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ORIGINAL ARTICLE

Development of a redox-related prognostic signature for predicting biochemical-recurrence-free survival of prostate cancer*

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Abstract

Objective Prostate cancer (PCa) is one of the most common malignancies among elderly males. However, effective prognostic biomarkers are currently lacking. Bioinformatic analysis was used to identify patients at high risk of biochemical recurrence (BCR).

Methods In our study, RNA sequencing and clinical data were downloaded from The Cancer Genome Atlas (TCGA) dataset to serve as the training and internal validation sets. The GSE84042 dataset was used as the external validation set. Batch effects were removed and normalized for the two datasets using "sva" package. Univariate Cox, least absolute shrinkage and selection operator (LASSO) Cox, and multivariate Cox regression analyses were successively performed to identify the redox-related gene (RRG) signature. After performing univariate Cox, LASSO Cox, and multivariate Cox regression analyses, a signature consisting of seven RRGs was established to predict BCR of patients with PCa, which included *TP53, ADH5, SRRT, SLC24A2, COL1A1, CSF3R*, and *TEX19*. Kaplan-Meier and receiver operating characteristic curve analyses showed good performance for the prognostic signature in the training and validation datasets.

Results Univariate and multivariate Cox analyses showed that the RRG signature was an independent prognostic factor for BCR of patients with PCa. Thereafter, the nomogram results revealed that it was able to predict BCR of patients with PCa with high efficiency.

Conclusion This study identified an independent prognostic signature and established a nomogram to predict BCR in PCa. This signature can be used to identify patients with PCa with a high risk of BCR, and personalized treatment can be applied.

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Key words: prostate cancer (PCa); redox; prognostic signature; prognosis; bioinformatic

Prostate cancer (PCa) is one of the most commonly diagnosed urogenital cancers in the elderly (age > 65 years) [1] and has the second highest male cancer-related mortality rate in the United States, accounting for approximately 20% of newly diagnosed cases in 2019 [2]. With advances in diagnosis and therapy, the clinical survival of patients with PCa has significantly increased. However, 20%–30% of patients experience biochemical recurrence (BCR) without clinical or radiographic metastases [3]. Without secondary treatment, the interval time from BCR to clinical progression is approximately 5–8 years, and 32%–45% of patients die of PCa within 15 years [4]. Therefore, a prognostic signature that can predict BCR-free survival is of tremendous clinical value.

Redox (reduction and oxidation) reactions are a series of reactions that transfer electrons between molecules. Redox reactions occur extensively throughout the body in response to both endogenous and exogenous stimuli. Redox reactions have important physiological functions such as transcriptional regulation, direct

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oxidative modification, regulation of redox-sensitive interacting proteins, regulation of redox-sensitive modifying proteins, and regulation of protein turnover [5]. The homeostasis of redox reactions refers to a delicate balance between the generation and removal of reactive oxygen species (ROS). Reactive oxidizing molecules are strongly oxidizing molecules that include free radicals. The excessive accumulation of these molecules is called "oxidative stress," which can destroy proteins, DNA and lipid macromolecules, and lead to DNA damage, signal transduction abnormalities and remodeling of the extracellular matrix [6]. Studies have shown that the imbalance of redox reactions is closely related to the development of many diseases, such as cancer, cardiovascular diseases, diabetes mellitus, and neurodegenerative diseases [7–9]. The accumulation of ROS has been linked to the occurrence and progression of various malignancies such as bladder, breast, liver, lung, ovarian, and prostate cancers [10–12]. The possible mechanisms of oxidative stress-induced cancers include the induction of genomic instability, abnormal epigenetic modifications, uncontrolled proliferation of initiated cells, and failure of apoptosis [10]. However, no studies have explored the association between redox-related genes (RRGs) and PCa prognosis.

In this study, The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) databases were used to analyze the association between RRGs and the prognosis of patients with PCa. Potential biomarkers were identified to improve the clinical outcome of patients with PCa.

Materials and methods

Data acquisition and processing

The RRGs were searched using the Genecard database (https://www.genecards.org/), NCBI gene function module (https://www.ncbi.nlm.nih.gov/gene/), OMIM database (https://www.oncomine.org/resource/), and GSEA-MsigDB (https://www.gsea-msigdb.org/gsea/msigdb) with the keyword "redox," and 4087 genes were obtained. We downloaded the transcriptomic data and associated clinical information for 499 PCa tumors from TCGA (https://portal.gdc.cancer.gov/), which contained 499 tumors and 52 surrounding normal tissues. Background correction and normalization of the RNA-seq data were performed using fragments per kilobase million (FPKM) [13]. The patients in TCGA cohort were randomly split into training and internal validation cohorts. Normalized mRNA expression data of the GSE84042 dataset with 73 PCa samples were downloaded from the GEO database, and clinicopathological data were obtained from the supplementary material of the original literature [14]. The GSE84042 dataset was used as the external validation cohort. Genes with expression values of 0 in more than half of the samples were deleted. The batch effect was eliminated by using the "sva" package in R (Version 4.1.0).

Construction and validation of RRG prognostic signature

To identify prognosis-related RRGs, we used data from TCGA cohort to perform univariate Cox proportional regression to evaluate the correlation between RRGs and BCR-free survival. The RRGs with P value < 0.00001 were selected, and then the better prognostic RRGs were screened by the least absolute shrinkage and selection operator (LASSO) regression analysis using the "glmnet" package. Finally, a prognostic signature was constructed using a multivariate Cox regression analysis. In order to reveal the biological functions of the selected RRGs, Gene Ontology (GO) and Kyoto Gene and Genome Encyclopedia (KEGG) enrichment analysis were performed by R packages "ggplot2" with P-value of < 0.05. The GO enrichment results are described in terms of three aspects: biological process (BP), cellular component (CP), and molecular function (MF). The following formula was used to compute the risk score of each patient: risk score = (exp Gene1 × coef Gene1) + (exp Gene2 × coef Gene2) +…+ (exp GeneN × coef GeneN). Here, exp represents the expression value of the selected genes, and coef represents the computed multivariate Cox regression coefficients.

The median risk score of the training cohort was used as the cut-off value for the training and validation cohorts. Patients were separated into high- and low-risk subgroups based on the cutoff values. The prognostic capacity of the gene signature was assessed using Kaplan-Meier curve analysis (using the "survival" package) and area under the receiver operating characteristic (ROC) curve (AUC) analysis (using the "timeROC" package). In addition, the internal validation dataset and GSE84042 cohort were employed as validation sets to verify the stability and correctness of the signature. The risk score for each patient in the validation set was calculated using the formula described above. Kaplan-Meier and ROC curve analyses were also performed on the validation set. The prognostic signature results were used to perform a principal component analysis (PCA). Statistical significance was set at $P < 0.05$.

Clinical relevance of RRG signature

Clinicopathological parameters including age at diagnosis, pathologic T stage (pT), Gleason grade score (GGS), and preoperative prostate-specific antigen (PSA) levels were used to stratify patients with PCa. Using the Kaplan-Meier "survival" package, Kaplan-Meier curve analysis was performed to evaluate the prognostic value of the signature in different subgroups. In addition,

we analyzed the differences in the signature-based risk score distribution between subgroups stratified by clinicopathological parameters. Statistical significance was set at $P < 0.05$.

Construction and validation of a nomogram

To identify independent prognostic indicators for PCa related to BCR-free survival, we used univariate and multivariate Cox analyses based on the prognostic gene signature and clinicopathological data such as age at diagnosis and pT, GGS, and PSA values. Then, using the "rms" package, we created a nomogram combining clinicopathological data and the gene signature to produce a quantitative strategy to predict the prognosis of patients with PCa. Finally, Kaplan-Meier survival analysis, AUC under the ROC curve analysis, and the C-index were performed to assess the accuracy and stability of the nomogram. The performances of the nomogram and clinical models were compared using decision curve analysis (DCA). Statistical significance was set at $P < 0.05$.

Results

Construction and validation of RRG prognostic signature

A flowchart of the process used in this study is shown in Fig. 1. In TCGA dataset, 429 patients with BCR-free survival status and time were collected to construct the RRGs signature. After performing univariate Cox proportional regression analysis, 19 RRGs were found to be significantly related to BCR-free survival ($P < 0.00001$). Next, LASSO Cox regression and multivariate Cox regression analyses were performed, and seven genes were identified: *TP53*, *ADH5*, *SRRT*, *SLC24A2*, *COL1A1*, *CSF3R*, and *TEX19*. The results are shown in Fig. 2 and 3. The results of GO and KEGG showed RRGs were mainly involved in cellular response to environmental stimulus, cellular response to abiotic stimulus and production of miRNAs involved in gene silencing by miRNA. Molecular functions of the differentially expressed RRGs were enriched for protease binding. KEGG analysis showed that these RRGs mainly enriched in the pathways of PI3K-Akt signaling pathway. The results were showed in Fig. 4. The risk score of each patient was calculated as follows: Risk score = (–0.3239 × TP53 exp) + (–0.6248 × ADH5 exp) + (1.4499 × SRRT exp) + (0.9269 × SLC24A2 exp) + (0.3841 × COL1A1 exp) + (1.5398 × CSF3R exp) + (1.5942 × TEX19 exp).

Patients were separated into high- and low-risk subgroups based on the cutoff values. Kaplan-Meier curve analysis of the TCGA training cohort revealed that patients in the high-risk group had a worse prognosis than those in the low-risk group ($P < 0.001$; Fig. 5a). The AUC under the ROC curve of different time points were calculated using the ROC curve. The AUC values for the first year were 0.837, 0.754 for the second year, 0.837 for the third year, 0.820 for the fourth year, and 0.846 for the fifth year, indicating that this model can accurately predict the BCR-free survival prognosis of patients with PCa (Fig. 5d). The TCGA validation cohort and GSE84042

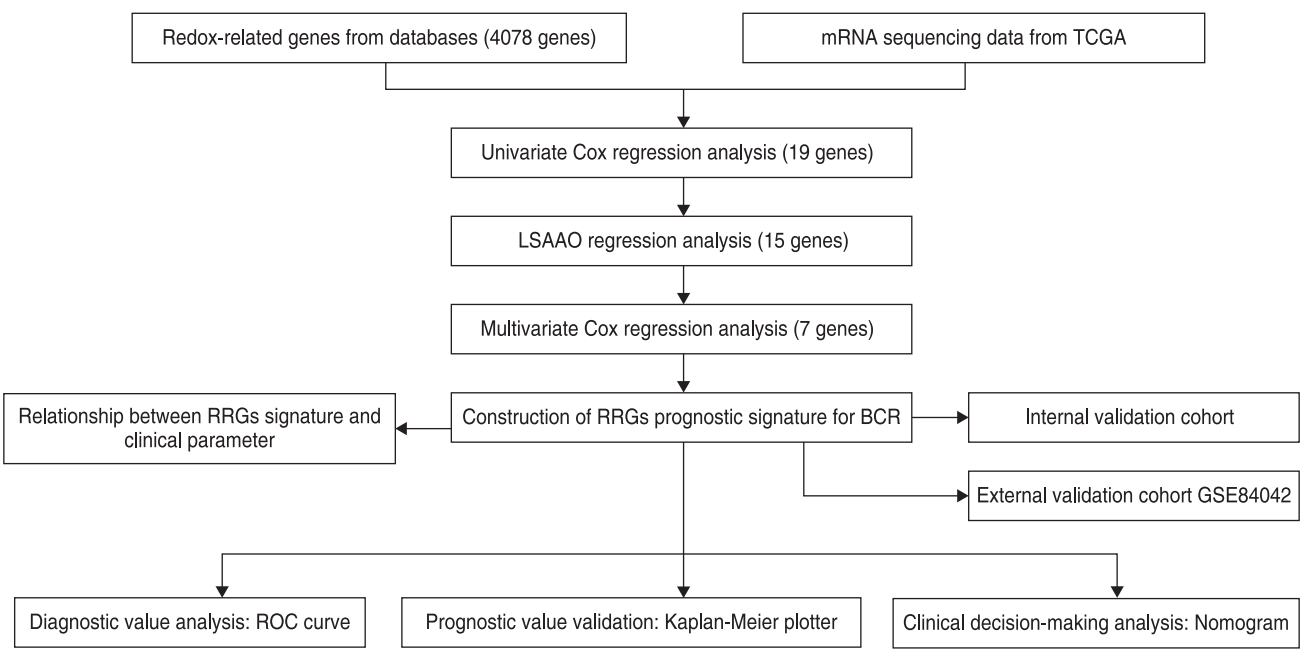

Fig. 1 Flowchart of the procedures performed in the study. TCGA: The Cancer Genome Atlas; PCa: prostate cancer; LASSO: the least absolute shrinkage and selection operator; ROC: receiver operating characteristic; RRGs: redox-related genes; BCR: biochemical recurrence

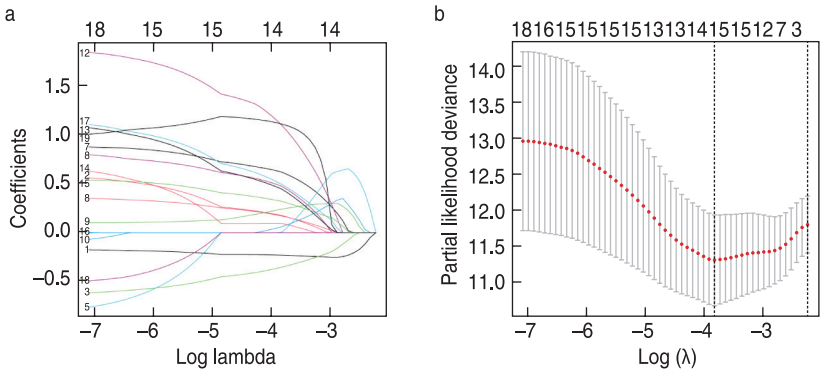

Fig. 2 Selection of prognostic RRGs by LASSO regression. (a) LASSO coefficient profiles of the prognostic RRGs. (b) Parameter selection in the LASSO model. RRGs: redox-related genes; LASSO: least absolute shrinkage and selection operator

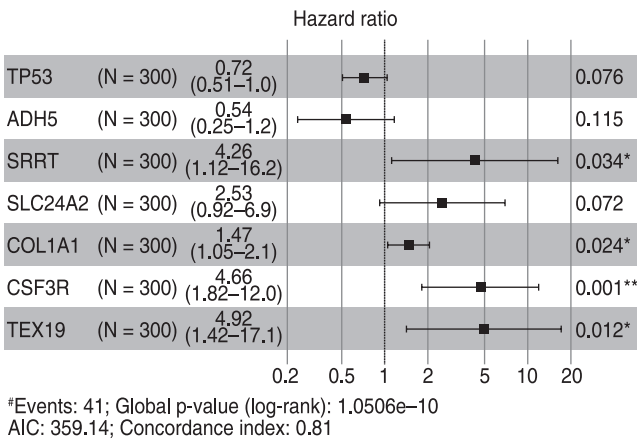

Fig. 3 Identification of prognostic RRGs by multivariate Cox regression analysis. RRGs: redox-related genes; * $P < 0.05$, ** $P < 0.001$

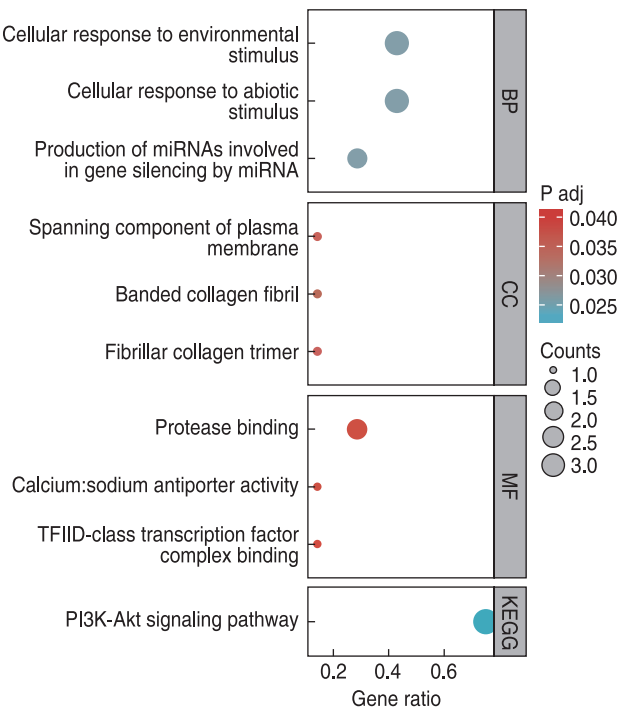

Fig. 4 GO and KEGG enrichment analysis. GO: Gene Ontology; KEGG: Kyoto Gene and Genome Encyclopedia; BP: biological process; CP: cellular component; MF: molecular function

cohort were used as validation sets to test the performance of the RRG signature. The results of the Kaplan-Meier survival analysis revealed that patients in the high-risk group had a worse BCR-free survival prognosis than those in the low-risk group (P = 0.015 in the TCGA validation cohort, Fig. 5b; P = 0.022 in the GSE84042 dataset, Fig. 5c). The AUC values of the 1st, 2nd, 3rd, 4th and 5th years were 0.762, 0.786, 0.849, 0.665, and 0.662, respectively, in the TCGA validation cohort (Fig. 5e) and 0.806, 0.742, 0.684, 0.713, and 0.722, respectively, in the GSE84042 dataset (Fig. 5f). The risk score curve, survival status, and gene expression heat maps of each patient in the TCGA training cohort, TCGA validation cohort, and GSE84042 dataset are shown in Fig. 5g–5o. Subsequently, the PCA results demonstrated that the RRGs signature could effectively distinguish patients with PCa with different BCR risks in the training and validation cohorts (Fig. 6). In addition, we used ROC analysis to compare the clinical performance of the prognostic signature and clinical parameters, including age, pT, GGS, and PSA. The AUC values of the prognostic signature, age, pT, GGS, and PSA levels were 0.803, 0.482, 0.682, 0.720, and 0.654, respectively (Fig. 7). This showed that the RRGs signature was a better model for predicting BCR of patients with PCa.

Clinical relevance of RRG signature

We used the Kaplan-Meier survival analysis of different clinicopathological stratifications to investigate the relationship between RRG-related prognostic signature and clinicopathological characteristics. Except for individuals with PSA > 4, the results showed that all high-risk groups had worse BCR-free survival outcomes

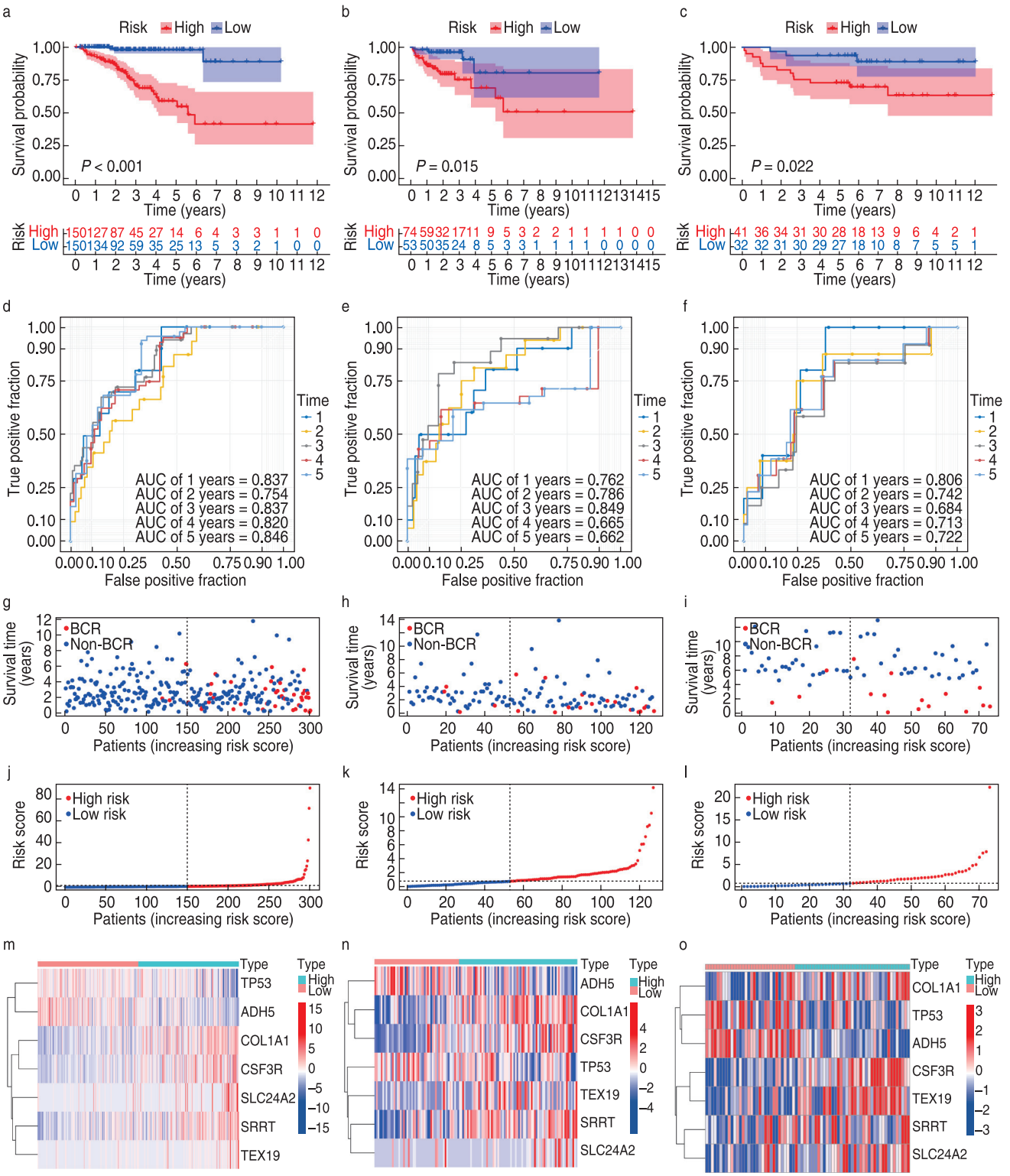

Fig. 5 Evaluation of the prognostic performance of the seven-RRG signature in the TCGA training cohort, TCGA internal validation cohort and GSE84042 external validation cohort. (a–c): Kaplan-Meier curve analysis in the high-risk and low-risk subgroups of the TCGA training cohort, TCGA internal validation cohort and GSE84042 external validation cohort. (d–f): The time-dependent ROC for 1st-, 2nd-, 3rd-, 4th- and 5th-year BCR predictions based on the RRG signature in the TCGA training cohort, TCGA internal validation cohort and GSE84042 external validation cohort. (g–o) The distribution of survival status, risk scores and expression of prognostic RRGs in the TCGA training cohort, TCGA internal validation cohort and GSE84042 external validation cohort

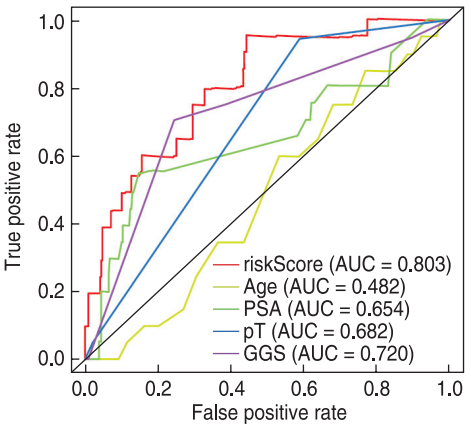

Fig. 6 The AUCs under ROC for comparing the diagnostic value among RRG signature, age, PSA, pT and GGS. AUC: area under ROC curve; ROC: receiver operating characteristic; RRG: redox-related gene; PSA: prostate specific antigen; pT: pathological T stage; GGS: Gleason grade score

than the low-risk groups (Fig. 8a–8h). We conclude that the RRGs-related prognostic signature could predict the prognosis of patients with PCa of different clinicopathological stratifications.

In addition, risk scores were compared based on clinicopathological status. The results showed that high pathological T stage, PSA value, and Gleason score were all linked to considerably higher RRG signature risk scores. The distribution of risk scores in the subgroups divided by age was not statistically different (P = 0.17, Fig. 9).

Identification of independent prognostic parameters

Univariate and multivariate Cox regression models were used to investigate the predictive value of different clinicopathological characteristics and RRG signature (Fig. 10). In the TCGA cohort, the Gleason score, pathological T stage, PSA value, and RRGs signature were significantly correlated with BCR-free survival. However, multiple regression analysis revealed that Gleason score, pathological T stage, and RRG signature were independent prognostic factors associated with BCR-free survival. In the GSE84042 cohort, the pathological T stage and the RRG signature were significantly correlated with BCR-free survival. After performing multivariate Cox regression analysis, these factors were identified as independent prognostic factors.

Construction and validation of a nomogram

We established a nomogram as a quantitative approach for predicting the prognosis of patients with PCa. In the TCGA cohort, the clinical parameters, age, and PSA were excluded from the nomogram because of their insignificant prognostic value. Gleason score, pathological T stage, and RRG signature were used to construct a nomogram (Fig. 11a). In both the TCGA and GSE84042 cohorts, the median risk score of the TCGA cohort was chosen as the cutoff value. The TCGA cohort was separated into high- and low-risk groups, and the high-risk group had a worse BCR-free survival outcome (P < 0.001; Fig. 11b). Patients in the GSE84042 cohort were similarly divided into two groups based on the same cut-off value, and the results revealed that those in the high-risk group had a worse prognosis (P < 0.001; Fig. 11c). Thereafter, we validated the clinical usefulness and availability of the nomogram using TCGA and GSE84042 cohorts. The AUCs for the first, second, third, fourth, and fifth years were 0.816, 0.775, 0.818, 0.806, and 0.850, respectively (Fig. 11d), and the C-index was 0.837 in the TCGA cohort (95% CI: 0.774–0.0.899, P < 0.0001). The AUCs were 0.919, 0.732, 0.776, 0.770 and 0.775 (Fig. 11e), and the C index was 0.808 in the GSE84042 cohort (95% CI: 0.728–0.888, P < 0.0001). The DCA curves demonstrated that the nomogram model was more effective than the clinical model in predicting BCR-free survival in patients with PCa (Fig. 11f and 11g).

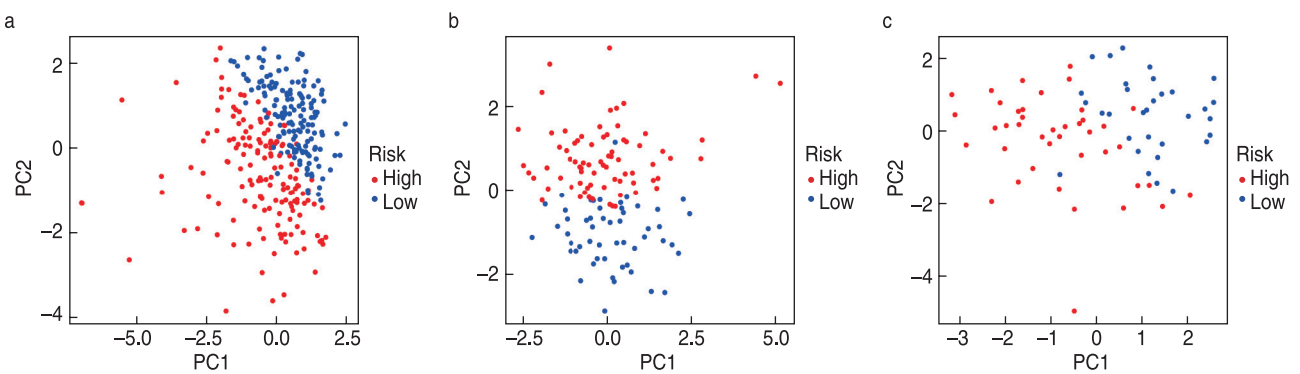

Fig. 7 (a) The results of PCA in the TCGA training cohort; (b) The results of PCA in the TCGA internal validation cohort; (c) The results of PCA in the GSE84042 external validation cohort. PCA: principal component analysis. TCGA: The Cancer Genome Atlas

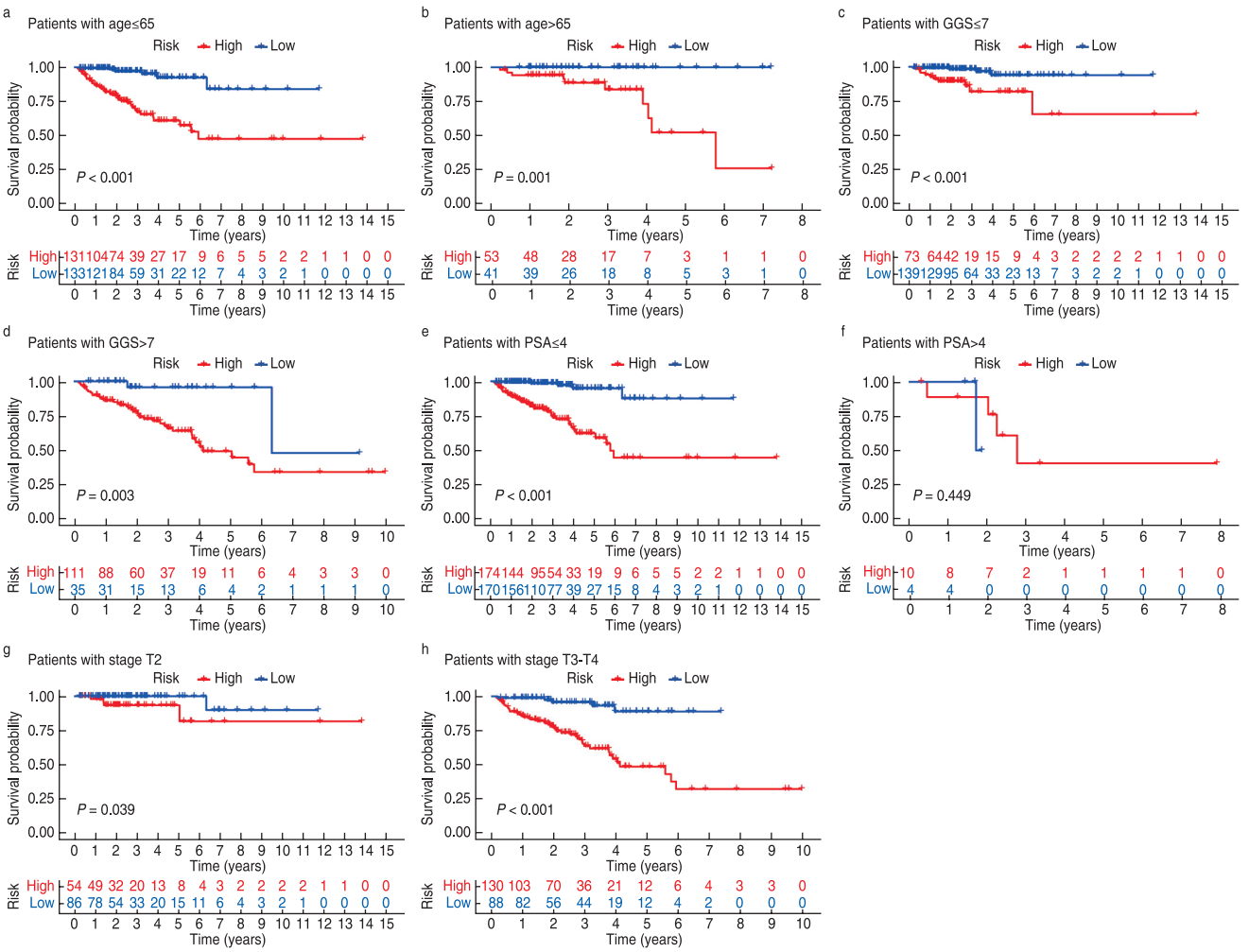

Fig. 8 Kaplan-Meier curve analysis of patients with PCa stratified by different clinicopathological stratifications. (a) Age ≤ 65 years; (b) Age > 65 years; (c) GGS ≤ 7; (d) GGS > 7; (e) pT: T2; (f) pT: T3–T4; (g) PSA value ≤ 4; (h): PSA value > 4. PCa: prostate cancer; GGS: Gleason grade score; pT: pathological T stage; PSA: prostate specific antigen

Discussion

In our study, we used the TCGA and GEO databases to retrieve transcriptome and clinicopathological data. Prognostic RRGs were identified by univariate, LASSO, and multivariate Cox regression analyses. Next, an RRGs signature was created to predict the BCR-free survival prognosis of patients with PCa. These genes included *TP53*, *ADH5*, *SRRT*, *SLC24A2*, *COL1A1*, *CSF3R*, and *TEX19*. The tumor suppressor gene *TP53* plays an important role in genomic integrity, cell cycle arrest, and other vital signaling pathways [15]. The wild-type *TP53* gene is lost in more than 50% of human cancers, and *TP53* mutations affect half of all metastatic PCa cases [16]. TP53 status has been shown to predict the clinical prognosis of castration-resistant prostate cancer and can be used as a biomarker for poor hormonal therapy responses [17]. *ADH5*, also known as S-nitrosoglutathione reductase (GSNOR), is a cellular denitrosylase that catalyzes the breakdown of SNOs to balance the intracellular thiol redox state [18, 19]. Studies have demonstrated that dysregulation of *ADH5* contributes to diseases such as asthma and breast cancer [18]. *SRRT*, also known as Ars2, plays a key role in sodium arsenite resistance [20]. It has been revealed that *SRRT* participates in the proliferation and migration of glioblastoma [21]. *SLC24A2* is a member of the solute carrier (SLC) family and is responsible for transporting compounds across biological molecules into cells [22]. SLC family members have been demonstrated to play roles in the carcinogenesis and prognosis of various cancers [23]. *COL1A1* participates in the encoding of type I collagen and belongs to the collagen family, which contributes to intercellular adhesion, cell differentiation and components of the extracellular matrix [24]. Gene dysfunction plays a critical role in the tumor development, metastasis, and prognosis of breast, lung,

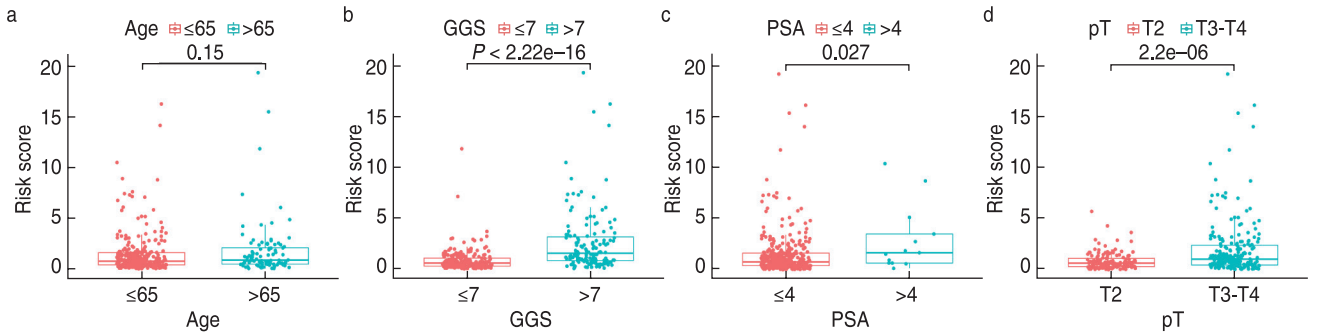

Fig. 9 The differential distribution of RRG signature risk scores between subgroups stratified by different clinical parameters and survival status. (a) Age; (b) GGS; (c) PSA; (d) pT. RRG: redox-related gene; GGS: Gleason grade score; PSA: prostate specific antigen; pT: Pathological T stage

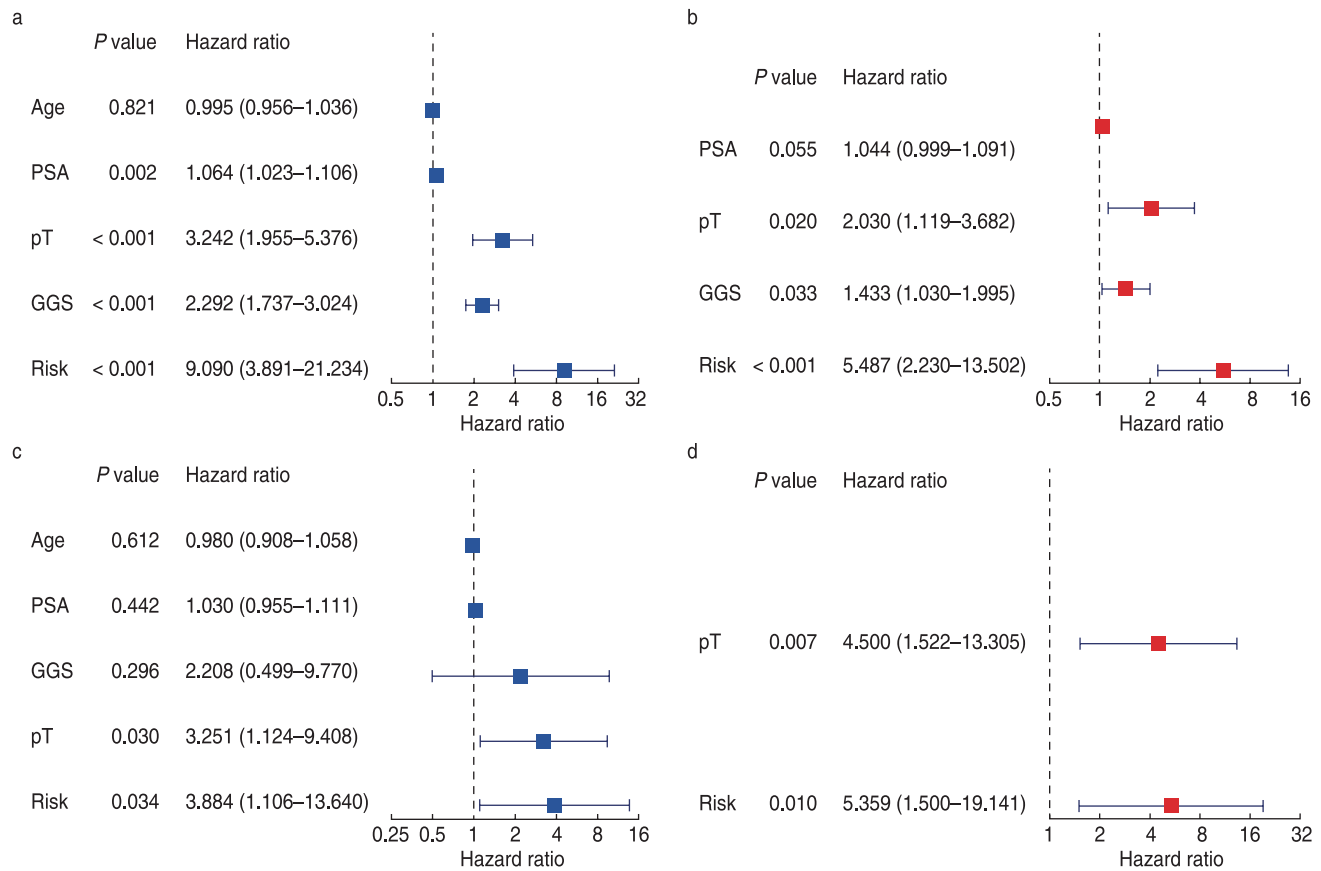

Fig. 10 Evaluation of independent prognostic factors based on clinicopathological parameters and the RRG signature in the TCGA and GSE84042 cohorts. (a) Univariate Cox regression analysis and (b) multivariate Cox regression analysis for evaluating independent prognostic factors in the TCGA cohort. (c) Univariate Cox regression analysis and (d) multivariate Cox regression analysis for evaluating independent prognostic factors in the GSE84042 cohort. RRGs: redox-related genes; TCGA: The Cancer Genome Atlas; PSA: prostate specific antigen; pT: pathological T stage; GGS: Gleason grade score

and hepatocellular cancers [24–26]. *CSF3R* is the colony-stimulating factor 3 receptor, and the encoded protein regulates the growth and differentiation of granulocytes [27]. A long-term survey revealed that patients with *CSF3R* mutations developed acute myeloid leukemia [28]. *TEX19* is an orphan gene expressed in adult testes, undifferentiated embryonic stem cells, and primordial germ cells [29]. *TEX19* has an impact on cancer cell proliferation and the initiation and prognosis of tumors [30].

We performed Kaplan-Meier and ROC curve analyses in the training and testing cohorts based on the RRGs signature, and the findings showed that the signature had an excellent prognostic ability to identify patients with a high risk for BCR. The patients were classified

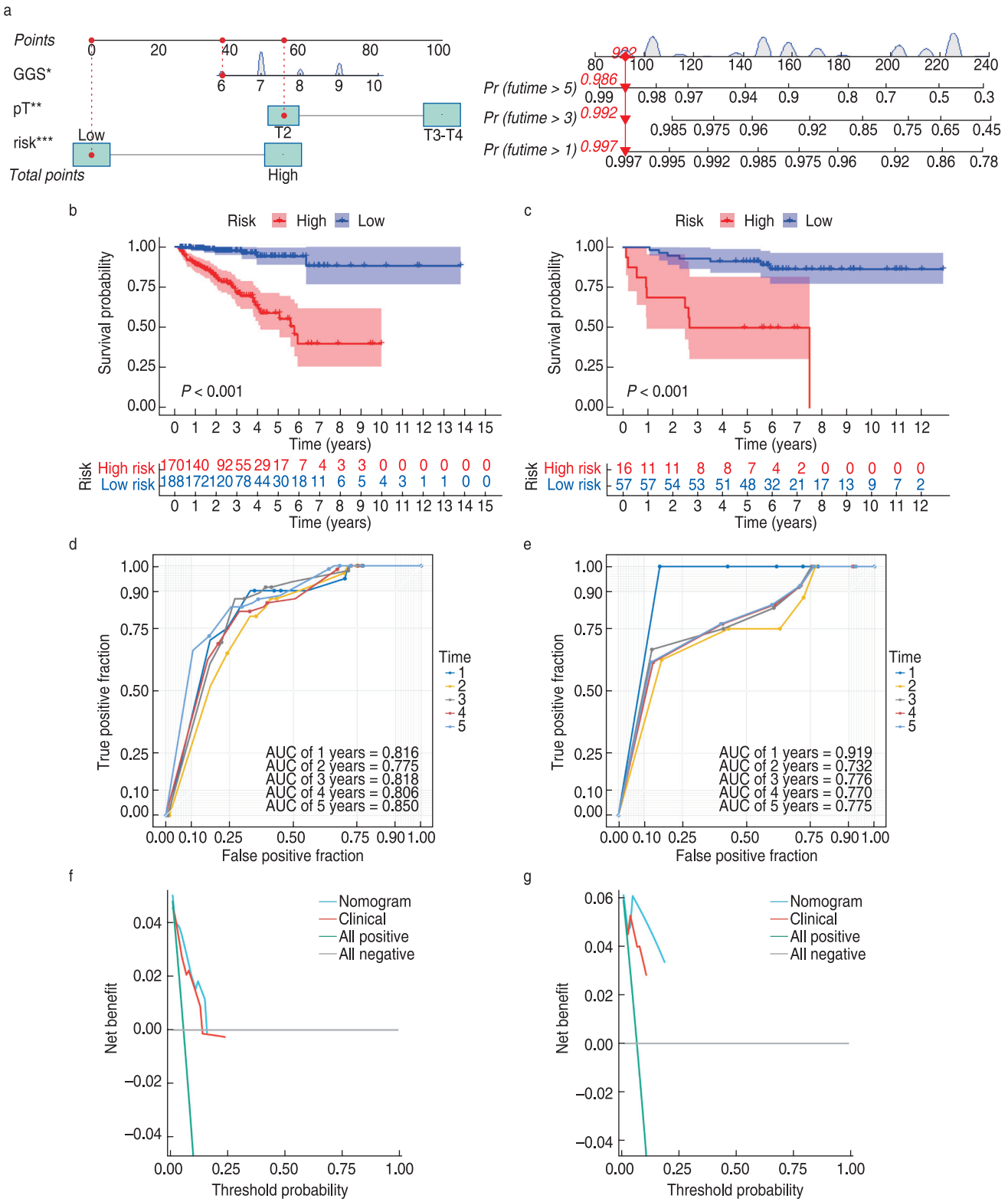

Fig. 11 The construction and validation of a nomogram. (a) Nomogram for predicting the 1st-, 3rd- and 5th-year BCR-free survival of patients with PCa in the TCGA cohort. (b and c) Kaplan-Meier curve analysis of the nomogram between high-risk and low-risk subgroups stratified by the cut-off value for the risk scores based on the nomogram model in the TCGA cohort and GSE84042 cohort, respectively. (d and e) The time-dependent ROC for 1st-, 2nd-, 3rd-, 4th- and 5th-year BCR predictions based on the nomogram model in the TCGA cohort and GSE84042 cohort, respectively. (f and g) The DCA curve of the nomogram in the TCGA cohort and GSE84042 cohort, respectively. *: $P < 0.05$, **: $P < 0.001$, ***: $P < 0.0001$; BCR: biochemical recurrence; PCa: prostate cancer; TCGA: The Cancer Genome Atlas; ROC: receiver operating characteristic; DCA: decision curve analysis

based on several clinical characteristics to investigate the relationship between the RRGs signature and clinical variables. We discovered that the RRGs signature could predict the prognosis of patients with PCa, except for those with PSA > 4 and that the signature was highly linked with clinical prognosis. It is possible that there were too few patients with PSA levels of > 4.

Additionally, a nomogram was developed to expand the clinical applications of the RRGs signature by combining clinical parameters. To verify the accuracy of the model in predicting PCa patient prognosis, Kaplan-Meier survival and ROC curve analyses were applied to TCGA and GSE84042 cohorts, and the results suggested that the model had good performance and efficiency in predicting prognosis.

Gene signatures based on different gene sets have been constructed to predict the prognosis of PCa. The Genomic Prostate Score (GPS) was based on 12 genes involved in PCa aggressiveness and 5 reference genes [31]. This score can evaluate the aggressiveness of PCa and help physicians to select the best therapy for patients [32]. Furthermore, GPS has significant predictive value for PCa recurrence [33]. The Prolaris Score is another polygenic genomic assay containing 31 genes involved in cell cycle progression that was established and confirmed to independently predict the BCR of PCa [34]. The Decipher genomic classifier is a gene profile comprising 22 genes created at the mRNA level to predict early metastasis and disease-specific mortality following radical prostatectomy [35].

In summary, our study provides new insights for the development of a novel signature based on RRGs to predict the clinical prognosis of patients with PCa. It has good predictive ability and clinical value and could help clinicians screen patients with a high probability of BCR and choose better treatment. However, our study has some limitations. First, the majority of patients in the training and validation cohorts were from North America; thus, caution should be taken when using the model for other nations. Secondly, the model was constructed and validated based on online data and should be validated using a prospective clinical cohort. However, the regulatory mechanisms underlying these prognostic RRGs require further investigation.

Conclusion

We established a novel RRGs prognostic prediction model using bioinformatic methods. This RRGs signature is an independent prognostic factor for assessing BCR survival in patients with PCa and could serve as a method for individualized risk stratification of patients with PCa. A nomogram was constructed to predict BCR survival, which would be useful for selecting personalized treatment.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Author contributions

Conception and design: PH and GS; Data curation and methodology: PH, BC, and GS; data analysis and interpretation: PH, BC, and GS; manuscript preparation: PH and GS; manuscript review: JM; Study supervision: JM.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

Ethical approval

Not applicable.

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