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ORIGINAL RESEARCH

# Different Role of TRF1 and TRF2 Expression in Non-Small Cell Lung Cancers

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**Background:** TRF1, TRF2, and TERT (Telomerase reverse transcriptase) are telomere-associated factors that regulate telomere length. Genetic changes in these genes may be associated with cancer pathogenesis; however, this relationship has not yet been comprehensively elucidated in lung cancer.

**Aim:** : Exploring the clinicopathologic and prognostic values of TRF1, TRF2, and TERT mRNA expression in non-small cell lung cancers (NSCLC).

**Methods:** : The clinical significance of TRF1, TRF2, and TERT expression in 141 patients with NSCLC was investigated. Additionally, these findings were supported by the open big data from The Cancer Genome Atlas (TCGA).

**Results:** : TRF1 and TRF2 expression levels tended to be associated with smoking, and TERT expression was positively correlated with age. The survival analysis showed that TRF1 expression predicted a better prognosis for squamous cell carcinoma (SCC), whereas TRF2 expression was associated with a shorter survival in adenocarcinoma. TCGA data also showed a better prognosis for SCC with TRF1 expression. However, the TRF2 results were not in agreement with our data.

**Conclusions:** : We present the clinical and prognostic values of TRF1, TRF2, and TERT expression in NSCLC tissues and TCGA. Our findings suggest that TRF1 expression is a possible prognostic marker for NSCLC, particularly SCC.

**Keywords:** TRF1, TRF2, TERT, telomere, lung cancer

## Background

Telomeres, comprised of TTAGGG repeat sequences, are nucleoprotein complexes that cap the ends of eukaryotic chromosomes.[1] Telomeres in normal somatic cells are shortened by approximately 0–200 base pairs at every cell division and have a critical length at which replicative senescence or apoptosis is initiated.[2,3] Therefore, the regulation of telomeres within an optimal length is essential for cell survival.[1–3] In cancer cells, preneoplastic or early stage of cancer cell suffer persistent telomere shortening leading to senescence, and then, this status is counteracted by the reverse transcriptase telomerase, whereas the remaining cells maintain telomere length via an alternative lengthening mechanism.[4,5] TRF1, TRF2, and TERT (Telomerase reverse transcriptase) are telomere-associated proteins that are part of the telomere structure and play essential roles in controlling telomere length.[6–8] TRF1 is a suppressor of telomere elongation.[6] TRF1 and TRF2 bind specifically to double-stranded TTAGGG repeats in the telomere. TRF2 is also a negative regulator of telomere length.[9] Therefore, overexpression of TRF2 results in progressive shortening of telomere length, similar to TRF1 overexpression. TERT is a ribonucleoprotein polymerase that maintains the telomere ends.[10] Its high expression sustains telomere length and genomic stability, thereby allowing cancer cells to divide continuously and preventing senescence or apoptosis.[11,12] To clarify the role of telomere regulation in cancer, mRNA expressions of TRF1, TRF2, and TERT should be comprehensively studied.

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Lung cancer is the leading cause of cancer-related deaths worldwide, with only 21% of lung cancer patients alive five years after diagnosis.[13] Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 85% of all cases.[14] Many causative factors for lung cancer have been identified, including active smoking, secondhand smoke, occupational agents, radiation, and environmental pollutants.[15] They may influence telomere regulation in human disease especially in NSCLC. Previous studies have suggested that deregulation of telomere length has the potential to serve as a prognostic marker in patients with NSCLC.[14,16] Therefore, we analyzed, for the first time, the clinical value of telomere regulatory genes in NSCLC.

Recent advances in genomic profiling using next-generation sequencing have made it possible to identify the genetic characteristics of cancers. Large-scale cancer genome studies such as The Cancer Genome Atlas (TCGA) have been conducted to investigate genes in different cancer types.[17,18] Moreover, TCGA can be used to investigate specific histological types of lung cancer, such as adenocarcinoma (AD) and squamous cell carcinoma (SCC), using histological data and clinical parameters. Therefore, we aimed to examine the clinicopathological and prognostic values of TRF1, TRF2, and TERT mRNA expression in NSCLC using patient tissues and TCGA datasets.

# Methods

## Patients and Tissues

A total of 141 patients (66.03 ± 8.19 years old, 42–84) were diagnosed as NSCLC and included in this study. Tissue samples from cancerous and paired adjacent non-cancerous tissues were obtained from the Keimyung Human Bioresource Bank, Korea. Data were obtained from patients who underwent surgery at the Dongsan Medical Center (Daegu, Korea) between April 2010 and January 2016. Our study complies with the Declaration of Helsinki. All patients were informed of the study purpose and informed consent was obtained from each participant before the research was conducted. Clinicopathological data of each patient were were re-evaluated during a review of their medical records. TNM staging of lung cancer was used according to the 8th AJCC staging system. This study was approved by the Institutional Review Board of Keimyung University Dongsan Medical Center (No. 2020–07-027).

## RNA Isolation and mRNA Expression Analysis

We extracted RNA from tissues using TRIzol reagent (Molecular Research Center Inc., Cincinnati, OH, USA). RNA quality was measured using a NanoDrop 1000 spectrophotometer (Thermo Scientific, Wilmington, Denmark). Each cDNA was synthesized from 2 μg of total RNA using M-MLV reverse transcriptase (Promega, Madison, WI, USA). qPCR was performed as previously described.[19,20] Each measurement was repeated in triplicate and five serially diluted control samples were included in each experiment.

## The Cancer Genome Atlas (TCGA) Data Analysis

Primary data from The Cancer Genome Atlas (TCGA) data portal were downloaded in March 2021. The TCGA dataset consisted of 1130 samples, including 1019 primary tumor tissues (517 AD and 502 SCC) and 111 normal solid tissues obtained from normal tissues adjacent to the tumor. To analyze the RNAseq data of NSCLC, AD and SCC datasets were sorted from TCGA with TZAP mRNA expression and clinical parameters. This study met the publication guidelines for using TCGA datasets (http://www.cancer.gov/about-nci/organization/ccg/research/structrual-genomics/tcga/using-tcga/citing-tcga). Overall survival (OS) was defined as the duration from the date of surgery to the date of the last follow-up visit or the date of death due to any cause, whereas disease-free survival (DFS) was defined as the duration from surgery to any type of recurrence.

## Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), version 24.0, for Windows (IBM, Armonk, NY, USA), was used for all statistical analyses. Chi-square and Mann–Whitney *U*-tests were used to analyze the relationships between variables. For survival analysis, the mean gene expression was used as a cutoff to divide patients into high- and low-expression groups. Survival analysis was performed using the Kaplan–Meier method, and the log rank test was used to identify statistically significant differences between the two groups. Statistical significance was defined as a two-tailed P value $< 0.05$.

## Results

TRF1, TRF2, and TERT expression were confirmed in 141 patients. The median value of TRF1, TRF2, and TERT expression was 1.30 ± 1.73, 1.47 ± 1.66, and 1.33 ± 1.78, respectively. Patients were divided into high and low expression group, and high expression of TRF1, TRF2, and TERT was found in 28.4%, 31.9%, and 24.0% of the NSCLC cases, respectively. The clinicopathological characteristics of NSCLC according to TRF1, TRF2, and TERT mRNA expression are summarized in Table 1. TRF1 and TRF2 expression were associated with smoking; however, this difference was not statistically significant (32.1% vs 15.6%, p = 0.068; 36.1% vs 18.2%, p = 0.053). Other variables did not correlate with TRF1 or TRF2 expression. TERT expression was significantly higher in older patients (32.3%) than in younger patients (11.9%) significantly (p = 0.02). TERT expression did not correlate with the other variables, such as TNM stage and EGFR mutation.

The median follow-up period in the cohort examined in the survival analysis was 80.7 ± 5.1 months (range: 0–155 months) in NSCLC. Univariate survival analysis revealed that OS in NSCLC patients was not associated with TRF1 (84.25 ± 9.0 vs 78.29 ± 5.90 months, P = 0.269), TFR2 (74.87 ± 9.24 vs 82.26 ± 6.03 months, P = 0.617), and TERT

**Table 1** Clinicopathological Characteristics of TRF1, TRF2, and TERT mRNA Expressions in NSCLC

| | TRF1 expression | | | TRF2 expression | | | TERT expression | | |
|---|---|---|---|---|---|---|---|---|---|
| | Low | High | P | Short | Long | P | Low | High | P |
| Total | 101 (71.6) | 40 (28.4) | | 96 (68.1) | 45 (31.9) | | 79 (76.0) | 25 (24.0) | |
| Age | | | 0.61 | | | 0.84 | | | 0.02 |
| ≤60 | 40 (74.1) | 14 (25.9) | | 38 (69.1) | 17 (30.9) | | 37 (88.1) | 5 (11.9) | |
| >60 | 61 (70.1) | 26 (29.9) | | 58 (67.4) | 28 (32.6) | | 42 (67.7) | 20 (32.3) | |
| Sex | | | 0.63 | | | 0.44 | | | 0.43 |
| Female | 24 (75.0) | 8 (25.0) | | 25 (73.5) | 9 (26.5) | | 19 (70.4) | 8 (29.6) | |
| Male | 77 (70.6) | 32 (29.4) | | 71 (66.4) | 36 (33.6) | | 60 (77.9) | 17 (22.1) | |
| Type | | | 0.32 | | | 0.15 | | | 0.35 |
| AD | 54 (77.1) | 16 (22.9) | | 52 (73.2) | 19 (26.8) | | 37 (72.5) | 14 (27.5) | |
| SCC | 37 (64.9) | 20 (35.1) | | 38 (66.7) | 19 (33.3) | | 37 (82.2) | 8 (17.8) | |
| Others | 10 (71.4) | 4 (28.6) | | 6 (46.2) | 7 (53.8) | | 5 (62.5) | 3 (37.5) | |
| Smoking | | | 0.07 | | | 0.05 | | | 0.80 |
| (-) | 27 (84.4) | 5 (15.6) | | 27 (81.8) | 6 (18.2) | | 21 (77.8) | 6 (22.2) | |
| (+) | 74 (67.9) | 35 (32.1) | | 69 (63.9) | 39 (36.1) | | 58 (75.3) | 19 (24.7) | |
| T stage | | | 0.45 | | | 0.62 | | | 0.73 |
| T1 | 34 (75.6) | 11 (24.4) | | 33 (73.3) | 12 (26.7) | | 25 (80.6) | 6 (19.4) | |
| T2 | 41 (65.1) | 22 (34.9) | | 41 (66.1) | 21 (33.9) | | 37 (74.0) | 13 (26.0) | |
| T3 | 17 (81.0) | 4 (19.0) | | 13 (59.1) | 9 (40.9) | | 11 (68.8) | 5 (31.2) | |
| T4 | 9 (75.0) | 3 (25.0) | | 9 (75.0) | 3 (25.0) | | 6 (85.7) | 1 (14.3) | |
| N stage | | | 0.79 | | | 0.73 | | | 0.67 |
| N0 | 74 (73.3) | 27 (26.7) | | 69 (68.3) | 32 (31.7) | | 56 (73.7) | 20 (26.3) | |
| N1 | 17 (68.0) | 8 (32.0) | | 18 (72.0) | 7 (28.0) | | 14 (82.4) | 3 (17.6) | |
| N2 | 10 (66.7) | 5 (33.3) | | 9 (60.0) | 6 (40.0) | | 9 (81.8) | 2 (18.2) | |
| Pathological stage | | | 0.28 | | | 0.49 | | | 0.58 |
| I | 55 (73.3) | 20 (26.7) | | 53 (71.6) | 21 (28.4) | | 43 (76.8) | 13 (23.2) | |
| II | 23 (62.2) | 14 (37.8) | | 23 (60.5) | 15 (39.5) | | 18 (69.2) | 8 (30.8) | |
| III | 23 (79.3) | 6 (20.7) | | 20 (69.0) | 9 (31.0) | | 18 (81.8) | 4 (18.2) | |
| Histology | | | 0.60 | | | 0.77 | | | 0.52 |
| Well/Moderate | 52 (72.2) | 20 (27.8) | | 48 (67.6) | 23 (32.4) | | 42 (80.8) | 10 (19.2) | |
| Poorly | 16 (66.7) | 8 (33.3) | | 17 (70.8) | 7 (29.2) | | 14 (73.7) | 5 (26.3) | |
| EGFR mutation | | | 0.56 | | | 0.66 | | | 0.93 |
| (+) | 13 (86.7) | 2 (13.3) | | 6 (60.0) | 6 (40.0) | | 11 (84.6) | 2 (15.4) | |
| (-) | 15 (78.9) | 4 (21.1) | | 11 (57.9) | 8 (42.1) | | 10 (83.3) | 2 (16.7) | |

(84.16 ± 10.98 vs 71.29 ± 5.9 months, P = 0.504) expression (Figure 1). When stratified by histology as squamous cell carcinoma and adenocarcinoma, higher TRF1 expression was associated with better survival results in squamous cell carcinoma (96.58 ± 12.75 vs 60.68 ± 8.38 months, P = 0.020; Figure 2A). Otherwise, higher TRF2 expression was associated with poorer survival result in adenocarcinoma (95.94 ± 8.0 vs 63.26 ± 10.87 months, P = 0.031; Figure 2B). The other variables did not have any effect on the prognosis of NSCLC.

To confirm these data from patient tissues, TCGA Big Data were used. Higher TRF1 expression was associated with better survival results in squamous cell carcinoma (2259.54 ± 148.74 vs 1907.52 ± 186.55 days, P = 0.011; Figure 3A). Survival analysis showed no prognostic value TRF2 expression in adenocarcinoma (2736.86 ± 377.25 vs 2355.92 ± 288.32 days, P = 0.795; Figure 3B). The other variables did not have any predictive potential for adenocarcinoma or squamous cell carcinoma.

## Discussion

In this study, we examine comprehensively the expression of TRF1, TRF2, and TERT in NSCLC tissues from patients and big data. Thus, these genes may play important roles in telomere regulation in various cancers.[5,10,16] Telomerase activation by the overexpression of these genes may favor cancer cell immortality and tumor progression. Short telomeres and telomerase activity are associated with poor survival in NSCLC.[21,22] And TRF2 and TERT expression showed poorer prognosis in NSCLS and telomere regulation suggested novel marker for NSCLS.[23] However, the role of

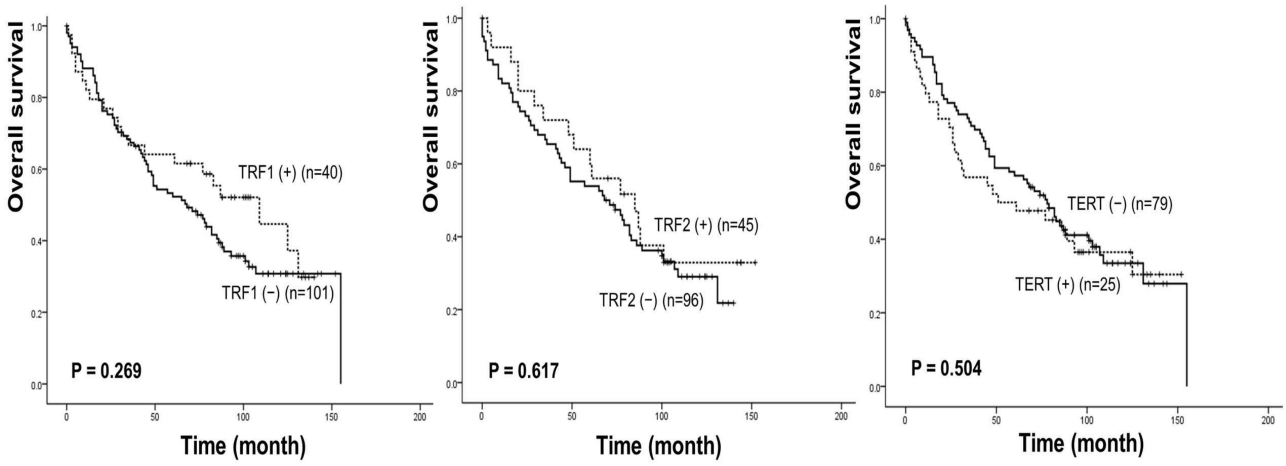


**Figure 1** Survival analysis in lung cancer according to TRF1, TRF2, and TERT expression.

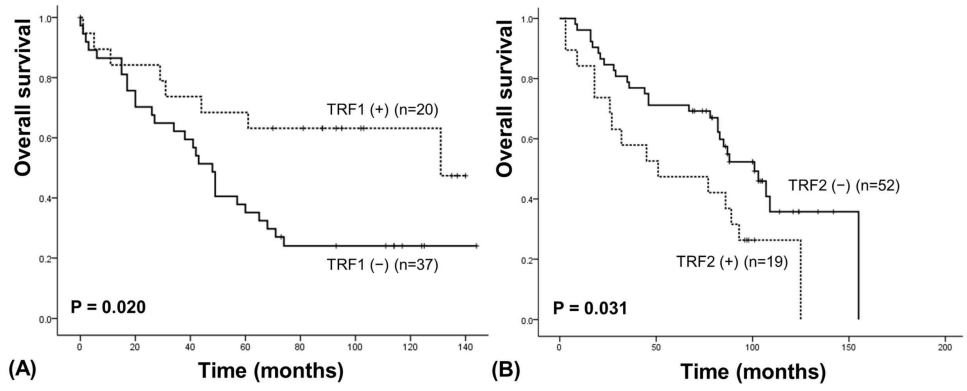


**Figure 2** Survival analysis of TRF1 in squamous cell carcinoma (**A**) and TRF2 in adenocarcinoma (**B**).

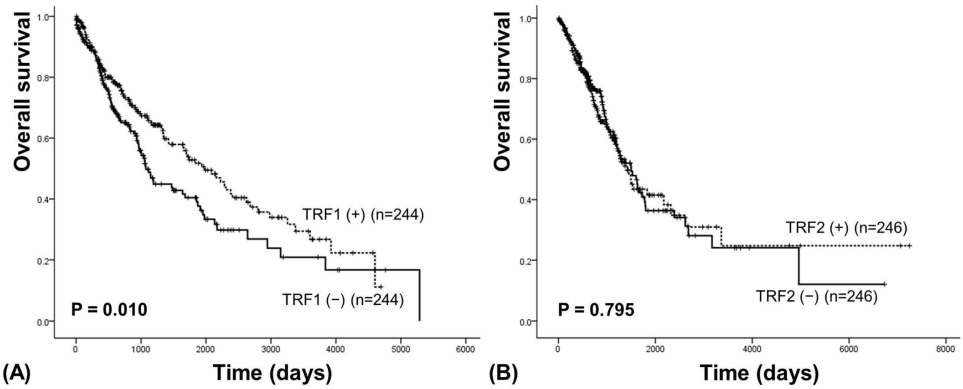


**Figure 3** Survival analysis of TRF1 in squamous cell carcinoma (**A**) and TRF2 in adenocarcinoma (**B**) by TCGA data.

telomeres in the prognosis of cancer remains unclear. To address this issue, we assessed the clinical characteristics and prognostic values of telomere regulatory genes in NSCLC patients.

We demonstrated that TRF1 and TRF2 expression levels were associated with smoking, although this association was not significant. TERT expression was higher in older patients with NSCLC. A previous study showed that the mRNA and protein levels of TRF1 and TRF2 were lower in smokers than in nonsmokers.[24] Smoking releases multiple toxic compounds that induce genetic instability. This status may involve the overuse of TRF1 and TRF2 to protect chromosome ends, and its level in cancer tissues is decreased.[25] Previous study showed that smoking induced lung carcinogenesis via various pathway such as COX, EGFR, and VEGF related pathways.[26,27] During lung carcinogenesis, TRF1 and TRF2 may increases gradually with with other pathways, and their co-expression may be extremely important.

Importantly, our results showed that TRF1 and TRF2 expression played different roles according to the NSCLC subtypes. In SCC, TRF1 expression was associated with better survival result, which is in agreement with the TCGA data. TRF2 expression has a prognostic value in AD; however, TCGA data did not show any statistical results. AD and SSC are widely believed to have different histological and biological signatures.[13,15] They are derived from different epithelial cells and have different genomic profiles. In prostate cancer, TRF1 expression is associated with a poor prognosis.[28] However, TRF1 may play a role for better result in SCC. TRF1 is essential for cellular pluripotency, tissue regeneration, and homeostasis.[29,30] TRF1 deletion induces telomere dysfunction and increases lung damage and inflammation.[31] This process may be associated with SCC carcinogenesis, supporting our result that TRF1 loss induced cancer progression in SCC. However, multivariate Cox-regression analysis showed that TRF1 and TRF2 did not have prognostic value when stratified by SCC and AD (Data not shown). It may be originated from unenough case number of cancer patients by stratified as SCC and AD. And important clinical characteristics such as pack-years, resection types, and et al was excluded in this study. Further study should be performed in various lung cancer cell lines and a large number of patient tissues.

## Conclusions

In conclusion, we studied the expression of TRF1, TRF2, and TERT in patients with NSCLC. Telomere changes are of great significance as clinical and prognostic markers of NSCLC. The results of the present study warrant future large-scale studies to elucidate the underlying molecular mechanisms of TRF1 and TRF2, and to determine their potential clinical utility.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Ethics Approval and Informed Consent

The human ethics and research ethics committees of Keimyung University Dongsan Medical Center approved the study (No. 2020-07-027).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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