

# Biomarker and Prognostic Value of Super-ARMS Detection for EGFR Mutation in Advanced NSCLC

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**Background:** ctDNA is a non-invasive and convenient method for detecting EGFR mutations in non-small cell lung cancer (NSCLC). However, its sensitivity is lower than that of tissue-based testing. To enhance ctDNA detection efficiency, we identified the patient population most suitable for ctDNA testing, assessed the relationship between ctDNA and tumor markers, and examined the clinical significance of ctDNA in medical practice.

**Methods:** A single-center retrospective study was conducted, including 135 patients with NSCLC who underwent histological and liquid Super-ARMS tests. Of these, 92 patients with EGFR mutations detected in both tumor tissue and plasma were classified into the EGFR<sup>tt</sup>, P<sup>+</sup> group, while 43 patients with EGFR mutations detected only in tumor tissue were classified into the EGFR<sup>tt</sup>, P<sup>-</sup> group. The clinical features and outcomes between these two groups were compared.

**Results:** The positivity rate of Super-ARMS test was 68.1% (92/135). The presence of EGFR<sup>tt</sup>, P<sup>+</sup> in the Super-ARMS test was significantly associated with pleural effusion, bone, liver, and multiple organ metastases. Compared to the EGFR<sup>tt</sup>, P<sup>+</sup> group, the EGFR<sup>tt</sup>, P<sup>-</sup> group had a significantly better PFS ( $P < 0.01$ ). Carcinoembryonic antigen (CEA) levels demonstrated a strong predictive value for identifying plasma EGFR-mutated patients (AUC 0.828, sensitivity 68.8%, specificity 84.4%), while Maximum Standardized Uptake Value (SUV<sub>max</sub>) also showed diagnostic value for plasma EGFR-mutated patients (AUC 0.78). Additionally, combination of TP53 and EGFR mutations in plasma provided improved risk stratification for PFS ( $P < 0.001$ ).

**Conclusion:** Patients exhibiting metastasis, elevated levels of tumor markers and SUV<sub>max</sub> are more suitable for plasma EGFR mutation testing in clinical NSCLC management. Moreover, a positive plasma ctDNA test not only guides targeted therapy but also predicts a worse prognosis.

**Keywords:** NSCLC, EGFR mutation, ctDNA, CEA, prognosis

## Introduction

Non-small cell lung cancer (NSCLC), which accounts for over 80%<sup>1</sup> of all lung cancers, is the primary cause of cancer-related deaths worldwide.<sup>2</sup> NSCLC is a highly malignant tumor, with the majority of patients diagnosed at an advanced stage. The five-year survival rate is approximately 21%.<sup>3,4</sup> For advanced NSCLC, conventional treatment methods primarily rely on chemotherapy and radiotherapy, though their efficacy is limited. In recent years, the prognosis of NSCLC patients has significantly improved with the use of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs).<sup>5-7</sup> EGFR-TKIs therapy is the standard first-line treatment for NSCLC patients with EGFR mutations. EGFR is the most common mutated target gene in NSCLC, with major mutation types including exon 19 deletions (19del), exon 21 missense mutations (L858R), and exon 20 mutations. Most mutations in exon 20 are associated with TKI resistance, particularly the T790M mutation. Unfortunately, fewer than 25% of patients benefit from targeted

therapy, and resistance almost invariably develops during treatment.<sup>8</sup> Therefore, early detection of target mutations and timely targeted treatment are crucial for NSCLC patients. At present, there are multiple methods for detecting EGFR mutations, with tissue samples analysis generally considered the “gold standard”.<sup>9</sup> However, sequencing often requires invasive tumor tissue biopsy, which carries risks<sup>10</sup> and have limitations in detecting tissue deficiencies and tumor heterogeneity.<sup>11–13</sup>

With advances in science and technology, circulating tumor DNA (ctDNA) testing has emerged as a non-invasive and easily reproducible method, becoming a prominent focus in oncology diagnosis and treatment. ctDNA-based genotyping can be performed at any stage of the disease, facilitating real-time detection and monitoring of genotypic changes. Some studies have shown that ctDNA testing can help predict early tumor recurrence and assess both the prognosis and therapeutic efficacy during and after treatment.<sup>14–18</sup> Main detection technologies for ctDNA include droplet digital polymerase chain reaction (ddPCR), tissue amplification refractory mutation system (ARMS), and next-generation sequencing (NGS).<sup>19–21</sup> Among these, ARMS-PCR is noted for its high sensitivity and specificity, offering a significantly higher detection rate for gene mutation compared to traditional PCR. It has become one of the most popular and important technologies for personalized molecular tumor detection due to its lower cost and shorter detection time compared to NGS.

Super-ARMS is an enhanced version of ARMS-PCR technology that preserves the key advantages of ARMS-PCR, including simplicity, speed, accuracy, high specificity, and ease of widespread adoption. It is especially effective for detecting EGFR gene mutations in blood samples.<sup>22,23</sup> Research indicates that Super ARMS has sensitivity close to ddPCR and offers distinct advantages over methods like NGS and ddPCR for clinical implementation.<sup>24,25</sup> Super-ARMS has been included in clinical expert consensus on liquid biopsy and, following clinical validation, has demonstrated effectiveness in guiding EGFR-targeted therapy.<sup>26,27</sup> However, Super-ARMS detection is associated with a certain false-negative rate, its sensitivity is lower than that of tissue-based testing. And there are currently few studies on its clinical value in detecting EGFR mutation in plasma ctDNA of advanced NSCLC.

Therefore, our study retrospectively collected data from 135 NSCLC patients with EGFR mutations confirmed by tumor biopsy sequencing to evaluate the performance of Super-ARMS in detecting EGFR gene mutations in plasma ctDNA. What's more, in order to improve the ctDNA detection performance, we identified the patient population most suitable for ctDNA testing, assessed the relationship between ctDNA and tumor markers, and examined the clinical significance of ctDNA in medical practice. This research is of significant importance for improving the efficiency of EGFR mutation ctDNA detection and guiding clinical targeted therapies.

## Methods

### Patients

We collected data from 135 EGFR-mutant patients with histologically confirmed NSCLC who underwent Super-ARMS testing and EGFR-TKIs treatment at the First Affiliated Hospital of Sun Yat-sen University from 01/01/2019 to 30/12/2022. The detailed inclusion and exclusion criteria were shown in [Supplementary Table 1](#). Baseline CT scans closest to the initiation of targeted drug therapy were reviewed by one clinical investigator and independently assessed by another for quality assurance, with the goal of determining the number and location of progressive disease sites. Metastatic sites were defined based on CT imaging, while progressive sites were defined as single lesions with at least a 20% increase in maximum dimension or the appearance of new lesions on CT imaging. Patients were grouped based on EGFR mutation results from histological and plasma ctDNA testing. Those with mutations detected by both methods were defined as the EGFR<sup>+</sup>, P<sup>+</sup> group, while those with mutations detected only by histology were defined as the EGFR<sup>+</sup>, P<sup>−</sup> group. We had access to information that could identify individual participants during or after data collection, and personal data were de-identified before analysis. This experiment was approved by the IRB of The First Affiliated Hospital of Sun Yat-sen University (approval no. [2022]049). This study was conducted in accordance with the Declaration of Helsinki. Patient consent was waived for this retrospective design. According to the approval requirements of the Ethics Committee of First Affiliated Hospital of Sun Yat-sen University, this study is a retrospective study. And since all the patient data used

are anonymous data, the Ethics Committee has approved that this study does not require the individual consent of the patients.

## Tissue and Blood Sample Detection

All collected tissue specimens were soaked in 4% formaldehyde solution, then embedded and fixed into paraffin sections for NGS detection. Plasma DNA was analyzed using the Super-ARMS EGFR method. We collected 10 mL of body fluid samples from NSCLC patients and processed using a two-stage centrifugation method: first at  $2000 \times g$  for 10 min, followed by a second centrifugation at  $8000 \times g$  for 10 min. Samples with severe hemolysis or excessively high lipid levels are not usable. The resulting supernatant had a final volume of not less than 2 mL. Free DNA was extracted using the Body Fluid Free DNA Isolation Kit (Xiamen Aide Biomedical Technology Co., Ltd.). The concentration of the extracted DNA was determined by the Nano Drop 2000 Nucleic Acid and Protein Quantification Instrument. The OD260/OD280 ratio of the DNA should be between 1.8 and 2.0, and the OD260/OD230 ratio should be greater than 2. EGFR gene mutations were detected following the operating procedures, the reagent kit includes both internal and external quality control samples, as well as positive and negative controls, to conduct testing as per the instructions for the EGFR gene mutation quantitative detection kit with result interpretation based on the instruction manual. We used Super-ARMS to detect these text limited reference samples for 20 times. With 95% positive detection rate as the standard for determining the minimum detection limit, it was found that Super-ARMS could be detected normally when the mutated DNA concentration was as low as 0.2%.

## <sup>18</sup>F-FDG PET/CT Image Acquisition and Analysis

PET/CT imaging was performed in 3D acquisition mode using a Gemini GXL 16 scanner (Philips, Best). The <sup>18</sup>F-FDG PET tracer, provided by our cyclotron center (Cyclone 10/5 Accelerator, IBA), had a radiochemical purity of over 95%. Patients fasted for at least 6 hours before receiving an intravenous injection of 5.55 MBq/kg of <sup>18</sup>F FDG, followed by whole-body emission scanning. CT parameters were set to 120 kV, 100 mA, with collimation and slice spacing of 5.0/0.75 mm. PET imaging was performed in a row-by-row manner using the same position acquired in 3D mode. All images were independently assessed by two PET/CT physicians with 3–9 years of clinical diagnostic experience, without prior knowledge of clinicopathologic information. The inter-reader consistency was assessed using a statistical measure, kappa coefficient, to evaluate the agreement between the two PET/CT readers. In case of any disagreements, consensus was reached through discussion. For each site of involvement, including primary tumor, metastatic lymph nodes, and distant metastases, a region of interest (ROI) was carefully delineated around the suspected lesion site and the maximum standardized uptake value ( $SUV_{max}$ ) was measured.

## Data Collection

Retrospective data collection based on electronic medical records included patients' age, sex, smoking status, tumor metastasis, tumor size, stage, tumor mutation typing, tumor markers, and treatment outcomes.

## Treatment and Follow-up

All patients diagnosed with EGFR mutations were treated with EGFR-TKIs. The cutoff for data was 30/12/2022. Treatment efficacy data were collected, objective response rate (ORR) and progression-free survival (PFS) were calculated. PFS is defined as the time from treatment initiation to disease progression or death. ORR is the percentage of tumors that have shrunk or disappeared after tumor treatment is administered.  $ORR = [(Number\ of\ Complete\ Response\ (CR)\ cases + Number\ of\ Partial\ Response\ (PR)\ cases) / Total\ evaluable\ population] \times 100\%$ . The response of lung cancer to treatment is measured every three months using the RECIST criteria.

## Statistical Analysis

All data were analyzed using SPSS26 and Graphpad8.0. Chi-square test and Fisher's exact test were used to compare differences in categorical data between groups. Kaplan–Meier curves were drawn and Log rank test were used to compare survival rates. All univariate regression analyses with *P* value less than 0.1 were included in multivariate Cox

proportional hazards model. The Cox proportional risk model was applied to estimate the hazard ratio (HR) for both multivariate and subgroup analyses. A two-sided *P* value of <0.05 was considered statistically significant.

## Results

### Patient Characteristics and the EGFR Mutation Status in Tissue and Plasma Samples

A total of 135 patients underwent both histological and plasma Super-ARMS mutation testing. There were 92 (68.1%, 0.595–0.760) patients in the EGFR<sup>tt</sup>, P<sup>+</sup> group, and 43 (31.9%) patients in the EGFR<sup>tt</sup>, P<sup>−</sup> group. Using histological testing results for EGFR mutations as a reference, the sensitivity of Super-ARMS test was 68.1%. Notably, in patients with multiple metastatic NSCLC, the sensitivity of Super-ARMS EGFR testing can reach up to 85% ([Supplementary Table 2](#)). During the data collection process, no tissue negative but plasma positive patients were found. This indicates that in our study, the Super-ARMS did not produce any false positives. Univariate analysis indicated that patients with pleural effusion (*P* = 0.002), bone metastases (*P* = 0.004), liver metastases (*P* = 0.009) and multiple organ metastases (*P* = 0.005) had higher Super-ARMS detection sensitivity. Specific details were provided in [Table 1](#)

**Table 1** Patient Characteristics

| Variables                               | All Patients<br>N=135 | EGFR <sup>tt</sup> , P <sup>+</sup><br>N=92 | EGFR <sup>tt</sup> , P <sup>−</sup><br>N=43 | χ <sup>2</sup> | P                        |
|---|-----------------------|---|---|----------------|--------------------------|
| <b>Age (years), n (%)</b>               |                       |   |   |                |                          |
| ≥60                                     | 81 (60.0)             | 53 (57.6)                                   | 28 (65.1)                                   | 0.699          | 0.403                    |
| <60                                     | 54 (40.0)             | 39 (42.4)                                   | 15 (34.9)                                   |                |                          |
| <b>Sex, n (%)</b>                       |                       |   |   |                |                          |
| Male                                    | 43 (31.9)             | 27 (29.3)                                   | 16 (37.2)                                   | 0.812          | 0.368                    |
| Female                                  | 92 (68.1)             | 65 (70.7)                                   | 27 (62.8)                                   |                |                          |
| <b>Smoking history, n (%)</b>           |                       |   |   |                |                          |
| Yes                                     | 34 (25.2)             | 22 (23.9)                                   | 12 (27.9)                                   | 0.439          | 0.508                    |
| No                                      | 101 (74.8)            | 70 (76.1)                                   | 31 (72.1)                                   |                |                          |
| <b>Pleural effusion, n (%)</b>          |                       |   |   |                |                          |
| Yes                                     | 49 (36.3)             | 42 (45.7)                                   | 7 (16.2)                                    | 9.842          | 0.002                    |
| No                                      | 86 (63.7)             | 50 (54.3)                                   | 36 (83.7)                                   |                |                          |
| <b>Intrapulmonary metastasis, n (%)</b> |                       |   |   |                |                          |
| Yes                                     | 46 (34.1)             | 31 (33.7)                                   | 15 (34.9)                                   | 0              | 1.000                    |
| No                                      | 89 (65.9)             | 61 (66.3)                                   | 28 (65.1)                                   |                |                          |
| <b>Brain metastasis, n (%)</b>          |                       |   |   |                |                          |
| Yes                                     | 61 (45.2)             | 45 (48.9)                                   | 16 (37.2)                                   | 2.024          | 0.155                    |
| No                                      | 74 (54.8)             | 47 (51.1)                                   | 27 (62.8)                                   |                |                          |
| <b>Bone metastasis, n (%)</b>           |                       |   |   |                |                          |
| Yes                                     | 60 (44.2)             | 48 (52.2)                                   | 12 (27.9)                                   | 8.326          | <b>0.004</b>             |
| No                                      | 75 (54.8)             | 44 (47.8)                                   | 31 (72.1)                                   |                |                          |
| <b>Liver metastasis, n (%)</b>          |                       |   |   |                |                          |
| Yes                                     | 12 (8.9)              | 12 (13.0)                                   | 0 (0)                                       |                | <b>0.009<sup>#</sup></b> |
| No                                      | 123 (91.1)            | 80 (87.0)                                   | 43 (100)                                    |                |                          |
| <b>Multiple Organ Metastases, n (%)</b> |                       |   |   |                |                          |
| Yes                                     | 40 (29.6)             | 34 (37.0)                                   | 6 (14.0)                                    | 9.647          | <b>0.002</b>             |
| No                                      | 95 (70.4)             | 58 (63.0)                                   | 37 (86.0)                                   |                |                          |
| <b>T Stage, n (%)</b>                   |                       |   |   |                |                          |
| ≤3cm                                    | 26 (19.3)             | 16 (17.4)                                   | 10 (23.2)                                   | 0.814          | 0.666                    |
| 3–5cm                                   | 38 (28.1)             | 27 (29.3)                                   | 11 (25.6)                                   |                |                          |
| ≥5cm                                    | 72 (52.6)             | 49 (53.3)                                   | 22 (51.2)                                   |                |                          |
| <b>Stage, n (%)</b>                     |                       |   |   |                |                          |
| III                                     | 3 (2.2)               | 1 (1.1)                                     | 2 (4.7)                                     |                | 0.248 <sup>#</sup>       |
| IV                                      | 132 (97.8)            | 91 (98.9)                                   | 41 (95.3)                                   |                |                          |

(Continued)

**Table 1** (Continued).

| Variables                   | All Patients<br>N=135 | EGFR <sup>tt</sup> , P <sup>+</sup><br>N=92 | EGFR <sup>tt</sup> , P <sup>-</sup><br>N=43 | $\chi^2$ | P     |
|-----------------------------|-----------------------|---|---|----------|-------|
| <b>Mutation type, n (%)</b> |                       |   |   |          |       |
| Deletion 19                 | 62 (45.9)             | 40 (43.5)                                   | 22 (51.2)                                   | 1.353    | 0.508 |
| Exon 21 (L858R)             | 65 (48.1)             | 47 (51.1)                                   | 18 (48.8)                                   |          |       |
| Rare mutation               | 8 (5.9)               | 5 (5.4)                                     | 3 (6.7)                                     |          |       |
| <b>TP53, n (%)</b>          |                       |   |   |          |       |
| Yes                         | 42 (31.1)             | 31 (33.7)                                   | 11 (25.6)                                   | 0.628    | 0.428 |
| No                          | 93 (68.9)             | 61 (66.3)                                   | 32 (74.4)                                   |          |       |

Notes: Statistically significant P values are given in bold. <sup>#</sup>Fisher's exact test.

and detailed PFS curves were shown in [Supplementary Figure 1](#). Furthermore, multivariate analysis demonstrated bone metastasis and CEA level were independent risk factors for positive EGFR ctDNA test in NSCLC ([Supplementary Table 3](#)).

## Diagnostic and Prognostic Value of Tumor Markers

In order to evaluate the diagnostic efficacy of ctDNA for patients in the EGFR<sup>tt</sup>, P<sup>+</sup> group, we constructed the receiver operating characteristic (ROC) curve and calculated the area under the ROC curve (AUC) of tumor markers in lung cancer. CEA demonstrated the highest accuracy in predicting ctDNA EGFR mutations (AUC 0.828, 95% CI 0.757–0.899, sensitivity 68.8%, specificity 84.4%, cutoff value 15.1) ([Figure 1A](#)). Further analysis categorized patients into high and low level groups based on cutoff value. Univariate analysis revealed that a high level of CEA or CFRA21-1 is associated with a poorer prognosis ( $P < 0.01$ ) ([Figure 1B](#) and [C](#)), but CA125 at 44.3 had no predictive value for prognosis ([Figure 1D](#)) ( $P > 0.05$ ).

## Diagnostic and Prognostic Value of SUV<sub>max</sub>

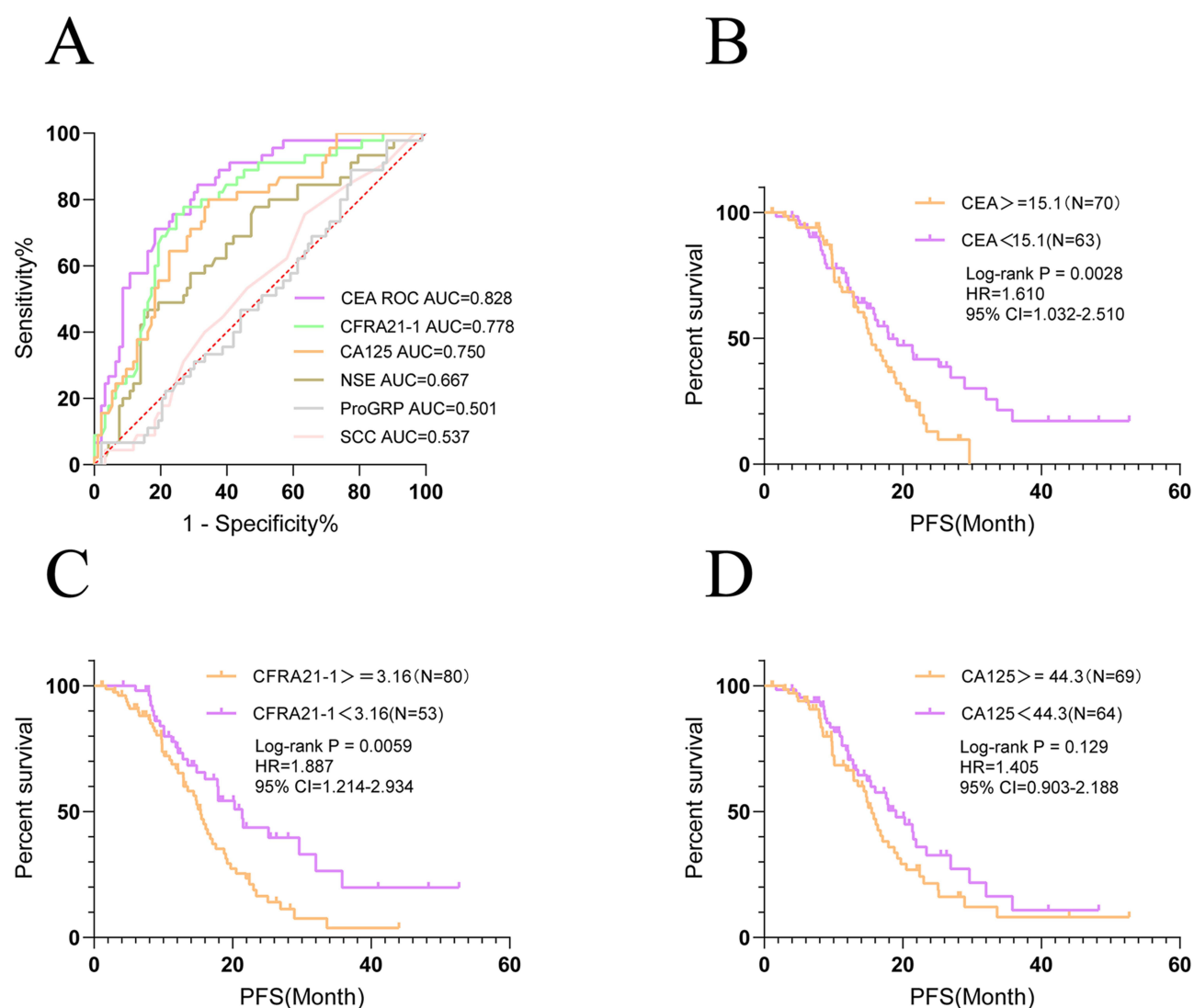
In the 135 NSCLC patients who underwent plasm Super-ARMS testing, 60 had an 18F FDG PET/CT scan. To identify patients with an increased probability of plasm EGFR mutations, ROC curve analysis was performed ([Figure 2A](#)). The SUV<sub>max</sub> of distant metastases (SUV<sub>max(M)</sub>) was identified as a predictive marker for plasm EGFR gene mutation. However, combining SUV<sub>max(T)</sub>, SUV<sub>max(N)</sub> and SUV<sub>max(M)</sub>, or combining SUV<sub>max(M)</sub> and CEA did not significantly improve AUC. Survival analysis based on the cutoff value grouping shows that patients with lower SUV<sub>max(M)</sub> have better PFS ( $P = 0.044$ ) ([Figure 2B](#)).

## Dynamics of ctDNA and Tumor Markers

There were 26 of 135 patients who underwent a second Super-ARMS test, with a median interval of 4.5 months between tests. We examined the relationship between ctDNA changes and serum biomarkers, and the waterfall plot demonstrated that patients with two consistent ctDNA tests had less variation in CEA levels compared to those with positive-negative or negative-positive transitions ([Supplementary Figure 2](#)), which suggested the magnitude of CEA change may predict alterations in the Super-ARMS assay.

## The Prognostic Value of ctDNA Testing

In the univariate analysis, the median survival times were 23.4 months in the EGFR<sup>tt</sup>, P<sup>-</sup> group and 15.37 months in the EGFR<sup>tt</sup>, P<sup>+</sup> groups. Compared to the EGFR<sup>tt</sup>, P<sup>+</sup> group, the EGFR<sup>tt</sup>, P<sup>-</sup> group had a better PFS ( $P = 0.001$ ) ([Figure 3A](#)). Meanwhile, EGFR<sup>tt</sup>, P<sup>-</sup> had a higher ORR than the EGFR<sup>tt</sup>, P<sup>+</sup> group ( $P = 0.005$ ) ([Figure 3B](#)). Moreover, after adjusted for other factors, positive EGFR ctDNA test still increased the risk of disease progression ( $P < 0.05$ ) ([Table 2](#)). We further performed subgroup analysis on the EGFR<sup>tt</sup>, P<sup>+</sup> group, the EGFR<sup>tt</sup>, P<sup>-</sup> group, and the forest plot is shown in the



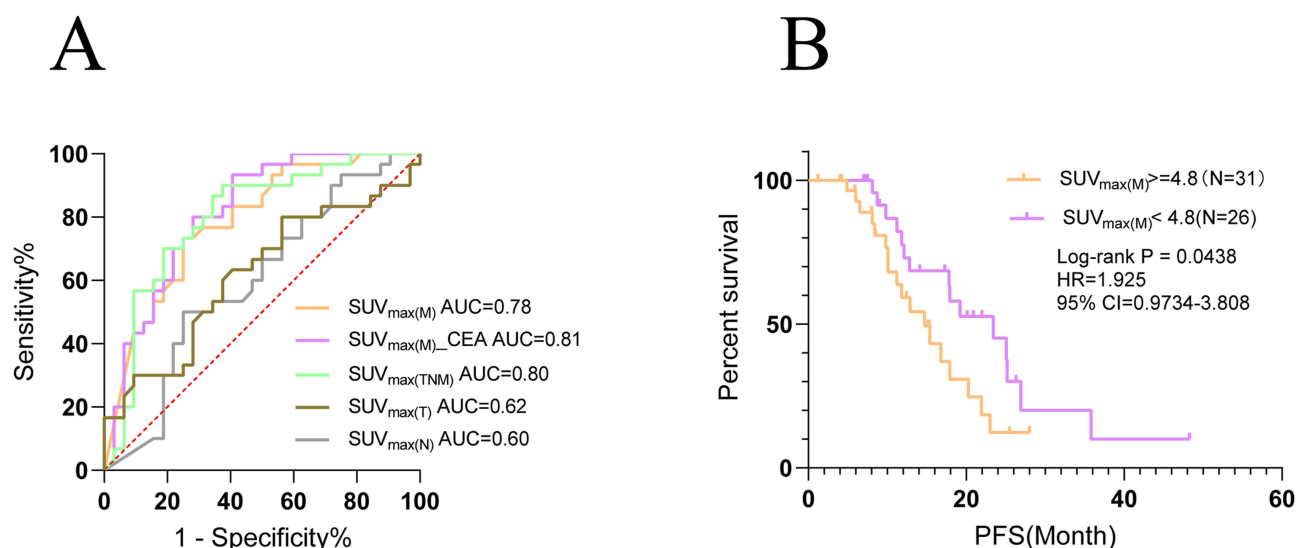
**Figure 1** ROC curve analyses and PFS of patients. **(A)** The sensitivity and specificity of tumor markers for predicting the presence of plasm EGFR mutation in patients with NSCLC. **(B)** PFS of patients in CEA $\geq 15.1$  group and  $< 15.1$  group. **(C)** PFS of patients in CA125 $\geq 44.3$  group and  $< 44.3$  group. **(D)** PFS of patients in CFRA21-1 $\geq 3.16$  group and  $< 3.16$  group. The cutoff value is defined based on the Youden index.

**Figure 4.** These results indicate that ctDNA test results have important prognostic value in NSCLC receiving EGFR-TKIs treatment.

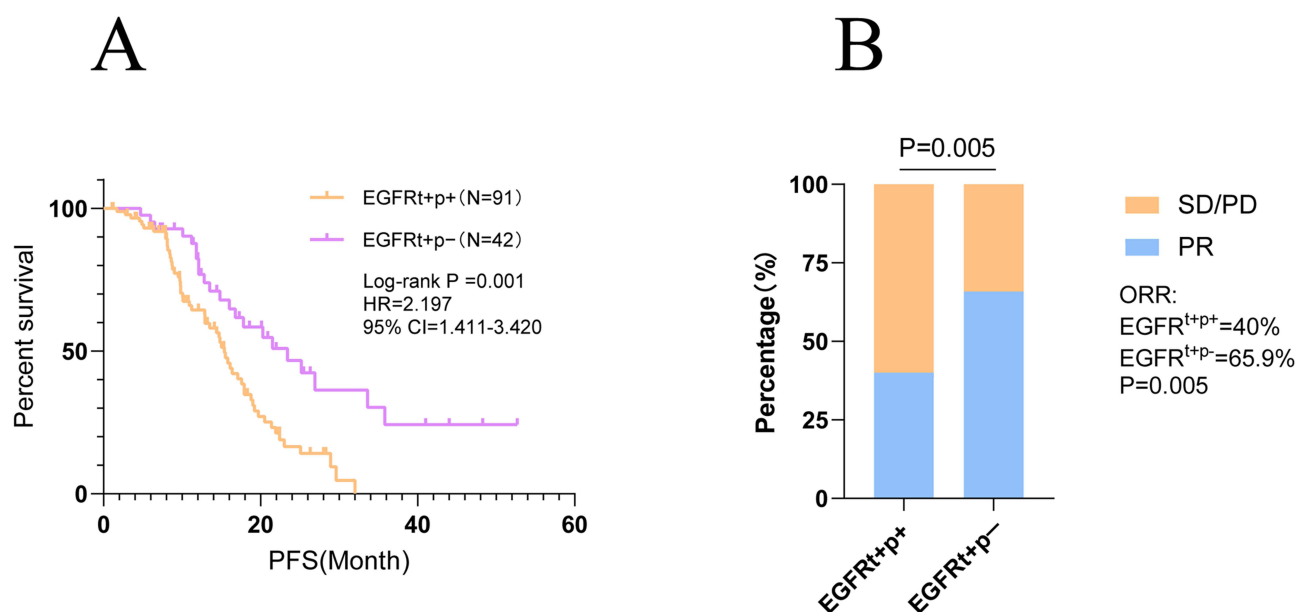
## The Prognostic Value of TP53 Mutation

In NSCLC, TP53 is the most commonly mutated gene. And our study showed that TP53 was an independent prognostic factor for PFS ( $P = 0.009$ ) (**Figure 5A**). Furthermore, we included TP53 and EGFR mutation status in the stratified analysis. Patients were categorized into four groups: EGFR<sup>tt</sup>, P<sup>+</sup> TP53 mutation group, EGFR<sup>tt</sup>, P<sup>+</sup> TP53 wild group, EGFR<sup>tt</sup>, P<sup>-</sup> TP53 mutation group and EGFR<sup>tt</sup>, P<sup>-</sup> TP53 wild group, with median survival of 13.5 months, 12.13 months, 16.37 months and 26.93 months, respectively (**Figure 5B**). Further stratification showed that patients without TP53 mutation and in EGFR<sup>tt</sup>, P<sup>-</sup> group had better clinical outcomes compared to other patients ( $P < 0.001$ ) (**Figure 5C**).





**Figure 2** ROC curve analyses and PFS of patients. **(A)** The sensitivity and specificity of  $SUV_{max}$  for predicting the presence of plasm EGFR mutation in patients with NSCLC. **(B)** PFS of patients in  $SUV_{max(M)} < 4.8$  group and  $SUV_{max(M)} \geq 4.8$  group. The cutoff value is defined based on the Youden index.



**Figure 3** PFS and ORR of patients. **(A)** PFS of patients in the EGFR<sup>+</sup>p<sup>+</sup> group and EGFR<sup>+</sup>p<sup>-</sup> group. **(B)** ORR of patients in the EGFR<sup>+</sup>p<sup>+</sup> group and EGFR<sup>+</sup>p<sup>-</sup> group.

## Discussion

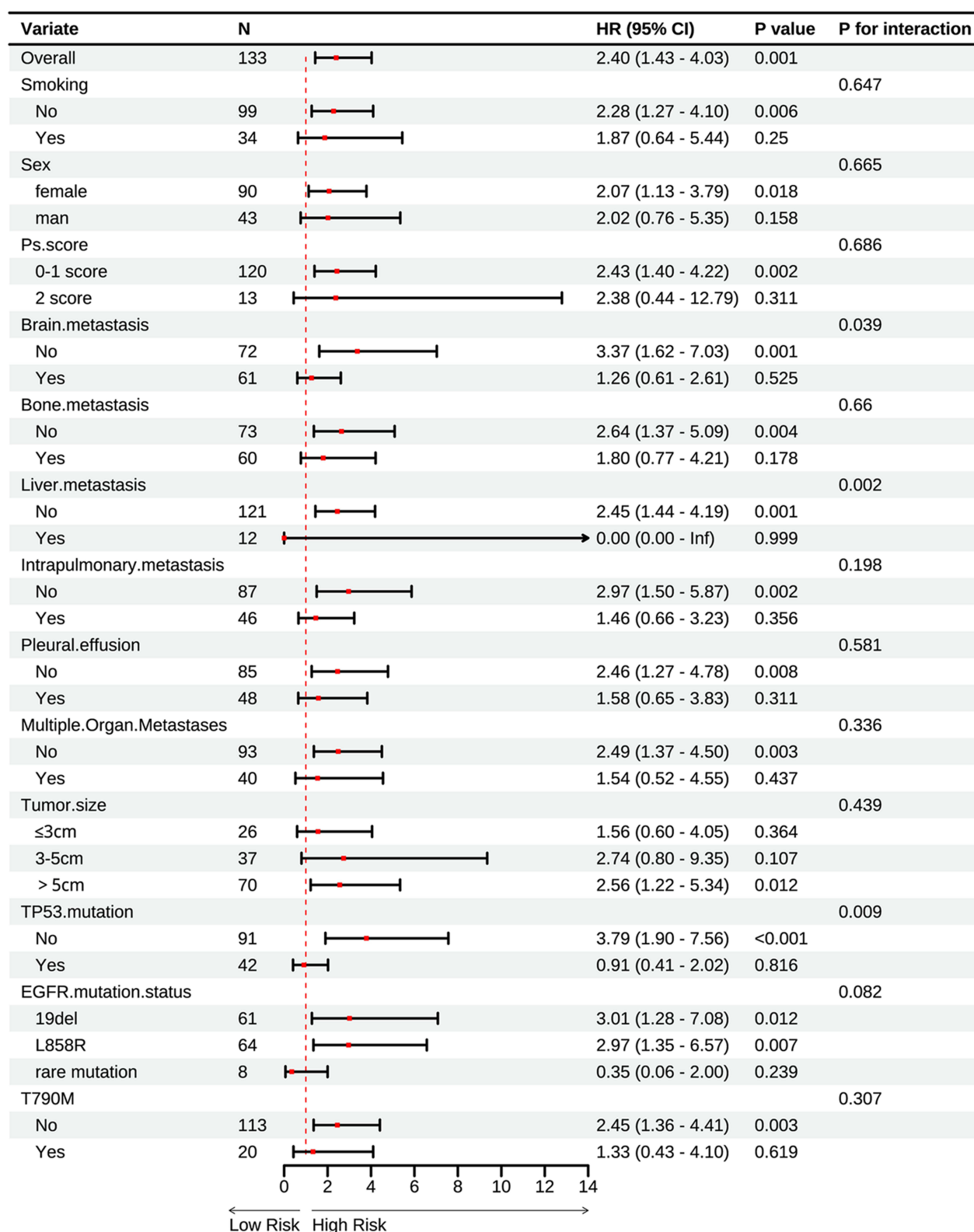
For advanced patients with NSCLC, EGFR-TKIs has become a standard treatment, significantly improving survival outcomes.<sup>28</sup> Consequently, the detection of EGFR mutations is crucial. Although tissue biopsy is considered the gold standard for EGFR mutation detection,<sup>29</sup> it also has many limitations.<sup>30</sup> Liquid biopsy has emerged as a clinically valuable alternative that addresses these limitations and offers a more comprehensive tumor mutation profile.<sup>31</sup> However, low tumor cell counts in liquid-based cell samples result in relatively low sensitivity for liquid biopsy, highlighting the urgent need to improve sensitivity. In our study, the sensitivity of Super-ARMS analysis for baseline patients was 68.1%, which is slightly lower than that of previous studies (71.4–79.5%) using tissue assays to detect EGFR mutations for targeted therapy in NSCLC.<sup>32,33</sup> This may be related to the sample size and patient inclusion selection bias.

**Table 2** Adjusted Association Between Patient Characteristics and PFS

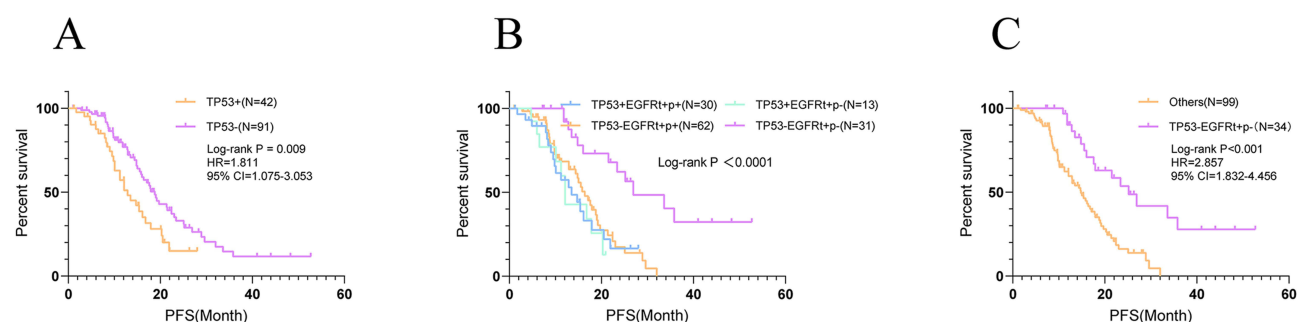
| Variables                          | Univariable Analysis<br>Log-Rank P | Multivariable Analysis |             |              |
|------------------------------------|------------------------------------|------------------------|-------------|--------------|
|                                    |                                    | HR                     | 95% CI      | P            |
| <b>Age (years)</b>                 |                                    |                        |             |              |
| ≥60                                | 0.236                              |                        |             |              |
| <60                                |                                    |                        |             |              |
| <b>Sex</b>                         |                                    |                        |             |              |
| Male                               | 0.111                              |                        |             |              |
| Female                             |                                    |                        |             |              |
| <b>Smoking history</b>             |                                    |                        |             |              |
| Yes                                | 0.206                              |                        |             |              |
| No                                 |                                    |                        |             |              |
| <b>Pleural effusion</b>            |                                    |                        |             |              |
| Yes                                | <b>0.002</b>                       |                        |             | 0.296        |
| No                                 |                                    |                        |             |              |
| <b>Intrapulmonary metastasis</b>   |                                    |                        |             |              |
| Yes                                | 0.579                              |                        |             |              |
| No                                 |                                    |                        |             |              |
| <b>Brain metastasis</b>            |                                    |                        |             |              |
| Yes                                | <b>0.003</b>                       |                        |             | 0.217        |
| No                                 |                                    |                        |             |              |
| <b>Bone metastasis</b>             |                                    |                        |             |              |
| Yes                                | 0.054                              |                        |             | 0.578        |
| No                                 |                                    |                        |             |              |
| <b>Liver metastasis</b>            |                                    |                        |             |              |
| Yes                                | <b>0.045</b>                       |                        |             | 0.147        |
| No                                 |                                    |                        |             |              |
| <b>Multiple Organ Metastases</b>   |                                    |                        |             |              |
| Yes                                | 0.005                              |                        |             | 0.647        |
| No                                 |                                    |                        |             |              |
| <b>T Stage</b>                     |                                    |                        |             |              |
| ≤3cm                               | 0.986                              |                        |             |              |
| 3–5cm                              |                                    |                        |             |              |
| ≥5cm                               |                                    |                        |             |              |
| <b>Stage</b>                       |                                    |                        |             |              |
| III                                | 0.205                              |                        |             |              |
| IV                                 |                                    |                        |             |              |
| <b>EGFR Mutation type</b>          |                                    |                        |             |              |
| Deletion 19                        | <b>0.006</b>                       | 0.294                  | 0.128–0.673 | <b>0.013</b> |
| Exon 21 (L858R)                    |                                    |                        |             |              |
| Rare mutation                      |                                    |                        |             |              |
| <b>T790M</b>                       |                                    |                        |             |              |
| Yes                                | <b>0.001</b>                       |                        |             | 0.496        |
| No                                 |                                    |                        |             |              |
| <b>TP53</b>                        |                                    |                        |             |              |
| Yes                                | <b>0.009</b>                       |                        |             | 0.149        |
| No                                 |                                    |                        |             |              |
| <b>EGFR</b>                        |                                    |                        |             |              |
| EGFR <sup>+</sup> , P <sup>+</sup> | <b>0.001</b>                       | 2.203                  | 1.303–3.725 | <b>0.003</b> |
| EGFR <sup>+</sup> , P <sup>−</sup> |                                    |                        |             |              |

**Note:** Statistically significant P values are given in bold.





**Figure 4** A forest plot of HRs for PFS.



**Figure 5** Risk stratification by EGFRm status and TP53. (A) PFS of patients in the TP53 mutation group and TP53 wild type group. (B) PFS of patients in the EGFR<sup>+</sup>, P<sup>+</sup> TP53 mutation group, EGFR<sup>+</sup>, P<sup>+</sup> TP53 wild group, EGFR<sup>+</sup>, P<sup>-</sup> TP53 mutation group and EGFR<sup>+</sup>, P<sup>-</sup> TP53 wild group. (C) PFS of patients between the EGFR<sup>+</sup>, P<sup>+</sup> TP53 mutation group and others.

The factors affecting the sensitivity of fluid-based assays are of considerable interest. As in previous studies,<sup>34–39</sup> we found that clinical indicators, including pleural effusion and organ metastasis were associated with higher assay sensitivity, likely due to the larger amounts of ctDNA released into the blood in these patients.<sup>40</sup> As a result, when patients have metastases, particularly bone and multiple metastases, suggesting the presence of a large tumor load, liquid biopsy may be considered an alternative to tissue biopsy for detecting EGFR mutations in patients with NSCLC. However, liquid biopsy is not a substitute for diagnostic tumor tissue biopsy, and repeat tumor tissue biopsy is recommended when the ctDNA test is negative.

Additionally, elevated levels of tumor markers, including CFRA21-1, CA125, and particularly CEA, were linked to the increased Super-ARMS sensitivity. Symonds et al found a significant correlation between ctDNA levels and tumor biomarkers in colorectal cancer.<sup>41,42</sup> However, research on the relationship between tumor biomarkers and ctDNA in lung cancer remains limited. Our study is the first to demonstrate that elevated levels of CEA, CFRA21-1, and CA125 are associated with high sensitivity in Super-ARMS testing in patients with NSCLC. These biomarkers can be used to predict positive detection. Additional ROC curve analysis reveals that tumor markers, specifically CEA, have significant diagnostic value in patients with positive Super-ARMS EGFR mutation tests. In the study of ctDNA dynamic changes, multiple studies have revealed that during tumor treatment response assessment, changes in ctDNA and tumor markers often occur synchronously or sequentially.<sup>43–45</sup> Our research also demonstrated that the dynamic change in CEA levels had predictive value for ctDNA testing. These results indicate that the level of tumor markers and their dynamic changes have predictive value for ctDNA detection results. The elevation of tumor markers usually reflects an increase in tumor size, possibly associated with distant metastasis, abnormal angiogenesis, or metabolic activity. These changes may all be linked to the increased cellular DNA entering the bloodstream. Therefore, in clinical practice, patients with lung cancer and higher levels of tumor markers are more suitable for ctDNA testing. Several studies have found a correlation between  $SUV_{max}$  and EGFR mutation,<sup>1,46,47</sup> although the results are not entirely similar. Ottestad et al found that ctDNA correlates with 18F-FDG PET/CT.<sup>40,48</sup> Our study further indicated that the  $SUV_{max}$  level holds predictive significance for ctDNA detection. This may be associated with higher  $SUV_{max}$  levels in patients, indicating active cell proliferation and apoptosis. These processes lead to increased DNA fragmentation, subsequently enhancing plasma ctDNA abundance, although the underlying mechanism remains elusive.

Many studies have revealed that ctDNA is an indicator of prognosis in patients undergoing treatment.<sup>49,50</sup> In this study, we concluded that the disparities between histology and plasma EGFR mutations could predict the prognosis of advanced patients with NSCLC undergoing EGFR-TKI treatment within a practical clinical context. This is consistent with the FLAURA study, which found that in NSCLC treated with osimertinib, the plasma ctDNA EGFRm-negative group observed a longer median progression-free survival compared to the plasma ctDNA EGFRm-positive group (23.5 versus 15.2 months).<sup>51</sup> This may be linked to patients with ctDNA-positive exhibiting a higher tumor burden, more extensive tumor dissemination, and enhanced immune escape.

In NSCLC, TP53 is the most mutated gene, and our study revealed that TP53 mutation is associated with the prognosis of patients with lung cancer. Moreover, the combination of TP53 and EGFR mutations provided a more precise

differentiation in prognosis, which was congruent with the results obtained in Xiao Liang's study.<sup>35</sup> This may be because individuals with TP53 mutations have disrupted apoptosis and increased genomic instability, which drives treatment resistance and tumor progression. Overall, combining TP53 plasma NGS and EGFR mutations using liquid biopsy optimizes the management of NSCLC.

Our study has certain limitations. First, it is a retrospective study with a relatively small sample size. Particularly, in the investigation focusing on assessing the relationship between the dynamic alterations of ctDNA and tumor markers, the sample quantity is insufficient. Hence, large-sample prospective cohort studies are warranted. Second, the follow-up duration is relatively brief, with the study endpoint being PFS rather than overall survival, potentially resulting in an inadequate comprehension of patients' survival states. Finally, this study is a single-center retrospective one, and a selection bias exists during the enrollment of study subjects. For example, patients with tumors may have differences in their prior treatment history and tumor heterogeneity, factors that could lead to bias in the results. Prospective and controlled studies need to be conducted to preclude biases stemming from relevant confounding factors and to manage irrelevant variables.

## Conclusions

Patients exhibiting metastasis, elevated levels of tumor markers and  $SUV_{max}$  are more suitable for plasma EGFR mutation testing. Moreover, a positive plasma ctDNA test not only guides targeted therapy but also predicts a worse prognosis.

## Abbreviations

EGFR, Epidermal Growth Factor Receptor; ctDNA, Circulating Tumor DNA; NSCLC, Non-Small Cell Lung Cancer; CEA, Carcinoembryonic Antigen;  $SUV_{max}$ , Maximum Standardized Uptake Value; PFS, Progression-Free Survival; EGFR-TKIs, Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors; AUC, Area Under the Curve.

## Data Sharing Statement

Availability of data and materials, the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This experiment was approved by the IRB of The First Affiliated Hospital of Sun Yat-sen University (approval no. [2022] 049). All procedures in the present study were conducted in accordance with the IRB of The First Affiliated Hospital of Sun Yat-sen University approved protocols.

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This study was carried out in the Critical Care Medicine, The First Affiliated Hospital of Sun Yat-sen University, located at No.58 Zhongshan Er Road, Yuexiu District, Guangzhou, Guangdong Province, P.R. China.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval to the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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