The Prognostic and Predictive Value of Pretreatment Serum Tumor Markers in Lung Adenocarcinoma with Different EGFR Status

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Abstract

**Background:** The prognostic value of carcinoembryonic antigen (CEA), cytokeratin-19 fragments (Cyfra21-1), neuron-specific enolase (NSE), Glycogen Antigen 153, Glycogen Antigen 199 has been investigated in Lung Adenocarcinoma (LUAD). However, few studies have directly focused on the association between serum tumor markers and epidermal growth factor receptor (EGFR) mutation status.

**Material and Method:** 146 patients with stage IIIIB and IV LUAD were enrolled between 2008 and 2018. Correlations between serum tumor marker levels, EGFR mutations and survival were analyzed and prognostic factors were identified.

**Result:** Of eligible 90 patients with EGFR-mutant LUAD, CA 15-3 (7 versus 9 months, 0.037 for PFS; 25 months versus 36 month, P = 0.003 for OS,) and Cyfra21-1 (7.0 versus 9.0 months, P =0.010 for PFS, 25 months versus 36 months, P=0.044 for OS,showed negatively significant correlation with overall survival and Progression free survival. For parents without EGFR-mutation, CA125 (month versus 8 months, P = 0.013 for DFS, 18 months versus 24 month, P = 0.016 for OS) also showed negatively significant correlation with overall survival and Progression free survival.

**Conclusion:** CA153 and Cyfra21-1 was a prognostic serum biomarker in EGFR-mutant LUAD patient, coincide with CA125 in EGFR-WT LUAD group.Cyfra21-1 levels was also a predictive serum biomarker for in EGFR-mutant LUAD patient who received EGFR-TKI treatment.

**Background**

The lung cancer in the morbidity and mortality was ranking first in various cancers worldwide. Only 10–15% of patients survive 5 years from diagnosis. Advanced NSCLC is fatal in 100% of cases (1), Lung adenocarcinoma (LUAD), which accounts for approximately 40% lung cancer, could be divided into EGFR-mutated LUAD group and EGFR-wild type LUAD group (2). EGFR-TKI therapy is a standard of treatment in advanced EGFR-mutant LUAD patients. EGFR exon 19 deletion (del19) and exon 21 Leu858Arg substitution (L858R) make up around 90% of all EGFR mutation-positive lung adenocarcinomas, which is closely associated with disease control rate and progression free disease (PFS) to EGFR tyrosine kinase inhibitors (3–4)

Measurement of serum tumor markers is a non-invasive means to monitoring efficacy of treatment and assess prognosis in cancers (5). Actually, serum cytokeratin 19 fragments (CYFRA 21 – 1), carcinoembryonic antigen (CEA) or neuron-specific enolase (NSE), Carbohydrate antigen 19 – 9, Carbohydrate antigen 125, Carbohydrate antigen 15 – 3 were used to be an independent prognostic marker and in non-small cell lung cancer (6–8). Some studies showed high level of serum Cytokeratin 19 was negatively correlated with Overall survival in LUAD (9), Other studies showed that Cytokeratin 19 level in serum has no prognostic value in patients with adenocarcinoma (10) CEA-high level was easier observed in LUAD harbored EGFR-mutation, but not be correlated with the EGFR-TKI effects of treatment (11). On the Contrary, pretreatment serum Tumor biomarker level such as CYFRA 21 – 1 was a
predictive marker of EGFR-TKI treatment in EGFR-mutated NSCLC patients (12). These data indicate that those tumor biomarkers may function differently in the initiation and progression of EGFR-mutant LUAD and EGFR-negative LUAD.

Herein, we identified that CYFRA 21 − 1 and CA153 was crucial in the prognostic of unrespectable LUAD patients with EGFR-mutated, while CA125 was of importance in the prognostic of those with EGFR-wildtype.

Material And Methods

Patient’s enrollment

Between April 2011 and April 2018, were diagnosed in Daping hospital and the EGFR status of these people was determined by DNA sequencing or qPCR. Diagnosis of LUAD was staged according to the TNM classification of the Union for International Cancer Control (8th edition). This study was approved by Daping Ethics Committee and conducted abided by the principle of the Declaration of Helsinki; a written consent was informed all patients. Primary treatment of was chemotherapy, radiotherapy, molecular targeting treatment either alone or in combination. Patients with EGFR-mutated received EGFR-TKI drugs were evaluated every 2 months by chest CT scans before treatment and then after 4 cycles of treatment. The tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST verus 1.1) (12). Progression disease free and overall survival was collected directly from the outpatient clinic records or from family contact. All the patients were followed at least two years.

Specimen Collection And Tumor Marker Assays

Specimen collection and tumor marker assays

The tumor serum biomarkers were detected before treatment initiation. Serum levels of CEA, CA199, CA125, CA153, NSE, CYFRA-21 were detected using electrochemiluminescence immunoassay on Roche Analytics E170 Immunology Analyzer (Roche Diagnostics, China). Based on manufacturer recommendation, the following cut-offs for serum marker levels were used: CEA 5.0 ng/ml, NSE 15.2 ng/ml, Cyfra21-1 3.3 ng/ml, CA153 28 U/mL, CA199 37U/mL, CA125 35U/mL.

Statistical analysis

Average value between groups was compared by using rank sum test for analysis. Progression-free survival (PFS) is defined as the time from the date of starting EGFR-TKI treatment to the date of tumor progression, the date of death or final follow-up. Overall survival (OS) was measured from the beginning of the date of diagnosis to death or the last follow-up. PFS and OS were determined the Log-rank test and by the Kaplan-Meier method for univariate analysis. And The Cox proportional hazards regression model was used to estimate the 95% confidence intervals (CIs) and hazards ratios (HR) in the univariate and
multivariate survival analyses. Data were analyzed using SPSS23.0 software (IBM Corp., Armonk, NY, USA). P values < 0.05 were considered statistically significant.

Results

Patient Characteristics

We retrospectively analyzed 146 patients diagnosed stage III-B-C or IV lung adenocarcinoma at Daping tumor Center General Hospital between April 2011 and April 2018. The clinic pathological characteristics were shown in Table 1. The population were included 73 males and 73 females, with a meanage of 51.1 years (range from 28 years to 80 years). Of 146 patients, 21 (14.38 %) patients had stage III-B-C disease, and EGFR Mutations were detected in 61.64% (90/146) adenocarcinoma cases. Among the 90 EGFR mutations, 37 were 19 exon del and 40 were L858R. Of the whole study population, 75 (51.37%) were bone metastasis and 46(31.51%)were brain metastasis. At the end of the last follow up, 100 patients had died and the median overall survival was 26.9 months, and the 2-year survival rate was 48.63 % for the whole group.
| Variable                  | Patients | %     |
|--------------------------|----------|-------|
| Gender                   |          |       |
| Male                     | 73       | 50.00 |
| Female                   | 73       | 50.00 |
| Age at diagnosis         |          |       |
| ⩽ 60                     | 88       | 60.27 |
| ≥ 60                     | 58       | 39.73 |
| Smoking history          |          |       |
| Never                    | 99       | 67.81 |
| Former/Current           | 47       | 32.19 |
| T stage                  |          |       |
| T1                       | 27       | 18.49 |
| T2                       | 55       | 37.67 |
| T3                       | 28       | 19.18 |
| T4                       | 36       | 24.66 |
| N stage                  |          |       |
| N0                       | 17       | 11.64 |
| N1                       | 18       | 12.33 |
| N2                       | 62       | 42.47 |
| N3                       | 49       | 33.56 |
| M stage                  |          |       |
| M0                       | 21       | 14.38 |
| M1                       | 125      | 85.62 |
| Bone metastasis          |          |       |
| Absent                   | 71       | 48.63 |
| Present                  | 75       | 51.37 |
| Brain metastasis         |          |       |
| Variable                  | Patients | %   |
|---------------------------|----------|-----|
| Absent                    | 100      | 68.49 |
| Present                   | 46       | 31.51 |
| EGFR mutation             |          |      |
| Wild-type                 | 56       | 38.36 |
| Positive                  | 90       | 61.64 |
| Exon 19 deletion          | 37       | 25.34 |
| L858R substitution        | 34       | 23.29 |
| Others                    | 19       | 13.01 |
| Total                     | 146      | 100  |

Association of CA153/CYFRA21-1/CA125 with PFS and OS in advanced NSCLC

Six serum tumor markers such as CYFRA21-1, CEA, NSE, CA125, CA199 and CA153 were routinely assessed during the visits of LUAD and predict the overall survival time. Among the 146 patients, 26 (17.8%) had high CA153 levels, 83 (47.9%) had high CA125 levels, 24 (16.4%) elevated Cyfra21-1, 85 (51.8%) had high CEA levels, 8 (5.4%) elevated NSE 34 (23.2%) elevated CA199 respectively (Table 2).
Table 2
Clinical characteristics of patients with advanced lung adenocarcinoma for further analysis.

| Variable           | LAC |         |     | LAC |         |     |
|--------------------|-----|---------|-----|-----|---------|-----|
|                    | n   | Median  | P-value | Median | P-value |
| Gender             |     | PFS(mo) |     | OS(mo) |     |
| Male               | 73  | 8       | 0.010 | 26    | 0.010 |
| Female             | 73  | 13      |       | 37    |       |
| Age at diagnosis   |     |         |       |       |       |
| <60                | 88  | 9       | 0.367 | 31    | 0.324 |
| ≥ 60               | 58  | 8       |       | 37    |       |
| Smoking history    |     |         |       |       |       |
| Never              | 99  | 10      | 0.025 | 36    | 0.028 |
| Former/Current     | 47  | 8       |       | 25    |       |
| Clinical stage     |     |         |       |       |       |
| I                 | 21  | 6       | 0.000 | 22    | 0.000 |
| II                | 125 | 10      |       | 36    |       |
| CEA                |     |         |       |       |       |
| <5ng/ml            | 61  | 8.5     | 0.944 | 32    | 0.922 |
| ≥ 5ng/ml           | 85  | 10      |       | 28    |       |
| CA153              |     |         |       |       |       |
| <31.3U/ml          | 120 | 9       | 0.037 | 36    | 0.003 |
| ≥ 31.3U/ml         | 26  | 7       |       | 25    |       |
| CA125              |     |         |       |       |       |
| <35 U/ml           | 77  | 10      | 0.074 | 37    | 0.062 |
| ≥ 35 U/ml          | 69  | 8       |       | 26    |       |
| CA199              |     |         |       |       |       |
| <35U/ml            | 112 | 9       | 0.208 | 35    | 0.249 |
| ≥ 35U/ml           | 34  | 6.5     |       | 25    |       |
| Variable | LAC | Median PFS(mo) | P-value | Median OS(mo) | P-value |
|----------|-----|----------------|---------|---------------|---------|
| NSE      |     |                |         |               |         |
| ≥25ng/ml | 138 | 9              | 0.011   | 31            | 0.168   |
| ≥ 25ng/ml| 8   | 4              |         | 18            |         |
| Cyfra21-1|     |                |         |               |         |
| ≥7 ng/ml | 122 | 10             | 0.010   | 32            | 0.044   |
| ≥ 7 ng/ml| 24  | 6              |         | 22            |         |
| Total    | 146 |                |         |               |         |

Out of the serum markers only CA 15–3 (7 versus 9 months, P = 0.037 for PFS, 25 months versus 36 month, P = 0.003 for OS, Fig. 1A, Table 2) and Cyfra21-1 (7.0 versus 9.0 months, P = 0.010 for PFS, Fig. 2C; 25 months versus 36 months, P = 0.044 for OS, Fig. 1B; Table 2) showed a negatively significant correlation with overall survival and Progression free survival.

However, Elevated CEA, CA199, CA125 patients did not exhibit any difference in OS nor PFS as compared with those with normal levels (Supplementary Fig. 1, Table 2). Furthermore, we found the patients with high level of NSE showed shorter PFS as compared with low level of NSE (Supplementary Fig. 1).

**Correlation ship of increased CA125/CYFRA21-1/CA153 with PFS and OS based on EGFR mutation status.**

In order to explore serum tumor biomarker in LUAD with different EGFR status, the population were divided into two groups: EGFR-mutant LUAD and EGFR-wild type LUAD. We found that the positive rate of CEA was significantly higher in EGFR-MT LUAD than that in EGFR-WT LUAD (63.33% versus 46.55%, P = 0.027). However, no significantly difference in others were observed in EGFR-MT LUAD group as compared with EGFR-WT NSCLC group (Table 4).
Table 4
Association between clinical characteristics and progression-free survival or overall survival among 90 patients with advanced stage lung adenocarcinoma with EGFR-mutant

| Variable                  | EGFR mutation | n  | Median PFS(mo) | P-value | Median OS(mo) | P-value |
|---------------------------|---------------|----|----------------|---------|---------------|---------|
| Gender                    |               |    |                |         |               |         |
| Male                      | 35            | 7  | 0.005          |         | 36            | 0.086   |
| Female                    | 55            | 16 |                | 43      |               |         |
| Age at diagnosis          |               |    |                |         |               |         |
| ≥60                       | 51            | 14 | 0.318          |         | 36            | 0.227   |
| ≥ 60                      | 39            | 17 |                | 42      |               |         |
| Smoking history           |               |    |                |         |               |         |
| Never                     | 71            | 15 | 0.058          |         | 39            | 0.365   |
| Former/Current            | 23            | 7  |                | 37      |               |         |
| Clinical stage            |               |    |                |         |               |         |
| □                         | 9             | 6  | 0.087          |         | 23            | 0.084   |
| △                         | 85            | 15 |                | 39      |               |         |
| CEA                       |               |    |                |         |               |         |
| ≥5ng/ml                   | 32            | 13 | 0.629          |         | 39            | 0.705   |
| ≥ 5ng/ml                  | 58            | 15 |                | 37      |               |         |
| CA153                     |               |    |                |         |               |         |
| ≥31.3U/ml                 | 75            | 15 | 0.022          |         | 39            | 0.006   |
| ≥ 31.3U/ml                | 15            | 10 |                | 24      |               |         |
| CA125                     |               |    |                |         |               |         |
| ≥35 U/ml                  | 45            | 16 | 0.205          |         | 42            | 0.223   |
| ≥ 35 U/ml                 | 45            | 11 |                | 37      |               |         |
| CA199                     |               |    |                |         |               |         |
| ≥35U/ml                   | 71            | 14 | 0.524          |         | 39            | 0.528   |
| ≥ 35U/ml                  | 19            | 15 |                | 32      |               |         |
EGFR-mutated LUAD patients with either elevated CA153 or Cyfra21-1 exhibited both shorter DFS and OS (CA153: 10.0 versus 15 months, P = 0.022 for PFS, Figure 2A; 24 months versus 39 month, P = 0.006 for OS, Fig. 2A; CYFRA21-1: 6.0 versus 15.0 months, P = 0.008 for PFS, Fig. 2C; 31 months versus 43 months, P = 0.017 for OS, Fig. 2B; Table 4). Abnormal CA125 levels were not correlated with DFS or OS in EGFR-mutated NSCLC (Fig. 2C;Table 4).

On the Contrary, EGFR-WT NSCLC patients with high expression of CA125 showed worse PFS and OS(CA125: 5 month versus 8 months, P = 0.013 for DFS, Fig. 3A,18 months versus 24 month, P = 0.016 for OS, Fig. 3B;Table 5)No relationship was found between increased CA153 or CYFRA21-1 in PFS or OS (Table 3).
| Variable | EGFR mutation | EGFR Wild-type | P-value |
|----------|---------------|----------------|---------|
|          | N = 90        | N = 56         |         |
| Positive (n) |              |                |         |
| CEA      | 57            | 27             | 0.027   |
| CA153    | 15            | 11             | 0.684   |
| CA125    | 45            | 24             | 0.401   |
| CA199    | 19            | 15             | 0.430   |
| NSE      | 4             | 4              | 0.486   |
| Cyfra21-1| 16            | 8              | 0.580   |
Table 5
Association between clinical characteristics and progression-free survival or overall survival among 56 patients with advanced stage LUAD with EGFR-wildtype

| Variable                     | EGFR wild-type |        |        | P-value |        | P-value |
|------------------------------|----------------|--------|--------|---------|--------|---------|
|                              | n              | Median | PFS(mo)|         | Median | OS(mo)  |
| Gender                       |                |        |        |         |        |         |
| Male                         | 38             | 8      | 0.189  | 22      | 0.748  |
| Female                       | 18             | 5.5    |        | 21      |        |
| Age at diagnosis             |                |        |        |         |        |         |
| <60                          | 37             | 7      | 0.748  | 24      | 0.363  |
| ≥ 60                         | 19             | 5      |        | 19      |        |
| Smoking history              |                |        |        |         |        |         |
| Never                        | 29             | 6      | 0.800  | 22      | 0.444  |
| Former/Current               | 27             | 8      |        | 21      |        |
| Clinical stage               |                |        |        |         |        |         |
| <5                           | 13             | 4      | 0.005  | 16      | 0.044  |
| ≥ 5                           | 43             | 8      |        | 24      |        |
| CEA                          |                |        |        |         |        |         |
| <5ng/ml                      | 29             | 6      | 0.914  | 22      | 0.626  |
| ≥ 5ng/ml                     | 27             | 8      |        | 22      |        |
| CA153                        |                |        |        |         |        |         |
| <31.3U/ml                    | 45             | 6.5    | 0.964  | 22      | 0.355  |
| ≥ 31.3U/ml                   | 11             | 7      |        | 25      |        |
| CA125                        |                |        |        |         |        |         |
| <35 U/ml                     | 32             | 8      | 0.013  | 24      | 0.031  |
| ≥ 35 U/ml                    | 24             | 5      |        | 18      |        |
| CA199                        |                |        |        |         |        |         |
| <35U/ml                      | 41             | 7      | 0.621  | 22      | 0.576  |
| ≥ 35U/ml                     | 15             | 6      |        | 19      |        |
Multivariate analysis of prognostic factors in EGFR-MT NSCLC and EGFR-WT advanced NSCLC

Multivariate analysis showed that CA153 (HR = 3.227 for DFS; P = 0.011 HR = 2.940, P = 0.015 for OS) and Cyfra21-1 (HR = 2.768 for DFS; P = 0.027 HR = 2.343, P = 0.027 for OS) were independent prognostic factors in all EGFR-mutated NSCLC patients. Furthermore, For EGFR-WT patients, CA125 (HR = 3.917 for PFS; P = 0.001 HR = 2.350, P = 0.018 for OS) and metastasis stage (HR = 3.917, P = 0.001 for PFS) were independent predictive and prognostic factors (Table 6).
Table 6
Multivariate analysis of PFS and OS for LUAD patients

| Variable                  | PFS          |            | OS           |            |
|---------------------------|--------------|------------|--------------|------------|
|                           | HR(95%CI)    | P-value    | HR(95%CI)    | P-value    |
| EGFR mutation (N = 90)    |              |            |              |            |
| Gender                    | 2.399 (1.118–5.151) | 0.025      | 1.839 (0.874–3.870) | 0.109      |
| Age at diagnosis          | 0.883 (0.462–1.686)  | 0.706      | 0.654 (0.338–1.267) | 0.208      |
| Smoking history           | 0.766 (0.281–2.086)  | 0.602      | 0.877 (0.363–2.120) | 0.771      |
| T stage                   | 1.814 (0.989–3.328)  | 0.054      | 1.245 (0.666–2.325) | 0.493      |
| N stage                   | 0.581 (0.280–1.203)  | 0.144      | 0.906 (0.450–1.826) | 0.783      |
| M stage                   | 2.674 (1.141–3.086)  | 0.003      | 2.509 (1.762–3.211) | 0.050      |
| CA153                     | 3.227 (1.310–7.952)  | 0.011      | 2.940 (1.232–7.019) | 0.015      |
| Cyfra21-1                 | 2.768 (1.122–6.828)  | 0.027      | 2.343 (1.104–4.971) | 0.027      |
| EGFR wild-type (N = 56)   |              |            |              |            |
| Gender                    | 0.875 (0.341–2.247)  | 0.782      | 1.141 (0.452–2.875) | 0.780      |
| Age at diagnosis          | 1.359 (0.681–2.713)  | 0.385      | 1.241 (0.642–2.400) | 0.522      |
| Smoking history           | 0.669 (0.270–1.658)  | 0.385      | 0.997 (0.410–2.425) | 0.994      |
| T stage                   | 1.149 (0.597–2.211)  | 0.677      | 1.366 (0.722–2.587) | 0.338      |
| N stage                   | 1.203 (0.493–2.935)  | 0.684      | 0.935 (0.398–2.195) | 0.877      |
| M stage                   | 0.198 (0.082–0.482)  | 0.000      | 0.366 (0.169–0.793) | 0.011      |

Patients Harboring Egfr-mutant Treated With Egfr-tki Therapy

In all EGFR-mutant LUAD patients, 82 (87.2%) patients were treated with EGFR-TKI therapy and/or chemotherapy, either gefitinib 250 mg/day, erlotinib 150 mg/day, or cetinib 375 mg/d. 27 as a second-line therapy, and 9 as third-line or thereafter. After fourth-cycle treatment, 39 (47.56%) patients were PR, 13 (15.85%) were SD, 30 (36.59%) were PD respectively. PR and SD were defined as effective, while PD was regarded as ineffective. It is noteworthy that serum CEA,NSE, CA153, CA125, CA199 could not predict therapeutic effect for patients treated with EGFR-TKIs, while elevated CYFR21-1 showed lower efficacy for EGFR-TKI resistance. 66.65% VS 85.64%, P < 0.05 Fig. 4.
Discussion

Advanced LUAD is a heterogeneous and complex disease with poor prognosis. However, due to the discovery of EGFR tyrosine kinase inhibitors, EGFR mutation subgroup shows longer progression free disease rate and over survival rate than EGFR-WT subgroup (14). Furthermore, serum tumor markers have been proven associated with EGFR mutation status and efficacy of EGFR-TKI treatment in lung cancer (15) However, there is no a consensus regarding appropriate tumor markers to distinguish the prognosis and efficacy of EGFR-TKI in advanced LUAD patients with different EGFR status. Herein, we screened and identified that CA153 and Cyfra21-1 was a prognostic marker in EGFR-mutant LUAD patient, coincide with CA125 in EGFR-WT LUAD group.

CA15-3, a tumor antigen recognized by two monoclonal antibodies DF3 and 115D8, was firstly a biomarker for breast cancer since 1980s (16). In previous study, the sensitivity and specificities of CA15-3 was lower than other serum biomarkers, such as CEA and CYFRA21 in LUAD (17). Furthermore, CA153 in pleural fluid was significantly highly expressed than that in serum in the lung cancer (18), indicating CA153 was of importance in distinguish the cancer patient. However, some other studies shows CA153 does not improve the diagnostic efficacy in lung cancer (19), indicating CA153 play a complex role in lung cancer. Herein, we firstly reported that high level of CA153 in serum shows longer than that with low in EGFR-mutant LUAD, while not in EGFR-WT LUAD. Meanwhile, Cyfra21-1 was a prognostic serum marker in EGFR-mutant LUAD patient (20), the reduction in serum level of CYFRA21-1 was a reliable biomarker to predict immunotherapy efficacy in NSCLC patients. In our study, we found the pretreatment of Cyfra21-1 was a predictive serum biomarker for EGFR-TKI treatment.

EGFR mutations occurring in the kinase domain are strongly associated with EGFR-TKI sensitivity. However, subsequent studies revealed that this relationship was not perfect and various predictive markers such as KRAS mutation, EGFR gene copy number have been reported (21). Given the level of tumor biomarkers was correlated with survival time, we highly suspected that the tumor biomarkers could be associated with EGFR-TKI sensitivity (22). Our research concluded that among the above six tumor biomarkers, only the level of CYFRA21-1 can show whether patients with EGFR-mutant are sensitive to EGFR-TKI drug, suggesting that Chemotherapy, apart from EGFR-TKI treatment, might be added to the first treatment of patients with high level of CYFRA21-1 and advanced EGFR-mutation LUAD (23).

CA125, a heavily glycosylated protein and was first identified as an ovarian cancer antigen, was increased in NSCLC but decreased in rectal cancer (24) It was reported that preoperative serum CA125 levels were related with TNM stage in operable NSCLC and was to monitor the tumor recurrence and disseminated failure post operation (25) However, other research suggested that elevated serum CA125 was not correlate with tumor recurrence (26), indicating CA125 plays a complex role in different gene background of lung cancer. To our knowledge, we described that CA125 was closely related with poor prognosis in EGFR-Wild LUAD, not in EGFR-mutant LUAD.

In conclusion, CYFRA21-1 and CA153 were two prognostic markers in unrespectable adenocarcinoma patients harboring EGFR mutations; However, CA125 was an independent prognostic factor only for EGFR
wild-type adenocarcinoma patients. Furthermore, the level of CYFRA21-1 was also a predictive maker for EGFR-TKI treatment, of course, a prospective clinical trial is necessary to testify our present findings.

**Conclusions**

In common tumor biomarker, we screened that CYFRA 21 – 1 and CA153 was crucial in the prognostic of unrespectable LUAD patients with EGFR-mutated, while CA125 was of importance in the prognostic of those with EGFR-wildtype.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethical Committee of Daping Hospital of the Third Military Medical University. We got the agreement and signed consent form of the patient reported in our paper.

**Consent for publication**

The patients included in this study allowed this paper to include some information of their disease for publication.

**Availability of data and materials**

All data generated or analysed during this study are included in this published article [and its supplementary information files].

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

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References

1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv192–237.

2. Da Cunha Santos G, Shepherd FA, Tsao MS. EGFR mutations and lung cancer. Annu Rev Pathol. 2011;6:49–69.

3. Noronha, V., et al. Patil VM, Joshi A, Menon N, Chougule A, Mahajan A, Janu A, Gefitinib Vers J Clin Oncol, 2020. 38(2): p. 124–136.

4. Mok TS, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947–57.

5. Sturgeon C, Thongprasert S, Yang CH, Chu DT, Saijo N. Sunpaweravong P Practice guidelines for tumor marker use in the clinic. Clin Chem. 2002;48(8):1151–9.

6. Ma S, Shen LY, Qian N, Chen KN. The prognostic values of CA125, CA19.9, NSE, AND SCC for stage I NSCLC are limited. Cancer Biomark. 2011;10(3–4):155–62.

7. Sato Y, Fujimoto D, Uehara K, Shimizu R, Ito J, Kogo M, Teraoka S, et al. The prognostic value of serum CA 19 – 9 for patients with advanced lung adenocarcinoma. BMC Cancer. 2016;16(1):890.

8. Wang H, Zhu Z, Xiao Y, Ma N, Li HM, Wen ZG, et al. The value of serum tumor marker CA125 and CEA in the diagnosis of non-small cell lung cancer]. Zhongguo Fei Ai Za Zhi. 2008;11(1):97–100. doi. 10.3779/j.issn.

9. Hsieh TC, et al. Diagnostic value of tumor markers in lung adenocarcinoma-associated cytologically negative pleural effusions. Cancer Cytopathol. 2013;121(9):483–8.

10. Kosacka M, Jankowska R. [The prognostic value of cytokeratin 19 expression in non-small cell lung cancer]. Pneumonol Alergol Pol. 2007;75(4):317–23.

11. Tanaka K, Hata A, Kaji R, Fujita S, Otoshi T, Fujimoto D, et al. Cytokeratin 19 fragment predicts the efficacy of epidermal growth factor receptor-tyrosine kinase inhibitor in non-small-cell lung cancer harboring EGFR mutation. J Thorac Oncol. 2013;8(7):892–8.
12. Torsello G, Polloniato PD, Pasini C. [The intravertebral vacuum phenomenon or gaseous dissection of the vertebral body]. Radiol Med. 1989;77(6):635–7.
13. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
14. Tomizawa Y, Iijima H, Sunaga N, Sato K, Takase A. Yoshimi Otani et al., Clinicopathologic significance of the mutations of the epidermal growth factor receptor gene in patients with non-small cell lung cancer. Clin Cancer Res. 2005;11(19 Pt 1):6816–22.
15. Feng LX, Wang J, Yu Z, Song SA, Zhai WX, Dong SH, et al., Clinical significance of serum EGFR gene mutation and serum tumor markers in predicting tyrosine kinase inhibitor efficacy in lung adenocarcinoma. 2019. 21(8): p. 1005–1013.
16. Li X, Xu Y, Zhang L. Serum CA153 as biomarker for cancer and noncancer diseases. Prog Mol Biol Transl Sci. 2019;162:265–76. doi. 10.1016/bs.pmbts.2019.01.005.
17. Wu H, Wang Q, Liu Q, Zhang Q, Huang Q, Yu Z. The Serum Tumor Markers in Combination for Clinical Diagnosis of Lung Cancer. Clin Lab, 2020. 66(3). http://doi: 10.7754/Clin.Lab.2019.190533.
18. Zou D, et al., [Expression and significance of CEA and CA153 in pleural fluid of patients with lung cancer]. Zhongguo Fei Ai Za Zhi, 2006. 9(4): 337–9. http://doi: 10.3779/j.issn.1009-3419.2006.04.08.
19. Wen Z, Huang Y, Ling Z, LUAD of Efficacy of Combined Carbohydrate Antigen Markers for Lung Cancer Diagnosis. 2020. 2020: p. 4716793.
20. Wang Q, Zheng H, Hu F, Zhang H, Hu Y, Li J, Zhang T, et al. [Serum CYFRA21-1 is Correlated with the Efficacy of Epidermal Growth Factor Receptor-tyrosine Kinase Inhibitor in Non-small Cell Lung Cancer Patients Harboring EGFR Mutations]. Zhongguo Fei Ai Za Zhi. 2016;19(8):550–8.
21. Uramoto H, Mitsudomi T. Which biomarker predicts benefit from EGFR-TKI treatment for patients with lung cancer? Br J Cancer. 2007;96(6):857–63.
22. Que D, Xiao H, Zhao BJ, Zhang X, Wang QS, Xiao HL, et al. EGFR mutation status in plasma and tumor tissues in non-small cell lung cancer serves as a predictor of response to EGFR-TKI treatment. Cancer Biol Ther. 2016;17(3):320–7.
23. Hosomi Y, et al. Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non-Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study. J Clin Oncol. 2020;38(2):115–23.
24. Zhang, M.,Morita S, Sugawara S, Kato T, Fukuhara T, Gemma A et al., Serum CA125 levels are decreased in rectal cancer but increased in fibrosis-associated diseases and in most types of cancers. Prog Mol Biol Transl Sci, 2019. 162: p. 241–252.
25. Gaspar MJ, Diez M, Rodriguez A, Ratia T, Duce AM, Galvan M, et al. Clinical value of CEA and CA125 regarding relapse and metastasis in resectable non-small cell lung cancer. Anticancer Res. 2003;23(4):3427–32.
26. Nuñez GR, Ito C, Del A, Giglio. Increased serum CA-125 levels in patients with lung cancer post thoracotomy. South Med J. 2009;102(4):427–8.
Figure 1

Kaplan-Meier survival curves of OS and PFS based on CA153/Cyfra21-1 levels in lung adenocarcinoma patients.
Figure 2

Kaplan-Meier survival curves of OS A and PFS B based on CA153/Cyfra21-1/CA125 levels in EGFR-mutant LUAD patients.
Figure 3

Kaplan-Meier survival curves of OS and PFS based on CA153/Cyfra21-1/CA125 levels in EGFR-WT LUAD patients.
Figure 4

χ² analysis showing the percentage of CEA, CA153, CA99, NSE, CA125, CYFRA21-1 in EGFR-TKI sensitive and EGFR-TKI resistant LUAD patients.

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