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Research article

Machine learning based androgen receptor regulatory gene-related random forest survival model for precise treatment decision in prostate cancer

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ABSTRACT

Background: It has been demonstrated that aberrant androgen receptor (AR) signaling contributes to the pathogenesis of prostate cancer (PCa). To date, the most efficacious strategy for the treatment of PCa remains to target the AR signaling axis. However, numerous PCa patients still face the issue of overtreatment or undertreatment. The establishment of a precise risk prediction model is urgently needed to distinguish patients with high-risk and select appropriate treatment modalities.

Methods: In this study, a consensus AR regulatory gene-related signature (ARS) was developed by integrating a total of 101 algorithm combinations of 10 machine learning algorithms. We evaluated the value of ARS in predicting patient prognosis and the therapeutic effects of the various treatments. Additionally, we conducted a screening of therapeutic targets and agents for high-risk patients, followed by the verification in vitro and in vivo.

Results: ARS was an independent risk factor for biochemical recurrence and distant metastasis in PCa patients. The enhanced and consistent prognostic predictive capability of ARS across various platforms was confirmed when compared with 44 previously published signatures. More importantly, PCa patients in the ARS^{high} group benefit more from PARP inhibitors and immunotherapy, while chemotherapy, radiotherapy, and AR-targeted therapy are more effective for ARS^{low} patients. The results of in silico screening suggest that AURKB could potentially serve as a promising therapeutic target for ARS^{high} patients.

Abbreviations: AR, androgen receptor; ARS, androgen receptor regulatory gene-related signature; PCa, prostate cancer; ADT, androgen deprivation therapy; PSA, prostate-specific antigen; DDR, DNA damage repair; ARSIs, AR signaling inhibitors; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus; TPM, transcripts per million; MSigDB, Molecular Signatures Database; ONC, oncogenes; TSG, tumour suppressor genes; HRR, homologous recombination genes; MMR, mismatch repair genes; CRPC, castration-resistant prostate cancer; CNVs, copy number variations; MMRDs, mismatch repair defects.

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Conclusions: Collectively, this prediction model based on AR regulatory genes holds great clinical translational potential to solve the dilemma of treatment choice and identify potential novel therapeutic targets in PCa.

1. Introduction

As the third most prevalent malignant neoplasm among newly diagnosed cases of cancer worldwide in 2020, prostate cancer (PCa) is the second most prevalent cancer and the fifth main cause of cancer-related mortality in males [1]. Current therapeutic modalities for PCa encompass active surveillance, radical prostatectomy, androgen deprivation therapy (ADT), poly(ADP-ribose) polymerase inhibitors, chemotherapy, and radiotherapy [2]. PCa progression is a complex process involving many genes and pathways, that displays significant inter-patient and intra-patient heterogeneity. It is necessary to incorporate patients' genomic profiles and clinical symptoms into treatment decision-making [3,4]. However, currently utilized clinical indicators and prognosis tools, such as prostate-specific antigen (PSA) testing, Gleason scoring, MRI, and DNA damage repair (DDR) gene detection, lack sufficient accuracy in predicting disease progression or guiding treatment strategies when facing complex disease progression conditions, potentially causing patients to be overtreated or undertreated [5–7]. Consequently, in the era of precision medicine, the identification of robust biomarkers to optimize prognostication and therapeutic outcomes in PCa is imperative.

As a hormone-dependent malignancy, the development and progression of PCa are strongly correlated with androgen receptor (AR) signaling pathway activity [8]. The androgen receptor, a nuclear transcription factor regulated by ligands and encoded by the NR3C4 gene, belongs to the superfamily of steroid hormone receptors [9,10]. AR and its signaling serve a crucial role in normal prostate development, whereas aberrant AR signaling has been linked to the pathogenesis and progression of PCa. Due to the crucial role that AR signaling plays in promoting PCa, therapy targeting the AR pathway has been the mainstay for treating metastatic PCa. AR signaling inhibitors (ARSIs), containing ADT and AR inhibitors, have been established as the cornerstone of treatment for advanced and metastatic PCa patients[11–13]. However, the therapeutic efficacy of ARSIs is often transient, as resistance to ARSIs frequently emerges within a relatively short period of 6–20 months after the initiation of treatment [14]. Persistent activation of AR signaling, such as mutations in AR and AR splice variants, may contribute to the progression of PCa and the failure of endocrine therapy [15]. Given the critical role of AR activation in PCa initiation and progression, the construction of a prediction model based on AR regulatory genes may have superior predictive power for patient prognosis and a close association with the efficacy of different medications.

Machine learning is a data-driven paradigm of artificial intelligence that enables systems to automatically learn and improve from data without the need for explicit programming [16]. Notably, the application of machine learning in the domain of healthcare is experiencing rapid expansion, being increasingly employed in disease diagnosis, prognosis prediction, and pathological image analysis [17,18]. In this study, we established a consensus machine learning-derived androgen receptor regulatory gene-related signature (ARS) by a total of 101 algorithm combinations of 10 machine learning algorithms. The performance of the ARS in predicting biochemical recurrence, metastasis, response to AR-targeted therapy, immunotherapy, PARP inhibitors, chemotherapy, and radiotherapy was evaluated. Furthermore, AURKB has been recognized as a promising therapeutic target for individuals with high ARS score, and the administration of its inhibitor, Tozasertib, resulted in substantial inhibition of PCa growth. In conclusion, our research presents a machine learning framework for developing an ARS with clinical implications for predicting patient prognosis and therapeutic vulnerabilities in PCa. The patient's prognosis signature holds great translation potential to guide the personalized treatment strategies in PCa.

2. Materials and methods

2.1. Collection and processing of public PCa cohorts

Transcriptional expression data, corresponding clinical information, somatic mutations and copy number alteration data of the PRAD cohort were retrieved from the Cancer Genome Atlas (TCGA) database. A total of 10 external validation datasets containing survival data (CPC, DKFZ-PRAD, GSE107299, GSE116918, GSE147250, GSE46602, GSE54460, GSE70770, MSKCC, and Su2c) were collected from the Gene Expression Omnibus (GEO) and cBioPortal (Table S1). Notably, the GSE111177 and GSE41408 cohorts, which contain distant metastasis information, were applied to assess the predictive value of the model for metastasis. Raw counts were computed as log2-transformed transcripts per million (TPM). As for the microarrays, we adjusted and normalized the background using the RMA algorithm in the "affy" package. Before model construction, each gene expression matrix was z-scaled across all cohorts.

To obtain the androgen receptor regulatory genes, we retrieved all gene sets correlating to the androgen receptor signaling pathway from the Molecular Signatures Database (MSigDB) (Table S2). The 101 algorithmic binary combinations were performed using the candidate genes screened from the TCGA-PRAD cohort and detected in 10 validation datasets. All genes were manually checked for their presence as aliases in each cohort and standardized to the same name, and if a gene was not detected in some cohort, it was discarded from further analysis. Genes were then screened by univariate Cox regression in the TCGA-PRAD cohort, and genes with a P-value <0.05 were selected as candidate genes to construct the ARS model.

2.2. Machine learning benchmark for the construction of the ARS

To construct a robust ARS with stable and accurate performance, we incorporated 10 machine learning algorithms, including RSF, Enet, stepwise Cox, CoxBoost, plsRcox, SuperPC, GBM, survival-SVM, Ridge, and Lasso. Then, a total of 101 individual or algorithmic binary combinations were generated (Table S3). The specifics of parameter optimization are delineated within the Supplementary Material. The C-index was calculated by R package "compareC" in both the training and validation sets for each model [19], and the model with the highest mean C-index was defined as the AR regulatory gene-related signature (ARS).

2.3. Evaluation of the ARS model

Multivariate Cox regression analyses were performed to assess the independence of the ARS from other clinicopathological characteristics. For prognosis prediction efficacy comparison, we retrospectively collected 44 published PCa signatures (Table S4). We determined the risk score of each patient using the method outlined in the original article (Table S4). The C-indexes were then calculated to compare the predictive capabilities of each signature with ARS in both the training and validation cohorts.

2.4. Genomic analysis of ARS

Somatic copy number variations were detected using GISTIC2.0 (GenePattern platform, https://cloud.genepattern.org/gp/pages/index.jsf). The oncogenes (ONC), tumor suppressor genes (TSG), homologous recombination genes (HRR), and mismatch repair genes (MMR) were compared between the ARS^{high} and ARS^{low} patients. To analyze somatic mutation data, we applied the "maftools" package and the MuTect2 pipeline. Furthermore, we compared the aneuploidy score, tumor neoantigens, and HRD score between the ARS^{high} and ARS^{low} groups in TCGA-PRAD cohort, which were obtained from a previous study [20].

2.5. Immune cell infiltration analysis and predictive ability of the ARS for immunotherapy

The "IOBR" package was employed to dissect patient immunological characteristics in the 11 datasets [21]. We applied the "xCELL" algorithm and calculated the correlation between the ARS and infiltration levels of 64 microenvironment cell types, encompassing both adaptive and innate immune cells, hematopoietic progenitors, epithelial cells, and extracellular matrix cells. (Table S5). Furthermore, we collected immunotherapy response-predictive pathways in a previous study [22]. The correlations of ARS with immunomodulators and related gene pathways were also evaluated. To better quantify the effectiveness of the ARS for immunotherapy response prediction, the Subclass Mapping module of GenePattern was utilized to infer the similarity of gene expression profiles between PCa patients and an immunotherapy cohort of melanoma patients accepting anti-CTLA4/PD-1 mono-clonal antibody [23,24].

2.6. Benefits of the ARS in aiding treatment decisions

Patients were stratified into high- and low-risk groups according to the median risk score. The gene sets revealing the response to androgen receptor were measured between ARS^{high} and ARS^{low} patients using the "ssgsea" algorithm in the 'GSVA' package. The AR signaling score was calculated using a gene expression signature comprised of 27 genes whose expression was strongly activated or inhibited in response to androgen stimulation [25]. The AR score of each patient in the Su2c cohort was utilized to compare its correlation with ARS in the dataset. Additionally, transcriptional data from PCa cell lines and IC50 or AUC values for various anti-cancer agents, such as anti-androgen drugs, chemotherapy, and PARP inhibitors, were obtained from the GDSC and PRISM databases to conduct drug sensitivity analysis using the "pRRophetic" package. GSE111177, which includes patients undergoing androgen deprivation therapy, was then used to validate the predictive capability of ARS for the efficacy of ADT. The PAM50 is a molecular subtype classifier which stratifies luminal and basal status in PCa, and has been demonstrated to be correlated to clinical outcome and response to androgen deprivation therapy [26]. The proportions of luminal A, luminal B, and basal-like subtypes in the ARS^{high} and ARS^{low} subgroups were also compared.

2.7. Prediction of therapeutic approaches for ARS^{high} patients

Due to the fact that a large proportion of proteins lack binding sites to be interfered, we compiled 2249 druggable targets (Table S6) from a previous study [27]. Utilizing Spearman's correlation analysis with criteria of Cor >0.30 and P-value <0.05, we identified targets that exhibited a positive correlation with ARS score. To mitigate potential biases stemming from individual cohorts, we specifically chose cohorts with over 200 candidate genes to generate the final gene list. The impact of gene loss on lethality can be assessed through the CERES score, which is utilized to gauge gene dependency levels in CRISPR-Cas9 essentiality screens. A lower CERES score suggests that the gene of interest is potentially vital for the survival of a specific cancer cell line. To investigate this further, we obtained CERES scores from the dependency map (https://depmap.org/portal/) and calculated the average CERES scores of candidate genes in all PCa cell lines. Additionally, we utilized compound data from the PRISM database (https://depmap.org/portal/prism/) to predict potential drugs that could be beneficial for patients with high ARS.

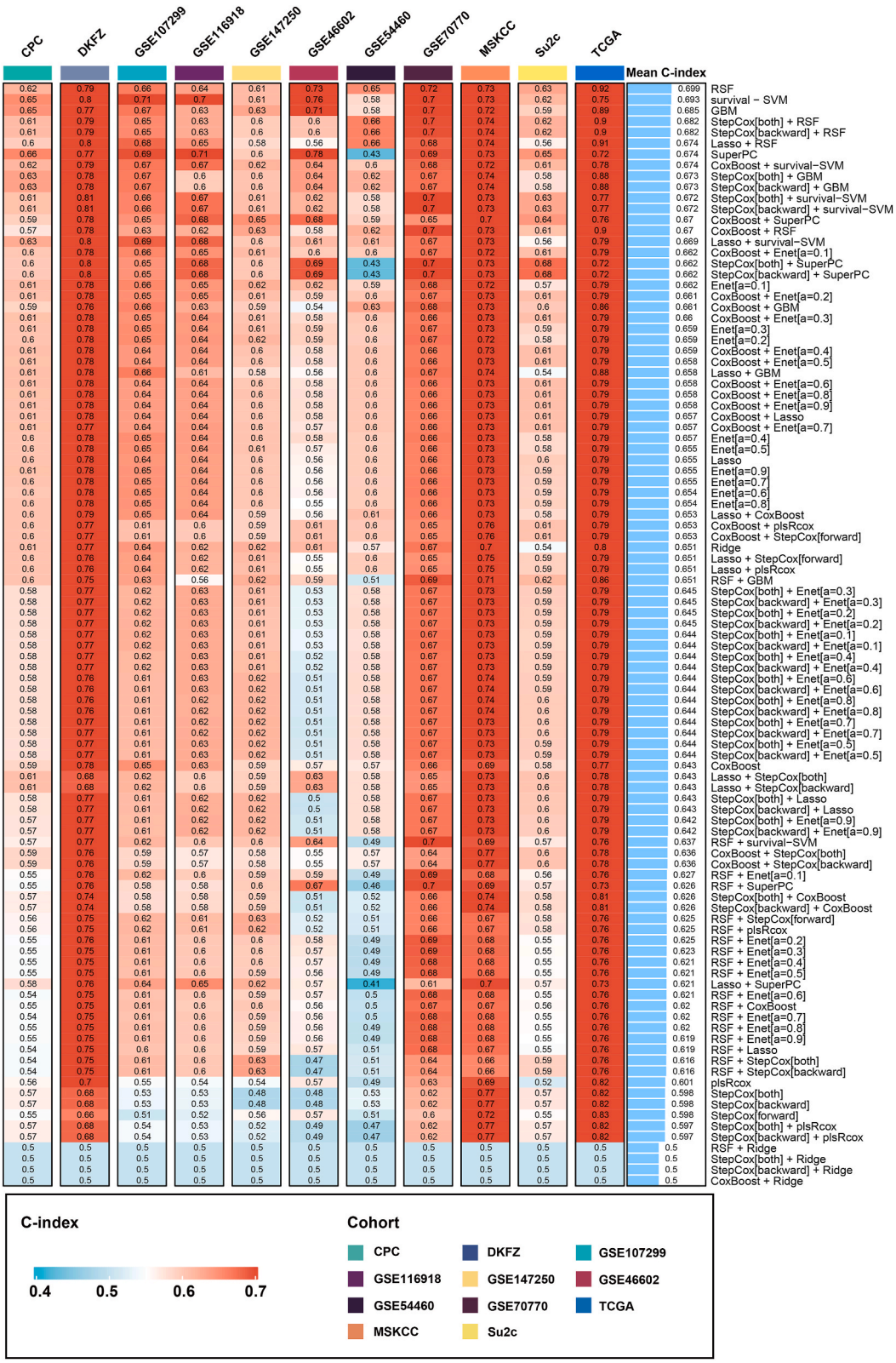


Fig. 1. A robust androgen receptor-associated signature (ARS) developed based on the machine learning-based scheme across 11 PCa datasets.

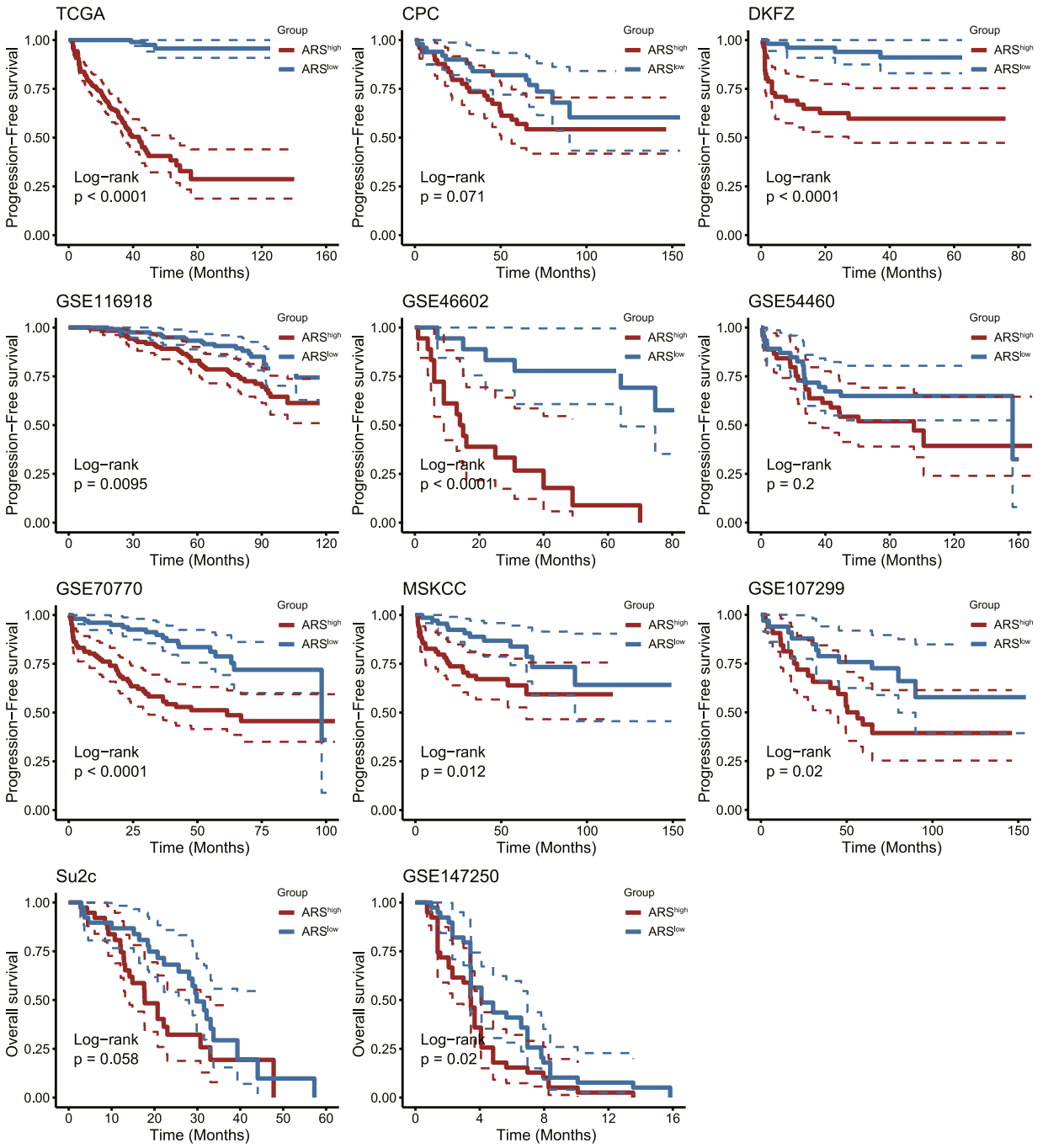
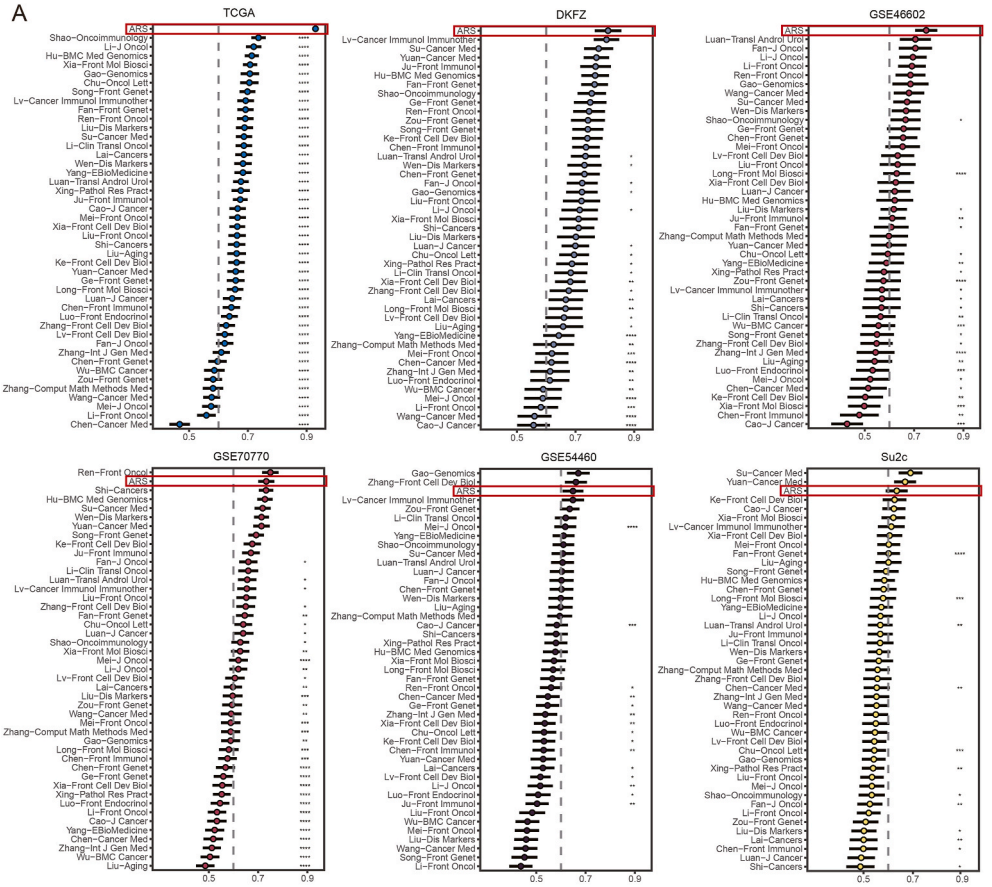


Fig. 2. Kaplan–Meier survival curve across the training and validation datasets between the ARS^{high} and ARS^{low} subgroups.

2.8. Cell culture and reagents

The PC-3 and 22RV1 cell lines were procured from the Shanghai Institute of Cell Biology in Shanghai, China. The enzalutamide-resistant C4-2B (C4-2B-ENZR) was generated through exposure of C4-2B cells to enzalutamide with incremental concentrations up to 10 μM, as detailed in a previous study [28]. Cell growth was sustained using RPMI 1640 medium supplemented with 10 % fetal bovine serum under standard laboratory conditions. Tozasertib, an inhibitor of AURKB, was obtained from Selleck Chemicals (Houston, USA).



B

Variable	HR	lower 95%CI	upper 95%CI	p value
TCGA				
age	1.001	0.968	1.035	0.958
gleason_score	2.740	1.491	5.035	<0.01**
T	1.503	0.697	3.239	0.298
N	0.963	0.591	1.569	0.88
M	2.277	0.300	17.279	0.426
RS	1.186	1.153	1.220	<0.001***
CPC				
ISUP_Grade	2.407	1.190	4.869	0.015 *
p_T	3.365	1.616	7.010	<0.01**
psa	0.971	0.900	1.049	0.457
age	0.987	0.938	1.038	0.607
RS	1.041	1.001	1.082	0.045 *
DKFZ				
age	0.895	0.764	1.048	0.169
psa	0.994	0.983	1.004	0.238
gleason_score	2.802	0.765	10.268	0.12
p_T	2.498	0.775	8.050	0.125
RS	1.068	1.024	1.114	<0.01**
GSE116918				
gleason_score	1.103	0.601	2.021	0.752
age	0.978	0.938	1.020	0.307
psa	1.004	0.996	1.013	0.321
c_T	1.783	0.938	3.387	0.078
RS	1.039	1.011	1.068	<0.01**
GSE46602				
age	0.927	0.840	1.023	0.131
gleason_score	4.625	1.017	21.036	0.048 *
psa	1.059	1.012	1.108	0.014 *
p_T	3.820	1.201	12.146	0.023 *
RS	1.095	1.029	1.164	<0.01**

Variable	HR	lower 95%CI	upper 95%CI	p value
GSE54460				
psa	1.086	1.051	1.123	<0.001***
gleason_score	1.017	0.393	2.631	0.972
c_T	1.851	0.792	4.328	0.155
RS	1.092	1.034	1.153	<0.01**
GSE70770				
gleason_score	4.078	1.200	13.858	0.024 *
age	1.029	0.953	1.112	0.462
psa	0.923	0.791	1.077	0.308
p_T	2.075	0.582	7.396	0.26
RS	1.098	1.043	1.157	<0.001***
MSKCC				
p_T	2.794	1.266	6.163	0.011 *
gleason_score	6.125	2.703	13.879	<0.001***
RS	1.022	0.996	1.048	0.092
Su2c				
age	1.046	0.986	1.110	0.14
psa	1.002	1.001	1.004	<0.001***
gleason_score	1.123	0.503	2.507	0.778
RS	1.061	1.006	1.118	0.028 *
GSE107299				
age	0.979	0.927	1.035	0.456
psa	0.999	0.910	1.097	0.982
c_T	1.178	0.537	2.582	0.683
RS	1.047	1.010	1.085	0.013 *
GSE147250				
PAM50	0.724	0.418	1.252	0.247
RS	1.049	1.017	1.082	<0.01**

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Fig. 3. Evaluation of the predictive performance of ARS.
(A) Comparison of the C-index in ARS and 44 published PCa signatures in TCGA, DKFZ, GSE46602, GSE70770, GSE54460, and Su2c. (B) The performance of the ARS was compared with that of other clinicopathological parameters in predicting prognosis via multivariate Cox regression analyses. (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001).

2.9. CCK-8 detection and colony formation assays

Cell viability experiments were performed using the Cell Counting Kit-8 (Boster, Wuhan, China) on PCa cells seeded in 96-well plates at a density of 3×10^3 cells per well. CCK-8 solution (10 μL) was added to each well at time intervals of 0, 24, 48, 72, and 96 h, followed by a 2-h incubation at 37 °C. The OD values at 450 nm were then measured using a microplate reader. Cells were seeded onto a 6-well plate at a density of 3×10^3 cells per well and subsequently treated with either Tozasertib or DMSO. Following a 14-day incubation period, the colonies were harvested and quantified for the purpose of statistical evaluation.

2.10. Flow cytometry

To determine the rate of apoptosis, cells were collected and subjected to a double wash procedure with PBS. Subsequently, the samples were subjected to a dual-staining protocol using Annexin V and PI (40303ES20, Yeasen Biotechnology, Shanghai, China). The cells were then incubated in a light-restricted environment at room temperature for 10–15 min. Flow cytometry data was acquired using a CytoFlex cytometer (Beckman Coulter, USA) and analyzed using FlowJo V10 software.

2.11. Animal study

The animal experiments conducted in this study were approved by the Institutional Animal Care and Use Committee of Huazhong University of Science and Technology (TJH-201901019). Male athymic nude mice, obtained from Shulaibao Biotechnology (Wuhan, China) at 5 weeks of age, were used. A total of 5.0×10^6 C4-2B-ENZR cells were subcutaneously injected into the mice. After allowing 7 days for tumor formation and development, the mice were randomly assigned to two groups, each consisting of five mice. Following daily intraperitoneal injections of Tozasertib (50 mg/kg), the control and treatment group underwent regular tumor volume measurements every 3 days. After an 18-day treatment period, the mice were euthanized, and their tumors were excised for immunofluorescence staining and TUNEL assay.

2.12. Statistical analysis

The R 4.1.0 software was used for all bioinformatic data processing, statistical analysis, and graphing. Spearman correlation was employed to analyze the correlation between two continuous variables. The wilcoxon test or *t*-test was applied to compare continuous variables, while the chi-square test was utilized to compare categorical variables. The survival differences were evaluated using the log-rank test. Using the "CompareC" package, the C-index of various signatures was compared. ROC curves were implemented using the "pROC" package to predict binary categorical variables. The statistical tests were all two-sided, with significance defined as a P-value <0.05.

3. Results

3.1. Identification of AR regulatory genes and construction of a consensus signature

A total of 926 genes associated with the AR signaling pathway were collected from the MSigDB database, and 722 of them were identified as present in the training and 10 validation sets. In the TCGA-PRAD dataset, 79 genes were identified as significantly associated with PCa progression-free survival via univariate Cox regression analysis (Table S7). These 79 genes were subjected to 101 algorithm combinations of 10 machine learning algorithms to generate a consensus ARS, and the C-index was computed for each model across all training and validation datasets. As shown in Fig. 1, the optimal model developed by machine learning algorithm was random survival forest, as it achieved the highest average C-index across all 11 datasets.

The random survival forest model was constructed in the training set and then applied to the validation cohorts, and risk scores were calculated for each patient. All patients were separated into high- and low-risk categories based on the median risk score. The ARS score distribution and survival status of patients in the training and validation cohorts were shown in Fig. S1. In the majority of datasets (except for CPC, GSE54460, and the SU2C cohort), the survival time of the high-risk group was significantly shorter than that of the low-risk group (Fig. 2).

3.2. Evaluation of the ARS model

Recent advances in next-generation sequencing have enabled the development of various predictive gene expression signatures for PCa [29,30]. To compare the efficacy of ARS to that of other signatures, we comprehensively retrieved published signatures in the past five years. We compared the ARS with 44 published PCa signatures and found that the ARS appeared to possess more robust

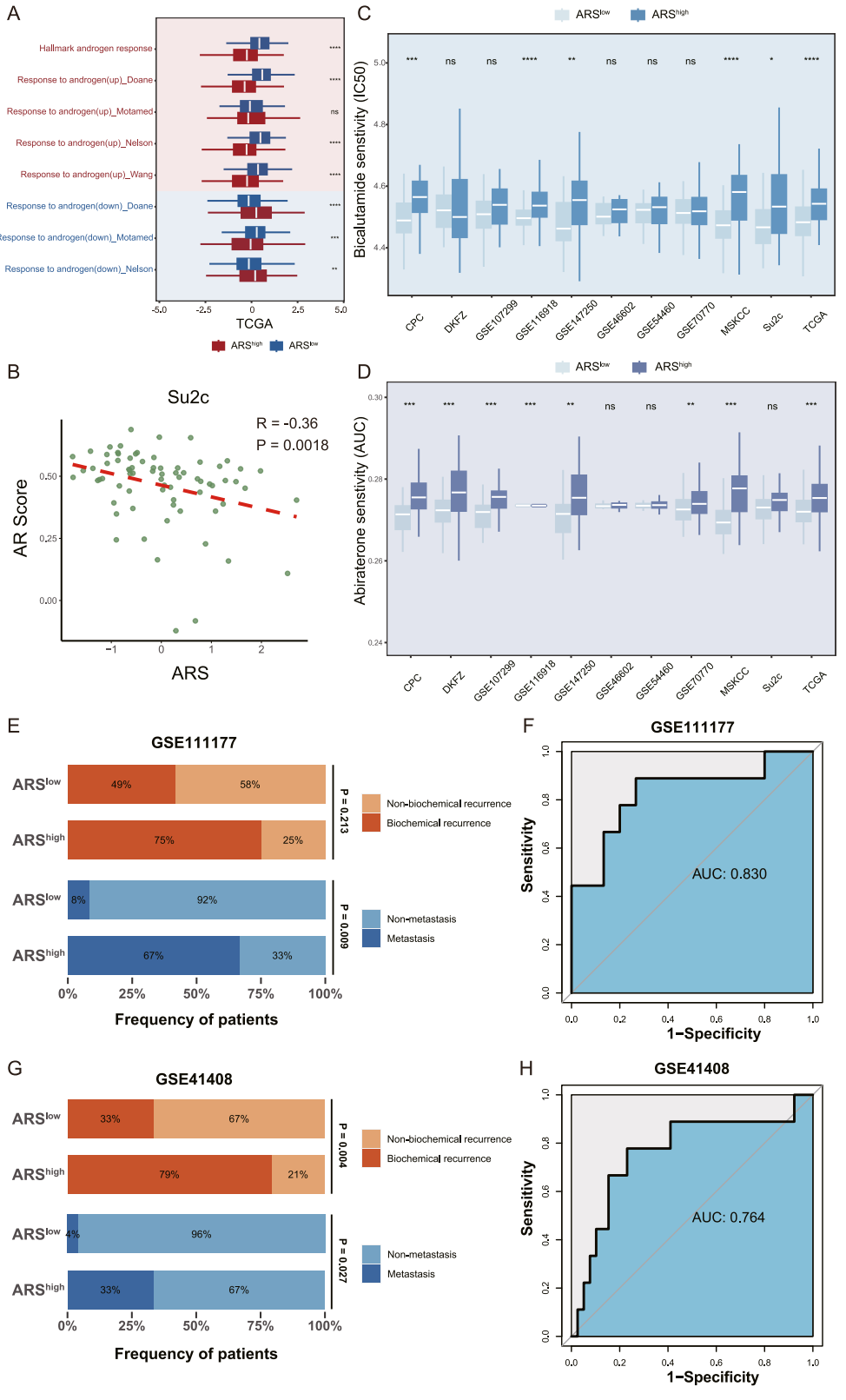

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Fig. 4. AR-targeted therapy prediction based on ARS.
(A) The androgen receptor pathway activity comparisons between the ARS^{high} and ARS^{low} groups in TCGA-PRAD cohort. (B) Correlation between the ARS and AR score in the Su2c cohort. (C-D) The inferred IC50 and AUC values of ARS^{high} and ARS^{low} patients across 11 PCa datasets. (E, G) The proportion of biochemical recurrence and metastasis of the ARS^{high} and ARS^{low} groups in GSE111177 (E) and GSE41408 (G). (F, H) ROC curves of ARS to predict the risk of metastasis in GSE111177 (F) and GSE41408 (H). (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001).

performance than the other signatures in the TCGA-PRAD cohort and 10 validation datasets (Fig. 3A and Fig. S2). We noticed that some signatures performed well in a few datasets (e.g., Ren-Front Oncol). However, they performed weakly in other datasets, suggesting limited stability. Considering that our signature was selected from 101 machine learning-based algorithm combinations across 14 prostate cohorts, the ARS had a better capacity for extrapolation.

Given that the management and prognosis of PCa frequently rely on clinical variables such as Gleason score, serum PSA levels, and TNM staging, we conducted a multivariate Cox regression analysis to ascertain the independent prognostic value of ARS in PCa patients. Our findings, as depicted in Fig. 3B, indicate that ARS can predict unfavorable outcomes independently in most datasets, underscoring the potential clinical relevance of this molecular signature.

3.3. Predictive ability of the ARS for AR-targeted therapy

Although there are several treatment options available for PCa patients, androgen deprivation therapy has been the cornerstone of PCa management. In nearly half of PCa cases, ADT is administered to patients [31]. Most prostate cancers initially respond to ADT, but the majority develop biochemical recurrence and progress into castration-resistant prostate cancer (CRPC) [32]. Owing to the fact that the response to ADT is closely related to patient prognosis, we conducted a thorough analysis of the predictive capability of the ARS in assessing the benefits of ADT. By comparing the activity of the AR signaling pathway between the ARS^{high} and ARS^{low} subgroups, we observed a notable decrease in AR activity within the ARS^{high} group (Fig. 4A). Additionally, in the Su2c cohort, a negative correlation was found between the AR score and ARS (Fig. 4B). Notably, previous research by Spratt et al. indicated that PCa with low AR activity exhibited reduced sensitivity to docetaxel and ADT [33]. Moreover, the GDSC database was utilized to analyze variations in anti-androgen drug sensitivity among ARS^{high} and ARS^{low} patient through IC50 calculations. In alignment with previous findings, individuals in the ARS^{high} group exhibited increased resistance to bicalutamide and abiraterone compared to those in the ARS^{low} group across various datasets (Fig. 4C and D). To further assess the predictive capability of the ARS for AR-targeted therapy, we calculated the risk score for the patients in GSE111177, which contained patients accepting ADT, and the risk score was significantly higher in patients with biochemical relapse or metastasis (Fig. S3). The patients in the ARS^{high} group displayed a significantly higher fraction of biochemical recurrence and metastasis (Fig. 4E). Considering that metastatic dissemination is the most significant event in PCa progression, we also evaluated the predictive abilities of the ARS for metastasis. The AUC of the ARS for predicting distant metastasis was 0.83 in GSE111177. Consistent with these results, in the dataset GSE41408, a higher incidence of metastasis was observed in the ARS^{high} group (Fig. 4G, Fig. S4). Furthermore, the ARS classifier demonstrated strong performance in predicting the presence of distant metastases, with an AUC of 0.764 (Fig. 4H).

3.4. Treatment guidance value of ARS for immunotherapy benefits

Cancer immunotherapy has become an important treatment modality in recent years [34]. The use of sipuleucel-T prolonged overall survival among men with metastatic CRPC [35]. However, it has exhibited modest efficacy for PCa patients in the past decades, which could partially be caused by the 'immune cold tumor' characteristics. Currently, the development of advanced molecular diagnostic platforms and neoadjuvant has led to the re-emergence of immunotherapy as a potential PCa treatment, especially for CRPC [36–38]. Aside from delving into immune mechanisms, efforts to identify biomarkers of immune response are also needed. To assess the role of the ARS in the immune characteristics of PCa, the correlations between the ARS and immune cell infiltration and well-known immune modulators were investigated. A positive correlation was found between the ARS score and infiltrating immune cells, such as natural killer T cells (NKT), $CD8^+$ effector memory T cells (CD8+_Tem), and $CD4^+$ central memory T cells (CD4+_Tcm) (Fig. 5A). Correspondingly, it was negatively correlated with smooth muscle and $CD4^+$ memory T cells. Moreover, the ARS score positively correlated with the majority of immune modulators, and a significant correlation was observed between the ARS score and classical immune checkpoint molecules, including PD-1, LAG3, CTLA-4, HAVCR2, PD-L2, TIGIT, and PD-L1, indicating that ARS^{high} patients might be the immunotherapy-adapted population (Fig. 5B).

To further investigate the predictive capacity of the ARS for the clinical outcome of immunotherapy, we evaluated the correlations between the ARS and the predicted ICB response signatures. ARS was positively correlated with the enrichment scores for the immunotherapy-related positive signatures (Fig. 5C). Additionally, we used an immunotherapy cohort (treated with CTLA-4/PD-1) as the reference to carry out subclass mapping in 11 datasets, and the results also confirmed that the ARS^{high} group was more likely to respond to anti-PD-1 or anti-CTLA-4 treatments (Fig. 5D).

3.5. Implications of ARS for PARP inhibitors, chemotherapy, and radiotherapy

Poly(ADP-ribose) polymerase inhibitors have recently been developed to treat PCa [39]. Numerous studies have demonstrated that treatment with the PARP inhibitor olaparib in patients with DNA repair gene mutations leads to a high response rate after standard

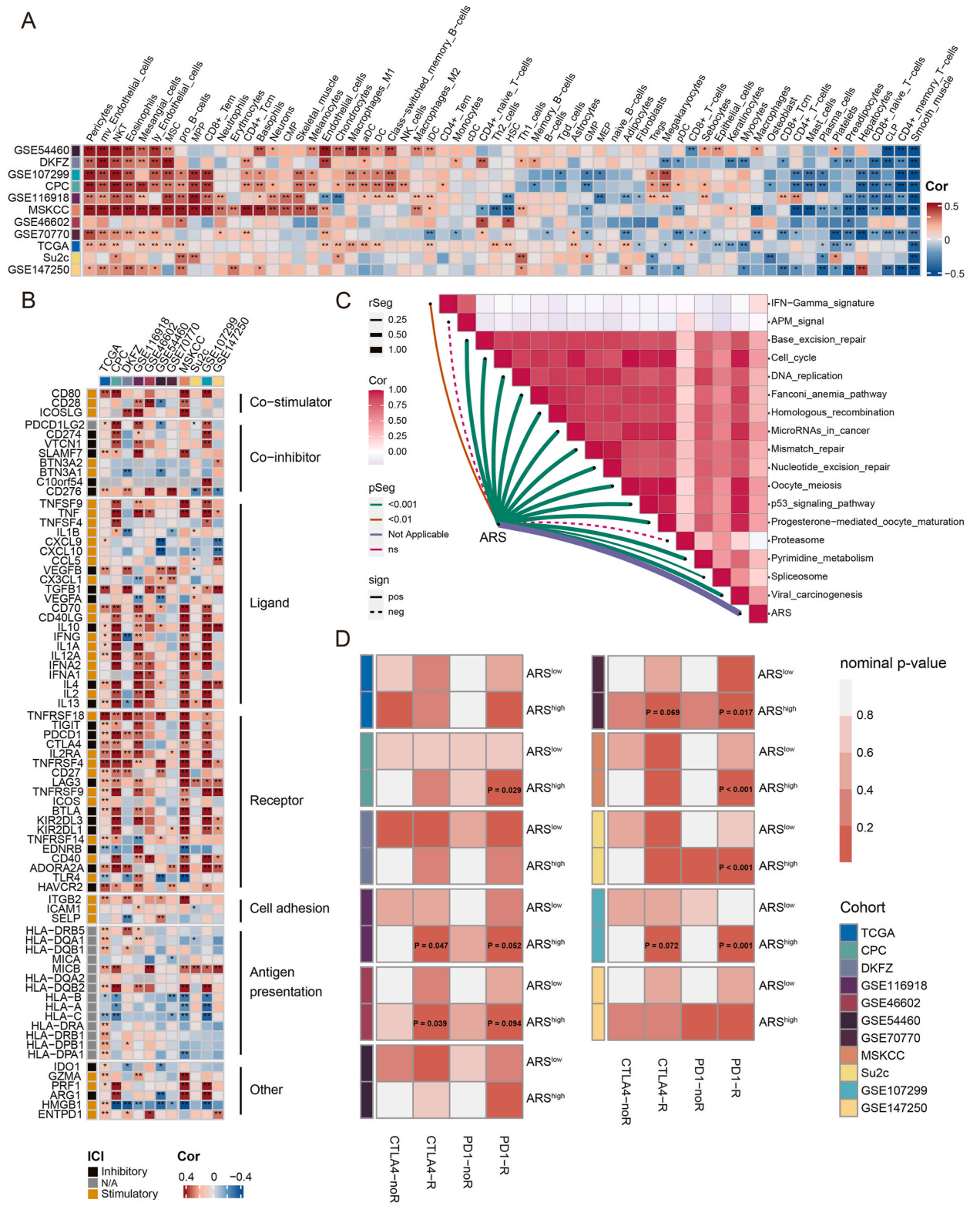

Fig. 5. Predictive value of the ARS for immunotherapy benefits.
(A-B) Correlations between ARS and immune cell infiltration levels (A) and immune modulators (B) across 11 PCa datasets. (C) Association between the ARS and the enrichment scores of immunotherapy-predicted pathways. (D) Subclass mapping results across 11 PCa datasets using an anti-PD-1/CTLA4-treated melanoma immunotherapy. (*p < 0.05, **p < 0.01).

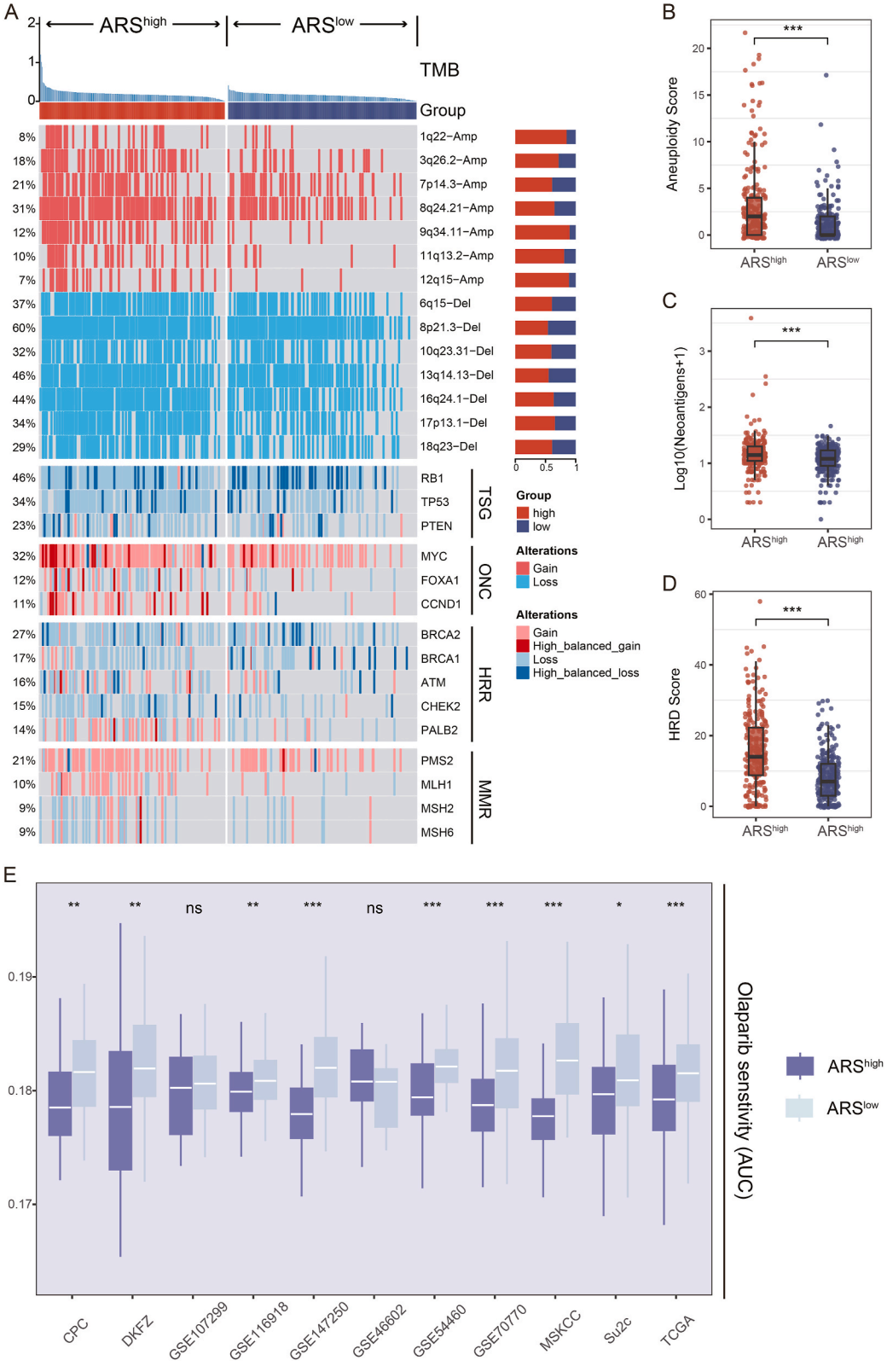

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Fig. 6. Implications of ARS for targeted therapy.
(A) Copy number amplification and deletion in the ARS^{high} and ARS^{low} groups: The upper bar plot illustrates the distribution of tumor mutation burden (TMB) among different patients, with the percentages on the left reflecting the prevalence of each CNV. The bar plot on the right displayed the distribution of this CNV among the ARS^{high} and ARS^{low} groups. (TSG: tumor suppressor gene; ONC: oncogene; HRR: homologous recombination repair; MMR: mismatch repair). (B-D) Comparison of the aneuploidy score (B), neoantigens (C), and HRD score (D) between the ARS^{high} and ARS^{low} groups in TCGA-PRAD cohort. (E) The predicted AUC values of olaparib between the ARS^{high} and ARS^{low} groups in 11 PCa datasets. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

therapies fail [40,41]. We performed genomic analysis to assess the correlation between ARS and copy number variations (CNVs) in patients. GISTIC2.0 revealed more recurrent copy number alterations in the ARS^{high} group than in the ARS^{low} group (Fig. S5). Many common gains and deletions in PCa, such as 8p21.3, 13q14.13, and 8q24.21, occurred more frequently in the ARS^{high} group than in the ARS^{low} group. Moreover, we assessed the copy number variations of several key genes that play a critical role in PCa. The ARS^{high} subgroup exhibited a higher frequency of deletions in tumor suppressor genes RB1, TP53, and PTEN, as well as amplifications in oncogenes MYC, FOXA1, and CCND1. Notably, an increased incidence of aberrations in HRR and MMR genes was observed in the subgroup with high ARS (Fig. 6A), indicating a potential susceptibility to PARP inhibitors in these individuals. Additionally, the elevated aneuploidy score, tumor neoantigen burden and HRD score in the ARS^{high} group further support this hypothesis (Fig. 6B–D). To corroborate this conjecture, we assessed the predicted sensitivity to olaparib in patients across 11 datasets. Consistently, a significantly lower AUC value indicated increased sensitivity to olaparib in patients within the ARS^{high} group (Fig. 6E). By comparing the frequency of somatic mutations in the ARS^{high} and ARS^{low} groups (Fig. S6), we discovered that TP53 was more frequently mutated in the ARS^{high} subgroup. This finding aligns with established guidelines for PCa treatment, since that TP53 mutations may confer resistance to abiraterone and enzalutamide therapy [42,43].

Since 2004, docetaxel has become the standard of care for mCRPC, which is the first adjuvant drug to show a survival benefit [44]. We evaluated the correlation between the ARS and chemosensitivity by using large-scale drug sensitivity data from the GDSC database. A significant difference was observed between the ARS^{high} and ARS^{low} groups in the predicted IC50s for docetaxel, paclitaxel, and etoposide (Fig. 7A). Patients with high ARS scores are more insensitive to docetaxel, paclitaxel, and etoposide. The PAM50 classifier was originally developed for breast cancer and applied to PCa, which categorizes PCa into luminal A, luminal B, and basal subtypes [45]. Androgen deprivation and docetaxel chemotherapy are highly effective against luminal A tumors, whereas basal tumors are largely resistant [26,46]. Interestingly, we observed that the ARS score was significantly higher in the basal subtype compared with other molecular subtypes (Fig. 7B). Correspondingly, the ARS^{high} group exhibited a significantly higher proportion of the basal subtype compared to the ARS^{low} group (Fig. 7C), indicating that patients with elevated ARS scores were less responsive to ADT and chemotherapy.

For locally advanced PCa, radiotherapy is still a treatment option [47]. The association between the ARS and patient benefit from radiotherapy was evaluated in GSE116918. This cohort consisted of localized advanced PCa patients undergoing radical radiotherapy (with ADT). The findings indicated a significant association between higher ARS scores and an increased likelihood of biochemical relapse or metastasis (Fig. S7). Similarly, patients classified in the ARS^{high} group demonstrated a heightened risk of experiencing biochemical relapse or metastasis following radical radiotherapy. (Fig. 7D).

3.6. Prediction of novel therapeutic targets and agents for high-risk patients

Given the findings presented above, which indicate that individuals in the ARS^{high} subgroup have a less favorable prognosis and limited response to various treatment options, it is imperative to explore new compounds and develop novel therapeutic approaches. Herein, we screened 2249 druggable targets summarized in a previous study to identify potential therapeutic agents. Across all 11 cohorts, we performed a correlation analysis of the association between ARS and the expression of druggable targets (Fig. 8A, S8). Ultimately, we merged the candidate key genes from seven cohorts and identified 7 potential therapeutic targets (AURKB, TACC3, PKLR, GRM2, FTL4, ADA, and PLCB2) (Fig. 8B). The CERES scores were employed to assess the essentiality of potential targets in seven PCa cell lines, revealing AURKB to have the lowest score, suggesting its crucial role in PCa cells (Fig. 8C). The expression of AURKB was found to be significantly elevated in PCa tissues compared to normal tissues, and patients with high AURKB expression exhibited a notably poorer prognosis, highlighting AURKB as a promising target for drug therapy (Fig. S9). To further select the most appropriate drugs for ARS^{high} patients targeting AURKB, we screened the PRISM database and compared the AUC values of different drugs between the ARS^{high} and ARS^{low} groups. Among them, we found that GSK1070916, MK−5108, Tozasertib and ZM−447439 consistently showed lower AUC values in the ARS^{high} groups in multiple cohorts and may be potentially effective drugs for ARS^{high} patients (Fig. 8D). After conducting a thorough review of current research on these drugs, we discovered that only Tozasertib had undergone a phase II clinical trial, demonstrating its safety and efficacy (Fig. 9A). Subsequently, a preliminary experimental investigation was conducted to assess the potential therapeutic effectiveness of Tozasertib for ARS^{high} PCa. The enzalutamide-resistant C4-2B (C4-2B-ENZR) cell line, previously constructed by our research group, was utilized as a model for ARS^{high} PCa. This cell line exhibited heightened malignant characteristics and maintained robust proliferative activity even when exposed to 10 μM enzalutamide [28]. Dose-response curves for Tozasertib were generated for C4-2B-ENZR, resulting in the determination of IC50 values (611.5 nM) (Fig. 9B). Based on these IC50 values, we selected concentrations of 400 nM for Tozasertib as the experimental concentrations. C4-2B-ENZR cells were treated with Tozasertib, and cell viability was assessed at 24, 48, 72, and 96 h. As shown in Fig. 9C, Tozasertib had a strong inhibitory impact on C4-2B-ENZR cell proliferation. Furthermore, we examined the effect of Tozasertib on the clonal formation ability of C4-2B-ENZR and other castration-resistant PCa cell lines (PC3 and 22RV1). The results of the colony formation

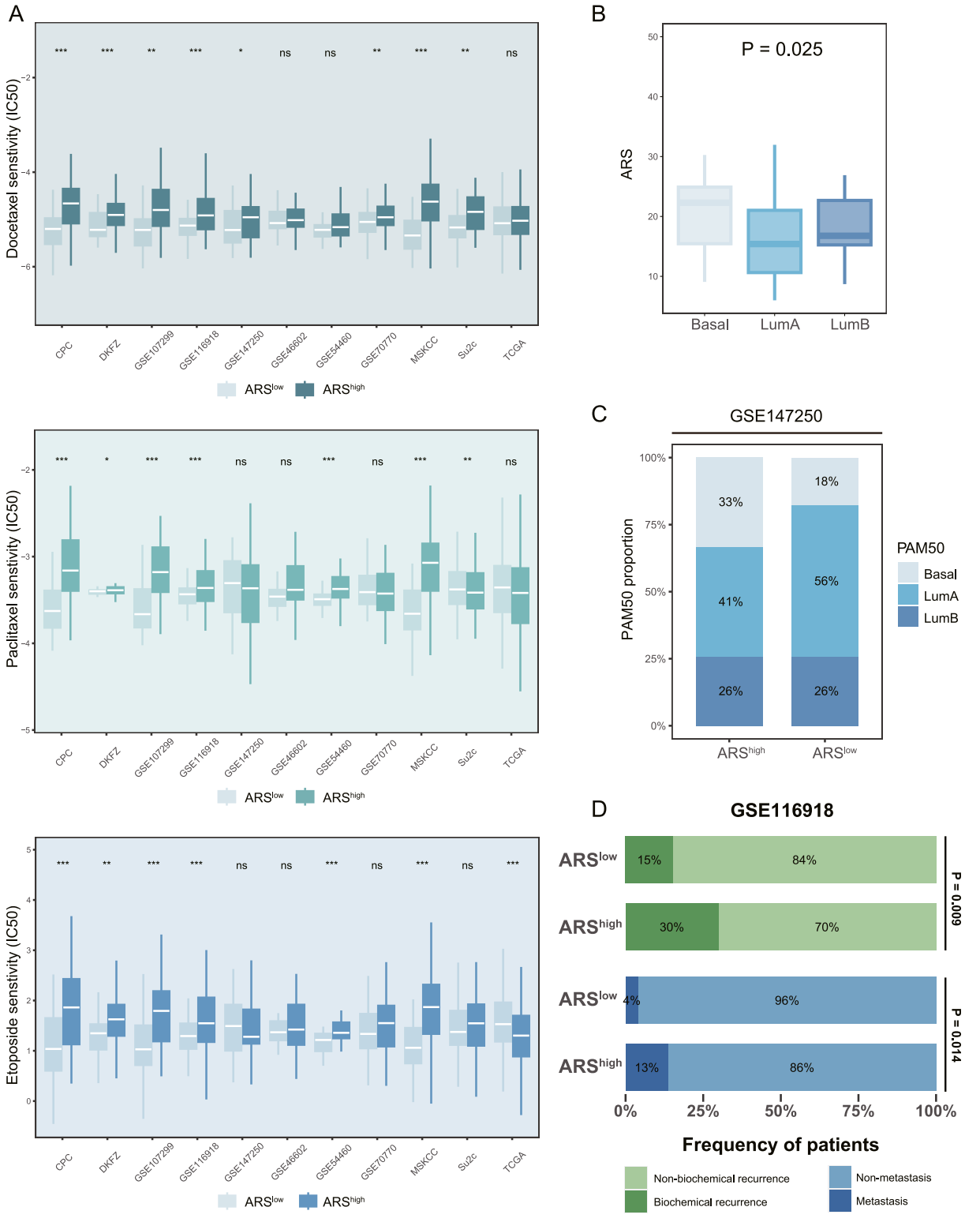

Fig. 7. ARS predicts chemotherapy and radiotherapy outcomes.
(A) The predicted AUC values of docetaxel, paclitaxel, and etoposide between the ARS^{high} and ARS^{low} groups in 11 PCa datasets. (B) The ARS score across the PAM50 molecular subtypes. (C) The proportion of different PAM50 tumor subtypes between the ARS^{high} and ARS^{low} groups. (D) The ratio of biochemical recurrence and metastasis in the ARS^{high} and ARS^{low} groups in GSE116918. (*p < 0.05, **p < 0.01, ***p < 0.001).

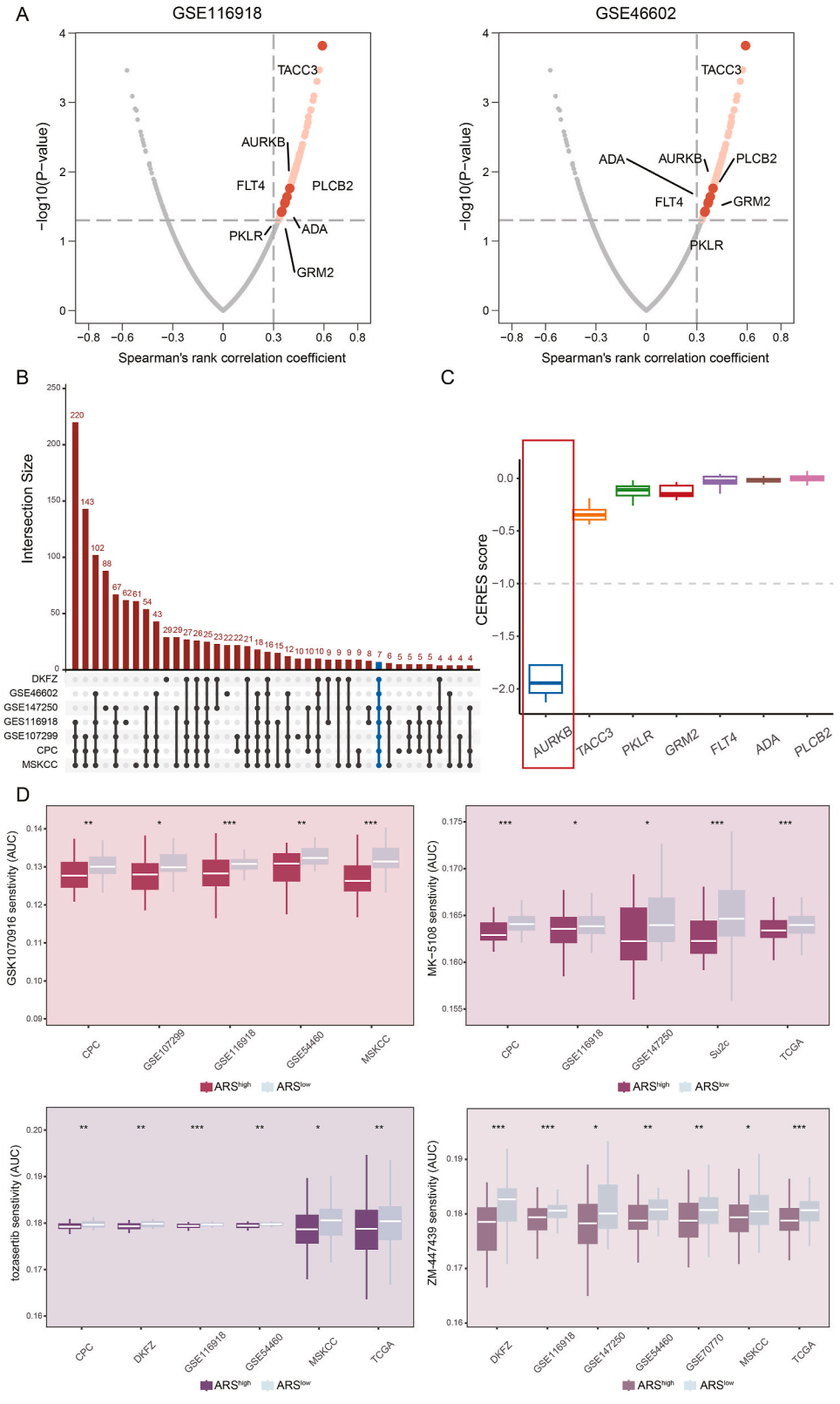

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Fig. 8. Target identification and agent selection for ARS^{high} patients.
(A) Correlation analysis between ARS and the expression of druggable target in the GSE116918 and GSE46602 cohort. (B) UpSet plot showing the intersection of potential targets across 7 datasets. (C) Prostate cancer cell line CERES scores for identified targets. (D) The predicted AUC values of AURKB inhibitors between the ARS^{high} and ARS^{low} groups. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

assay indicated a marked reduction in the proliferative capacity of these castration-resistant PCa cells following treatment with Tozasertib (Fig. 9D). Additionally, our findings indicate that the introduction of Tozasertib resulted in a marked increase in apoptosis rate in C4-2B-ENZR (Fig. 9E). Subsequently, we confirmed the therapeutic efficacy of Tozasertib for C4-2B-ENZR in an in vivo setting. Specifically, our results demonstrate that Tozasertib effectively inhibited subcutaneous tumor growth in C4-2B-ENZR (Fig. 9F). Furthermore, the group treated with Tozasertib showed a significant reduction in Ki-67-positive cells and a noticeable increase in the proportion of TUNEL-positive cells (Fig. 9G–H). Collectively, our findings suggest that targeting AURKB may represent a promising therapeutic strategy for managing ARS^{high} patients, a subgroup characterized by poor prognosis and resistance to AR-targeted therapy.

4. Discussion

PCa diagnosis and postoperative management have made significant strides in recent years [48,49]. Currently, further requirements for restricting overtreatment and accurately choosing therapy options for patients have been proposed by precision medicine [50]. These standards primarily include: i) distinguishing between patients with inert progression and those with rapid progression or metastasis; ii) avoiding premature postoperative adjuvant interventions; and iii) assisting in assessing the advantages of adjuvant treatment and directing the patients' personalized treatment strategy. It has been recognized that predictive risk assessment based on conventional clinical indicators, including serum PSA, ISUP grading, and TNM staging, has several drawbacks in clinical practice because of the great heterogeneity of tumors [51]. High-throughput gene expression sequencing has produced a wealth of data, and machine learning analysis approaches have yielded a substantial impact on the clinical management of PCa [52]. It is essential to properly summarize massive independent cohorts across different clinical therapy scenarios and to evaluate the data objectively using machine learning techniques to produce robust predictive models.

Genomic events and regulators of the androgen receptor-related signaling pathway have been well recognized as key factors driving the progression of PCa and determining sensitivity to ADT [53]. Widespread interest has been shown in the use of AR-related regulators as indicators of PCa progression and response to treatment. In fact, AR-V7, a novel molecular marker, has been utilized to predict a lower survival benefit to anti-androgen therapy (enzalutamide, abiraterone) [54]. This study suggests that, compared to 44 published gene signatures, the random forest survival model generated from AR-related regulators possesses a stronger and more compatible prediction capability. The majority of gene signatures exhibited inconsistent performance across the 11 PCa cohorts, with the C index outperforming ARS in some cohorts but not in others. This result may be due to the following reasons: i) The predetermined gene set used for gene signature development may be one of the aspects impacting PCa progression, but it cannot be recognized as the primary motivating factor. ii) Another possible explanation is that the applied analysis methods are not sufficiently comprehensive. Most of these gene signatures were constructed using the Lasso regression method for dimensionality reduction, which has been shown to be susceptible to overfitting and thus lead to limited abduction stability. Some of the original studies compared several popular machine learning techniques to obtain the best model, while we conducted dimensionality reduction on a total of 101 binary combinations of 10 machine learning methods and demonstrated the superiority of this approach. iii) The diverse clinical circumstances of PCa were not well covered in these published studies. This study comprised up to 13 clinical cohorts with backgrounds that included various clinical stages (primary disease, distant metastases, castration sensitivity, and resistance), as well as different treatment modalities (ADT, radiation, and chemotherapy).

Androgen deprivation therapy is the cornerstone of advanced PCa treatment, including surgical castration, LHRH agonists and antagonists, androgen receptor inhibitors (enzalutamide, bicalutamide), and androgen synthesis inhibitors (abiraterone). We demonstrate that the ARS is correlated with poorer ADT treatment outcomes, and the correlation between the ARS and the AR response signals, AR scores, and simulated sensitivity to bicalutamide/abiraterone provided supportive evidence. Compared to many other cancer types, PCa has a higher burden of chromosomal structural variation, including insertion, deletion, inversion, translocation, gene fusion, and tandem duplication [55]. It has been proven that postoperative biochemical recurrence and distant metastasis are related to increased CNA burden [56,57]. The ARS^{high} group exhibited higher aneuploid scores and tumor neoantigen loading. Not only the copy number of the oncogenes MYC, FOXA1, and CCND1 dramatically increased in the ARS^{high} group, but also the tumor suppressor genes TP53, PTEN, and RB1 showed higher copy number loss, indicating enhanced malignant proliferation in the ARS^{high} group. DNA homologous recombination repair is the main repair mode for DNA double-strand damage. HRD produces specific, quantifiable, and stable genomic alterations, leading to genomic and chromosomal instability, and has been approved by the FDA as a marker for PARP inhibitor application. There was a strong correlation between the ARS^{high} group and higher olaparib sensitivity in 9 cohorts, proving that the ARS was helpful in determining PARPi use. Mismatch repair is the main DNA single-strand damage repair approach, and tumors with mismatch repair defects (MMRDs) exhibit a large number of single nucleotide substitutions and frameshift mutations. MMRD is linked to microsatellite instability (MSI-H), and patients with high levels of MMRD are considered suitable for ICB therapy. There is still an absence of further information from the real-world PCa immunotherapy cohort, despite the fact that the analysis results from immune cell infiltration levels, anti-tumor immune response signals, key molecule expression levels, and immunotherapy responsiveness inference are highly consistent in accordance with theoretical cognition. It is recognized that PCa is a typical "immune cold" tumor with a low total tumor mutation burden and insufficient infiltration of effector T cells. With a single drug objective

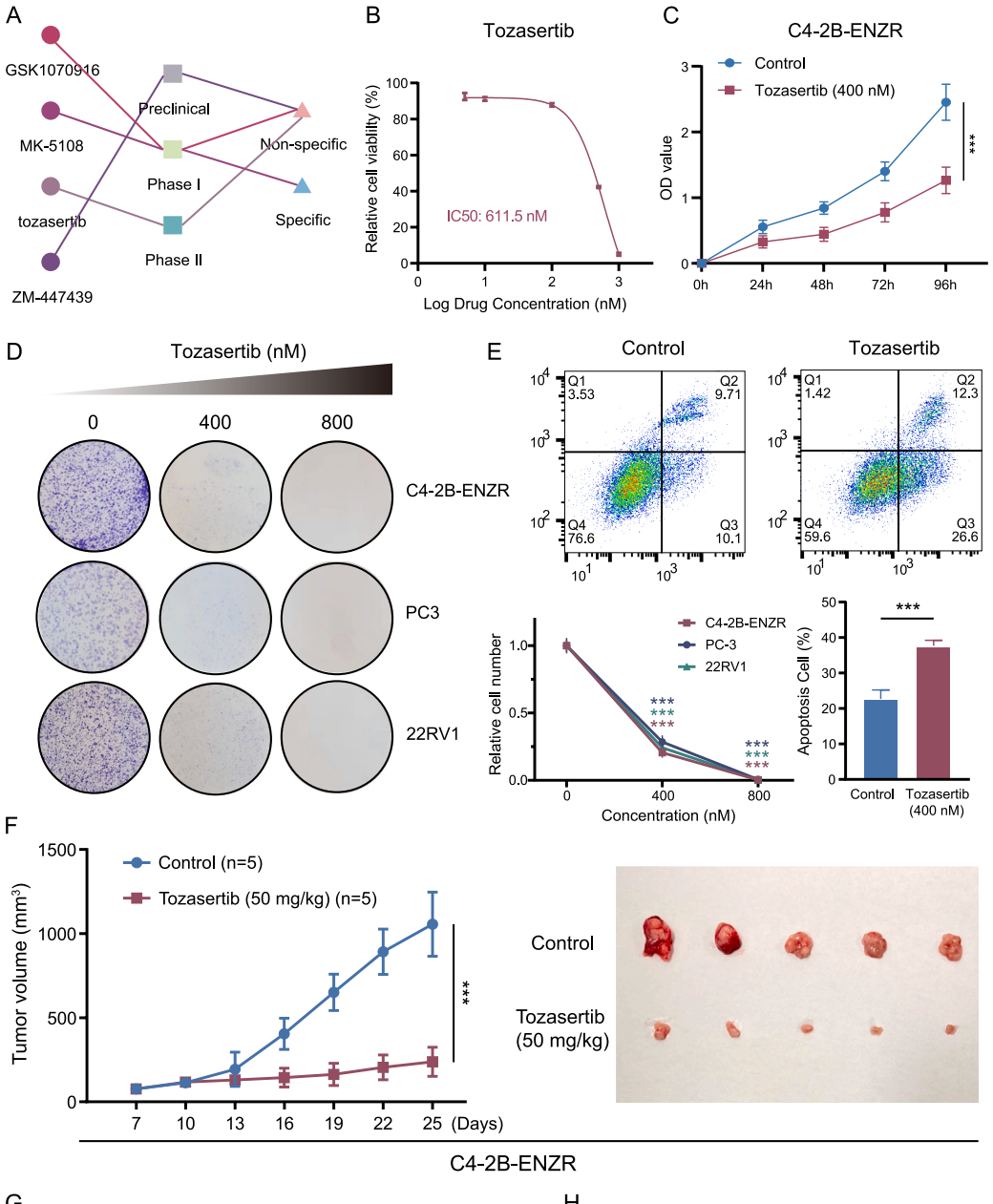

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Fig. 9. Tozasertib suppressed cell proliferation and promoted apoptosis in C4-2B-ENZR.
(A) Detailed information concerning the clinical status of selected inhibitors of AURKB and their target specificity. (B) The dose-effect curves of Tozasertib for C4-2B-ENZR. (C) The effect of Tozasertib on C4-2B-ENZR cell viability at different time points (0–96 h). (D) Colony formation assays were conducted based on three castration-resistant PCa cell lines (C4-2B-ENZR, PC3, and 22RV1) treated with Tozasertib using gradient concentrations. (E) Apoptosis rates following Tozasertib administration were determined by flow cytometry. (F) A subcutaneous injection of C4-2B-ENZR cells was performed in nude mice (five in each group), and the treatment group was administrated with Tozasertib (50 mg/kg). A three-day interval was monitored with tumor size measurements. Then, mice were sacrificed and tumor volume was determined. (G-H) An immunofluorescence staining to determine Ki-67 expression levels. Scale bar, 100 μm; TUNEL analysis to determine cell apoptosis in each group. Scale bar, 100 μm. (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

response rate of less than 10 %, CTLA-4 inhibitors and PD-1 inhibitors have thus far both failed in trials of immunotherapy for PCa. Zhao et al. applied the PAM50 classification approach to separate PCa into basal and luminal A/B subtypes and demonstrated that while luminal B has the worst prognosis, it is the only subtype that benefits from ADT therapy [26]. Coleman et al. further confirmed that luminal subtypes have superior responsiveness to docetaxel and AR signaling inhibitors in patients with mCRPC [26]. Our analysis showed that basal PCa has a much higher ARS, and drug sensitivity inference demonstrates that low ARS groups are more sensitive to chemotherapy (i.e., docetaxel, paclitaxel, and etoposide). Overall, the ARS has exhibited excellent discriminative efficacy in differentiating PCa patient treatment options.

Tozasertib, small-molecule inhibitors targeting AURKB, hold the greatest potential among these prospective therapeutic agents for high ARS PCa patients identified in this study. AURKB is a serine/threonine protein kinase that participates in the progression of the cell cycle during mitosis. AURKB is significantly overexpressed in PCa and has been linked to malignant events such as tumor staging, a higher tumor grade, and seminal vesicle invasion [58], according to earlier reports. It is important to note that, in contrast to androgen-sensitive LNCap and EPN cell lines, aberrant AURKB expression is more pronounced in androgen-independent PC3 and DU145 cell lines [59]. According to Addepalli et al.'s report, downregulating AURKB can drastically reduce PCa cell proliferation and, as a result, slow tumor growth in vivo [60]. AURKB was recently reported to be elevated in mCRPC that had become resistant to abiraterone treatment by Sicote et al., suggesting that targeting AURKB may help reverse abiraterone resistance [61]. In fact, it has been reported that Tozasertib reduces PCa cell survival and shows promising results in vitro and in vivo [58,62]. In the present investigation, it was observed that Tozasertib exhibited a stronger efficacy in inhibiting tumor growth for C4-2B-ENZR, which suggested that it may be a potential therapeutic approach for CRPC.

We must acknowledge several inherent limitations before applying the random forest survival model developed based on AR-related regulators to clinical translation, despite the model's considerable potential for managing PCa prognosis. First, the development of the ARS is based on a retrospective meta-cohort study. In the future, the ARS should also be verified in a prospective multicenter study. Second, a variety of models or gene signatures have been developed to manage PCa prognosis, and we only retrospectively collected 44 published gene signatures. It is necessary to conduct a more thorough comparative study to show the superiority of ARS before further promoting its use in clinical applications. For example, ARS should be further compared with the commercial prognostic tools Prolaris ® (Myriad Genetics Inc.), Decipher ® (GenomeDX Inc.), OncotypeDX GPS ® (Genomic Health Inc.) [63]. Third, our study only utilized the previously established C4-2B-ENZR cell line for representing the ARS^{high} patients. Additional cell lines resistant to anti-androgen drugs are needed for further validation. Finally, there is still an indispensable gap to confirm the utility of the ARS for immunotherapy response due to a dearth of real-world PCa immunotherapy cohorts.

5. Conclusion

In summary, we constructed a robust prediction model based on AR-related regulators using multiple machine-learning algorithms. ARS is an independent risk factor for the survival of PCa patients. Additionally, PCa patients with a high ARS benefit more from olaparib and immunotherapy, while those with a low ARS are sensitive to chemotherapy, radiotherapy, and AR-targeted therapy. Additionally, we identified Tozasertib, inhibitor targeting AURKB, for ARS^{high} patient and verified by in vitro and in vivo experiments.

Data and code availability

Data will be made available on request.

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CRediT authorship contribution statement

Qinyu Li: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Yanan Wang:** Investigation, Formal analysis. **Junjie Chen:** Investigation, Data curation. **Kai Zeng:** Writing – review & editing, Funding acquisition. **Chengwei Wang:** Writing – review & editing. **Xiangdong Guo:** Writing – review & editing. **Zhiquan Hu:** Writing – review & editing. **Jia Hu:** Writing – review & editing. **Bo Liu:** Writing – review & editing. **Jun Xiao:** Writing – review & editing, Visualization, Supervision. **Peng Zhou:** Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37256.

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