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# The relationship between thyroid transcription factor-1 positivity and epidermal growth factor receptor mutation in lung adenocarcinoma and its prognostic significance

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## Abstract:

**BACKGROUND AND AIM:** Thyroid transcription factor-1 (TTF-1) is a good prognostic factor and is also thought to be associated with driver mutations in lung cancer. This study aimed to evaluate the relationship between TTF-1 expression and prognosis and driver mutations in lung adenocarcinomas.

**METHODS:** We analyzed the data of 307 patients who were diagnosed with lung adenocarcinoma and underwent TTF-1 testing in two centers between January 2018 and January 2021.

**RESULTS:** Of the 307 patients included in the study, 231 were TTF-1 positive, 23 were weakly positive, and 53 were negative. There was no statistically significant relationship between TTF-1 positivity and progression-free survival (PFS) (p=0.492). However, overall survival (OS) was significantly longer in TTF-1 positive patients (p=0.005). Both PFS and OS were significantly longer in TTF-1 positive patients with multiple metastates (p=0.001, p=0.013). Of the 199 patients who underwent epidermal growth factor receptor (EGFR) mutation analysis, EGFR positivity was detected in 62 of them, and 58 patients were found to be in the TTF-1 positive group (p=0.022).

**CONCLUSIONS:** Thyroid transcription factor-1 positivity in lung adenocarcinomas is a good prognostic factor that often accompanies EGFR positivity.

## Keywords:

Epidermal Growth Factor Receptor (EGFR), lung adenocarcinoma, prognosis, Thyroid Transcription Factor-1 (TTF-1)

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## Introduction

Lung adenocarcinomas account for 40% of all lung cancers and are the leading cause of cancer death worldwide.[1] Thyroid transcription factor-1 (TTF-1), a 38 kDa nuclear protein, is encoded by a gene on the q13 arm of chromosome 14.[2] Thyroid transcription factor-1 is released from the fetal thyroid, lung, and brain during embryogenesis, and plays a role in the development of these organs. In adults, TTF-1 is released from the thyroid tissue and type 2 pneumocytes and contributes to the function of cells in the terminal respiratory unit.[1,3,4] Thyroid transcription factor-1 is an immunohistochemical (IHC) marker widely used in lung cancer diagnosis, and is secreted in 60-90% of lung adenocarcinomas.[5] Thyroid transcription factor-1 is mostly negative in other organ adenocarcinomas and squamous cell lung cancers, and is commonly used in the differential diagnosis of primary lung adenocarcinomas from metastatic lung adenocarcinomas.[5,6]

The relationship between TTF-1 positivity and prognosis in lung adenocarcinomas is conflicting. While many studies suggest TTF-1 as a good prognostic factor, some studies do not find any relationship between them.[3,7]

Epidermal growth factor receptor (EGFR) protein is associated with abnormal proliferation of cancer cells and has been detected in many malignant epithelial tumors, including non-small cell lung cancers.[8] Detecting EGFR mutation rates at a higher rate in TTF-1 positive patients is important because their life spans significantly increase with the development of EGFR tyrosine kinase inhibitors (TKIs).[9]

Several studies have investigated the relationship between TTF-1 and overall survival in lung adenocarcinomas, but the results remain controversial. The aim of this study was to examine whether expression is a good prognostic factor in lung adenocarcinomas and to explore the associations of other genetic mutations that have positive effects on survival, such as EGFR and Anaplastic Lymphoma Kinase (ALK), which are more common in TTF-1 positive patients.

## Materials and Methods

We conducted a retrospective review of the medical records of 352 patients diagnosed with lung adenocarcinomas at two medical oncology centers between January 2018 and January 2021. We excluded 45 patients from the study because they either did not undergo TTF-1 testing or their follow-up and treatment was conducted in another center. We collected data on age, gender, smoking history, stage, metastasis status, date of diagnosis, TTF-1, EGFR, ALK and c-ros oncogene 1, receptor tyrosine kinase (ROS-1) status, treatments received, treatment responses, dates of progression, and dates of death of the 307 patients from their medical records.

Progression-free survival (PFS) was calculated based on the date of progression from the diagnosis date of the patients or the last data entry date for patients who did not progress. Overall survival (OS) was calculated from the diagnosis date of the patients to the date of death or the last data entry date for surviving patients.

The Ventana device and TTF-1 (8G7G3/1) Mouse Monoclonal Antibody kit were used to detect TTF-1. Thyroid transcription factor-1 examination, which is an IHC method, was performed on 4-micron-thick tissue sections fixed with formalin and embedded in a paraffin block. Pathologists considered tumor cells positive when stained with TTF-1, negative when no staining was observed, and weakly positive when a few of the cells stained pale. Patients diagnosed with lung adenocarcinoma and at all stages, regardless of their stage, were included in the study, provided that they had undergone a TTF-1 test.

The real-time Polymerase Chain Reaction (PCR) method was used for EGFR mutation testing, and the Fluorescence In Situ Hybridization (FISH) method was used for ALK and ROS-1 testing.

All of the patients included in the study were diagnosed in a single center, and their diagnoses were confirmed by joint evaluation of all pathologists.

This study was approved by the hospital's Institutional Review Board on 13/01/2021 and conducted in accordance with the Helsinki Declaration. Informed consent was not required as it is a retrospective study.

### Statistical analysis

The data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 25.5 (IBM, NY, USA). The normality of the data was assessed using Shapiro-Wilk and Kolmogorov-Smirnov tests. Descrip-

**Table 1: Demografic data of the patients**

| | n | % | | n | % |
|---|---|---|---|---|---|
| Age (year) (mean±SD) | 62.6±10.3 | | RT and/or CT | 83 | 27.0 |
| Sex | | | Palliative | 26 | 8.5 |
| Female | 94 | 30.6 | SBRT | 6 | 2.0 |
| Male | 213 | 69.4 | Target-specific | 74 | 24.1 |
| Smoking | | | TTF-1 (n=307) | | |
| Current+ex | 224 | 73.0 | Positive | 231 | 75.2 |
| Never | 83 | 27.0 | Negative | 53 | 17.3 |
| Stage | | | Weak positive | 23 | 7.5 |
| Stage I+II | 100 | 32.6 | EGFR (n=199) | | |
| Stage IIIA | 35 | 11.4 | Positive | 62 | 31.1 |
| Stage IIIB | 18 | 5.9 | Negative | 137 | 68.8 |
| Stage IV | 154 | 50.2 | ALK (n=196) | | |
| Metastasis | | | Positive | 37 | 18.8 |
| No | 154 | 50.2 | Negative | 159 | 81.1 |
| Oligo | 79 | 25.7 | ROS-1 (n=156) | | |
| Multiple | 74 | 24.1 | Positive | 3 | 1.9 |
| Bone metastasis | 74 | 24.1 | Negative | 153 | 98.0 |
| Cerebral metastasis | 39 | 12.7 | Progression | 189 | 61.6 |
| LAP metastasis | 34 | 11.1 | Follow-up period (months) (mean±SD) (min-max) | 31.0±25.9 (1.0-166.4) | |
| Pleura metastasis | 43 | 14.0 | | | |
| Treatment | | | Mortality | 132 | 43.0 |
| Surgery | 118 | 38.4 | | | |

SD: Standard deviation, LAP: Lymphadenopathy, RT: Radiotherapy, CT: Chemotherapy, SBRT: Stereotactic body radiation therapy, TTF-1: Thyroid transcription factor-1, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ROS-1: Receptor tyrosine kinase

tive statistics were used to summarize the data. The Chi-Square test was used to compare categorical variables between groups, while the Mann-Whitney U test and Student's t-test were used for comparison of continuous variables. The results were presented as median (min-max), mean±SD, number and percentage (%). Kaplan-Meier analysis was used to evaluate the effect of TTF-1 positivity and negativity on survival. The results were presented with both mean and median values, with 95% confidence intervals. A p-value <0.05 was considered statistically significant in all statistical analyses.

## Results

Of the 307 patients included in the study, 213 (69.4%) were male and 94 (30.6%) were female, with a mean age of 62.6 ± 10.3 years. Of these patients, 224 (73.0%) had a history of smoking. At the time of diagnosis, 135 (44.0%) patients were in stage 1, 2, or 3A, while 172 (56.0%) patients were in stage 3B or 4. Metastases were absent in 50.2% of the patients, with bone, pleura and brain metastases being the most common. Thirty-eight point four percent of the patients had undergone surgery, 27.0% had received chemotherapy and/or radiotherapy, and 8.5% followed only supportive treatment due to advanced age, poor performance, or the patient's refusal to receive any treatment. Table 1 presents all demographic data for the patients.

During a mean follow-up period of 31.0 ± 25.9 months, progression was observed in 186 (61.6%) patients, and 132 (43.0%) patients died during treatment or follow-up.

We detected TTF-1 positivity in 231 (75.2%) patients, weakly positive in 23 (7.5%), and negative in 53 (17.3%) patients. EGFR mutation analysis was performed on 199 patients, with EGFR mutation positivity found in 62 (31.1%) of these patients. Of the EGFR-positive patients, 58 (34.3%) were also TTF-1 positive, while only 4 (13.3%) were TTF-1 negative (p=0.022). Thirty-two (19.3%) ALK-positive patients were also TTF-1 positive, while five (16.7%) ALK positive patients were TTF-1 negative. Although three (2.3%) patients with ROS-1 positivity were found to be TTF-1 positive, the relationship between TTF-1 positivity and both ALK and ROS-1 was not statistically significant (p=0.737 and p=0.445, respectively) (Table 2). In the correlation analysis, a weak but statistically significant correlation was found between TTF-1 and EGFR (r=0.208, p=0.003). No statistically significant correlation was found between TTF-1 and ALK or ROS-1.

**Table 2: Comparison of TTF-1 groups with EGFR, ALK, and ROS-1 positivity and negativity**

| | TTF-1 positive+weak positive | | TTF-1 negative | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| EGFR | | | | | |
| Positive | 58 | 34.3 | 4 | 13.3 | 0.022 |
| Negative | 111 | 65.7 | 26 | 86.7 | |
| ALK | | | | | |
| Positive | 32 | 19.3 | 5 | 16.7 | 0.737 |
| Negative | 134 | 80.7 | 25 | 83.3 | |
| ROS-1 | | | | | |
| Positive | 3 | 2.3 | 0 | 0.0 | 0.445 |
| Negative | 128 | 97.7 | 25 | 100.0 | |

TTF-1: Thyroid transcription factor-1, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ROS-1: Receptor tyrosine kinase

When we evaluated the patients overall, we observed that the stage and number of metastases were directly associated with the rate of progression and mortality (p<0.001). We also observed that bone, liver, adrenal, and brain metastases, in particular, had a negative impact on progression (p<0.001, p=0.007, p=0.009, p=0.035, respectively). Bone, liver, brain, adrenal, and lymph node metastases were found to be associated with higher mortality rates (p<0.001, p=0.004, p=0.004, p=0.007, p=0.007, respectively). Mortality was lower in EGFR-positive patients (p=0.021), and the mortality rate was also lower in female patients (p=0.009). While the progression rate was similar between the female and male groups, all data are presented in Table 3.

The PFS was 53.3±5.5 months in TTF-1 positive patients and 40.4±6.7 months in negative patients (p=0.492). The mean OS was 82.7±6.4 months in TTF-1 positive patients and 53.8±7.7 months in negative patients (p=0.005) (Table 4) [Fig. 1]. The progression free survival was calculated as 19.0±3.1 months, and OS was 26.8±3.7 months in TTF-1 positive patients with multiple metastases, while PFS was 5.8±1.7 months and OS was 10.2±2.7 months in TTF-1 negative patients. Progression-free survival and OS were longer in patients with multiple metastates who showed TTF-1 positivity (p=0.001, p=0.013, respectively) (Table 5). When only stage 4 patients were evaluated, OS was found to be statistically significantly longer in the TTF-1 positive group than in the focally positive and TTF-1 negative groups (median OS: 32.1 months, 8.6 months, and 5.2 months, respectively, p=0.009). In addition, in these patients, PFS was found to be statistically significantly longer in the TTF-1 positive group than in the focally positive and TTF-1 negative groups (median PFS: 15.4 months, 4.6 months, and 3.5 months, respectively, p=0.002).

## Discussion

Lung cancer is the most common type of cancer in the world, primarily due to its high blood supply. It also tends to metastasize to the lungs more frequently than other organs, making it a leading cause of cancer-related deaths.[10] Thyroid transcription factor-1 is a diagnostic biomarker for lung adenocarcinoma and small cell lung carcinoma (SCLC), and also an important prognostic factor for survival.[11,12] In this study, we investigated the impact of TTF-1 release on prognosis and its correlation with EGFR, ALK, and ROS-1 mutations in a large population of patients diagnosed with primary lung adenocarcinoma.

In this study, 231 (75.2%) patients showed TTF-1 positivity, while 53 (17.3%) were TTF 1 negative, and 23 (7.5%) were weakly positive. Due to limited availability, we could not perform genetic mutation analysis on every patient. However, out of the total patient population, 199 patients underwent EGFR mutation analysis, while 196 patients had ALK, and 156 patients had ROS-1 examinations. When we analyzed the relationship between all three mutations and TTF-1 expression, we found positivity in 62 (31.1%) out of 199 patients who underwent EGFR mutation analysis. Out of the TTF-1 positive patients, 58 (34.3%) were also EGFR positive, while only four (13.3%)

**Table 3: Comparison of demographic and clinical characteristics of patients with and without progression and mortality**

| | Progression present n=189 | | Progression absent n=118 | | p | Mortality present n=132 | | Mortality absent n=175 | | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | | n | % | n | % | |
| Sex | | | | | | | | | | |
| Female | 56 | 29.6 | 38 | 32.2 | 0.634 | 30 | 22.7 | 64 | 36.6 | 0.009 |
| Male | 133 | 70.4 | 80 | 67.8 | | 102 | 77.3 | 111 | 63.4 | |
| Stage | | | | | | | | | | |
| Stage I+II | 39 | 20.6 | 61 | 51.7 | <0.001 | 20 | 15.2 | 80 | 45.7 | <0.001 |
| Stage IIIA | 18 | 9.5 | 17 | 14.4 | | 9 | 6.8 | 26 | 14.9 | |
| Stage IIIB | 17 | 9.0 | 1 | 0.8 | | 14 | 10.6 | 4 | 2.3 | |
| Stage IV | 115 | 60.8 | 39 | 33.1 | | 89 | 67.4 | 65 | 37.1 | |
| Metastasis | | | | | | | | | | |
| No | 74 | 39.2 | 80 | 67.8 | <0.001 | 43 | 32.6 | 111 | 63.4 | <0.001 |
| Oligo | 56 | 29.6 | 23 | 19.5 | | 40 | 30.3 | 39 | 22.3 | |
| Multiple | 59 | 31.2 | 15 | 12.7 | | 49 | 37.1 | 25 | 14.3 | |
| Liver metastasis | 21 | 11.1 | 3 | 2.5 | 0.007 | 17 | 12.9 | 7 | 4.0 | 0.004 |
| Adrenal metastasis | 20 | 10.6 | 3 | 2.5 | 0.009 | 16 | 12.1 | 7 | 4.0 | 0.007 |
| Bone metastasis | 59 | 31.2 | 15 | 12.7 | <0.001 | 47 | 35.6 | 27 | 15.4 | <0.001 |
| Cerebral metastasis | 30 | 15.9 | 9 | 7.6 | 0.035 | 25 | 18.9 | 14 | 8.0 | 0.004 |
| LAP metastasis | 26 | 13.8 | 8 | 6.8 | 0.058 | 22 | 16.7 | 12 | 6.9 | 0.007 |
| Other | 11 | 5.8 | 3 | 2.5 | 0.181 | 10 | 7.6 | 4 | 2.3 | 0.028 |
| TTF-1 | | | | | | | | | | |
| Positive | 141 | 74.6 | 90 | 76.3 | 0.697 | 93 | 70.5 | 138 | 78.9 | 0.239 |
| Negative | 35 | 18.5 | 18 | 15.3 | | 27 | 20.5 | 26 | 14.9 | |
| Weak positive | 13 | 6.9 | 10 | 8.5 | | 12 | 9.1 | 11 | 6.3 | |

In the comparison between groups, the Student's t-test was used for normally distributed continuous parameters, the Mann-Whitney U test for non-normally distributed continuous variables, and the Chi-square and Fisher's exact tests for categorical parameters. Results are presented as mean ± SD, median (min-max), and n (%). A p-value of <0.05 was considered statistically significant. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used for normality testing. LAP: Lymphadenopathy, TTF-1: Thyroid transcription factor-1

of the TTF-1 negative patients showed EGFR positivity. We observed a strong linear relationship between EGFR positivity and TTF-1 positivity (p=0.022). In a study conducted by Chen et al.,[8] they evaluated 213 patients with lung adenocarcinoma in terms of the relationship between TTF-1 and EGFR, and found that the incidence of EGFR mutation increased as TTF-1 expression increased, similar to our study. They observed EGFR mutations in 48 (52.74%) out of 91 TTF-1 strongly positive patients (p<0.001), while only 15 (22.40%) out of 67 TTF-1 negative patients were EGFR positive.

In our study, we evaluated the relationship between ALK expression and TTF-1, and found positivity in 37 (18.8%) out of 196 patients. Out of these, 32 (19.3%) were from the TTF-1 positive group, and only five (16.7%) were from the negative group. We identified three ROS-1 positive patients out of 156 patients, all of whom were TTF-1 positive (2.3%). However, there was no statistically significant difference found for either ALK or ROS-1, possibly due to the insufficient number of patients and tests. In a study by Warth et al.,[13] they examined a population of 412 patients with lung adenocarcinoma and found that only six ALK positive patients were in the TTF-1 positive group of 360 patients. However, this was still not statistically significant.

Interestingly, in another study, they investigated 211 patients with 168 TTF-1 positive and found that three (7%) of the five ALK positive patients were in the TTF-1 negative group, while two (1.19%) were in the TTF-1 positive group. This relationship between TTF-1-negative patients and ALK positivity was statistically significant (p=0.018). However, we could not find any other studies that supported Rodriguez's study.[14] When we analyzed the study of Koh et al.,[15] they found that 12 (26.7%) ALK positive patients were from the TTF-1 positive group, which is in correlation with our data. They also found that there was no patient in the negative arm, and that 12 (26.1%) EGFR positive patients were from the TTF-1 positive group, while three (6.5%) were from the TTF-1 negative group, similar to our study (p=0.045).

**Table 4: Comparison of TTF-1 status with PFS and OS**

| | Mean | | Median | | |
|---|---|---|---|---|---|
| | PFS (months) | 95%CI | PFS (months) | 95%CI | p |
| TTF-1 status | | | | | |
| Positive | 53.3±5.5 | 42.5–64.1 | 22.0 | 18.5–25.5 | 0.492 |
| Negative | 40.4±6.7 | 27.3–53.6 | 15.1 | 8.1–22.2 | |
| Weak positive | 27.0±5.5 | 16.2–37.7 | 13.4 | 0.0–31.7 | |
| | OS (months) | 95%CI | OS (months) | 95%CI | p |
| TTF-1 status | | | | | |
| Positive | 82.7±6.4 | 70.2–95.3 | 61.2 | 46.9–75.4 | 0.005 |
| Negative | 53.8±7.7 | 38.7–69.0 | 35.0 | 19.0–51.0 | |
| Weak positive | 35.1±6.4 | 22.5–47.6 | 22.5 | 1.1–43.8 | |

Kaplan-Meier analysis was performed. Results are presented as median and mean with 95% confidence intervals. A p-value of <0.05 was considered statistically significant. TTF-1: Thyroid transcription factor-1, PFS: Progression-free survival, OS: Overall survival, CI: Confidence Interval

**Table 5: The relationship of metastasis status with PFS and OS according to TTF-1 expression**

| | Mean | | Median | | |
|---|---|---|---|---|---|
| | PFS (months) | 95%CI | PFS (months) | 95%CI | p |
| Nonmetastatic | | | | | |
| TTF-1 status | | | | | |
| Positive | 71.5±7.8 | 56.2–86.8 | 37.3 | 26.6–47.9 | 0.200 |
| Negative | 75.0±9.5 | 56.4–93.6 | – | – | |
| Oligometastasic | | | | | |
| TTF-1 status | | | | | |
| Positive | 23.1±2.6 | 17.9–28.3 | 17.7 | 14.1–21.4 | 0.783 |
| Negative | 28.0±10.2 | 7.8–47.8 | 12.8 | 5.3–20.3 | |
| Multiple metastasic | | | | | |
| TTF-1 status | | | | | |
| Positive | 19.0±3.1 | 12.9–25.1 | 11.5 | 8.4–14.6 | 0.001 |
| Negative | 5.8±1.7 | 2.4–9.2 | 3.7 | 1.7–5.6 | |
| | OS (months) | 95%CI | OS (months) | 95%CI | p |
| Nonmetastatic | | | | | |
| TTF-1 status | | | | | |
| Positive | 105.1±8.0 | 89.3–120.8 | – | – | 0.877 |
| Negative | 74.2±15.0 | 44.8–103.6 | – | – | |
| Oligometastatic | | | | | |
| TTF-1 status | | | | | |
| Positive | 38.1±3.6 | 31.0–45.2 | 36.9 | 28.7–45.1 | 0.768 |
| Negative | 54.4±13.4 | 28.0–80.7 | 35.0 | 20.4–49.6 | |
| Multiple metastasic | | | | | |
| TTF-1 status | | | | | |
| Positive | 26.8±3.7 | 19.6–34.0 | 17.3 | 2.8–11.7 | 0.013 |
| Negative | 10.2±2.7 | 4.9–15.6 | 5.8 | 0.6–4.6 | |

Kaplan-Meier analysis was performed. Results are presented as median and mean with 95% confidence intervals. A p-value of <0.05 was considered statistically significant. PFS: Progression-free survival, OS: Overall survival, TTF-1: Thyroid transcription factor-1

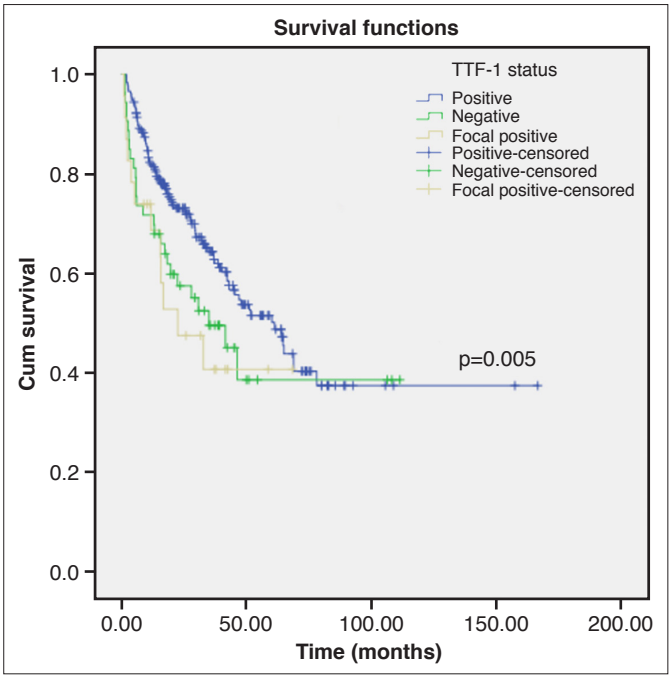


**Figure 1:** Kaplan-Meier analysis of OS according to TTF-1 expression
TTF-1: Thyroid transcription factor-1, OS: Overall survival

Although many publications have mentioned the association of TTF-1 expression with a good prognosis, there are not many studies on PFS.[16,14] Therefore, we examined the association of TTF-1 expression with PFS and OS in our study. We calculated the mean PFS as 53.3±5.5 months in our TTF-1 positive patients and 40.4±6.7 months in our negative patients. Although PFS was not statistically significant (p=0.492), it showed a longer time in terms of months. However, when stage 4 patients were evaluated separately, a statistically significant relationship was also found between TTF-1 and PFS (p=0.002). In contrast to our study, Oktay et al.[1] found the mean PFS as 7.7 months in TTF-1 positive patients and 8.8 months in TTF-1 negative patients.

When we evaluated the OS, we found that it was 82.7±6.4 months for TTF-1 positive patients and 53.8±7.7 months for negative patients, and it was statistically significant (p=0.005). Li et al.[16] found OS as 22.7 months in TTF-1 positive patients and 11.8 months in TTF-1 negative patients (p<0.0001). In a meta-analysis including 21 studies and 6451 patients with nonsquamous non-small cell lung cancer (NSLC), TTF-1 expression was more significant in the early stage of the disease. It has been documented that TTF-1 positivity is associated with a longer OS not only in the early stage but at each stage (p<0.00001).[3] Considering these and similar studies, we can say that TTF-1 expression is a good prognostic factor that positively affects the survival of the disease.

When we looked at the association of TTF-1 positive and negative patients with other clinical features, we could not find any significant difference for PFS and OS. However, when we considered patients according to their metastasis status, the mean PFS was 19.0±3.1 months in multiple metastatic TTF-1 positive disease and 5.8±1.7 months in negative patients (p=0.001). The OS was 26.8±3.7 months in TTF-1 positive patients and 10.2±2.7 months in negative patients (p=0.013). We attributed our inability to detect this correlation in non-metastatic group to the fact that most of the patients in this group had undergone surgery. In solitary metastatic disease, we thought that lung surgery and metastasectomy operations were also effective in survival. We could not find any other study in the literature examining the effect of TTF-1 positivity and metastatic status on the prognosis of the disease.

The fact that our study was retrospective and the lack of patients' performance status in the patient records were limiting factors.

In conclusion, although TTF-1 is widely used in the differential diagnosis of lung adenocarcinomas, we found that it is also a good prognostic marker for survival. Thyroid transcription factor-1 positivity is associated with a better OS, and these patients also have a higher EGFR mutation frequency, which provides a better alternative treatment with the use of EGFR tyrosine kinase inhibitor (TKI).

## Conflicts of interest
There are no conflicts of interest.

## Ethics Committee Approval
The study was approved by the University oh Health Sciences Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee (No: 4, Date: 13/01/2021).

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## Peer-review
Externally peer-reviewed.

## Authorship Contributions
Concept – N.K.; Design – N.K., M.A.; Supervision – N.K.; Materials – N.K., M.A.; Data collection &/or processing – N.K., N.A.; Analysis and/or interpretation – N.K., P.Ç.; Literature search – N.K.; Writing – N.K., P.Ç.; Critical review – N.K., P.Ç., M.A.

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