| <0.001     | 26            | 0.218     |           |
| Survival analysis   |              |                |                |            | I², %         |           |           |
| Multivariate        | 5            | 584            | 2.80 (1.83–4.29)| <0.001     | 40            | 0.156     | 0.125     |
| Univariate          | 9            | 1050           | 2.12 (1.71–2.62)| <0.001     | 23            | 0.242     |           |
| Clinical trial      |              |                |                |            | p-Value***    |           |           |
| No                  | 5            | 584            | 2.80 (1.83–4.29)| <0.001     | 40            | 0.156     | 0.125     |
| Yes                 | 9            | 1050           | 2.12 (1.71–2.62)| <0.001     | 23            | 0.242     |           |

Note: *Significance within groups; **significance of heterogeneity; ***significance between groups.

Abbreviations: HR, hazard ratio; NGS, next-generation sequencing; OS, overall survival; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.
Austria), and meta, metafor, dmetar packages. The random-effects model was used to calculate the pooled HR values and assess the association of EGFR plasma status with survival outcomes. HR > 1 indicates an inferior survival for the patients with T+P+ mutations. In contrast, HR < 1 is the indicator of superior survival for T+P+ subjects. HR = 1 suggests that no correlations exist between EGFR plasma mutations and survival outcomes.

The heterogeneity of effect size (HR) between studies was measured by Higgin's and Thompson's $I^2$-statistics. Heterogeneity was determined as significant if $I^2 > 50\%$ and $p < .05$. Accordingly, the subgroup analyses were performed to explore sources of heterogeneity that may come from clinical characteristics. Furthermore, we used the Leave-one-out statistic to detect studies with extreme effect sizes (outliers). Then, the pooled HR was estimated once removed outliers from the analysis and checked for the consistency of overall results. The potential of publication bias in the meta-analysis was detected by the linear regression test for funnel plot asymmetry. In case of significant bias presence ($p < .05$), we used the Trim-and-fill method to impute missing studies and calculate the adjusted HR values.

3 | RESULTS

3.1 | Study characteristics

Among 35 studies included in this meta-analysis,5–14,19–41 21 studies reported the association of EGFR mutations in prior-treatment plasma
(prior-EGFR) with survival outcomes, including seven studies for PFS, three and 11 studies for OS, and both survival outcomes (Additional file 1: Table S1). Twenty-two studies presented data related to the post-treatment EGFR-plasma mutations (post-EGFR), which consists of 11 reports for PFS, three and 11 studies for OS, and both survival outcomes. The total number in prior-treatment studies is 2483 patients, and in post-treatment are 1623 cases. Ten studies used osimertinib in NSCLC treatment (two with first-line and eight with second-line), while others used the first- or second-generation EGFR TKIs with/without chemotherapy. The polymerase chain reaction (PCR) methods were used in almost all studies, while the next-generation sequencing (NGS) technique was only used in four reports to detect EGFR-plasma mutations. The NOS score above six indicated that all included studies are of high quality.

### 3.2 Association of prior-treatment EGFR plasma with survival outcomes

Among 2483 patients in the studies with prior-EGFR, 1524 patients have the T+P+ EGFR mutations, whereas 959 others have the T+P- results. The PFS time of T+P+ patients was from 3.7 to 15.6 months, and of T+P- subjects were 8.3 months to “not reached” (NR). These OS values were 8.2–28.8 months and 25.3–NR months, respectively. The overall estimated HR for PFS was 2.00 (95% CI: 1.73–2.31, \( p < .001 \), Figure 2A), which indicated that EGFR+ in both tumor tissue and plasma at baseline is the worse prognostic factor for NSCLC treated with EGFR TKIs. Similarly, the analysis has shown that T+P+ EGFR mutation is the inferior factor for OS (HR = 2.31, 95%CI: 1.89–2.83, \( p < .001 \), Figure 2B). The heterogeneity in these analyses for PFS (I² = 32%, \( p = .093 \)) and OS (I² = 33%, \( p = .113 \)) were not statistically significant. Besides, funnel plot asymmetry tests indicated a lack of publication bias in these analyses (Figure 3A,B).

The subgroup analysis results for PFS and OS are presented in Tables 1 and 2, respectively. Although significant heterogeneity exists in some subgroups (Caucasian, osimertinib treatment, and non-clinical trials), overall effect sizes are not significantly different between them (\( p > .05 \)).

### 3.3 Association of post-treatment EGFR plasma with survival outcomes

After treatment with EGFR TKIs (22 studies), EGFR clearance in plasma (T+P/C0) was recorded in a total of 1123 patients, while the persistence or recurrence of this mutation (T+P+) was noted in 500 cases. The median PFS of T+P+ patients was 1.8–11.1 versus 9.8–
NR months in T + P− subjects. These OS values in T + P+ and T + P− patients were 7.5–27.0 and 23.7–NR months, respectively. Meta-analyses have shown that EGFR+ in post-treatment plasma is associated with shorter PFS (HR = 3.84, 95% CI: 2.96–4.99, p < .001, Figure 4A) and OS (HR = 3.22, 95% CI: 2.35–4.42, p < .001, Figure 4B). While the heterogeneity in OS analysis was relatively low (I² = 39%, p = .083), this parameter in the PFS analysis was substantial (I² = 68%, p < .001). This phenomenon also was observed in subgroup meta-analyses (Tables 3 and 4). Subsequently, four studies that contributed most to overall heterogeneity in PFS analysis were detected by influence analysis (Figure 5A). By excluding outliers from the analysis model, the heterogeneity dropped to 22% (p = .196), whereas the analyzed result remained significant (HR = 3.49, 95% CI: 2.85–4.27, p < .001). Because of the potential publication bias (Figure 5B,C), we used the Trim-and-fill statistics to implement missing studies (Figure 5D,E) and showed an adjusted HR value of 2.93 (95% CI: 2.34–3.68, p < .001) for PFS, and 2.48 (95% CI: 1.78–3.46, p < .001) for OS.

4 | DISCUSSION

Several studies have been conducted to assess the prognostic role of the EGFR-plasma test in NSCLC treated with EGFR TKIs, however, with different conclusions.3–14 Thus, it has not been recommended to use in prognosis yet.1 We performed the meta-analysis on EGFR positive tumor NSCLC from 35 studies and noted that EGFR+ in both tumor tissue and plasma at baseline is the worse prognostic factor for PFS and OS. Additionally, the maintained detectable EGFR \( E_{19}^{\text{del}} \) and EGFR \( B^{858R} \) or recurrence of the mutation in plasma after EGFR TKI initiation is the inferior factor for survival outcomes. Significantly, the prognosis role of the EGFR-plasma test is also validated in treatment with third-generation EGFR TKI, and for different techniques as PCR clamping, allele-specific PCR, digital PCR, and NGS.

Patients with plasma concurrent EGFR mutations are classified into the shedding tumor group and associated with poor performance status, advanced clinical stage, increased metastatic site, and large tumor volume.7,8,42 In addition, EGFR plasma concomitance is correlated with a higher percentage of driver mutations and gene alterations (TP53, CDK4/6, CTNNB1, AR, PIK3CA, MYC, CCNE1, KRAS, PDGFRα, NF1...).43 It explains why the T + P− patients are less sensitive to EGFR TKIs and have shorter survival compared to those with non-shedding EGFR mutations. Moreover, baseline EGFR-plasma and coexisting alterations are related to the mutation persisting in post-treatment samples28 and the development of secondary mutations as EGFR 790M, EGFR 779S, and other acquired genetic changes.43–45 These are consistent with the meta-analyzed results that maintenance of initial EGFR mutations (with or without secondary mutations) in plasma is the worse signature. Thanks to the benefit of prognosis, clinicians should require additional EGFR-plasma mutation testing even

### Table 4 Subgroup meta-analyses of post-EGFR for OS

| Variable               | No. of study | No. of patient | HR (95%CI)   | p-Value* | Heterogeneity |
|------------------------|--------------|----------------|--------------|----------|---------------|
|                        |              |                |              |          | **I²**, %      |
|                        |              |                |              |          | p-Value**   |
|                        |              |                |              |          | p-Value***  |
| Ethnicity              |              |                |              |          |               |
| Asian                  | 5            | 301            | 2.62 (1.71–4.03) | <0.001   | 36   | 0.183 | 0.093       |
| Caucasian              | 6            | 440            | 3.84 (2.49–5.92) | <0.001   | 34   | 0.180 |            |
| Treatment              |              |                |              |          |               |
| 1st-/2nd-gen TKI       | 8            | 595            | 2.80 (2.00–3.92) | <0.001   | 35   | 0.149 | 0.044       |
| Osimertinib            | 3            | 146            | 4.68 (2.77–7.93) | <0.001   | 0    | 0.407 |            |
| Technique              |              |                |              |          |               |
| asPCR                  | 2            | 220            | 3.22 (1.04–9.95) | 0.042    | 76   | 0.041 | 0.087       |
| dPCR                   | 5            | 324            | 4.30 (2.89–6.42) | <0.001   | 0    | 0.458 |            |
| PCR clamping           | 2            | 120            | 1.95 (1.29–2.95) | 0.002    | 0    | 0.723 |            |
| NGS                    | 1            | 59             | 3.22 (1.35–7.69) | 0.008    | -    | -     |            |
| Other*                 | 1            | 18             | 5.48 (1.42–21.09) | 0.013    | -    | -     |            |
| HR extraction method   |              |                |              |          |               |
| Direct                 | 8            | 530            | 3.32 (2.30–4.78) | <0.001   | 36   | 0.141 | 0.973       |
| Indirect               | 3            | 211            | 3.27 (1.49–7.15) | <0.001   | 62   | 0.071 |            |
| Survival analysis      |              |                |              |          |               |
| Multivariate           | 5            | 407            | 2.61 (1.88–3.63) | <0.001   | 18   | 0.302 | 0.109       |
| Univariate             | 6            | 334            | 4.59 (2.50–8.41) | <0.001   | 52   | 0.064 |            |
| Clinical trial         |              |                |              |          |               |
| No                     | 4            | 349            | 2.82 (1.87–4.26) | <0.001   | 31   | 0.226 | 0.684       |
| Yes                    | 7            | 392            | 3.81 (2.31–6.28) | <0.001   | 50   | 0.059 |            |

Note: Significance within groups; ** significance of heterogeneity; *** significance between groups.

*BEAMing, PANAMutyper, MBP-QP; 1st-/2nd-gen: first-/second-generation.

Abbreviations: HR, hazard ratio; NGS, next-generation sequencing; OS, overall survival; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.
though it has been confirmed positive in the tumor tissues. Also, bi-monthly repeated monitoring of \( EGFR \) mutations in plasma after \( EGFR \) TKI initiation should be done in NSCLC management.

This study highlights the prognostic role of the \( EGFR \)-plasma test in NSCLC treated with \( EGFR \) TKIs. However, some limitations still exist. First, substantial heterogeneity and publication bias is present in post-treatment analyses, although non-trial studies without adjusted HR values have been excluded. It might be due to differences in patient characteristics, therapy regimen, and HR extraction method between studies. Thus, cautious use of results is needed. Second, the sample size in some study arms is limited, while not all individual HR values are extracted directly, which might affect the overall results.

**FIGURE 5** Outliers (A) and funnel plots for publication bias in analyses with post-\( EGFR \) for PFS and OS (B and C), and for PFS, OS after imputing missing studies (D and E). OS, overall survival; PFS, progression-free survival
Third, this study only finishes with the prognostic role of EGFR-plasma as a single gene, which requires further clinical trials with a complex gene model to continue to update our results.

In conclusion, the results of this study indicated that NSCLC patients harboring EGFR-plasma mutations have poorer outcomes compared to those with tumor-only mutations during EGFR TKI therapies. Besides, the persistence of EGFR mutations in post-treatment plasma is the worse factor for PFS and OS.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Conceptualization, data curation, formal analysis, investigation, methodology, software, supervision, validation, writing—original draft, writing—review and editing, T.P.; Data curation, formal analysis, investigation, resources, validation, writing—review and editing, V.T.; Data curation, formal analysis, investigation, validation, writing—original draft, writing—review and editing, B.-T.T.; Data curation, formal analysis, investigation, resources, validation, visualization, writing—review and editing, T.H.; Data curation, investigation, validation, writing—review and editing, S.P.; Investigation, validation, writing—review and editing, V.L.; Data curation, investigation, validation, writing—review and editing, A.L.; Data curation, investigation, validation, writing—review and editing, H.N.; Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, writing—review and editing, S.N.

ETHICAL STATEMENT
Not applicable.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION
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