Original Article

Telomere-related prognostic signature for survival assessments in lung adenocarcinoma

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Background: Telomere-related genes (TRGs) are important in many different types of cancers. However, there is a lack of research on the relationship between their expression and prognosis in lung adenocarcinoma (LUAD) patients. This study is to investigate the prognostic value of TRGs in LUAD and to develop a TRG signature that can predict patient survival.

Methods: A total of 2,086 TRGs were obtained from a database of genes involved in telomere maintenance (TelNet), while the clinical information and tumor RNA expression profiles of 513 LUAD patients were acquired from The Cancer Genome Atlas (TCGA) database. Statistical methodologies, such as least absolute shrinkage and selection operator (LASSO)-Cox, were employed to construct a prognostic model with predictive capabilities.

Results: We analyzed 1,339 telomere-associated differentially expressed genes and identified a ten-gene predictive signature for LUAD. This signature exhibited effective prognostic classification capabilities across multiple datasets, including GSE3141 (58 samples), GSE8894 (63 samples), GSE50081 (127 samples), and GSE72094 (398 samples). Furthermore, we screened tumor-sensitive drugs targeting this signature. High telomere levels were associated with reduced survival in lung cancer patients who underwent surgery. Compared to the traditional TNM (tumor node metastasis classification) grading method, our telomere-associated gene panel demonstrated superior prediction accuracy. Notably, patients in the high-risk group, defined by the telomere-associated signature, exhibited improved responses to immunotherapy, suggesting potential benefits for this subgroup of patients.

Conclusions: This study presents a comprehensive molecular signature comprising TRGs, which holds potential for functional and therapeutic investigations. Additionally, it serves as an integrated tool to identify crucial molecules for immunotherapy in lung cancer.

Keywords: Telomere-related gene (TRG); prognosis signature; lung adenocarcinoma (LUAD); nomogram

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Introduction

Telomeres are highly conserved nuclear protein structures located at the ends of eukaryotic linear chromosomes (1,2). They are composed of TTAGGG repeating nucleotide sequences and are involved in maintaining genomic integrity by preventing the activation of the DNA damage response (DDR) (2). In reality, because DNA polymerase cannot fully duplicate the ends of linear chromosomes, telomere length actually decreases with each somatic cell division (3); however, this is not the case in cancer cells. Turning on the telomere maintenance mechanism (TMM)

can prevent the gradual telomere shortening activation that occurs in cancer cells, it comes in two primary forms: alternative-lengthening of the telomere (ALT) and telomerase activation (4). Due primarily to telomerase's late activation during tumorigenesis, telomeres in telomerase-positive cancer cells are typically significantly shorter than those in normal cells, despite the fact that these cells can activate telomerase to maintain telomere length and achieve infinite proliferation (5). In contrast, telomeres in ALT-dependent cancers are longer but exhibit more heterogeneity. The most prevalent cancer in the world is lung cancer, and one of its main histologic subtypes is lung adenocarcinoma (LUAD) (6). Age, complications, and tumor-related characteristics such tumor stage, node stage, and metastatic stage are often the conventional prognostic variables of LUAD (7). Owing to advancements in sequencing technology, many genetic signature-based models have been investigated recently to assess the prognosis of LUAD patients (8). A handful of these models may also point to LUAD's putative carcinogenesis process in addition to demonstrating these models' encouraging prediction accuracy. Cell cycle stoppage due to telomere attrition may be followed by cell division and a particular state of illness (9).

Many illnesses, including cancer, dyskeratosis congenita, and heart disease, can be brought on by telomere disorders (10). Because 3'-end erosion is a process inherent to linear chromosome replication, maintaining telomere length is essential for the unchecked growth of human cancer cells (11). By inducing senescence or death, continuous telomere shortening prevents somatic cells from proliferating abnormally and becoming tumors (12). Telomere length variation is associated with an increased risk of lung cancer and may be used to predict a patient's prognosis (13). Recent research suggests that the mechanism behind telomere preservation in cancer is a complex one linked to hundreds of different genes (14). The prognosis of many cancer types has also demonstrated a noteworthy correlation with these telomere-related genes (TRGs). A risk score for kidney renal clear cell carcinoma derived from TRG expression levels is associated with immunological subtypes, tumor mutation load, and may also be used to forecast the prognosis of kidney cancer patients (2). To assess tumor immunity and forecast the response to programmed cell death 1 ligand 1 (PDL-1) blocking immunological treatment, an 18-telomere length-related gene prognostic signature is created in the study by Chen *et al.* (13) for non-small cell lung cancer. Nonetheless, the research only included 168 TRGs, despite the fact that over 2,000 TRGs have been identified as being important in telomere preservation. Consequently, in order to fully comprehend the signature of TRGs in lung cancer, a more thorough investigation is required. Our goal in this article is to thoroughly examine the unique characteristics of TRGs in LUAD. We created a risk model based on the TRGs to forecast the prognosis of LUAD, and we then looked into the possibility that this risk model may be used to choose therapy drugs. This work highlights the comprehensive exploration of telomere-related molecular markers in LUAD, providing a more profound genetic knowledge of this malignancy and aiding in the creation of treatment strategies tailored to individual LUAD subtypes. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-767/rc).

Highlight box

Key findings

- We identified a telomere-related prognostic signature that effectively predicts survival outcomes in lung adenocarcinoma (LUAD) patients.

What is known and what is new?

- Telomere dysfunction is associated with cancer progression and poor prognosis.
- This study introduces a novel telomere-related prognostic signature specific to LUAD, providing a new tool for survival assessment.

What is the implication, and what should change now?

- The identified telomere-related signature could be used in clinical settings to improve risk stratification and personalized treatment strategies for LUAD patients.
- Future research should focus on integrating this signature into standard prognostic models to enhance the accuracy of survival predictions and inform therapeutic decisions.

Methods

Data sources and study population

We used The Cancer Genome Atlas (TCGA) (15) to obtain RNA-seq data and clinical information for LUAD patients, providing a reliable basis for conducting thorough genomic and clinical analysis. We transformed the count-type values into counts per million (CPM) and eliminated

Table 1 Overview of datasets utilized in this investigation

Datasets	Platform	Country	No. of patients	No. of controls	Cancer type	Prognostic information
GSE131907	10x Genomics	Korea	44	11	NSCLC	–
GSE3141	GPL570	USA	58	–	LUAD	Yes
GSE8894	GPL570	South Korea	63	–	LUAD	Yes
GSE50081	GPL570	Canada	127	–	LUAD	Yes
GSE72094	GPL15048	USA	398	–	LUAD	Yes
TCGA-LUAD	IlluminaHiSeq	USA	513	59	LUAD	Yes

LUAD, lung adenocarcinoma; TCGA, The Cancer Genome Atlas; NSCLC, non-small cell lung cancer.

samples lacking clinical data. A total of 2,086 Telomere-relevant genes were obtained from TelNet database (16). Four patient prognostic datasets (GSE3141, GSE8894, GSE50081, and GSE72094) were utilized to validate the Telomere-Riskscore prediction accuracy. In addition, we performed external validation using the online tool of a single-cell database, NSCLS_GSE131907 (http://tisch.comp-genomics.org/home/), as described in *Table 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Screening for differentially expressed TRGs

We used the DESeq2 R/Bioconductor package to develop a predictive risk model for differentially expressed TRGs, as previously described (17). The DESeq2 uses a model based on the negative binomial distribution to provide statistical routines for determining differential expression in digital gene expression data.

Telomere-Riskscore genes panel generation

To identify the gene expressions that are most correlated with prognosis, we employed a LASSO (least absolute shrinkage and selection operator). LASSO is a regression analysis method that performs both variable selection and regularization in order to enhance the prediction accuracy and interpretability of the statistical model it produces. LASSO analysis will identify the gene with the lowest penalty parameter (λ) to create a prognostic risk score (Telomere-Riskscore). Next, we divided the LUAD patients in the datasets into two subgroups based on an optimal range of risk scores determined using the R "survminer" package. We utilized the "pheatmap" code to display gene expression in Telomere-Riskscore. The survival rate was calculated using the Kaplan-Meier approach and statistically evaluated using the log-rank test. We conducted univariate and multivariate cox regression analysis to determine if Telomere-Riskscore was an independent prognostic factor. The "survivalROC" package's time-dependent receiver operating characteristic curve (TDROC) was used to assess Telomere-Riskscore's predictive performance over 1, 3, and 5 years (18). Additionally, we have also analyzed the squamous cell carcinoma (SCC) data from TCGA, constructed a model based on risk genes, and predicted its accuracy.

Valuation immunological features and estimation immune subtypes

CIBERSORTx was used to analyze the expression profiles of various genes in the LUAD tumor microenvironment, including macrophages, $CD4^+$ T cells, $CD8^+$ T cells, and B cells. The study also examined the correlation between 28 immune cell types and the Telomere-Riskscore (19).

Prediction of chemotherapy response

We utilized the R package "pRRophetic" and TCGA-LUAD data to estimate medication sensitivity for each patient group (20). Ridge regression was used to predict the sample's highest half-inhibitory concentration (IC_{50}), while ten-fold cross-validation was employed to assess accuracy.

Construction and verification of prognostic nomogram

The "rms" R package was used to create a prognostic nomogram that predicted 1-, 3-, and 5-year survival rates based on Telomere-Riskscore, age, and pathologic stage. To validate the nomogram in the training set, the calibration curve and receiver operating characteristic (ROC) curve

were plotted at 1-, 3-, and 5-year intervals to determine its accuracy in predicting prognosis using R's rms, pROC, and timeROC packages (version 4.2.2) (20).

Statistical analyses

To compare normally distributed data, we utilized the Student's *t*-test or one-way analysis of variance (ANOVA) test. Nonnormally distributed data were analyzed using the Mann-Whitney *U* test or the Kruskal-Wallis test. The prognostic nomogram was created using the R package "rms" and Iasonos' instructions. R version 4.0.3 was used for all statistical tests and visual analysis.

Results

Determination of telomere-associated genes and their functions

To determine the differentially expressed TRGs between cancerous and adjacent tissues, an initial identification of 11,335 differentially expressed genes (DEGs) was conducted between 59 normal and 513 LUAD samples in the TCGA database (*Figure 1A*). Subsequently, out of these, 1,339 telomere junction-associated DEGs were recognized (*Figure 1B*). These genes were further screened using the LASSO method for model creation (*Figure 1C*). A ten-gene model was identified as the best performing one following a 10-fold cross-validation employing a random sampling technique (*Figure 1D*). DEGs with higher expression in cancers were deemed risk genes, while those with lower tumor expression were labeled as protective genes. When patients were classified into high-risk or low-risk groups based on risk score thresholds, those in the high-risk group exhibited significantly poorer survival outcomes (*Figure 1E,1F*). Utilizing the model correlation coefficient, we established a telomere-risk score gene panel to predict the prognosis of LUAD patients. Collectively, our findings led to the development of a ten-TRG model capable of predicting patient prognosis. To further analyze the performance of the ten-TRG model in SCC data, we constructed a ten-TRG prognostic model (Figure S1). The results were similar to those in LUAD, where high expression of these risk genes indicated a poor prognosis.

Telomere-Riskscore = −0.0218 × ExpDHDDS + 0.0055 × ExpDSG2 + 0.0116 × ExpFOSL1 + 0.0664 × ExpIGF2BP1 + 0.1395 × ExpLDHA − 0.0202 × ExpPIK3CG + 0.0976 × ExpPLCD3 + 0.0332 × ExpTEAD4 + 0.0589 × ExpTRIM7 − 0.0528 × ExpZKSCAN4

Evaluation of independent prognosis-predictive factors

To identify independent prognostic variables for assessing clinical characteristics and risk ratings, both univariate and multivariate Cox analyses were utilized in this study. In terms of prediction, the Telomere-Riskscore surpassed the performance of the T, M, and N stages (*Figure 2A,2B*). The predictive classifier exhibited superior performance with 1-, 2-, and 3-year AUCs of 0.849, 0.784, and 0.891 respectively (*Figure 2C-2E*). Hence, we posit that the Telomere-Riskscore serves as a novel prognostic prediction tool that operates independently of traditional clinical evaluation indicators. This model demonstrates high accuracy in predicting the prognosis of LUAD patients.

Verification of the Telomere-Riskscore in multiple additional datasets

We employed a similar strategy to construct risk scores for patients in the GSE3141, GSE8894, GSE50081, and GSE72094 datasets, and validated this signature across these cohorts. As per the Kaplan-Meier survival analysis (*Figure 3A*), higher risk scores were significantly correlated with decreased overall survival rates, demonstrating a strong prognostic ability of this signature according to ROC analysis (*Figure 3A*). Additionally, we performed external validation using an online single-cell database tool. LDHA and DSG2 were extracted for validation, revealing that their expression levels were significantly elevated in both the tumor and metastasis groups compared to the normal group (*Figure 3B*). Altogether, the model we constructed accurately predicted patient prognosis in the validation set as well.

Relationship between the Telomere-Riskscore and tumor immunity

The ssGSEA method was utilized to calculate infiltration scores for 28 distinct immune cell types from high and low groups. Statistically significant differences in infiltration levels among 15 immune cell types were observed in the study (*Figure 4A*). Subsequently, a correlation analysis was conducted between cell types closely related to tumor immunity (such as CD8T cells, neutrophils, natural killer cells, and B cells) and telomere-related model genes. The findings indicated negative correlations between DHDDS

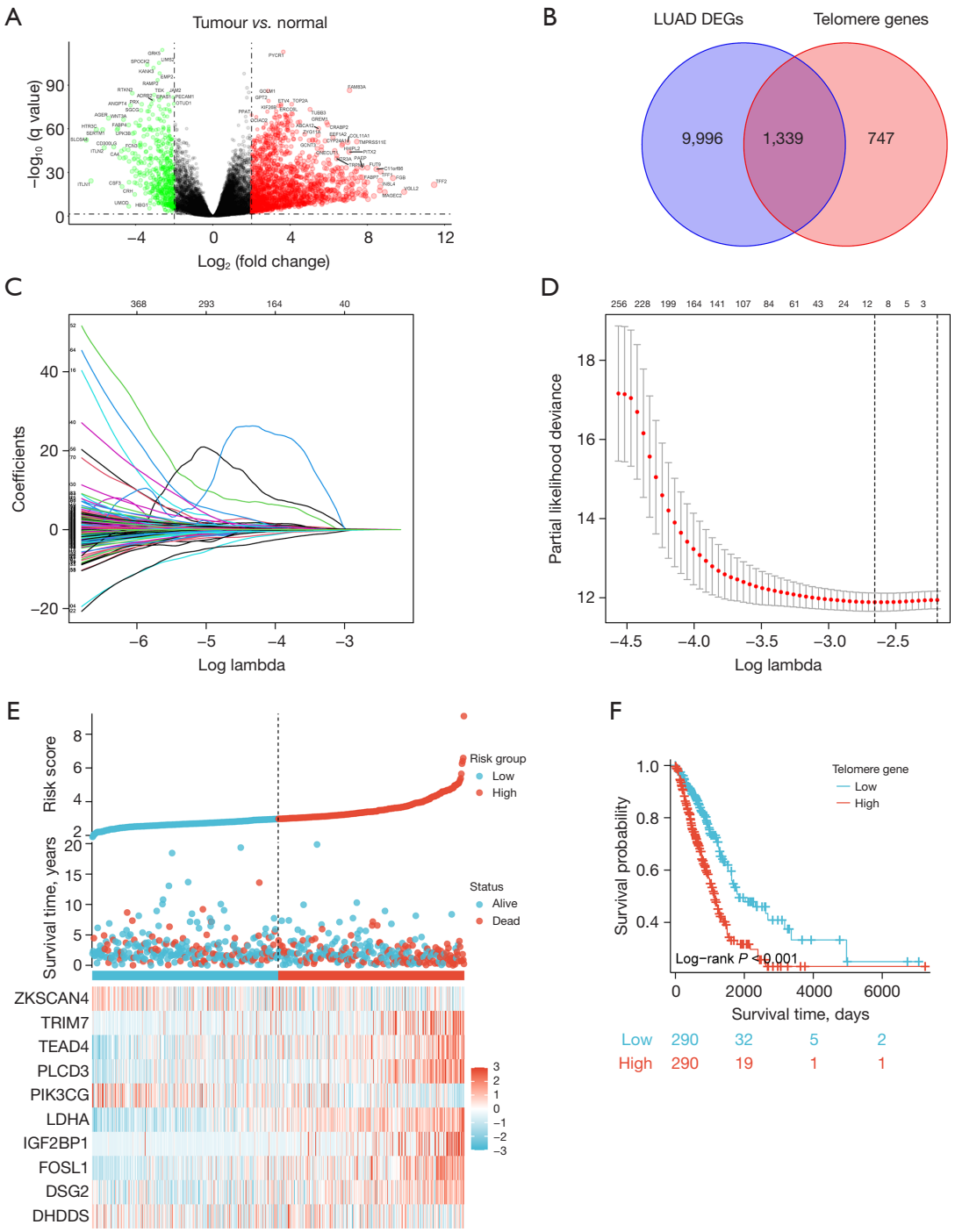

Figure 1 Identification of telomere-related DEGs and establishment of telomere-related subtypes. (A) DEGs between the 59 normal tissues and 513 LUAD tissues, with red indicating significantly upregulated genes in tumor tissues, green indicating significantly downregulated genes, and black indicating non-significant genes. (B) 1,339 overlapping genes were identified as telomere-related DEGs. (C,D) LASSO-Cox regression analysis. (E) The scores of patients and their distribution. (F) Patients with elevated risk scores demonstrated significantly reduced survival rates. LUAD, lung adenocarcinoma; DEGs, differentially expressed genes; LASSO, least absolute shrinkage and selection operator.

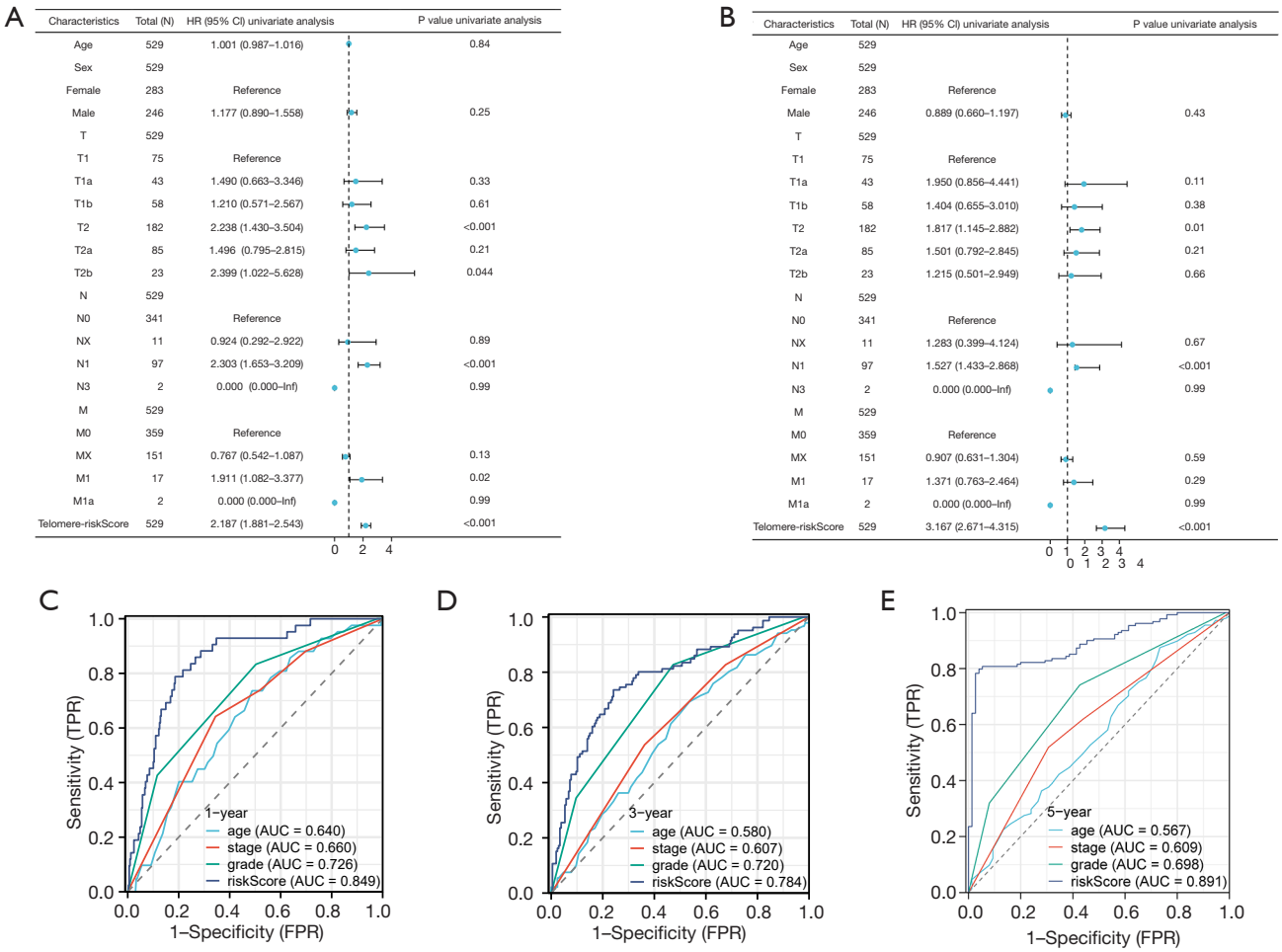

Figure 2 Evaluation of independent prognosis-predictive factors. (A,B) Forest plots of the univariate and multivariate Cox regression analyses among Telomere-Riskscore and clinical factors. (C-E) Time-dependent receiver operating characteristic curves at 1-, 3-, and 5-year. HR, hazard ratio; CI, confidence interval; TPR, true positive rate; AUC, area under the curve; FPR, false positive rate.

and CD8T cell infiltration, and between IGF2BP1, LDHA and natural killer cell infiltration. Conversely, FOSL1 exhibited a positive correlation with neutrophil infiltration, while TEAD4 demonstrated a negative correlation with B cell infiltration (*Figure 4B*). In summary, our results suggest that the extent of immune cell infiltration within the tumor microenvironment and the expression of TRGs offer valuable insights and explanatory power.

Telomere-Riskscore predicts the therapeutic benefits of chemotherapy

Adjuvant chemotherapy is a primary treatment approach for LUAD patients post-surgery. We selected six commonly utilized chemotherapy drugs for LUAD patients and evaluated the chemotherapy sensitivity of individuals with varying Telomere-Riskscores. LUAD samples were categorized as high-risk or low-risk based on their Telomere-Riskscores. Fifty-nine paracancerous tissues from the TCGA-LUAD dataset were used as a control group. The chemotherapeutic sensitivity levels among the three groups were compared (*Figure 5A*). No significant differences in IC_{50}s for cisplatin and paclitaxel were observed between the low Telomere-Riskscore LUAD and control groups. However, the high Telomere-Riskscore LUAD group exhibited enhanced responsiveness to cisplatin, docetaxel, paclitaxel, etoposide, and gemcitabine compared to the control group. We then performed a correlation analysis to ascertain the relationship between these drugs' IC_{50} and the Telomere-Riskscore (*Figure 5B*). Our results

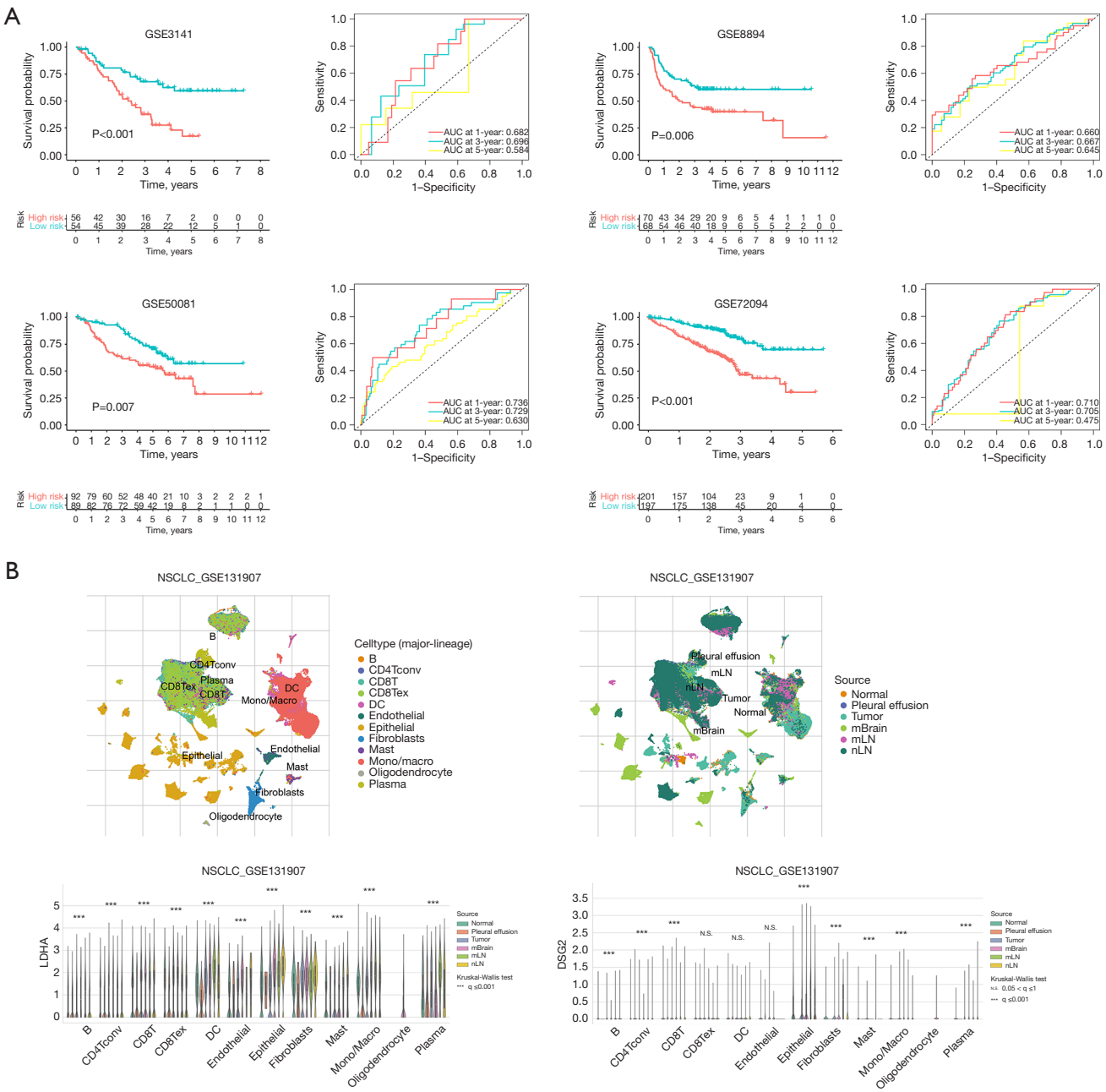

Figure 3 External verification of Telomere-Riskscore using six microarray cohorts. (A) Each cohort was equally divided into high- and low-risk group based on the value of Telomere-Riskscore. Kaplan-Meier analysis and time-dependent receiver operating characteristic curves of each cohort are displayed. (B) External validation using the online tool of a single-cell database, NSCLC_GSE131907. AUC, area under the curve; DC, dendritic cell; mLN, mesenteric lymph nodes ; nLN, normal lymph node; LDHA, lactate dehydrogenase A gene; DSG2, desmoglein 2 gene; NSCLC, non-small cell lung cancer.

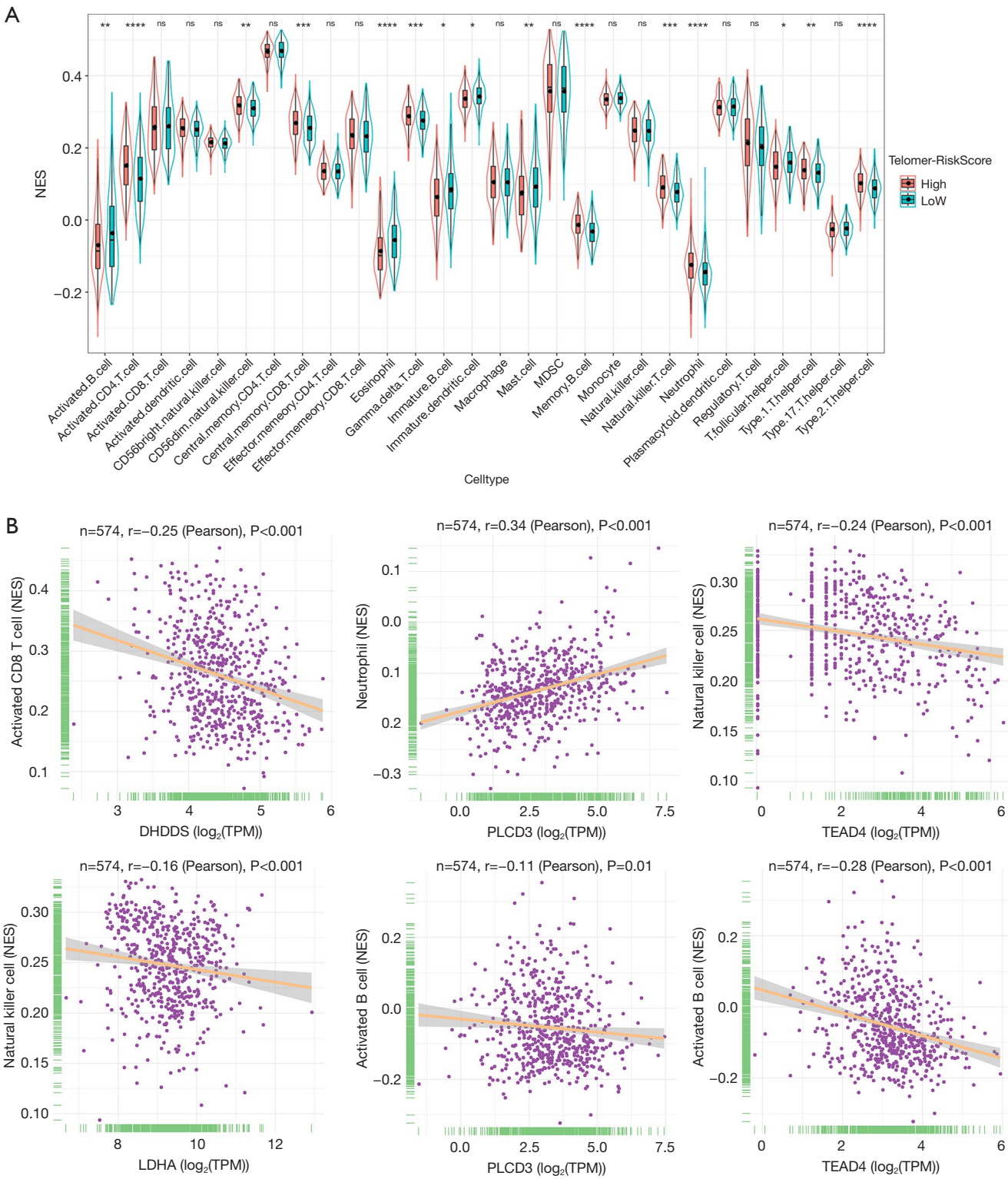

Figure 4 Correlation analysis between Telomere-Riskscore model genes and immune cell infiltration. (A) Immune cell infiltration analysis in low and high group. (B) Correlation analysis between panel genes and immune cell infiltration. *, P<0.05; **, P<0.01; ***, P<0.001; ****, P<0.0001. NES, normalized enrichment score; MDSC, myeloid-derived suppressor cell; TPM, transcript per million.

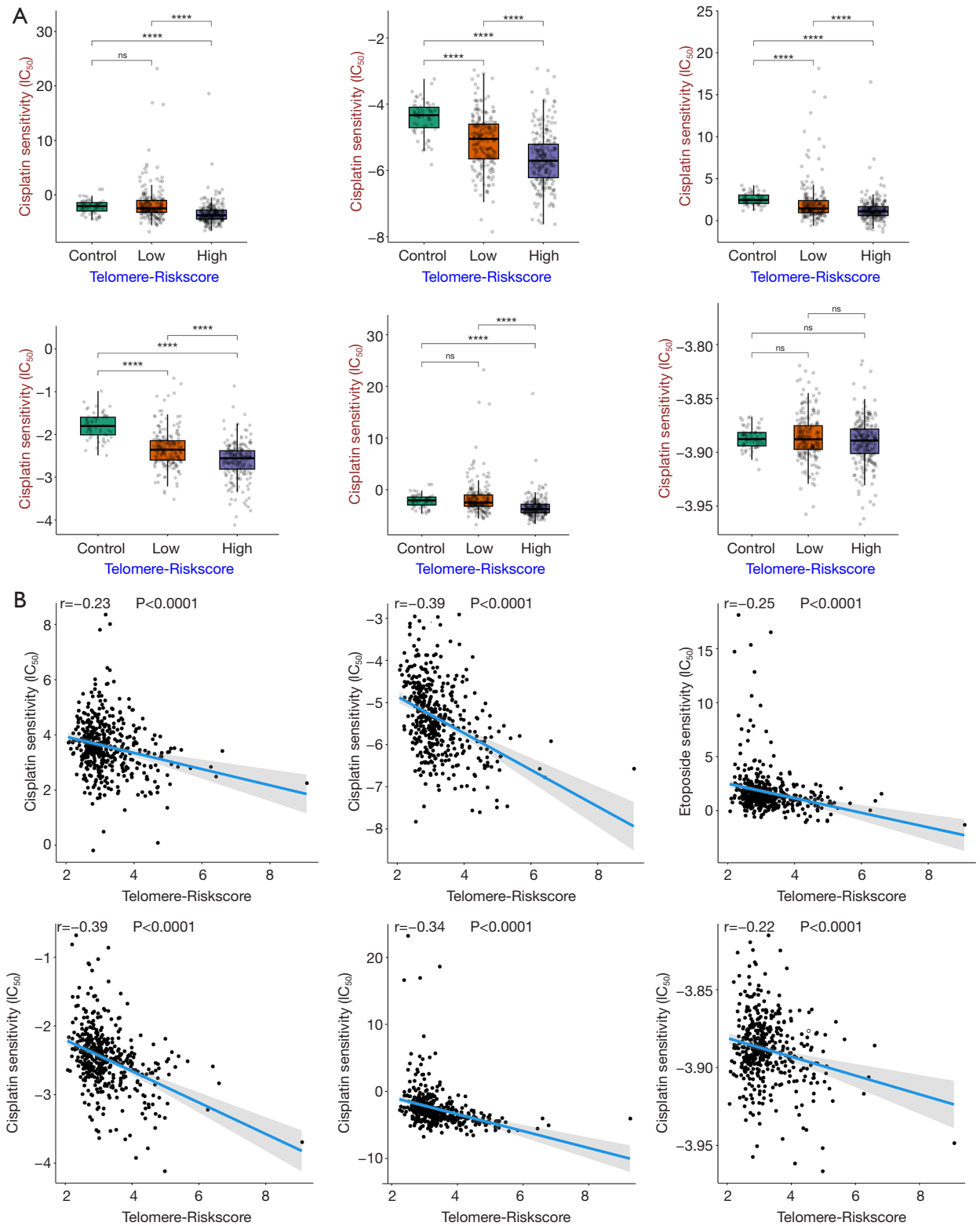

Figure 5 Differences in sensitivity of patients with different Telomere-Riskscore to chemotherapy. (A) The box plots of the estimated IC_{50} for commonly used chemotherapy drugs. (B) Correlation analysis between IC_{50} of six drugs and Telomere-Riskscore. ns, not significant; ****, P<0.0001. IC_{50}, highest half-inhibitory concentration.

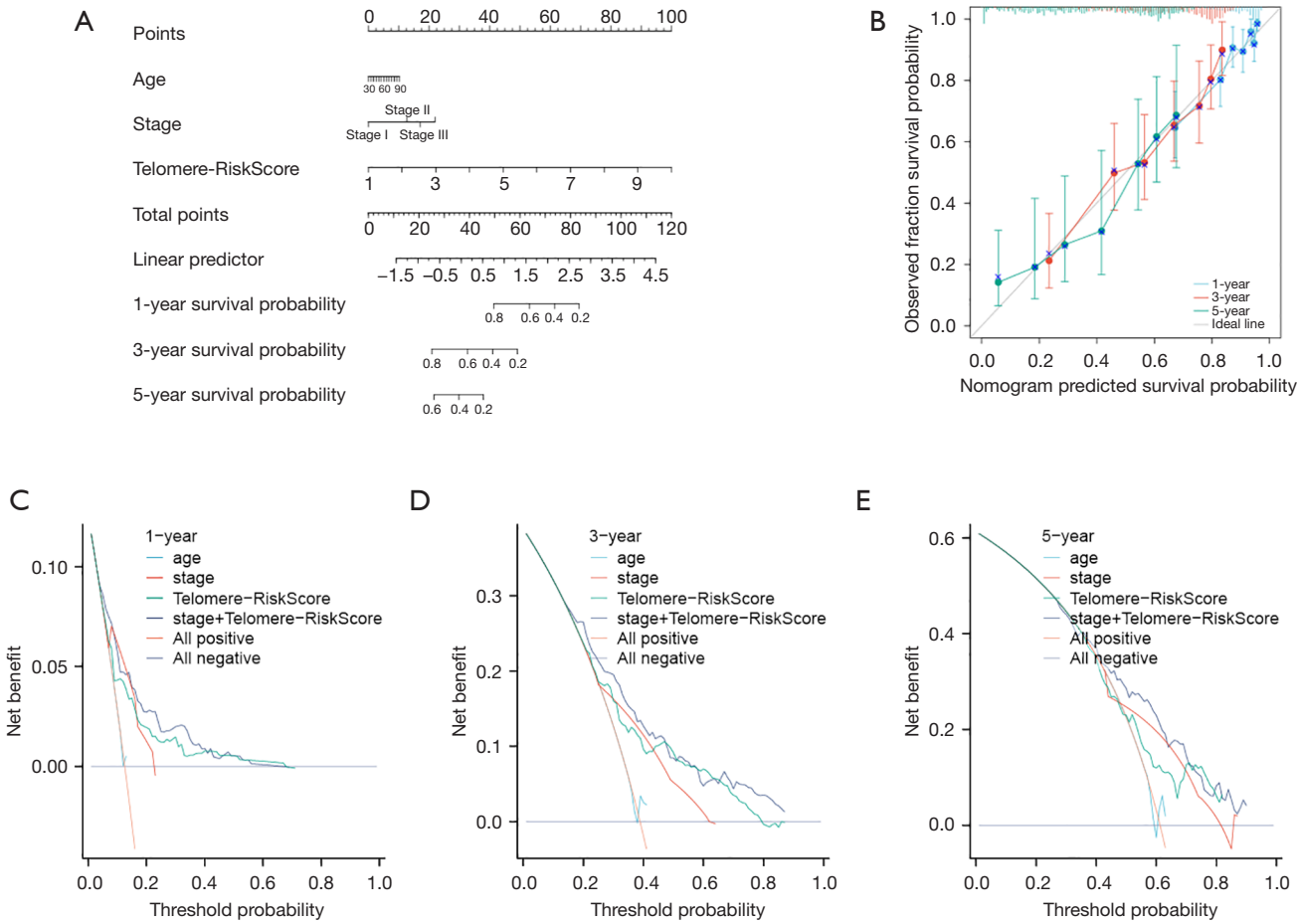

Figure 6 Establishment and validation of a prognostic nomogram utilizing Telomere-Riskscore. (A) A nomogram for predicting 1-, 3-, and 5-year survival possibilities of individual LUAD patients. (B) Plots depict the calibration of the nomogram based on Telomere-Riskscore in terms of consistency between predicted and observed 1-, 3- and 5-year outcomes. (C-E) Decision curve analyses of the nomogram for 1-, 3- and 5-year risk. LUAD, lung adenocarcinoma.

suggest that a higher Telomere-Riskscore corresponds to a lower IC_{50}, implying that these medications may be beneficial for individuals with high Telomere-Riskscores.

Development of a prognostic nomogram based on Telomere-Riskscore

In order to enhance prediction accuracy and practical utility, we developed a nomogram that integrates the Telomere-Riskscore with clinical prognostic variables for estimating patient survival rates over 1, 3, and 5 years (*Figure 6A*). A patient's prognosis can be determined by summing the contribution scores of each component. Compared to an ideal model, our nomogram exhibited superior performance in terms of 1-, 3-, and 5-year calibration charts (*Figure 6B*). The decision curve analysis demonstrated that our nomogram's clinical value considerably exceeded that of the clinical characteristics alone (*Figure 6C-6E*). Our study suggests that combining the Telomere-Riskscore with clinical factors can enhance the prognosis predictions for a larger number of patients.

Discussion

Due to the prevalent phenomenon of telomere shortening and activation, telomeres play a crucial role in the progression of LUAD (21). TRGs play a critical role in maintaining telomere length and stability. Telomeres, the protective caps at the ends of chromosomes, prevent genomic instability by protecting chromosomal ends from

degradation and inappropriate repair. TRGs encode proteins involved in telomere elongation, protection, and repair, such as telomerase reverse transcriptase (TERT) and shelterin complex components. TRGs are involved in the regulation of cell proliferation and senescence. Dysregulation of TRGs can lead to uncontrolled cell division or premature cellular aging, both of which are hallmarks of cancer. For instance, overexpression of TERT, which maintains telomere length, is commonly observed in various cancers and is associated with tumor progression and poor prognosis. Ongoing research is exploring TRG-targeted therapies as a novel approach to cancer treatment. Inhibitors of telomerase activity, such as imetelstat, have shown promise in preclinical and clinical studies by selectively targeting cancer cells with high telomerase activity. Additionally, strategies to disrupt the shelterin complex, which protects telomeres, are being investigated to induce telomere dysfunction and cancer cell death. Furthermore, immunotherapy targeting telomerase in tumor cells has no detrimental effect on normal cells as telomerase is repressed in most human somatic cells (22). Telomerase activity has been detected in small subpopulations of normal human cells, including stem/progenitor cells, activated lymphocytes, and highly proliferative cells (23). These cells exhibit significantly longer telomere lengths compared to cancer cells, suggesting that telomerase inhibition therapy may be particularly effective against tumor cells. By specifically targeting telomeres in tumor cells, we can avoid damaging healthy human cells that express telomerase. Low residual levels of telomerase activity prior to the removal of telomerase function may influence the effectiveness of telomerase-targeted therapy (24). Consequently, our research focused on alterations in telomere gene expression within LUAD. In our study, we have extended the analysis to include SCC data in addition to LUAD. To do this, we utilized SCC data from the TCGA database and constructed a ten-TRG prognostic model for SCC. Similar to LUAD, we identified a set of ten TRGs that were significantly associated with the prognosis of SCC patients. In both SCC and LUAD, high expression levels of the identified risk genes were associated with poorer overall survival. This suggests that telomere-related mechanisms may play a crucial role in the progression and prognosis of different types of lung cancer.

Initially, we analyzed the differentially expressed genes between LUAD and normal tissues, identifying 1,339 TRGs. Through LASSO-Cox regression, we further refined this list to ten genes (*ZKSCAN4*, *TRIM7*, *TEAD4*, *PLCD3*, *PIK3CG*, *LDHA*, *IGF2BP1*, *FOSL1*, *DSG2*, *DHDDS*), which were then used to construct a prognostic panel named Telomere-Riskscore.

Among the genes of Telomere-Riskscore, desmoglein-2 (DSG2), a gene in the Telomere-Riskscore, is a calmodulin-class cell adhesion protein vital for cardiomyocyte function (25). It also modulates telomerase activity. While some studies link aberrant DSG2 expression to carcinogenesis, its role remains contentious (26). High DSG2 expression correlates with poor prognosis in cutaneous SCC and cervical cancer (27). Its downregulation curbs colon cancer cell proliferation and non-small cell lung cancer progression. Despite typically low expression in pancreatic cancer, our study found considerable DSG2 expression in LUAD compared to normal tissues, correlating with poor prognosis, possibly due to LUAD patient tumor heterogeneity. Lactate dehydrogenase A (LDHA), a key player in the glycolytic pathway, contributes significantly to carcinogenesis (28). Aberrant LDHA expression driven by hypoxia governs gastric cancer progression (29). LDHA is targeted by platinum complexes, thereby impeding the metabolism and migration of triple-negative breast cancer cells (30). Under hypoxic conditions, LDHA can generate erythropoietin L-2HG to maintain an appropriate balance in pancreatic cancer stem cell development (31). Our study confirmed that LDHA, a TRG, accurately predicts the prognosis of LUAD patients.

The Telomere-Riskscore, derived from the ten aforementioned genes, surpasses clinical characteristics in predicting LUAD patient prognosis (*Figure 2*). Notably, we validated our findings across multiple external datasets (*Figure 3*), underscoring their robustness. The Telomere-Riskscore reliably and effectively predicts LUAD patient prognosis in external validations, demonstrating its utility as a prognostic tool.

Our analysis of immune infiltration in high-risk and low-risk groups revealed correlations between specific gene expressions and distinct immune cell infiltrations (*Figure 4*). We performed a comprehensive analysis of immune cell infiltration in LUAD samples using bioinformatics tools. Our findings indicated that TRG expression levels were significantly correlated with the presence of various immune cell types, such as $CD8^+$ T cells, B cells, and neutrophils cells. Notably, higher expression of certain TRGs was associated with increased infiltration of immunosuppressive cells, including NK cells and neutrophils. These results suggest that TRGs may contribute to an immunosuppressive tumor microenvironment, which can facilitate tumor

growth and metastasis. TRGs that are significantly associated with poor prognosis and immune evasion in LUAD can be identified as potential therapeutic targets. By targeting these genes or their pathways, we can develop novel immunotherapy strategies aimed at reducing tumor immunosuppression and enhancing anti-tumor immune responses. Based on the positive correlation between TRG expression and immune checkpoint molecules (such as PD-1, PD-L1, and CTLA-4), combining TRG-targeted therapies with existing immune checkpoint inhibitors could provide a synergistic effect. This approach may enhance the efficacy of immunotherapy by simultaneously inhibiting immune checkpoints and modulating the tumor microenvironment to be less immunosuppressive. We utilized the R software package "pRRophetic" and mRNA expression profiles to predict patient responses to six drugs, providing preliminary insights that require further clinical trial verification (*Figure 5*).

We developed a nomogram integrating the Telomere-Riskscore with clinical characteristics for practical clinical application (*Figure 6*). Nomograms are widely used for cancer prognosis prediction, offering more accurate forecasts than single-stage cancer due to various considerations. Calibration chart and decision curve analyses demonstrated that our nomogram enhanced prediction accuracy, potentially benefiting a greater number of patients.

Our research presents a novel LUAD prognostic model based on the Telomere-Riskscore. Our model identified genes associated with LUAD patient prognosis, such as *DSG2*, *LDHA*, *ZKSCAN4*, and *FOSL1*, previously unexplored in lung cancer studies, laying groundwork for future inquiries into lung cancer mechanisms.

The greatest advantage of the risk model presented in this study is its high prognostic accuracy. The model effectively stratifies patients into high-risk and low-risk groups with significant differences in overall survival. This allows for better prediction of patient outcomes and more informed clinical decision-making. The model enables the identification of high-risk patients who may benefit from more aggressive treatment strategies or closer monitoring. This targeted approach can potentially improve patient outcomes and optimize the use of healthcare resources. Our model incorporates a multi-gene signature of TRGs, which provides a comprehensive view of the genetic factors influencing prognosis. This integrative approach captures the complexity of tumor biology better than single-gene markers.

Our study provides a comprehensive analysis of TRGs and their prognostic value in LUAD. By integrating multi-omics data and performing extensive bioinformatics analyses, we have characterized key TRGs and their association with immune infiltration and clinical outcomes. This approach highlights the potential of TRGs as novel biomarkers for cancer prognosis and therapeutic targets. Our findings contribute to the growing body of research aimed at identifying molecular targets for cancer immunotherapy. While our study offers valuable insights, it is not without limitations. One of the main limitations is the focus on TRGs in LUAD, which may not capture the full spectrum of key molecules involved in cancer immunotherapy across different cancer types. To provide a more comprehensive pattern of characterizing key molecules, future studies should include a broader range of cancer types and molecular pathways. Additionally, functional validation experiments are necessary to confirm the biological roles of TRGs in immune modulation and tumor progression. Our next plan is to extend the analysis to other cancer types, such as SCC and breast cancer, to determine the generalizability of our findings. By including diverse cancer types, we aim to identify common and unique TRGs across different malignancies.

There are limitations in this study, including the reliance on transcriptome data rather than polymerase chain reaction (PCR) data for panel construction. The biggest challenge we face is the need for extensive validation of the risk model across diverse patient cohorts. While our model shows strong performance in the cohorts analyzed, its generalizability to different populations and clinical settings must be confirmed. Another challenge is the need to further elucidate the biological mechanisms underlying the association between TRG expression and prognosis. Understanding these mechanisms will enhance the clinical utility of the model and potentially reveal new therapeutic targets. Further determination is needed for the optimal cut-off value when using gene expression data as categorical variables in Cox regression. Additionally, the retrospective nature of the study and the heterogeneous patient population could potentially bias our findings.

Conclusions

In summary, the Telomere-Riskscore gene panel serves as a valuable tool for predicting survival rates in LUAD patients and can potentially guide clinical chemotherapy decisions. However, further clinical investigations are necessary to

validate our findings.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-767/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-767/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-767/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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