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A 6 transcription factors-associated nomogram predicts the recurrence-free survival of thyroid papillary carcinoma

Tao Wang, MD, Kun Tian, MD, Xie Ji, MD, Feixue Song, MD*

Abstract

Various researches demonstrated that transcription factors (TFs) played a crucial role in the progression and prognosis of cancer. However, few studies indicated that TFs were independent biomarkers for the prognosis of thyroid papillary carcinoma (TPC). Our aim was to establish and validate a novel TF signature for the prediction of TPC patients' recurrence-free survival (RFS) from The Cancer Genome Atlas (TCGA) database to improve the prediction of survival in TPC patients.

The genes expression data and corresponding clinical information for TPC were obtained from TCGA database. In total, 722 TFs and 545 TPC patients with eligible clinical information were determined to build a novel TF signature. All TFs were included in a univariate Cox regression model. Then, the least absolute shrinkage and selection operator Cox regression model was employed to identify candidate TFs relevant to TPC patients' RFS. Finally, multivariate Cox regression was conducted via the candidate TFs for the selection of the TF signatures in the RFS assessment of TPC patients.

We identified 6 TFs that were related to TPC patients' RFS. Receiver operating characteristic analysis was performed in training, validation, and whole datasets, we verified the high capacity of the 6-TF panel for predicting TPC patients' RFS (AUC at 1, 3, and 5 years were 0.880, 0.934, and 0.868, respectively, in training dataset; 0.760, 0.737, and 0.726, respectively, in validation dataset; and 0.777, 0.776, and 0.761, respectively, in entire dataset). The result of Kaplan–Meier analysis suggested that the TPC patients with low scores had longer RFS than the TPC patients with high score ($P = .003$). A similar outcome was displayed in the validation dataset ($P = .001$) and the entire dataset ($P = 2e\text{-}05$). In addition, a nomogram was conducted through risk score, cancer status, C-index, receiver operating characteristic, and the calibration plots analysis implied good value and clinical utility of the nomogram.

We constructed and validated a novel 6-TF signature-based nomogram for predicting the RFS of TPC patients.

Abbreviations: HR = hazard ratio, LASSO = least absolute shrinkage and selection operator, RFS = recurrence-free survival, ROC = receiver operating characteristic curve, TCGA = The Cancer Genome Atlas, TFs = transcription factors, TPC = thyroid papillary carcinoma.

Keywords: nomogram, recurrence-free survival, TCGA, thyroid papillary carcinoma, transcription factors

1. Introduction

Thyroid papillary carcinoma (TPC) is the most common form and accounts for the majority of all thyroid cancers. Despite a good prognosis, some patients with TPC suffer from local recurrence and/or distant metastasis.[1,2] An enormous negative effect on the quality of life and psychology is very common in patients with TPC.[3–5] Thus, an effective and exhaustive treatment approach for patients with TPC is urgently needed. Furthermore, identification of sensitive and specific biomarkers for prognosis may help provide individualized treatment for patients with TPC.

Various researches demonstrated that transcription factors (TFs) played a crucial role in the progression and prognosis of cancer. For instance, Hirao et al reported that TF homeobox D9 was associated with the malignant phenotype of cervical cancer via direct binding to the human papillomavirus oncogene promoter.[6] Zablockis et al revealed a significant prognostic role of thyroid TF-1 expression in patients with advanced lung adenocarcinoma.[7] Wu et al suggested that spalt-like TF 4 served as a potential diagnostic and prognostic biomarker of colorectal cancer.[8] Zhang et al indicated that lack of caudal-type homeobox TF 2 expression functioned as a prognostic biomarker in metastatic colorectal carcinoma.[9] Therefore, TFs may be potential predictive biomarkers to help doctors offer individualized treatment for cancer and may prolong patients' survival time. For example, Li et al suggested that overexpression of Forkhead box Q1, a member of the forkhead TF family, was correlated with poor prognosis in papillary thyroid carcinoma.[10] In addition, several studies revealed prognostic and

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The datasets generated during and/or analyzed during the current study are publicly available.

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predictive biomarkers for TPC. For example, Luzón-Toro et al demonstrated that lncRNA LUCAT1 served as a novel prognostic biomarker for patients with TPC.[11] Scheffel and Maia reported that the long and still uncertain journey of BRAF functioned as a prognostic signature in patients with TPC.[12] Liu et al revealed a key prognostic value of a 2-microRNA signature for TPC.[13] However, few studies have indicated that TFs were independent biomarkers for TPC prognosis. It is essential to identify TFs as independent and valuable signatures for TPC prognosis with a comprehensive and systematic method.

In this study, genes expression data and corresponding clinical information for TPC were retrieved from The Cancer Genome Atlas (TCGA) database and relevant TFs and eligible patients were screened to explore the application of TF signature analysis for cancer prognosis. According to bioinformatics methods, we developed and verified a novel 6-TF signature via risk score in prognostic assessment for TPC. Finally, a nomogram was performed and the result demonstrated the good value and clinical application of the nomogram.

2. Materials and methods

2.1. Data source and processing

We searched TCGA database based on TCGAbiolinks package[14] to obtain genes expression data and relevant clinical information for TPC. In addition, this study was performed from April 2020 to July 2020. In total, 24,991 genes and 545 TPC patients with complete clinical information were included. Samples without prognostic information or non-TF genes were excluded for the following analysis. TFs were screened by TRRUST database.[15] We converted raw counts of expression matrix to transcripts per million. Genes with 0 expression more than 20% of the samples were excluded. Finally, 722 TFs and 545 patients with TPC were determined for subsequent univariate Cox regression analyses.

2.2. Statistical analysis

To select TFs related to TPC patients' recurrence-free survival (RFS), an univariable Cox regression analysis was employed to assess the relationship between the TFs expression and TPC patients' RFS. Subsequently, the selected TFs were used to perform least absolute shrinkage and selection operator (LASSO) analysis for selecting the candidate TFs related to TPC patients' RFS. Then, multivariate Cox regression was acted with the candidate TFs to identify the TF-based signature for predicting RFS of TPC patients.

We classified 545 samples into a training set (n = 381) and a testing set (n = 164). The training cohort was applied for the selection of prognostic TF biomarkers. A 6-TF prognostic signature was determined via a linear combination of the regression coefficient according to the multivariate Cox regression analysis. The TF risk score formula was developed to obtain survival RFS risk scores for every patient with the coefficients from the multivariate Cox regression analysis. Patients with TPC were stratified into high- and low-risk groups with the median

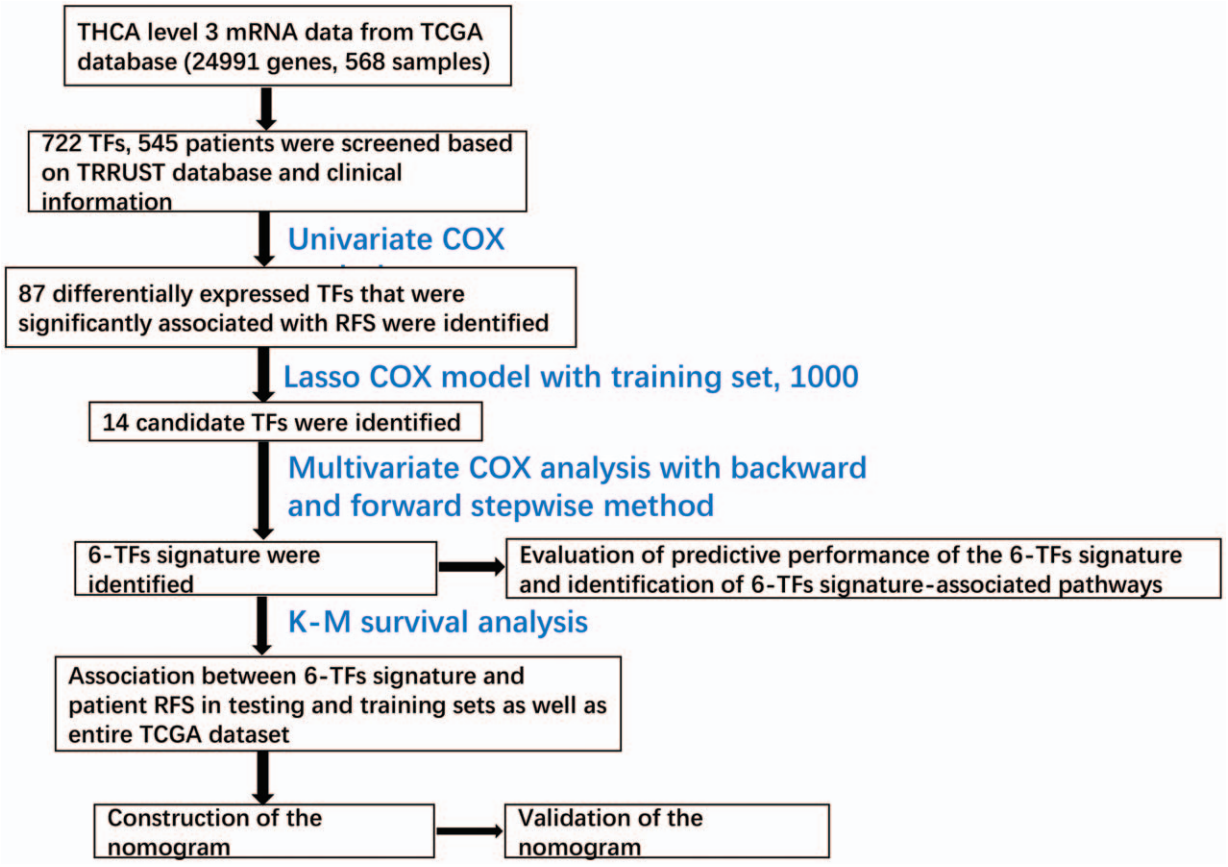

Figure 1. The flowchart of this study.

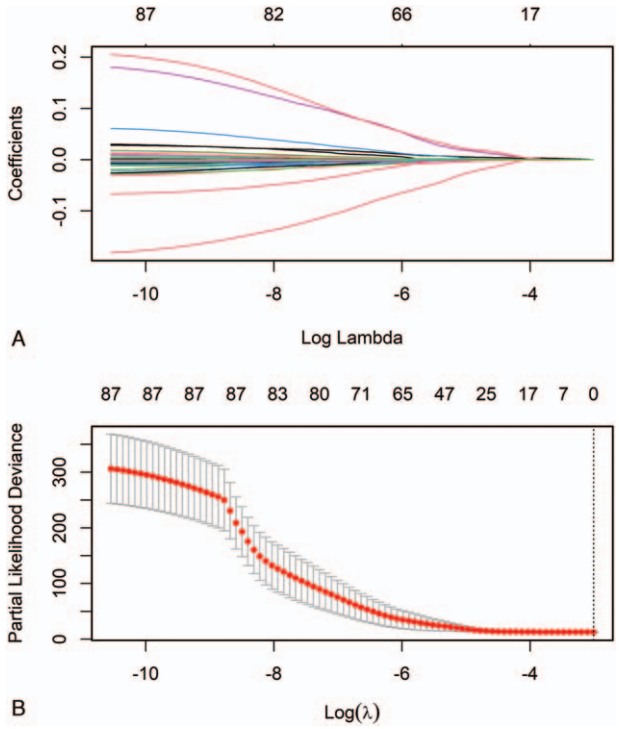

Figure 2. Candidate TFs selection in the light of the LASSO Cox regression model. (A) 10-fold cross-validation for tuning parameter selection in the LASSO model by minimum criteria (the 1-SE criteria). (B) LASSO coefficient profiles of the 87 TFs. A coefficient profile plot was created against log (lambda) sequence. Vertical line was performed at the value selected with 10-fold cross-validation, where optimal lambda resulted in 14 non-zero coefficients. LASSO = least absolute shrinkage and selection operator, TFs = transcription factors.

risk score as the cutoff. The time-dependent receiver operating characteristic (ROC) curve was built to weigh the predictive value of the TF signature for RFS with the R package "survivalROC." The model with a greater AUC value had a higher predictive value. The Kaplan–Meier survival curve and a log-rank test were used to test the survival difference in the high- and low-risk group via the R package "survival." The predictive performance of the TF signature was further examined in the testing training group and the entire group. All ROC and Kaplan–Meier curves were performed with R (version 3.6.1).

2.3. Gene set variation analysis

To evaluate the TF signature-linked signaling pathways. We performed single sample gene sets enrichment analysis in accordance with TPC mRNA information by gene set variation analysis package.[16] The top 20 critical pathways which had positive linkage to risk score were selected. In addition, patients with TPC were stratified into high- and low-risk groups with the median risk score as the cutoff.

2.4. Construction of the nomogram

The univariate Cox proportional hazard analysis and multivariate Cox proportional hazard analysis were executed through risk scores and other clinicopathological factors. To evaluate clinical procedure, a nomogram, combining the 6-TF signature with clinicopathological risk factors with significant P value ($P < .05$) from multivariate Cox regression analysis was developed as a quantitative prediction method to assess clinical prognosis. The prognostic power of the nomogram was tested by C-index, ROC, and calibration plots. The outcome of the nomogram was presented in the calibrate curve.

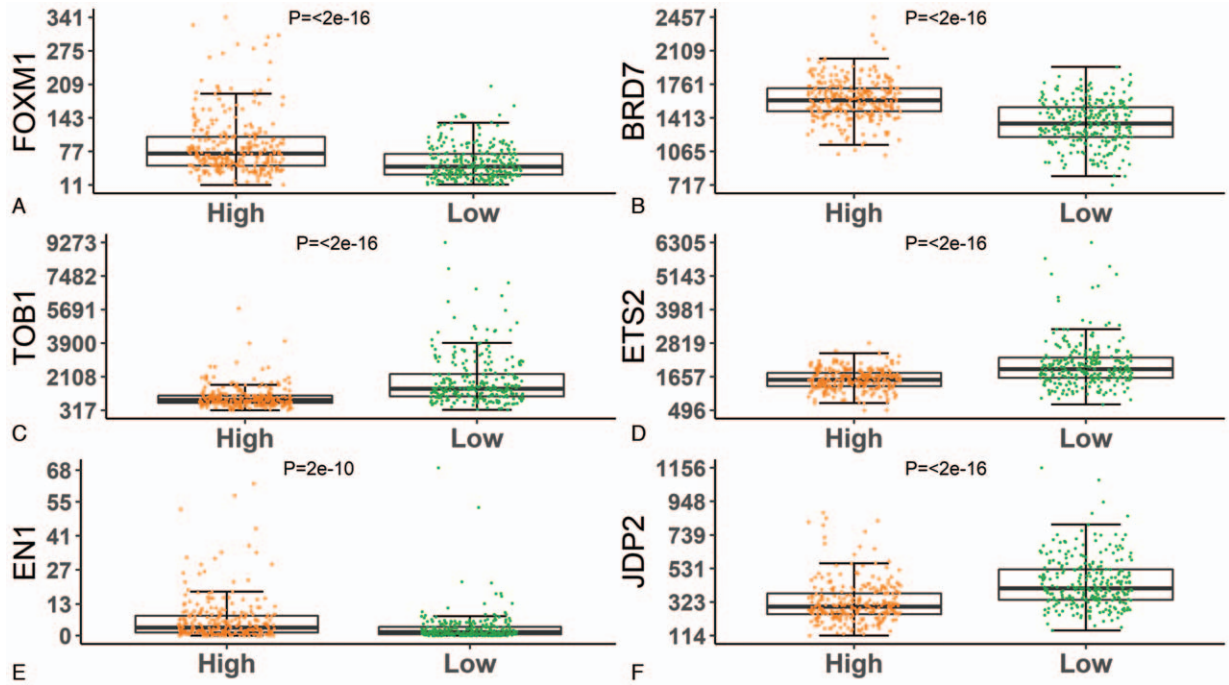

Figure 3. Boxplots of the 6 TFs expression values against risk group in the TCGA dataset. "High" and "Low" stood for the high-risk and low-risk groups, respectively. The differences between the 2 groups were examined by Mann–Whitney U test, and P values were summarized in the graphs. TCGA = The Cancer Genome Atlas, TFs = transcription factors.

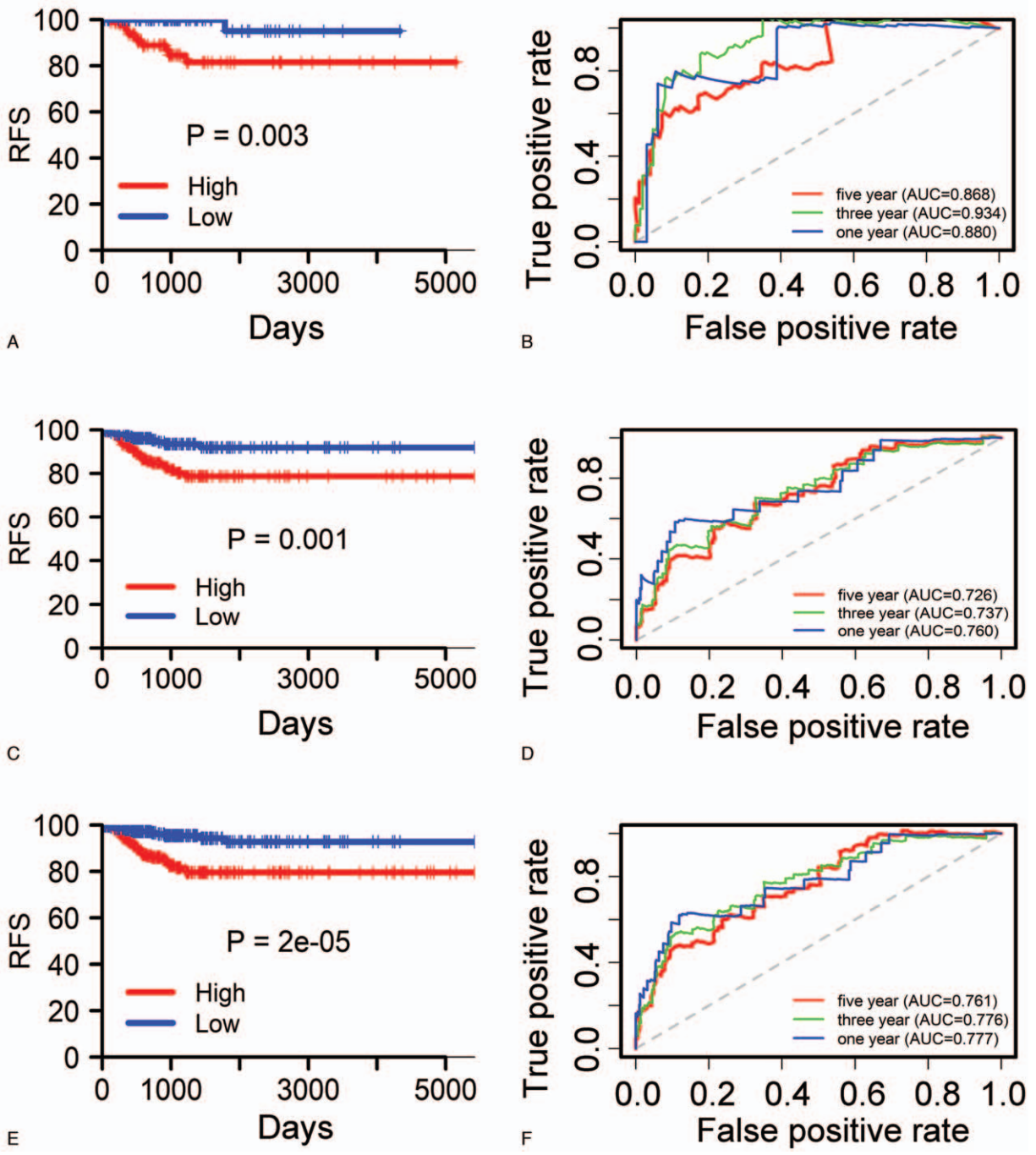

Figure 4. Kaplan–Meier and ROC analysis of patients with TPC in training dataset and validation dataset as well as the whole dataset. (A, C, E) Kaplan–Meier analysis for TPC patients between the low-risk and high-risk. (B, D, F) ROC curves showing the predictive ability of the signature for 1-, 3-, and 5-year RFS. RFS = recurrence-free survival, ROC = receiver operating characteristic curve, TPC = thyroid papillary carcinoma.

3. Results

3.1. Clinical characteristics of the study populations

The study was performed on 545 TPC patients who were clinically and pathologically diagnosed with TPC. Of these patients, 147 (26.97%) were male and 398 (73.03%) were female. The median age at diagnosis was 46 years (range, 15–89) and the median RFS was 908 days. The 3-year RFS rate of all patients was 37.36%. The pathologic stage was defined through the American Joint Committee on Cancer (AJCC) Cancer staging manual. The stage of TPC patients ranged from I to IV, and 314 (57.61%) patients in state I, 57 (10.46%) patients in stage Il, 118 (21.65%) patients in stage Ill, and 54 (9.91%) in stage IV, in addition, 2 (0.37%) patients' stage was not available. Histological type of the eligible patients included TPC-classical/usual 401 (73.58%), TPC-follicular (≥99% follicular patterned) 106

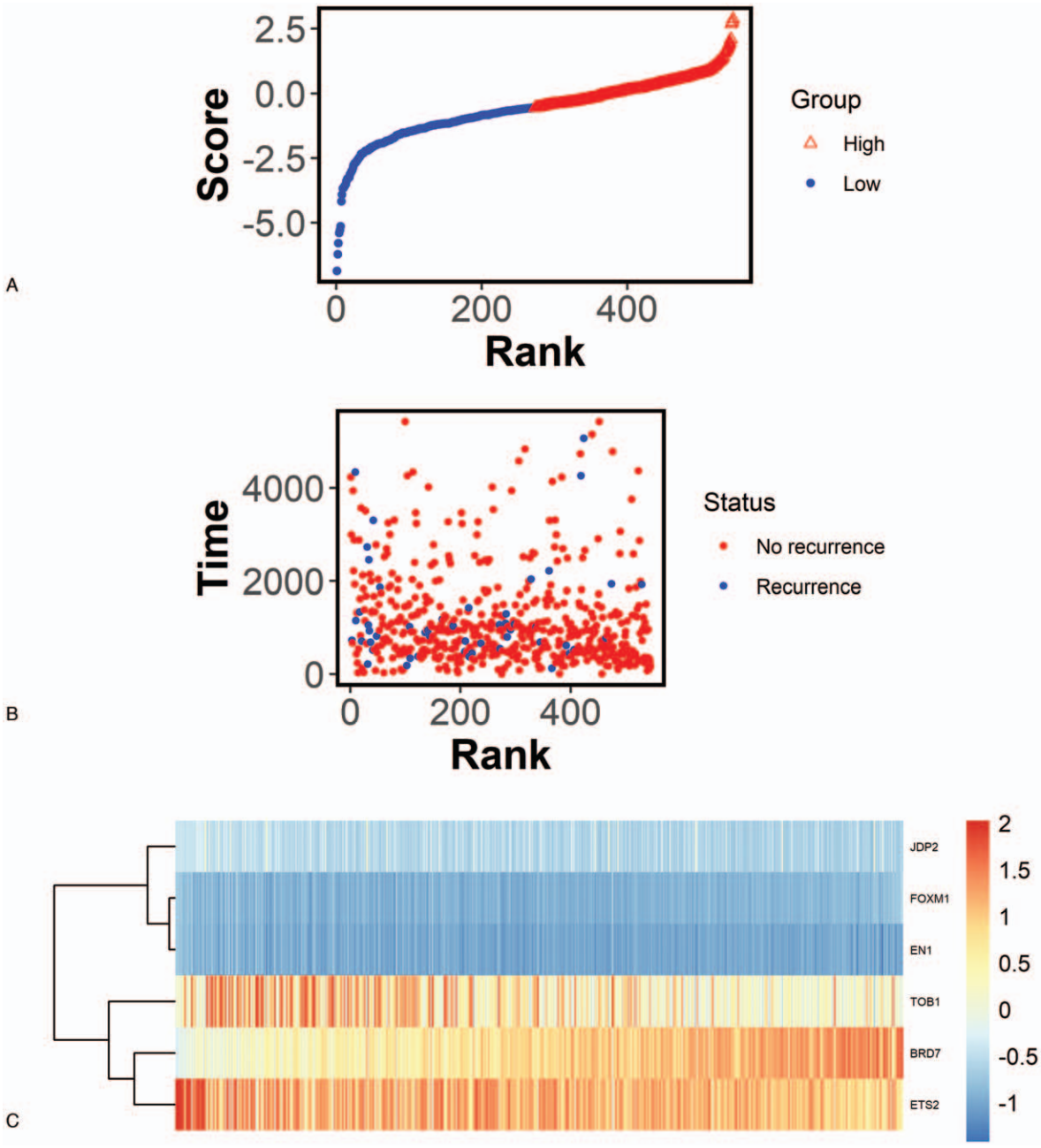

Figure 5. TF risk score analysis of 545 TPC patients in the TCGA dataset. (A) The distribution of the risk scores of the 545 total included cases. The red triangle stood for the high-risk cluster, the blue circle stood for the low-risk cluster. (B) Status of TPC patients. The red ball referred to the high-risk group, the blue ball referred to the low-risk group. (C) Heatmap of the 6 TFs in TPC patients. Each row of the heat map stood for a radiomics characteristic and each column stood for a TPC patient. TFs = transcription factors, TGGA = The Cancer Genome Atlas, TPC = thyroid papillary carcinoma.

(19.45%), and TPC-tall cell (≥50% tall cell features) 38 (6.97%), respectively. Patients were separated into 4 groups according to the residual tumor, that is, R0 418 (76.7%), R1 53 (9.72%), R2 3 (0.55%), and other 71 (13.03%). In addition, TPC patients were divided into 5 groups based on primary thyroid gland neoplasm location anatomic site: bilateral group, isthmus group, left lobe group, right lobe group, and other groups. Right lobe group was the most common type 238 (43.67%). Table S1, Supplemental Digital Content, http://links.lww.com/MD/G423 showed the characteristics of the study populations. Figure 1 listed the workflow chart of this study.

3.2. Identification of TFs significantly related to RFS and establishment of prognostic signatures

Fourteen TFs (Fig. 2A and B) were suggested to be significantly correlated with TPC patients' RFS by univariate Cox regression analysis and LASSO Cox regression analysis (Table S2, Supplemental Digital Content, http://links.lww.com/MD/G424). Finally, 6 TFs (JDP2, FOXM1, EN1, TOB1, BRD7, and ETS2) were revealed to be significantly involved in TPC patients' RFS based on multivariate Cox analysis ($P < .05$). By linearly combining the expression values of determined TFs measured via their coefficients derived from the multivariate Cox regression model,

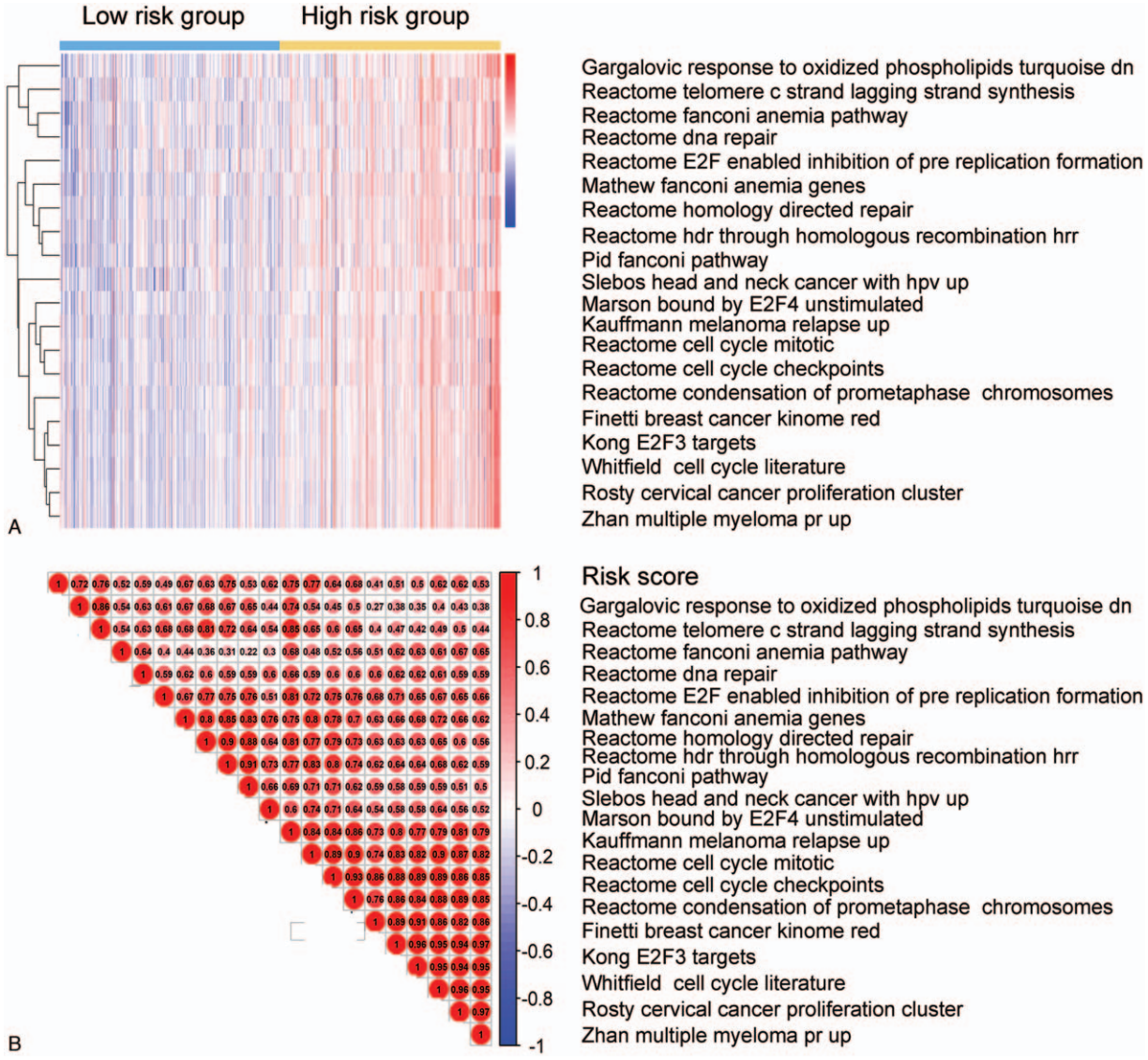

Figure 6. Evaluation of the 6 TF signature-linked signaling pathways. (A) Heatmap of top 20 enriched pathways involved in high-risk group. Each row of the heat map referred to a radiomics characteristic and each column represented a TPC patient. (B) Association graph between risk scores and top 20 pathways. Each red ball represents a pathway, and each line represents 1 patient. The score characteristic of each patient can be observed from the graph. TFs = transcription factors, TPC = thyroid papillary carcinoma.

we developed a prognostic formula. Risk score = 00915 * FOXM1 + 0.00118 * BRD7 – 0.00029 * TOB1 – 0.00102 * ETS2 + 0.03078 * EN1 – 0.00231 * JDP2, which was used to assess RFS risk scores of each patient enrolled in this study. The 6-TF signature was used for predicting the RFS of TPC patients. Obviously, the high TF expression of FOXM1, BRD7, and EN1 has involved a high risk. Whereas, the low TF expression of TOB1, ETS2, and JDP2 was correlated with a higher risk (Fig. 3).

3.3. Relationship between the 6-TF signature and TPC patients' RFS in training dataset and validation dataset as well as the whole dataset

The patients with TPC were stratified into high- and low-risk groups using the median risk score as the cutoff. The Kaplan–Meier analysis was employed to test the difference in RFS between the 2 groups. The result of training set showed that the TPC patients with low-scores had better RFS than the TPC patients with high-score ($P = .003$) (Fig. 4A). A similar outcome was displayed in the validation dataset ($P = .001$) (Fig. 4C) and the whole dataset ($P = 2e\text{-}05$) (Fig. 4E).

3.4. Evaluation of the predictive ability of the 6-TF signature using ROC analysis

Time-dependent ROC curves were carried out to assess the predictive strength of the 6-TF signature. The AUC of the 6-TF signature at 1, 3, and 5 years were 0.880, 0.934, and 0.868, respectively (Fig. 4B) in training dataset, 0.760, 0.737, and 0.726, respectively (Fig. 4D) in validation dataset, and 0.777, 0.776, and 0.761, respectively (Fig. 4F) in entire dataset. The result

Table 1

Univariate Cox regression analysis and multivariate Cox regression analysis outcome according to risk score and other clinical variables.

	Univariate Cox analysis				Multivariate Cox analysis			
ID	HR	HR.95L	HR.95H	*P* value	HR	HR.95L	HR.95H	*P* value
Cancer status	3.137530042	2.32086661	4.241559907	1.06E-13	2.63613922	1.889203904	3.678390643	1.18E-08
Score	2.718281828	2.04154101	3.619352274	7.60E-12	2.22334172	1.666402953	2.966418417	5.60E-08
Stage	1.398291239	1.183014651	1.65274233	8.49E-05	1.16805096	0.889716357	1.533458437	.263337059
T	1.454638123	1.180289556	1.79275675	.000440668	1.16555336	0.889053027	1.528046792	.267513637
Neoplasm dimensionneoplasm depth	1.570201152	1.182759874	2.084558085	.001802426	0.83864552	0.444078038	1.58378989	.587501814
Neoplasm dimensionneoplasm width	1.335644155	1.060299786	1.682491436	.014008163	1.1014961	0.632404001	1.91854203	.732766019
N	1.409484551	1.046612542	1.898168253	.023824733	1.10331334	0.798598096	1.524296564	.551044972
Sex	1.832947007	1.047937173	3.206007781	.033661191	1.08566677	0.560358443	2.103425668	.807555294
Age at initial pathologic diagnosis	1.017709658	1.000843233	1.034860319	.03951178	0.99441844	0.970001114	1.019450416	.659019261
Neoplasm dimension neoplasm length	1.167144595	1.005616409	1.354618414	.041986269	0.95104497	0.715956145	1.263326734	.728987523
M	1.667988447	0.997018798	2.790504517	.0513441				
Residual tumor	1.39888024	0.995731838	1.965253949	.052953074				
Extrathyroid carcinoma present extension status	1.240056499	0.962436661	1.597757215	.096136795				
Number of lymphnodes positive by HE	1.022255762	0.980216085	1.066098444	.304259225				
Primary neoplasm focus type	1.121921285	0.84922029	1.482191824	.418123446				
Race	1.116371133	0.818589047	1.522478846	.486790347				
Ethnicity	1.16616657	0.723866838	1.878721884	.527513274				
Primary thyroid gland neoplasm location anatomic site	1.033624458	0.872927108	1.223904621	.701273747				
Histological type	0.938332279	0.657706237	1.338694111	.725530066				
Patient personal medical history	0.982533261	0.713118526	1.353732338	.914183461				

HR = hazard ratio.

demonstrated that the 6-TF signature was a reliable predictor for RFS of TPC patients.

Furthermore, patients were ranked with the risk scores (Fig. 5A), and the scatter plot presented the relationship between survival status (Fig. 5B). The outcome indicated that the high-risk cohort had a worse survival than the low-risk cohort. Heatmap of 6 TFs grouped through risk score was shown in Fig. 5C, which confirmed our previous boxplot. Besides, subgroup analysis was executed with a few clinicopathological factors consisting of age, gender, stage, histologic grade, residual tumor, ethnicity, and medical history. The result demonstrated a good predictive ability of the 6-TF in most of the sub-groups (Figs. S1–S7, Supplemental Digital Content, http://links.lww.com/MD/G416, http://links.lww.com/MD/G417, http://links.lww.com/MD/G418, http://links.lww.

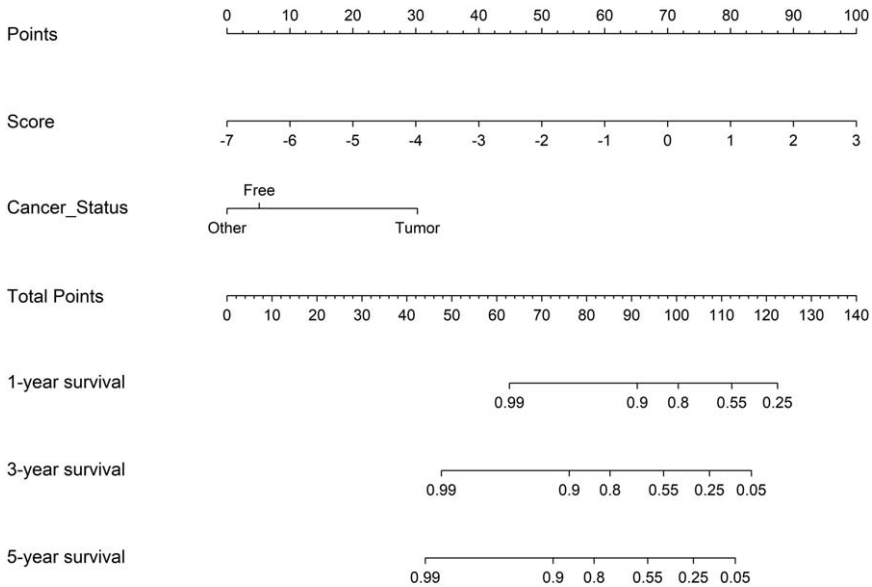

Figure 7. TF-based nomogram for predicting RFS in TPC patients. The nomogram was constructed in accordance with the entire TCGA set, with a risk score, cancer status. C-index, ROC, and the calibration plots were defined as evaluation indexes for the nomogram. RFS = recurrence-free survival, ROC = receiver operating characteristic curve, TFs = transcription factors, TGGA = The Cancer Genome Atlas, TPC = thyroid papillary carcinoma

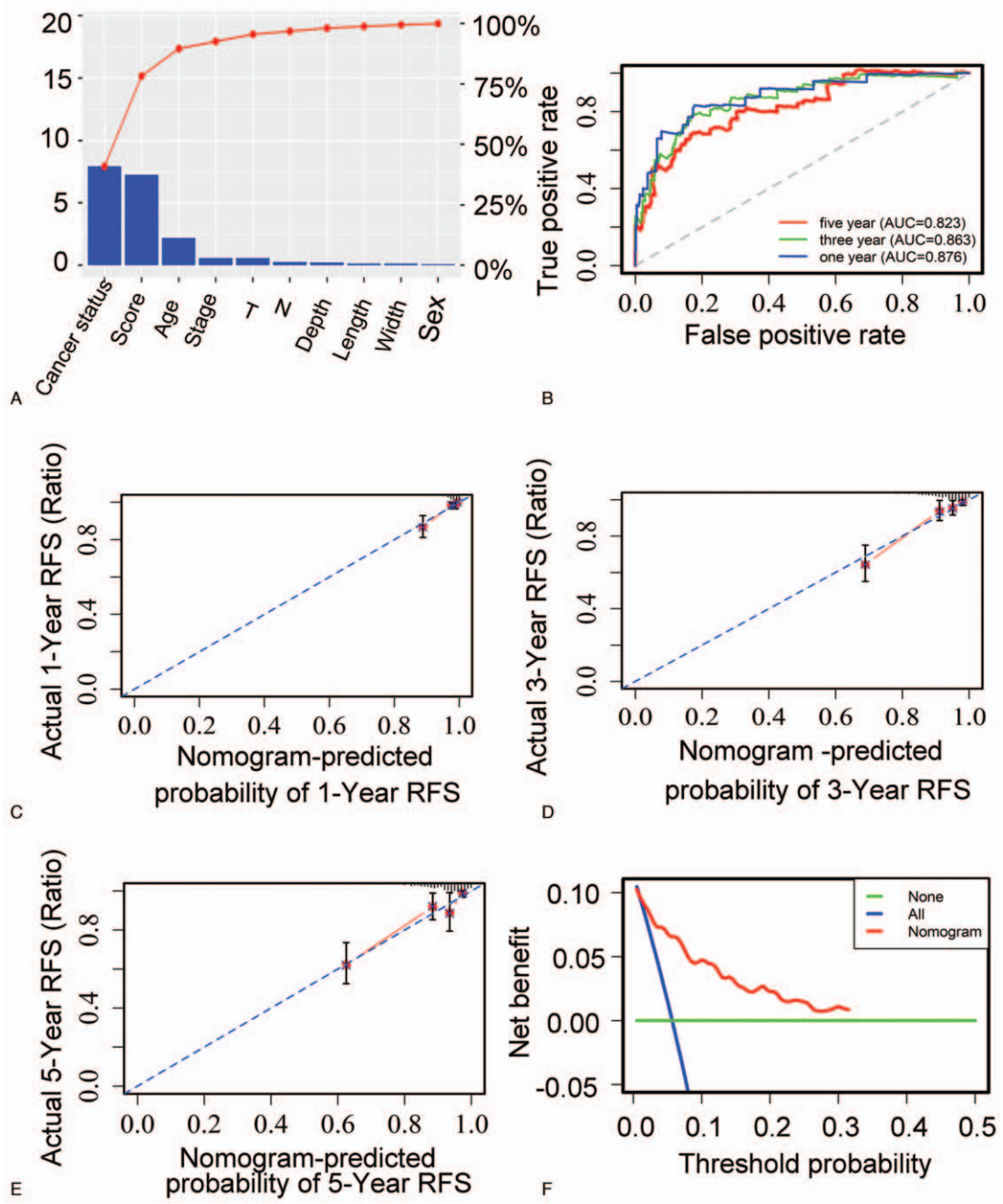

Figure 8. The 6-TF-based nomogram based on the entire TCGA dataset. (A) Barplot stood for the importance of each clinical variable. The horizontal axis referred to clinical factors, the vertical axis referred to the percentage of importance. (B) 1-, 3-, and 5-year ROC curves for the 6-TF-based nomogram. (C, D, E) Stood for the 1-, 3-, and 5-year nomogram calibration curves, respectively. (F) The decision curve analysis for the nomogram. The red line referred to the nomogram. The blue line referred to the treat-all and the green line referred to the treat-none. ROC = receiver operating characteristic curve, TFs = transcription factors, TGGA = The Cancer Genome Atlas.

com/MD/G419, http://links.lww.com/MD/G420, http://links.lww.com/MD/G421, and http://links.lww.com/MD/G422).

3.5. Evaluation of the 6 TF signature-linked signaling pathways

The patients with TPC were stratified into high- and low-risk groups using the median risk score as the cutoff. The top 20 core pathways which had positive linkage to TF risk score were assessed (Fig. 6A) (Table S3, Supplemental Digital Content, http://links.lww.com/MD/G425). A positive correlation between the enriched signaling pathways and the TF risk score was further described in Figure 6B.

3.6. Nomogram development

We conducted univariate and multivariate Cox model through TF-related risk scores and some clinicopathological factors to examine the independence of the 6-TF signature as a prognostic predictor of TPC patients. Hazard ratios (HRs) showed that the

6-TF signature was importantly involved in the RFS of TPC patients ($P < .001$, HR 2.22, 95% CI 1.67–2.97) based on the Cox regression analysis (Table 1), implying that the 6-TF signature may be an independent prognostic predictor. The importance among different clinical variables in the nomogram was summarized in (Fig. 8A). The nomogram (Fig. 7) showed that C-index (0.836, 95%CI: 0.804–0.868), AUC (0.876, 0.863, and 0.823) (Fig. 8B) and calibration plot presented a good performance (Fig. 8C–E). The result showed that the nomogram generated a good performance as the desired model both in the whole TCGA set. On the other hand, the DCA suggested that the nomogram had key clinical utilization for prognosis prediction of TPC patients than that in the treat all or treat none cluster (Fig. 8F).

4. Discussion

We determined a combination of 6 TFs (JDP2, FOXM1, EN1, TOB1, BRD7, and ETS2) which can effectively predict RFS in TPC patients based on the univariate Cox proportional hazard analysis, the LASSO Cox regression analysis, and multivariate Cox proportional hazard analysis. Various experiments have suggested that the above 6 TFs were significant in cancer development. For instance, Liu et al reported that JDP2 suppressed the epithelial-to-mesenchymal transition in pancreatic cancer BxPC3 cells.[17] Song et al demonstrated that UCHL3 promoted pancreatic cancer progression and chemo-resistance via FOXM1 stabilization.[18] Peluffo et al suggested that EN1 served as a transcriptional dependency in triple-negative breast cancer involved in brain metastasis.[19] Guo et al indicated that microRNA-371a-3p promoted the progression of gastric cancer through targeting TOB1.[20] Niu et al implied that BRD7 repressed the Warburg effect and tumor progression by inactivation of HIF1α/LDHA axis in breast cancer.[21] Wallace et al reported that ETS2 in tumor fibroblasts enhanced angiogenesis in breast cancer.[22] We speculated that these 6 TFs were associated with TPC patients. The result of Figure 4B, D, and F revealed the values of the 6-TF signature for predicting RFS of TPC patients (AUC at 1, 3, and 5 years were 0.880, 0.934, and 0.868, respectively, in training dataset; 0.760, 0.737, and 0.726, respectively, in validation dataset; and 0.777, 0.776, and 0.761, respectively, in entire dataset, and entire TCGA dataset 0.741, 0.748, and 0.781, respectively), suggesting a great value of the 6-TF signature. The significance of the 6-TF signature for the prognosis of TPC patients will not be fully realized until additional treatments are available for patients with TPC destined to have poor survival after conventional chemotherapy. In this regard, TFs might not only predict the RFS of TPC patients but might also generate clues on individual TF related to tumor development. Therefore, identification of the 6-TF signature could greatly promote prognosis and our power to develop effective treatment protocols. Whereas, there were still a few crucial virtues in the study. We developed a nomogram that combined both the 6-TF signature and the conventional clinicopathological factors to predict 3- and 5-year TPC patients' RFS. As demonstrated in Figure 8B, the result of the nomogram showed that C-index (0.836, 95%CI: 0.804–0.868) and AUC (0.876, 0.863, and 0.823). The outcome indicated the good power of our nomogram for predicting RFS of TPC patients in the clinical routine, which made our study more forceful. Furthermore, we LASSO Cox regression analysis to explore the candidate TFs significantly linked to TPC patients' RFS which can filter the variables between univariate and multivariate Cox analysis. In other words, the application of LASSO Cox regression can improve the predictive ability of the 6-TF signature.

Nevertheless, there were a few limitations in this study. Firstly, the lack of an independent external validation set was a hindrance for implementation in the clinical setting. Otherwise, more associated clinical factors might be enrolled in the nomogram model to make the study more reliable. In addition, the value of the 6-TF signature for the prognosis of TPC patients needed to be examined in clinical practice.

5. Conclusions

We successfully constructed and validated a novel 6-TF signature and a nomogram for predicting the RFS of TPC patients.

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Conceptualization: Feixue Song.
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Formal analysis: Tao Wang, Xie Ji.
Funding acquisition: Feixue Song, Tao Wang, Kun Tian.
Investigation: Tao Wang, Kun Tian, Xie Ji.
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Project administration: Kun Tian.
Resources: Tao Wang, Kun Tian, Xie Ji.
Software: Tao Wang, Xie Ji.
Supervision: Feixue Song.
Validation: Kun Tian.
Visualization: Tao Wang.
Writing – original draft: Tao Wang, Kun Tian.
Writing – review & editing: Feixue Song, Xie Ji.

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