Thyroid Research

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A new Tec family-based clinical model predicts survival in differentiated thyroid cancer patients via machine learning

Ziyu Luo[1], Wenhan Li[1], Jianhui Li[1] and Ying Zhang[1*]

Abstract

Background The Tec family of proteins has been identified as a key player in numerous diseases. However, no studies on the associations of Tec family proteins with overall survival (OS) in differentiated thyroid cancer (DTC) patients have been conducted.

Methods RNA sequencing (RNA-Seq) and clinical data were downloaded from The Cancer Genome Atlas (TCGA) database. LASSO-Cox, random forest, and eXtreme Gradient Boosting (XGBoost) analysis methods were used to screen for the genes encoding Tec family proteins that were most closely associated with DTC. A predictive model was developed to estimate the OS of DTC patients. The validity of the prediction model was evaluated via receiver operating characteristic (ROC) curves, decision curve analysis (DCA), and fivefold and 200-fold cross-validation. In addition, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to investigate the biological functions of the most significant genes.

Results The *AC007494.3* and *AC019226.2* genes were most strongly associated with the OS of DTC patients. Therefore, the model can be used to predict the OS of DTC patients. Functional annotation analysis revealed characteristics similar to those of other Tec kinases.

Conclusions We found that the *TEC* gene has significant predictive value for the prognosis of DTC patients. The *TEC* gene has potential value as a target for future drug development. In addition, we recommend more comprehensive treatment and closer monitoring of high-risk populations.

Keywords Tec, Differentiated thyroid cancer, Overall survival, Machine learning

Introduction

Thyroid cancer is the most common cancer of the endocrine system as well as a common tumour in women [1]. Despite the excellent prognosis of patients with differentiated thyroid cancer (DTC), 3–10% of patients still die [2]. In recent years, the development of next-generation sequencing technology and omics technology has enabled the effective stratification of risk factors among patients with DTC via genetic testing [3, 4].

The Tec family is a novel subfamily of non-receptor protein tyrosine kinases (PTKs) that has emerged in recent years, named after the first member of the family. This family consists of five members: Tec, Btk, Itk/Emt/Tsk, Bmx, and Txk/Rlk [5]. Tec kinase is characterized by discrete proline-rich regions and pleckstrin homology domains, which are indispensable for the complete activation of phospholipase C-γ (PLC-γ) and the subsequent mobilization of calcium ions in response to antigen receptor stimulation [6]. Associations between the Tec family and the development of cardiovascular disease,

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rheumatoid arthritis, and multiple myeloma have been established. Furthermore, preclinical studies of related drugs have been conducted [7–9]. Research has demonstrated that calcium channels are integral to the proliferation and invasion of papillary thyroid carcinoma [10, 11]. However, the correlation between the Tec family and the overall survival (OS) of DTC patients has not been investigated. To date, no study has been conducted to construct a Tec family prediction model for the OS of DTC patients.

The objective of this study was to examine the relationship between DTC and Tec family members and to develop a predictive model. This study offers a new approach to predicting the occurrence of DTC, provides insights that can aid in drug research, and proposes a useful tool for postoperative monitoring.

Materials and methods

Patients and The Cancer Genome Atlas (TCGA) database

Clinical information and RNA sequencing (RNA-Seq) data from patients with DTC were downloaded from the TCGA database (https://portal.gdc.cancer.gov/repository). Specifically, we downloaded open, transcriptomic RNA-Seq data from TCGA-THCA. A total of 139 patients with unknown TNM stages were excluded. Ultimately, 210 patients were included in this study.

The main outcome measure was OS. Clinical characteristics such as age, sex, race, and TNM stage were collected.

Methods used to screen relevant genes

A total of 1057 RNA-Seq results in which Tec family members were identified were selected. A total of 45 genes related to OS were screened. These 45 genes were selected as candidates for further analysis.

LASSO-Cox dimension reduction analysis: The analysis was performed with the "glmnet" and "survival" packages in R. The λ value corresponding to the minimum partial likelihood deviation was selected as the optimal λ. The nonzero features corresponding to the optimal λ and their corresponding regression coefficients were visualized. The signature genes that were more important for OS were selected.

Random forest (RF) algorithm: Analysis was performed with the "randomForestSRC" package in R. RF builds a bagging ensemble on the basis of a decision tree (DT) and introduces random attribute selection into the training process of the DT. This method can effectively improve the classification accuracy of new samples [12]. The very important genes identified by the model were those linked to OS.

eXtreme gradient boosting (XGBoost) feature selection: Our analysis utilized the "XGBoost" package in R. XGBoost merges predictions from a sequence of weak regression trees and progressively adds them to the model to achieve optimal prediction performance while minimizing model complexity [13]. Simultaneously, XGBoost improves the model's control of complexity and learns from the RF to decrease computation, thus preventing overfitting. The gain values for all the features were ranked, and the 15 most significant variables were selected and displayed. These variables are among the most crucial genes linked to mortality in papillary carcinoma patients.

AC007494.3 and *AC019226.2* were the genes most strongly associated with OS, identified by intersecting the important genes selected from the above three algorithms. The corresponding lambda values are 0.116396434 and 0.209657018, respectively. The risk score for each patient was calculated using the following formula: $\text{RiskScore} = \text{exprAC007494.3} \times \lambda\text{AC007494.3} + \text{exprAC019226.2} \times \lambda\text{AC019226.2}$, where expr is the expression level of the gene and λ is the corresponding lambda value.

Development and evaluation of prediction models

Clinical information was utilized with the risk score to construct univariate and multivariate Cox proportional hazards models, with the aim of analysing risk factors related to OS. The outcome of the multivariate Cox proportional hazard model was then used to construct a forest plot to predict the OS of patients with DTC. Receiver operating characteristic (ROC) curves were used to assess the discriminatory ability of the model, and the area under the curve (AUC) was subsequently utilized to demonstrate the model's efficacy. Internal validation of the model was conducted through fivefold and 200-fold cross-validation. Decision curve analysis (DCA) was used to evaluate the clinical benefit of the model [14].

Statistical analysis

A t test was used for the statistical analysis of genes associated with OS. Additionally, survival analysis was performed via the Kaplan–Meier method and log-rank test. We addressed overfitting via fivefold cross-validation [15, 16]. Gene Ontology (GO) analysis was performed via the DAVID portal (https://david.ncifcrf.gov/summary.jsp). $p < 0.05$ was regarded as statistically significant. All the statistical analyses were performed with R 4.1.2 (http://www.rproject.org/) software and the rms package (https://cran.r-project.org/web/packages/rms/).

Results

Patient characteristics

A total of 210 patients were ultimately included in the study. Among these patients, 161 (76.7%) were female,

Table 1 Characteristics of 210 DTC patients

Characteristic	N (%)
Sex	
Male	49 (23.3)
Female	161 (76.7)
Age (years)	
≤ 55	148 (70.5)
> 55	62 (29.5)
Race	
White	156 (74.3)
Other	54 (25.7)
T stage	
T1/T2	131 (62.4)
T3/T4	79 (37.6)
N stage	
N0	104 (49.5)
N1	106 (50.5)
M stage	
M0	207 (98.6)
M1	3 (1.4)
Follow-up	
median [IQR]	2.66 [1.67, 4.18]

Abbreviations: DTC differentiated thyroid cancer, *IQR* interquartile range

and 148 (70.5%) were under 55 years of age (Table 1). A total of 156 (74.3%) patients were white, and 54 (25.7%) were of other races. Among the 210 patients, 79 (37.6%) were diagnosed tumours staged as T3/T4, and 106 (50.5%) had lymph node metastasis (N1). Three patients had distant metastases (M1). The mean follow-up duration was 2.66 years, ranging from 1 month to 14 years.

Relationships between the RiskScore and clinicopathological features

The correlations between the RiskScore and clinicopathological factors were further examined. The results revealed that the RiskScore was not correlated with age, sex, race or TNM stage (all $p > 0.05$).

Construction of the prediction model

High expression levels of 45 genes in the Tec family were associated with OS (Fig. 1). LASSO-Cox dimension reduction analysis identified 12 important genes associated with OS, namely, *AC006065.6*, *AP003499.4*, *AC005858.1*, *AC139792.3*, *AC019226.2*, *AC007494.3*, *AC002540.1*, *AL162727.3*, *AL132796.3*, *AL160274.1*, *AC091912.2*, and *AC092139.1* (Fig. 2(A)(B)(C)). The RF algorithm identified 20 important genes related to OS, namely, *AC019225.2*, *AC005858.1*, *AL356266.1*,

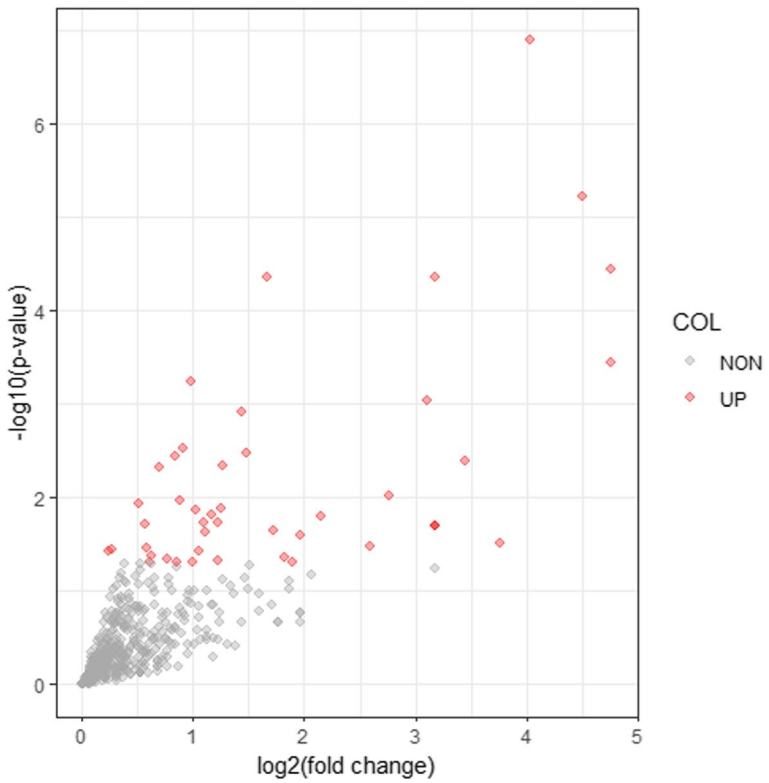

Fig. 1 Highly activated biological processes in deceased patients. Red dots represent significantly elevated BPs, and grey dots represent non-significant changed BPs

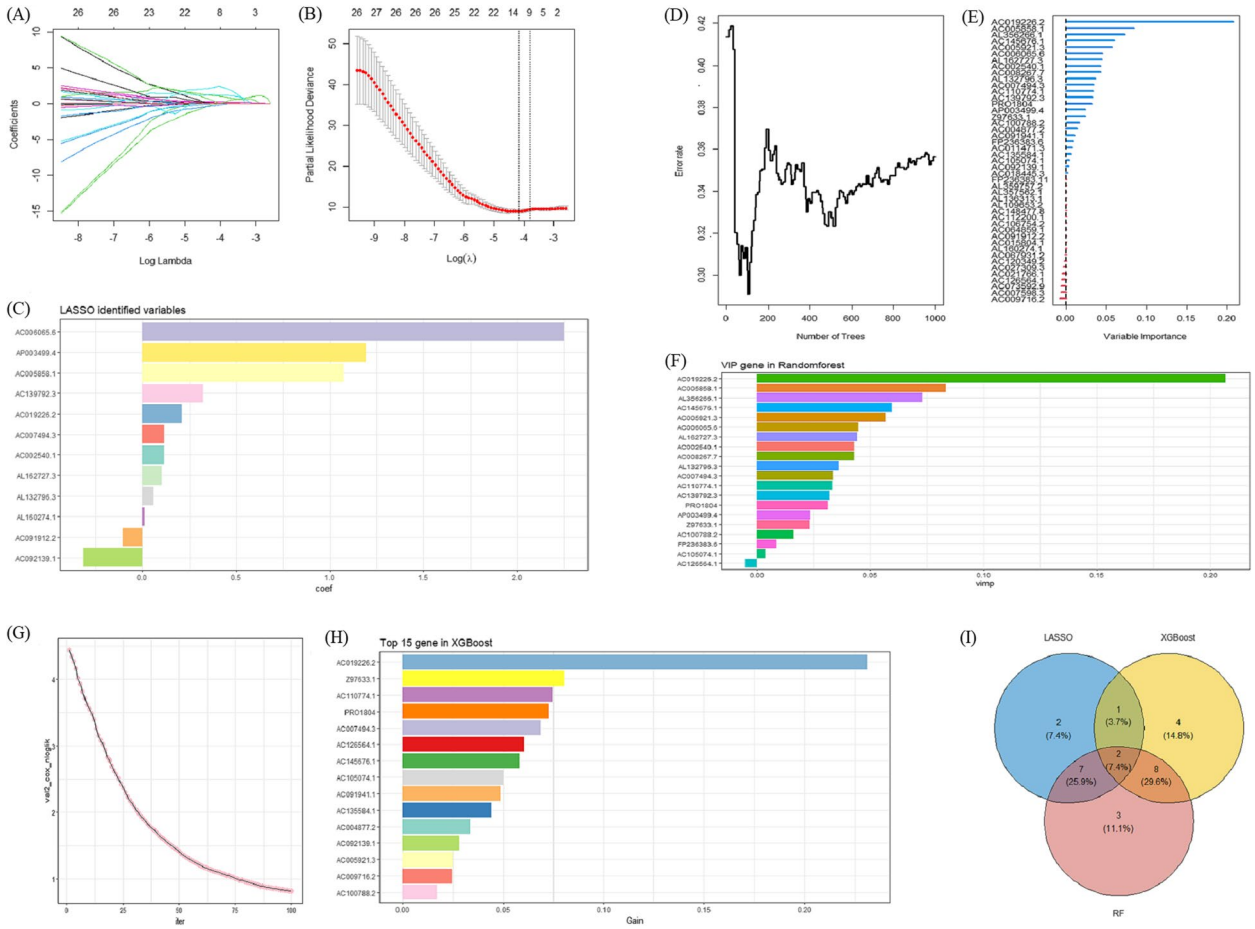

Fig. 2 **A**, **B** Screening the 12 most representative genes expressed in response to TEC genes by LASSO-Cox analysis. **C** Histogram describing the important features of the LASSO-Cox predictive model for OS. **D, E** Relationship between the error rate and number of classification trees. **F** Histogram describing the important features of the random forest predictive model for OS. **G** The negative partial log-likelihood of the Cox proportional hazards regression in the XGBoost model changes as the number of iterations increases. **H** Histogram describing the important features of the XGBoost predictive model for OS. **I** Intersection of the genes identified by the three algorithms

AC145676.1, *AC005921.3*, *AC006065.6*, *AL162727.3*, *AC002540.1*, *AC008267.7*, *AL132796.3*, *AC007494.3*, *AC110774.1*, *AC139792.3*, *PRO1804*, *AP003499.4*, *Z97633.1*, *AC100788.2*, *FP236383.6*, *AC105074.1* and *AC126564.1* (Fig. 2(D)(E)(F)). XGBoost identified 15 important genes related to OS, namely, *AC019226.2*, *Z97633.1*, *AC110774.1*, *PRO1804*, *AC007494.3*, *AC126564.1*, *AC145676.1*, *AC105074.1*, *AC091941.1*, *AC135584.1*, *AC004877.2*, *AC092139.1*, *AC005921.3*, *AC009716.2* and *AC100788.2* (Fig. 2(G)(H)). After intersecting the results of the above three methods, two common genes were obtained, namely, *AC007494.3* and *AC019226.2* (Fig. 2(I)).

Univariate Cox proportional hazards models revealed that the risk score was significantly correlated with OS (hazard ratio [HR] 3.04, 95% confidence interval [CI] 1.9–4.85). A multivariate Cox proportional hazards model revealed that T3/T4 stage (HR 14.28, 95% CI 1.59–94.65) and the RiskScore (HR 4.32, 95% CI 2.31–8.45) were independent risk factors for OS (Table 2). The forest plot established based on the results of the multivariate analysis is shown in Fig. 3(A).

Evaluation of prediction models

The model yielded 5-year and 10-year AUC values of 73.4% and 76.5%, respectively (Fig. 3(B)). The DCA curves at both 5 and 10 years revealed substantial net benefit (Fig. 3(C)). The 5-year and 10-year AUC values of cross-validation were between 0.7 and 0.8 (Fig. 3(D)).

Survival analysis and preliminary exploration of gene function

The Kaplan–Meier curve indicated a significant difference between the two groups ($p = 0.049$) (Fig. 4).

Table 2 Univariate and multivariate Cox proportional hazard models to predict OS in DTC patients

Characteristics	Univariate model		Multivariate model	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)				
≤ 55	reference			
> 55	-	0.99		
Sex				
Male	reference			
Female	0.96 (0.20 to 4.64)	0.96		
Race				
White	reference			
Other	1.00 (0.21 to 4.82)	0.99		
T stage				
T1/T2	reference		reference	
T3/T4	4.78 (0.98 to 23.17)	0.05	14.28 (1.59 to 94.65)	0.01
N stage				
N0	reference			
N1	1.87 (0.47 to 7.47)	0.37		
M stage				
M0	reference			
M1	4.09 (0.50 to 33.5)	0.19		
RiskScore	3.04 (1.90 to 4.85)	< 0.001	4.42 (2.31 to 8.45)	< 0.001

Abbreviations: DTC differentiated thyroid cancer, *OS* overall survival

AC007494.3 and *AC019226.2* were associated with the biological process terms positive regulation of calcium ion-dependent exocytosis, cilium movement, folic acid transport, regulation of the ciliary beat frequency and calcium ion-regulated exocytosis (Fig. 5(A)); the cellular component terms extracellular region, extracellular space, axoneme, acrosomal vesicle and terminal bouton (Fig. 5(B)); and the molecular function terms folic acid binding, serine-type endopeptidase activity, chemokine activity, methotrexate transporter activity and SNARE binding (Fig. 5(C)). The significant signalling pathways of *AC007494.3* and *AC019226.2* included antifolate resistance, viral protein interaction with cytokines and cytokine receptors, cytokine–cytokine receptor interaction, fructose and mannose metabolism and the IL-17 signalling pathway (Fig. 5(D)).

Discussion

In this study, we analysed Tec genes associated with DTC in the TCGA database. Our findings indicate a correlation between *AC007494.3* and *AC019226.2* and OS. Based on the results of our analysis, we developed a prediction model utilizing clinical data that effectively predicts the OS of DTC patients. Our prediction model highlights the potential of molecular profiling to guide patient follow-up in DTC. In addition, it can provide novel insights for drug development.

We found that T stage was associated with OS in DTC patients. Wang et al. also reported a correlation between higher T stage and disease-specific survival in DTC patients [17]. Tang et al. reported that T stage was associated with poor prognosis in DTC patients [18]. Cao et al. developed a clinical prediction model that confirmed that T stage was associated with the survival of DTC patients. Their model had a C index of 0.71, which was similar to our results [19].

Our research revealed that the age of 55 was not significantly associated with OS in DTC patients. This finding aligns with recent studies. For instance, van Velsen et al. demonstrated that advanced age had a significant negative impact on disease outcomes specifically within the high-risk DTC population [20]. The optimal age cutoff for predicting prognosis differs between papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Ganly et al. reported that the mortality rate of DTC increased progressively with age. To date, there is no universally accepted age cutoff for risk stratification in DTC patients [21]. Peng et al. identified 67 years as the optimal cutoff age for predicting DTC mortality, rather than 55 years [22].

Furthermore, distant metastatic sites in DTC exhibit varying correlations with patient survival. Prior research has established that distant metastasis is linked to disease-specific mortality. Chen et al. highlighted the critical role of lung metastasis in both disease-specific and overall survival [23]. One study, with a follow-up period extending up to 29 years (median follow-up time of 6.9 years), found that age over 55 and distant metastasis were unfavorable prognostic factors, increasing the risk of death [24]. In contrast, our study, which had a 14-year follow-up period (median follow-up time of 2.66 years), did not find a significant correlation with OS. Therefore, a longer follow-up period is necessary to further elucidate the relationship between these factors and survival outcomes.

Numerous studies have aimed to develop predictive models for genes related to DTC. Chen et al. discovered three differentially expressed genes linked to survival

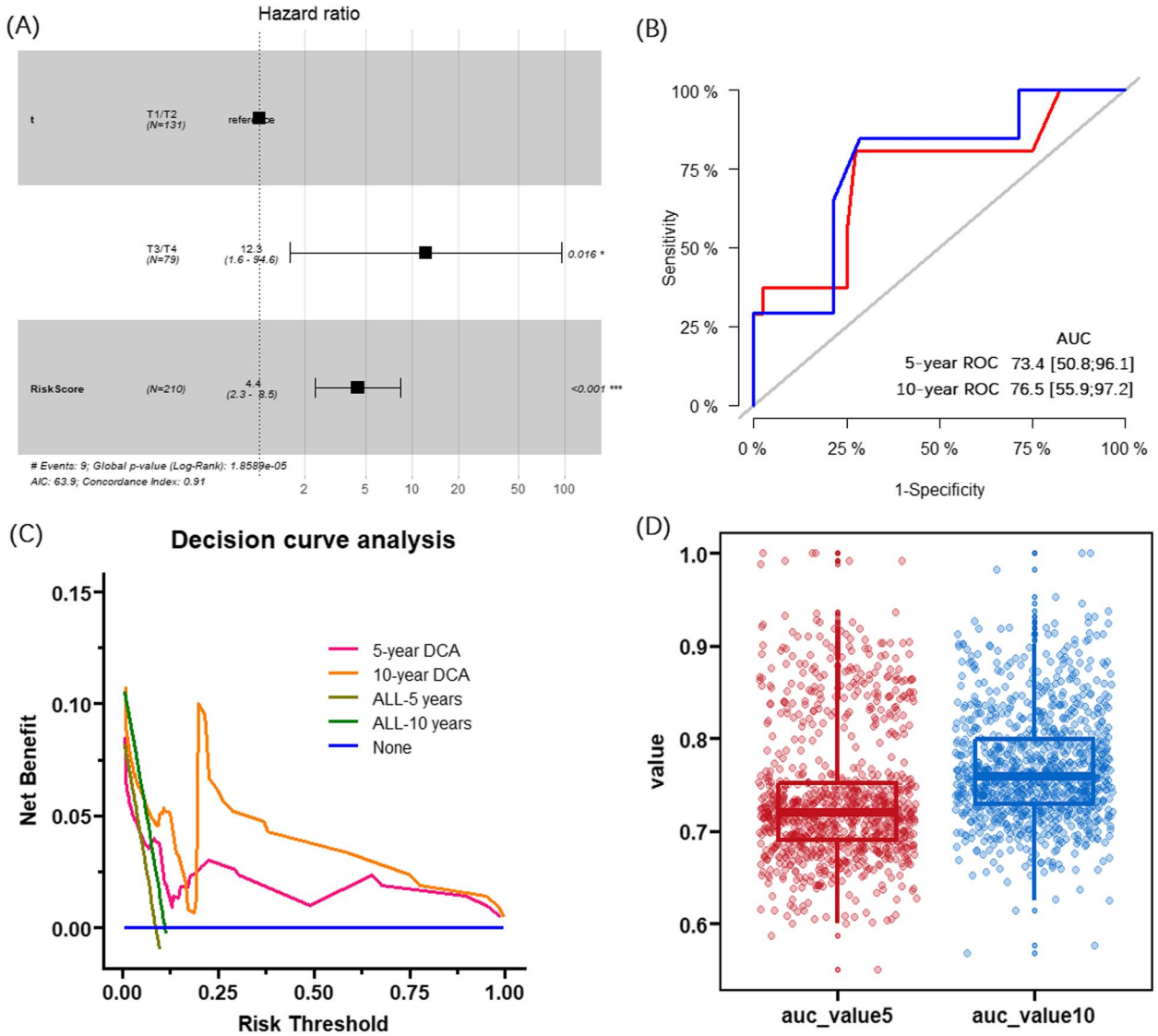

Fig. 3 **A** Forest plot predicting the OS of DTC patients. **B** ROC curve evaluation of the model's OS prediction. **C** Decision curve analysis to predict 5-year and 10-year OS of DTC patients (**D**) The model's AUC value was evaluated using fivefold and 200-fold cross-validation

and constructed a predictive model [25]. The ferroptosis gene has been used to establish a model to predict the survival of DTC patients [26, 27]. Su et al. searched for long noncoding RNAs (lncRNAs) associated with m6A to predict the prognosis of DTC [28]. Wang et al. developed a model for DR-lncRNAs linked to the survival of DTC patients and conducted drug sensitivity analyses. The team discovered that DR-lncRNAs have potential value as prognostic biomarkers and therapeutic targets [29]. A study by Yang et al. demonstrated that four miRNA signatures possess robust prognostic value in DTC. These findings indicate the significant potential value of these signatures in predicting DTC outcomes [30]. Ding et al. identified four differentially expressed genes and established a nomogram using the genes combined with clinical information [31]. The nomogram provided excellent prediction for DTC prognosis. Xia et al. combined six lncRNA molecules that are independently associated with lactate metabolism with clinical features to construct a nomogram. Their model demonstrated remarkable prediction performance [32]. However, none of these studies investigated the correlation between the Tec family genes and the OS of DTC patients. Our study is the first to examine the association of the Tec family with

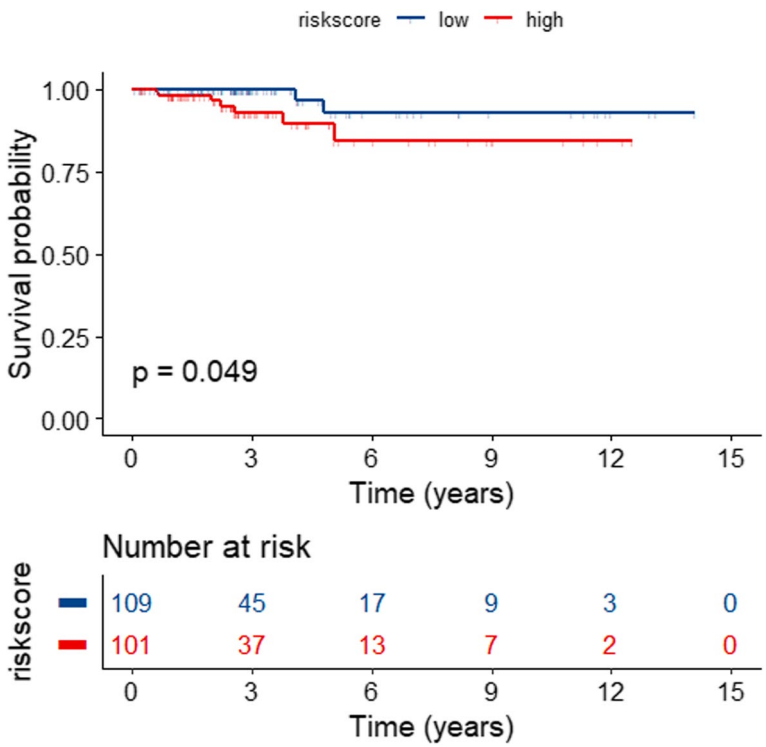

Fig. 4 Kaplan–Meier curve for OS analysis. The analysis showed a significant difference in OS between the high-risk and low-risk group ($P = 0.049$)

OS in DTC patients. Additionally, the prediction model constructed in combination with clinical characteristics exhibited a high level of predictive ability.

The Tec family is a recently discovered subfamily of non-receptor PTKs, with Tec as its first and representative member. The family includes Tec, BTK, ITK/EMT/TSK, BMX, and TXK/RLK. The family is characterized primarily by a pleckstrin homology (PH) domain in its protein structure [5, 33, 34]. Non-receptor PTKs play crucial roles in modulating cellular responses to numerous external stimuli and are important targets for drug discovery in the management of cancer and infectious diseases [35]. The cellular expression and function of these kinases suggest that they could serve as promising drug targets for treating malignant tumours and autoimmune diseases [9].

Tec kinases play pivotal roles in immune activation via lymphocyte action and in cytokine-mediated intracellular signalling, contributing to paracrine- and cytokine-mediated regulation of the tumour microenvironment [36]. The effects of Tec kinases on cellular physiology suggest that these kinases play a role in regulating various cellular processes beyond calcium mobilization [6, 37]. Additionally, the kinases play significant roles in regulating the mobilization of PLC-γ and calcium ions following the activation of lymphocyte surface antigen receptors [38]. Our study revealed similarities between the results of the cellular functional analyses of *AC007494.3* and *AC019226.2* and previous conclusions.

Tec kinase is implicated in the onset and progression of illnesses such as ischaemic heart disease, atherosclerosis, and myocardial infarction [7]. The BTK protein in the Tec family is the subject of extensive study. Research has shown that BTK deficiency is linked to numerous diseases related to B cells [39]. Furthermore, the levels of BTK in prostate cancer tissues are positively correlated with tumour grade. Consequently, inhibiting BTK expression can selectively impede the growth of prostate cancer cells [40]. Liu et al. proposed the use of BTK expression as a prognostic marker for multiple myeloma patients [41]. These findings demonstrate the potential of Tec proteins for clinical application.

Our research has several limitations. First, the TCGA database lacks additional clinicopathologic data. Second, the TCGA database lacks recurrence data. Third, more studies are needed to prove the specific functions of these two genes. Fourth, external data are needed to validate the model.

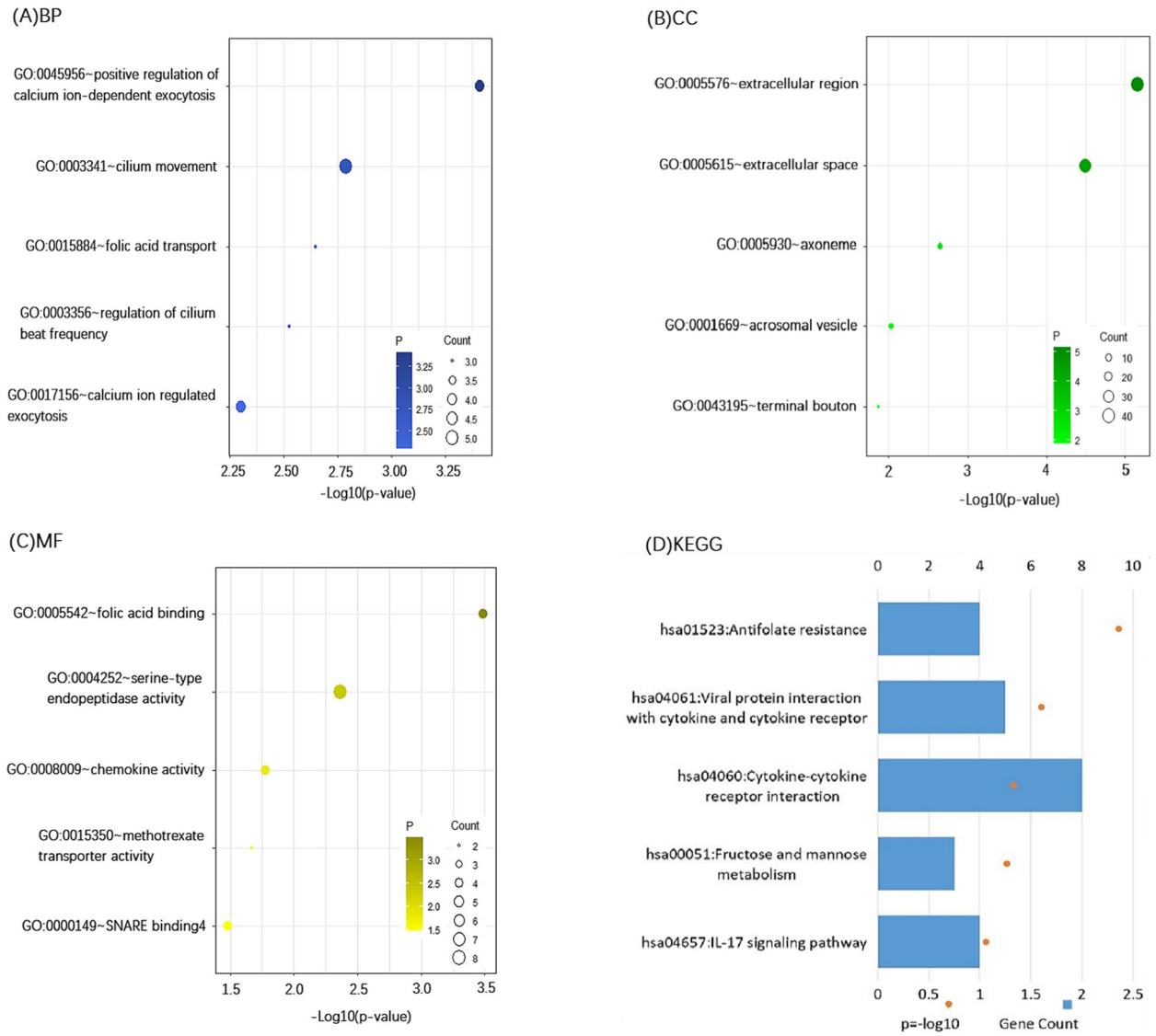

Fig. 5 Risk score is closely related to the regulation of cell cycle processes in DTC. **A** Biological process (BP) terms; **B** cellular component (CC) terms; **C** molecular function (MF) terms; **D** Kyoto Encyclopedia of Genes and Genomes (KEGG) results

The results of our investigation suggest a notable correlation between Tec proteins and OS in DTC patients. It is therefore recommended that mutations of the genes in this family be considered in pathological examination. Furthermore, *AC007494.3* and *AC019226.2* are expected to be targets for future drug development. High-risk patients should also be followed up more closely.

Authors' contributions

Ziyu Luo –- Study conception and design, Acquisition of data, Analysis and interpretation of data, Drafting of manuscript. Wenhan Li –- Acquisition of data, Critical revision of manuscript. Jianhui Li –- Study conception and design, Critical revision of manuscript. Ying Zhang –- Study conception and design, Acquisition of data, Critical revision of manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Competing interests
The authors declare no competing interests.

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