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ORIGINAL RESEARCH

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Prognostic role and therapeutic implications of phosphatidylinositol transfer protein cytoplasmic 1 in primary prostate cancer

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Abstract

Phosphatidylinositol transfer protein cytoplasmic 1 (PITPNC1) has been implicated in some tumor types, but its role in primary prostate cancer (PCa) remains unexplored. This study investigates the prognostic significance of PITPNC1 in PCa. RNA sequencing (RNA-seq), mutation data and clinical information on PCa cohorts were retrieved from the The Cancer Genome Atlas Program (TCGA) and Gene Expression Omnibus (GEO) databases. Data analysis revealed that PITPNC1 expression was significantly lower in PCa tissues compared to benign tissues, and this reduced expression correlated with earlier biochemical recurrence and decreased overall survival. Functional enrichment analysis indicated that PITPNC1 activates pathways related to cell adhesion and immune receptor signaling while inhibiting RNA metabolism pathways. Additionally, high Tumor Protein P53 (*TP53*) mutation frequency was observed in the low PITPNC1 expression group. In immunotherapy cohorts, lower PITPNC1 expression was associated with poorer outcomes. Furthermore, Rucaparib was identified as a potential therapeutic agent for patients with low PITPNC1 expression. Collectively, we identified PITPNC1 as a promising prognostic marker in PCa. Its expression levels can predict immunotherapy responses, and it holds potential as a target for precision therapies.

Keywords

Prostate cancer; PITPNC1; Biochemical recurrence; TP53; Immunotherapy

1. Introduction

According to epidemiological statistics, prostate cancer (PCa) remains one of the most common cancers affecting male reproductive and urinary health, ranking second in incidence and fifth in mortality globally [1]. In the United States, PCa has become the most commonly diagnosed cancer among men, with mortality rates now the second highest [2]. Data from the 2016 cancer registry in China indicate that the age-standardized incidence rate of PCa is the sixth highest among all male malignancies, accounting for 6.72% of all male cancer cases [3]. These statistics highlight the significant threat that PCa poses to male health.

The development of PCa is usually slow in its early stages, and for such cases, surgical resection and radiation therapy have been shown to be effective for managing its development [4]. However, due to the variability in PCa characteristics, prognostic outcomes vary widely among patients. Approximately 20–40% of patients experience biochemical recurrence (BCR) within ten years after radical prostatectomy (RP), defined as consecutive serum Prostate Specific Antigen (PSA) levels of $\geq$0.2 ng/mL [5–7]. Thus, clinicians face a significant challenge in stratifying patients by risk to avoid both undertreatment and overtreatment [8].

PCa is often diagnosed at an advanced stage, necessitating complex treatment strategies [9, 10]. For hormone-sensitive metastatic prostate cancer (mHSPC), androgen-deprivation therapy (ADT) is the primary treatment, sometimes augmented with additional hormonal therapies [9, 10]. In cases of metastatic castration-resistant prostate cancer (mCRPC), treatment options have expanded over the past two decades to include chemotherapy, androgen receptor signaling inhibitors and immunotherapies [11, 12]. However, identifying specific

patient subsets remains a significant challenge, underscoring the need for precise biomarker identification to optimize treatment outcomes [13].

Members of the phosphatidylinositol transfer protein (PITP) family facilitate the transport of phospholipids across cellular membranes [14]. Class I PITPs, namely PITPα (PITPNA) and PITPβ (PITPNB), can selectively bind phosphatidylinositol (PI) or phosphatidylcholine (PC). In contrast, PITPNC1, classified under Class II, primarily interacts with PI and phosphatidic acid (PA), but not PC [15]. PITPNC1 initially drew attention due to its amplification in human breast cancer and its increased expression in tissues from breast, colon and melanoma metastases. In these contexts, PITPNC1 has been shown to promote a pro-metastatic phenotype by secreting factors that enhance invasiveness and angiogenesis [16]. Subsequent studies have associated elevated PITPNC1 expression with unfavorable prognostic outcomes in gastric cancer and radioresistance in rectal cancer [17]. However, the role of PITPNC1 in PCa remains unclear.

Due to the significant heterogeneity in PCa, identifying novel biomarkers presents numerous challenges [18]. In recent years, with the advancement of biotechnology, multi-omics has emerged as an integrative approach that combines different omics research methods, offering a more comprehensive understanding of tumor heterogeneity and aiding in the identification of biomarkers [19]. Among these, transcriptomics provides extensive public resources and reliable experimental techniques. Notably, datasets like TCGA not only offer clinical follow-up information centered on transcriptomics but also enable multi-omics analyses, including genomics and epigenomics [20]. Although recent developments in proteomics are increasingly promising [21], the comprehensiveness of proteomic data still lags behind that of transcriptomics. However, in the foreseeable future, proteomics will undoubtedly become an indispensable part of cancer research.

As shown in Fig. 1, in this study, by integrating multi-omics and multi-cohort PCa data, we identified PITPNC1 as a potential biomarker for PCa. This finding was corroborated through local cohort. Subsequent functional enrichment analyses, predictions of drug effects, and multi-omics assessments further deepened our understanding of PITPNC1's role in PCa.

2. Materials and methods

2.1 Data processing workflow

The data processing methodology employed in this study aligns with our previously published work [22]. In summary, we initiated the study by downloading RNA-seq data, mutation data and clinical information for the TCGA and GEO databases. To convert Ensembl Identifiers (ID) to SYMBOL IDs in the RNA-seq data, we used the R packages clusterProfiler (version 4.8.1) and org.Hs.eg.db (version 3.17.0) [23]. To address batch effects, we applied the ComBat function from the sva R package (version 3.48.0). The datasets employed in this study are in **Supplementary Table 1**.

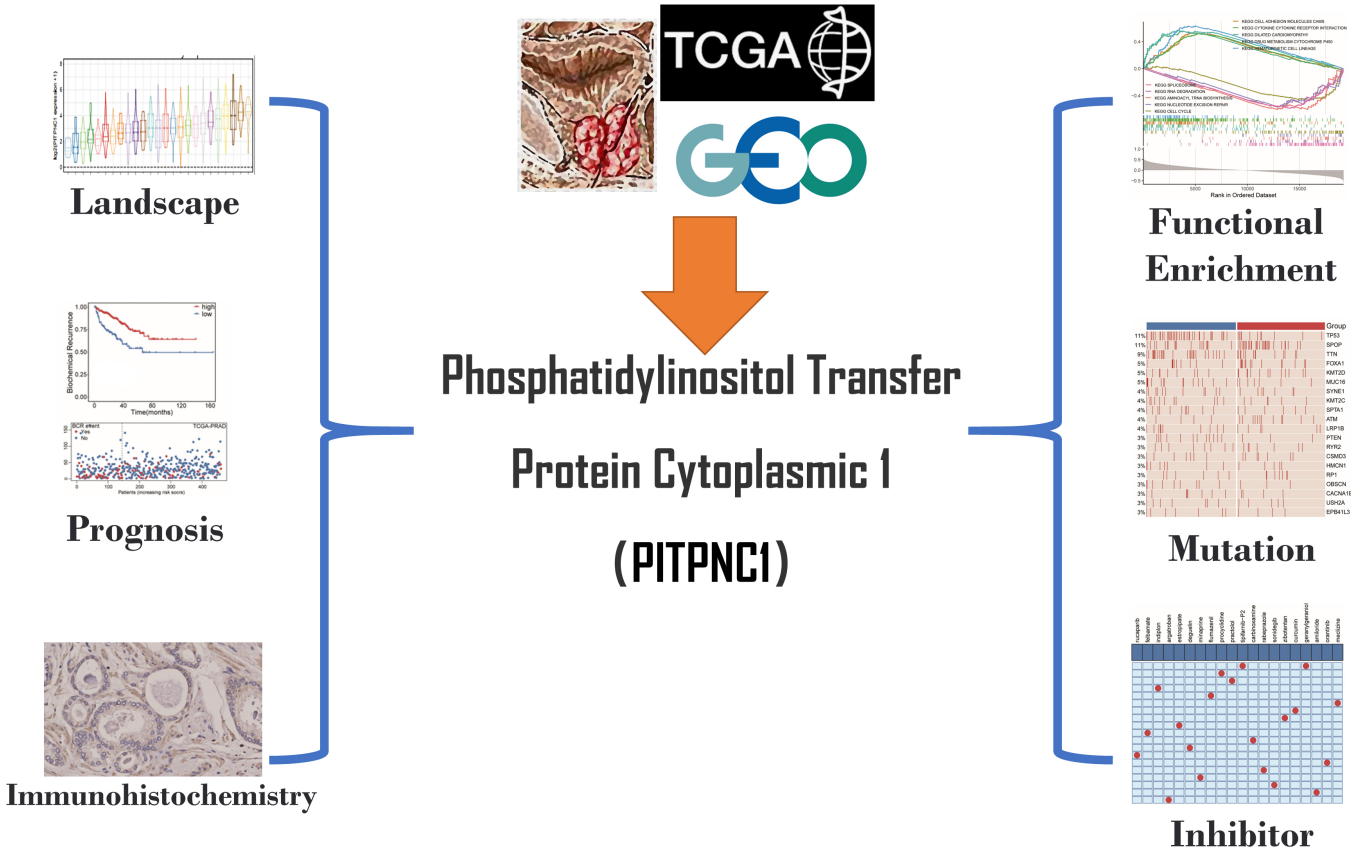

FIGURE 1. Study flowchart. TCGA: The Cancer Genome Atlas Program; GEO: Gene Expression Omnibus.

2.2 Prognostic assessment

To assess the prognostic significance of gene expressions in PCa, we conducted univariate Cox regression and Kaplan-Meier (KM) analyses using the R package "survival" (version 3.5-5).

2.3 Functional enrichment

We employed the Spearman correlation method to evaluate the relationship between PITPNC1 expression and the expression of all other messenger RNAs (mRNA). The resulting ranked gene list was subsequently analyzed with the "clusterProfiler" package (version 4.8.1) to perform Gene Set Enrichment Analysis (GSEA). This analysis focused on identifying enriched pathways and gene sets, including Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

2.4 Immunohistochemistry (IHC)

Local cohort samples for this study were obtained from a tissue microarray (TMA, HProA120Su01) provided by Shanghai Outdo Biotech Limited Company. Following protocols established in our previous studies [24], a summary of the IHC procedure is as follows. Anti-PITPNC1 antibody (NBP2-97834, Novus Biologicals, Minneapolis, MN, USA) was employed for staining. Tissue samples were initially fixed in 4% paraformaldehyde and then embedded in paraffin. Sections of 4 μm thickness were treated with 1% H_2O_2 solution to block endogenous peroxidase activity, followed by blocking with non-immune goat serum. Sections were incubated overnight at 4 °C with primary antibodies, and subsequently with biotinylated secondary antibodies for 30 minutes at room temperature. The IHC results were scored by summing the percentage of positively stained cells and the staining intensity. The scoring criteria for cell percentages were: 0 (0%), 1 (1–10%), 2 (11–50%) and 3 (>50%). Staining intensity was scored as: 0 (negative), 1 (weak), 2 (moderate) and 3 (strong).

2.5 Mutation analysis

To investigate the differential genomic mutations between high and low PITPNC1 expression groups, stratified by the median expression level, we utilized the "maftools" R package (version 2.16) [25]. Statistical significance of the differences was determined using the Wilcoxon rank-sum test.

2.6 Therapy response evaluation

We employed the online tool "BEST" (https://rookieutopia.com/app_direct/BEST/) to predict patient responses to immune checkpoint blockade (ICB) therapy [26]. Transcriptomic expression patterns were analyzed between patient groups with varying levels of PITPNC1 expression and different immunotherapy outcomes. Anti-Programmed Death-1 (Anti-PD-1) immunotherapy samples were categorized based on optimal PITPNC1 expression cut-off values for survival analysis. Additionally, we utilized the Connectivity Map (CMap) [27] (https://www.broadinstitute.org/connectivity-map-cmap), a data-driven approach for identifying relationships among genes, chemical substances and biological conditions, to pinpoint potential compounds targeting PITPNC1-associated pathways in PCa. Further analyses using the CMap tool were conducted to elucidate mechanisms of action (MoA) and drug targets with greater specificity.

2.7 Statistical analysis

Data analysis and visualization were conducted using R version 4.3.1, with additional visualizations performed via the Sanger Box bioinformatics analysis online tool [28]. Statistical analyses were executed using GraphPad Prism 8.0 software (San Diego, California, USA) under a licensed agreement. Comparisons between two groups were made using the Wilcoxon rank-sum test. All p-values reported are two-sided, with statistical significance indicated by $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$.

3. Results

3.1 PITPNC1 is downregulated in PCa tissues

In two human tissue datasets, PITPNC1 was found to rank third in terms of expression in the The Human Protein Atlas (HPA) cohort and seventh in the The Genotype-Tissue Expression (GTEx) cohort, indicating moderate to high levels of expression across different normal organ tissues (Fig. 2A). In contrast, PITPNC1 expression in PCa cell lines ranks second to last in the Cancer Cell Line Encyclopedia (CCLE), surpassing only that in mesothelioma (Fig. 2B). Varied expression patterns of PITPNC1 are observed across different cancer types in matched and unmatched sample classifications within TCGA (Fig. 2C,D), with significantly higher levels in benign tissues compared to PCa. These findings suggest that PITPNC1 holds potential as a biomarker for PCa.

3.2 PITPNC1 as a prognostic factor in primary PCa

In this study, we compiled RNA expression and prognosis data for primary PCa from global public databases, including datasets from the United States TCGA- Prostate Adenocarcinoma (PRAD), gene expression data series (GSE) 54460, GSE21034), Europe (CancerMap, GSE70768) and Canada (CPC). Kaplan-Meier analyses (Fig. 3A–F) indicate that lower PITPNC1 expression correlates with earlier BCR across these datasets. Univariate Cox regression analysis identified PITPNC1 as a protective factor against BCR (Fig. 3G). Multivariate Cox regression consistently showed hazard ratios (HR) less than 1 for PITPNC1 across multiple datasets, with significant p-values ($p < 0.05$) in GSE54460, CancerMap and CPC (Fig. 3H). These results indicate PITPNC1 as a favorable prognostic marker for BCR in primary PCa.

3.3 IHC validation of PITPNC1 in local cohort

The prognostic significance of PITPNC1, initially confirmed through RNA-seq data from Western populations, necessitated further validation in clinical samples. We performed immuno-

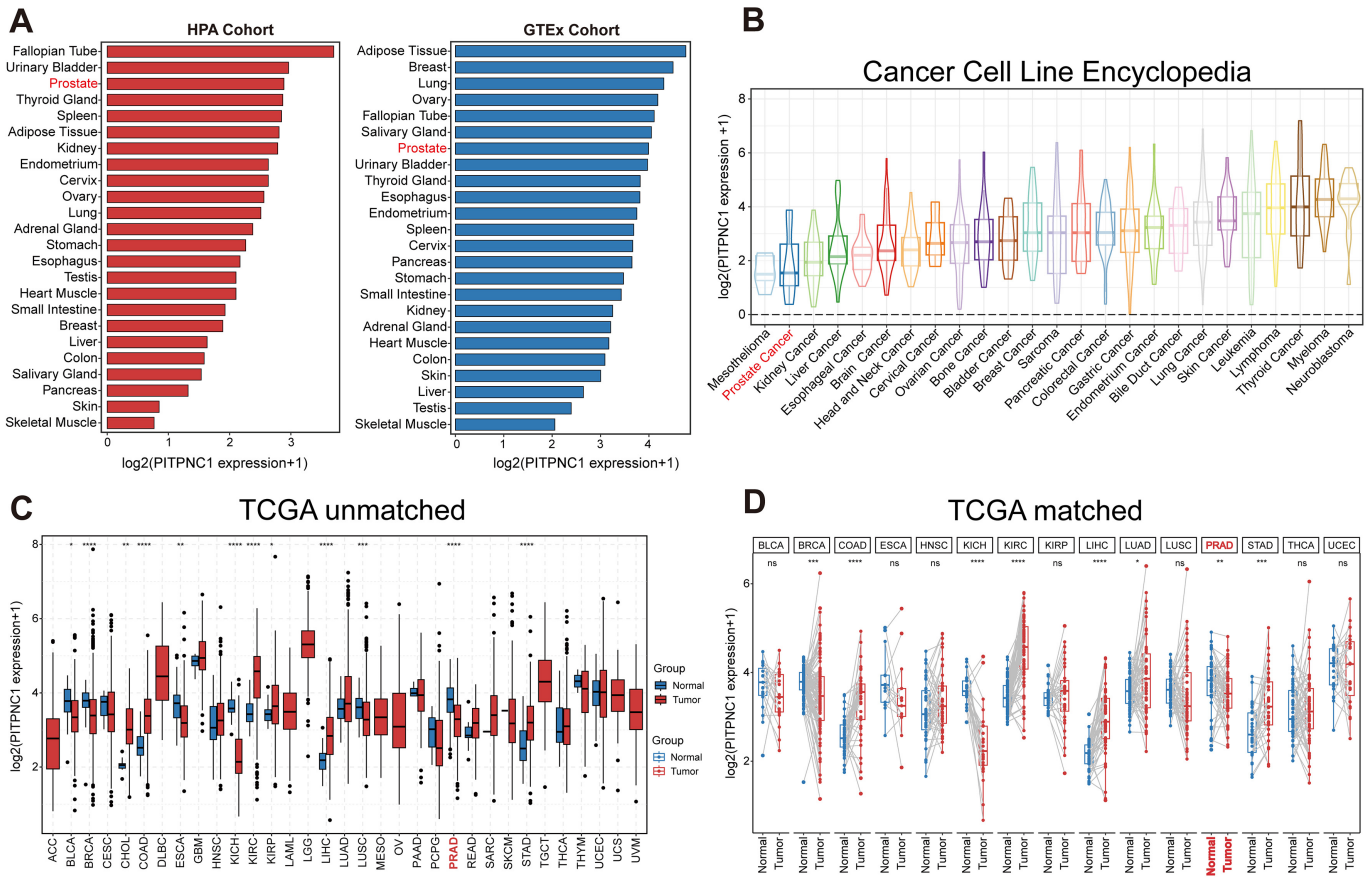

FIGURE 2. PITPNC1's expression pattern different tissues. (A) RNA Expression level of PITPNC1 in normal tissues (HPA & GTEx database). (B) PITPNC1 RNA expression levels in cancer cell lines (CCLE database). (C) Unmatched samples differential expression genes analysis in TCGA pan-cancer. (D) Matched samples differential expression genes analysis in TCGA pan-cancer. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$; $****p < 0.0001$; NS, No Significance. TCGA: The Cancer Genome Atlas Program; HPA: The Human Protein Atlas; GTEx: The Genotype-Tissue Expression.

histochemistry (IHC) to assess PITPNC1 protein expression at local cohort using a Chinese cohort. The results revealed predominant cytoplasmic localization of PITPNC1 (Fig. 4A). Overall, PITPNC1 expression was also found to be lower in PCa tissues compared to benign tissues (Fig. 4A). Additionally, follow-up data indicated that patients with low PITPNC1 expression had lower overall survival rates (Fig. 4B), suggesting PITPNC1's potential as a PCa biomarker based on its protein expression pattern.

3.4 Functional enrichment analysis

Following the identification of PITPNC1's prognostic significance, we explored the biological functions associated with PITPNC1 using Gene Set Enrichment Analysis (GSEA) across Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways (Fig. 5A–D, **Supplementary Table 2**). The top five GO pathways influenced by PITPNC1 were ranked based on Normalized Enrichment Scores (NES). Similarly, PITPNC1 affected the top five KEGG pathways, revealing activation of cell adhesion and immune receptor signaling pathways, and inhibition of RNA metabolism pathways such as RNA localization, export, synthesis and splicing. These findings provide valuable insights for further research into PITPNC1's biological functions.

3.5 Mutation landscape related to PITPNC1 expression in PCa

It is well established that the mutational burden in primary PCa is generally lower compared to many other cancer types. Interestingly, the group with low PITPNC1 expression was found to have a higher TP53 mutation frequency of 17.2%, contrasting with just 5.1% in the high PITPNC1 expression group. Furthermore, the low PITPNC1 expression group had increased mutation frequencies in Titin (*TTN*) (12.2%) and Phosphatase and Tensin Homolog Deleted on Chromosome Ten (*PTEN*) (5.4%), while Ataxia Telangiectasia Mutated (*ATM*) mutation frequency was decreased (1.8%) (Fig. 6A,B). Additionally, significant differences in high-frequency arm-level copy number alterations (CNA) were observed between the groups (Fig. 6C), with losses at 8p21-3-Del, 8p23-1-Del and 16q24-1-Del being more frequent in the low PITPNC1 expression group (72.4%, 59.7% and 54.3%, respectively). These findings suggest that the poorer prognosis associated with low PITPNC1 expression may be linked to the heterogeneity of these gene mutations.

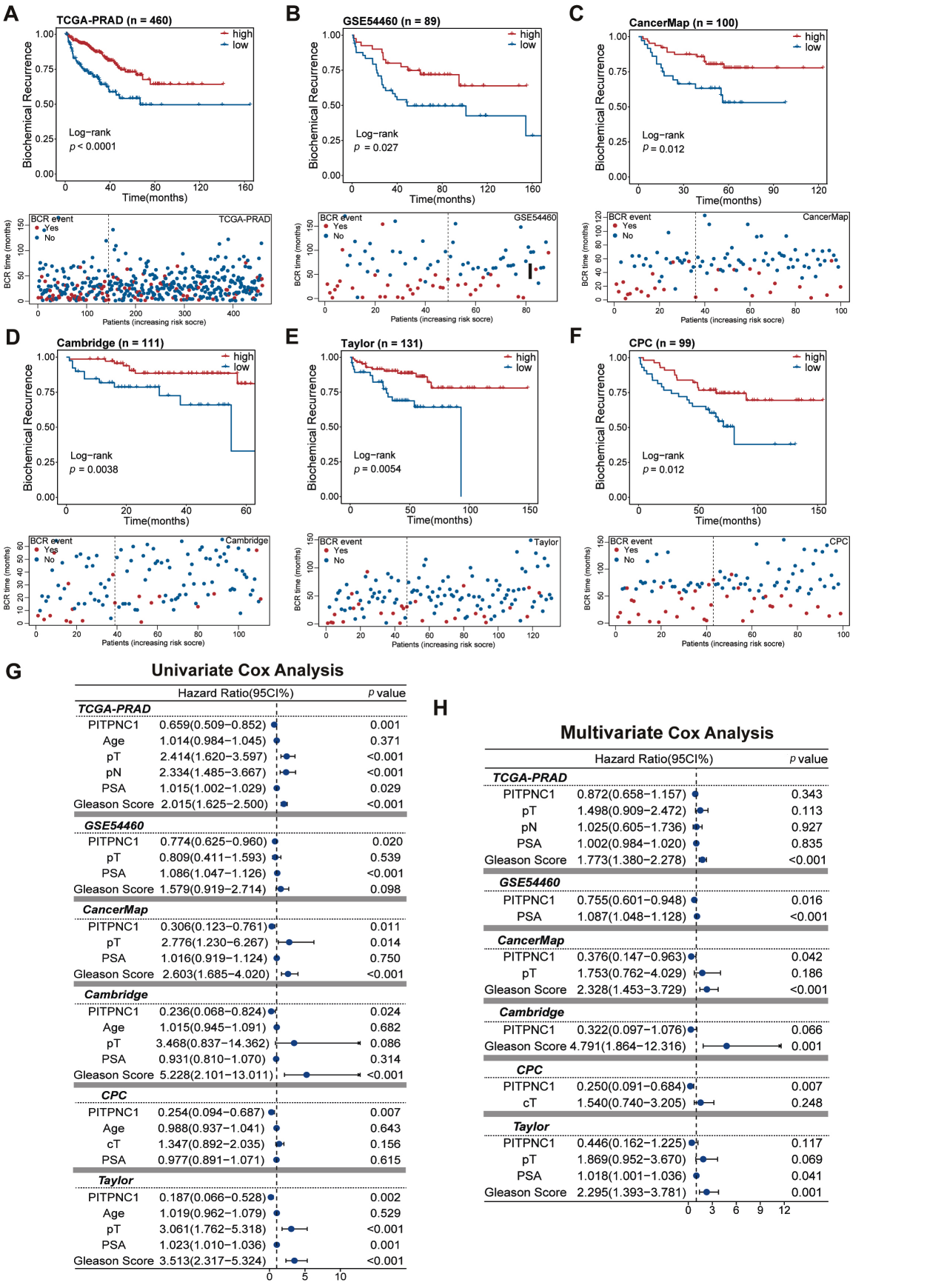

FIGURE 3. PITPNC1 serves as a biomarker for PCa prognosis. (A–F) Kaplan-Meier survival analyses for PITPNC1 across TCGA-ACC and GEO datasets. (G,H) Univariate and 0 multivariate cox regression. TCGA: The Cancer Genome Atlas Program; GSE: gene expression data series.

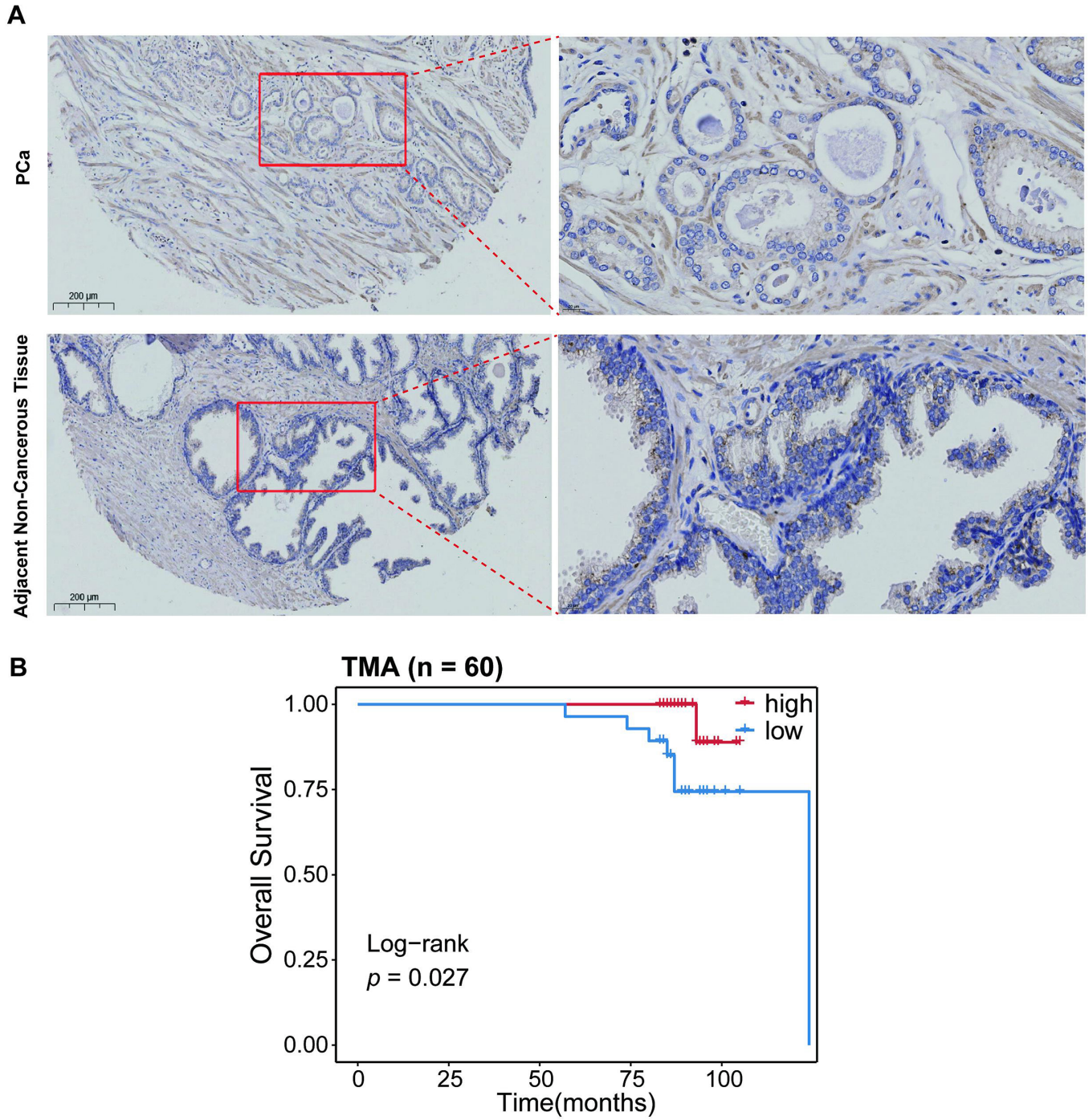

FIGURE 4. IHC validation of PITPNC1 in local cohort. (A) Immunohistochemistry staining of PITPNC1 in PCa and Begin tissue. (B) Survival analysis of PITPNC1 IHC score. PCa: Prostate cancer; TMA: Tissue microarray; IHC: immunohistochemistry.

3.6 Prospects of PITPNC1 in drug therapy

After identifying the prognostic significance of PITPNC1 in PCa, we investigated its potential association with therapy response. Analysis of four cohorts treated with Anti-PD-1/PD-L1 and Cytotoxic T Lymphocyte-Associated Antigen-4 (Anti-CTLA-4) (Fig. 7A–D) consistently shows better outcomes in patients with high PITPNC1 expression. In Cho's non-small cell lung cancer cohort (Fig. 7A), PITPNC1 expression level was found to be associated with treatment response, with an Area Under the Curve (AUC) of 0.87, and significantly higher expression in responders. Analysis of the TCGA-PRAD (Fig. 7E,F) identifies rucaparib and Farnesyltransferase inhibitors as potential PITPNC1-targeting therapies, highlighting avenues for further investigation.

4. Discussion

Primary PCa typically progresses slowly, often with asymptomatic or mildly symptomatic presentations such as prostate hyperplasia. Notably, some patients experience excellent 10-year cancer-specific survival rates exceeding 94% [29–31]. RP

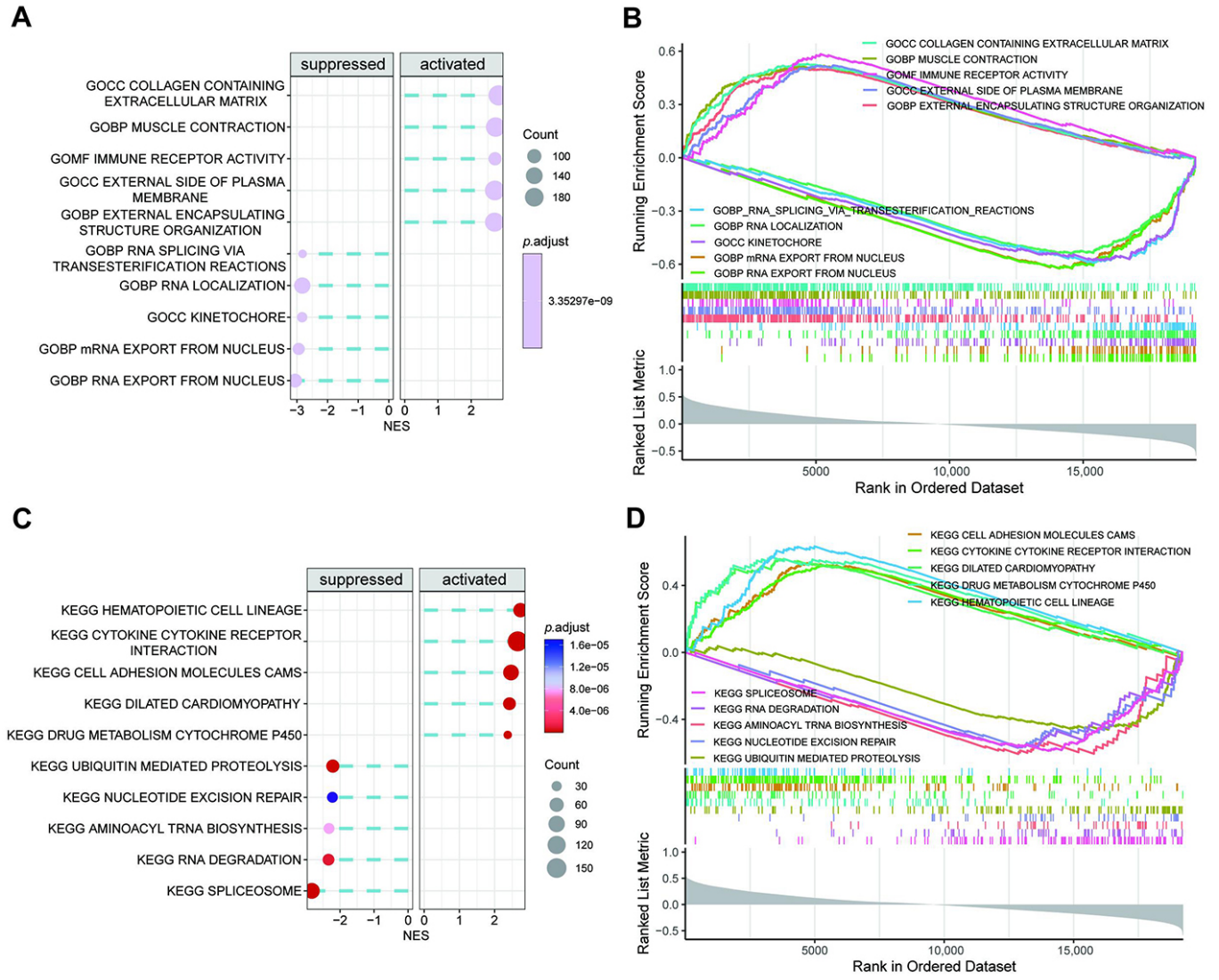

FIGURE 5. Functional enrichment. (A,B) Top 10 activated and suppressed GO terms ranked by NES. (C,D) Top 10 activated and suppressed KEGG pathways ranked by NES. GO: Gene Ontology; KEGG: Kyoto Encyclopedia of Genes and Genomes; NES: Normalized Enrichment Score.

is the standard treatment for primary PCa, but BCR following RP represents a critical phase that may necessitate treatment adjustments. Without additional interventions such as radical radiotherapy or endocrine therapy, approximately 34% of BCR patients may progress to develop distant metastases, leading to clinical recurrence [32]. Current clinical prediction of BCR risk post-RP relies on indicators such as PSA levels, Gleason score and surgical margins. However, studies indicate that even with these combined clinical factors, the accuracy of predicting PCa prognosis remains around 75–85%, potentially resulting in both over- and undertreatment [33–35]. Hence, there is an urgent need for novel prognostic biomarkers to better stratify BCR risk in patients with primary PCa post-RP.

In this present study, we assessed cohorts of PCa from China, the United States, Europe and Canada, and identified PITPNC1 as a promising biomarker associated with better patient prognosis. PITPNC1 belongs to the PITPs family, known for its role in various cellular processes, including lipid metabolism [36]. It functions by binding and transporting phosphatidic acid to facilitate phosphatidic acid metabolism.

PITPNC1 has been implicated in various tumors. For instance, it has been associated with radioresistance and modulation of fatty acid metabolic reprogramming in gastrointestinal tumors [36]. Additionally, direct interaction between PITPNC1 and Fatty Acid Synthase (FASN) regulates fatty acid metabolism, suppresses Cytotoxic T Lymphocytes ($CD8^+$ T cells), and promotes radioresistance in rectal cancer [37]. Furthermore, PITPNC1 has been found to link Kirsten ratsarcoma viral oncogene homolog (KRAS) to myelocytomatosis oncogene (MYC), inhibiting autophagy in lung and pancreatic cancers and thereby promoting tumor progression [14]. However, its role in PCa remains largely unexplored. Previous studies have primarily linked PITPNC1 to lipid metabolism in tumors [36]. Nonetheless, our functional enrichment analysis revealed that PITPNC1 activates pathways related to cell adhesion and immune receptors, while inhibiting pathways associated with RNA metabolism, including RNA localization, export, synthesis and splicing. This suggests that PITPNC1 may play

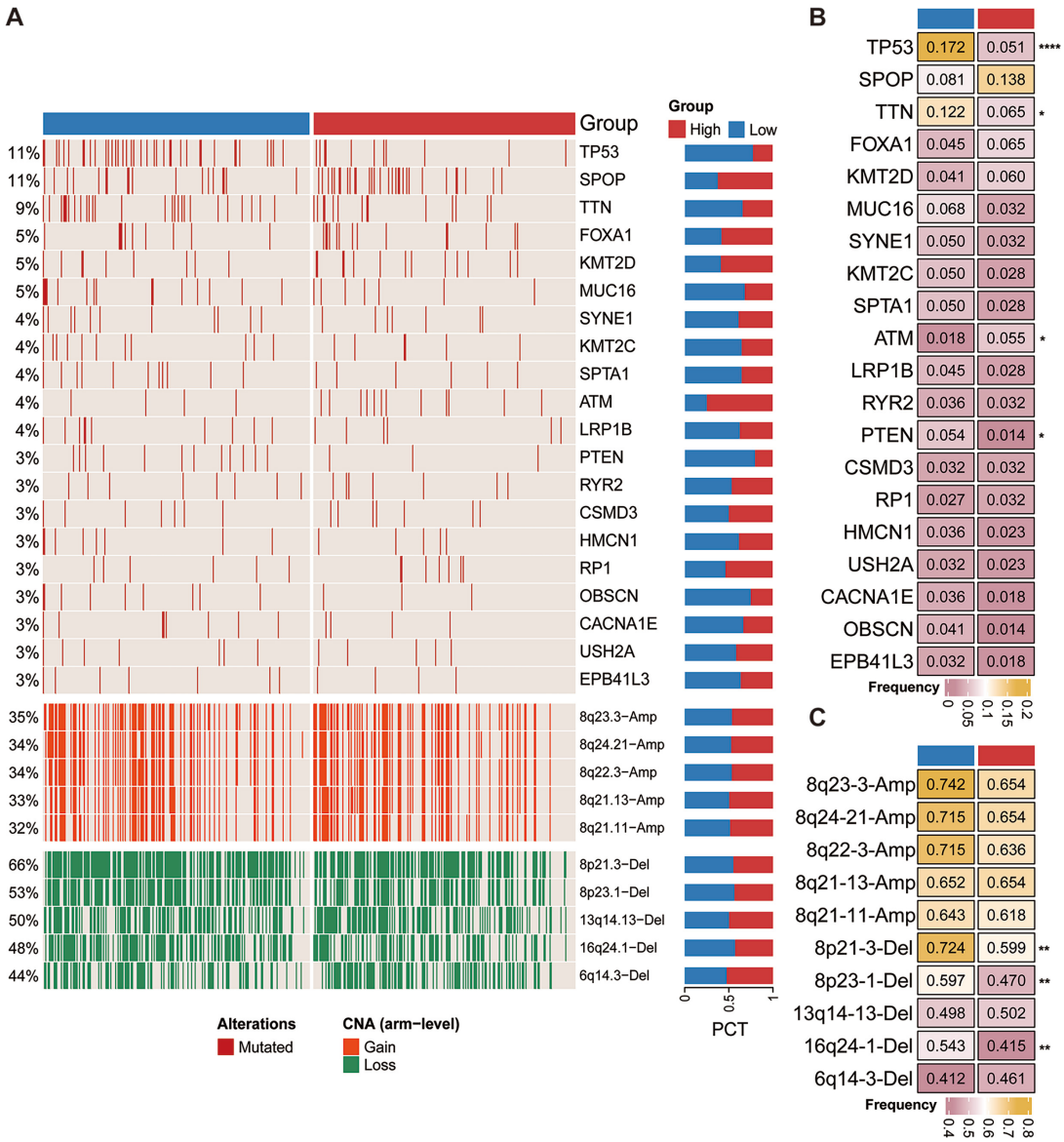

FIGURE 6. Mutation landscape. (A) Integrative landscape illustrating the relationship between PITPNC1 expression with gene mutation and CNA. (B,C) Statistical Analysis of PITPNC1 Expression in Relation to Gene Mutations and CNA Frequencies. *$p < 0.05$; **$p < 0.01$; ****$p < 0.0001$. CAN: Copy Number Alteration.

a distinct role in PCa compared to other tumors. However, further experimental validation is necessary to confirm these findings.

Based on the results shown in Fig. 2, PITPNC1 expression is higher in cancer than in normal tissue for colorectal adenocarcinoma (COAD), stomach adenocarcinoma (STAD), kidney renal clear cell carcinoma (KIRC) and liver hepatocellular carcinoma (LIHC). Conversely, in PRAD, breast cancer (BRCA), kidney chromophobe (KICH) and lung squamous cell carcinoma (LUSC), PITPNC1 expression is higher in normal tissue. We attribute these differences to two possible reasons. First, PITPNC1 may exhibit strong tissue specificity across different cancer types; for example, despite both being renal cancers, KIRC and KICH show markedly different levels of PITPNC1 expression. Additionally, PITPNC1 primarily functions in signal transduction, and the variability in signaling pathway activity among different tumors could account for the observed differences in PITPNC1 expression.

Our mutational analysis revealed a significant finding: higher frequencies of TP53 mutations were observed in the group with low PITPNC1 expression. TP53, a well-established tumor suppressor gene, encodes the p53 protein, which is crucial for maintaining cellular integrity. It orchestrates responses to various stress signals, including metabolic stress, oncogene activation and DNA damage, by regulating processes such as cell cycle arrest, DNA repair, senescence and apoptosis. Through these mechanisms, p53 plays a pivotal role in preserving genomic stability [38]. In PCa, numerous studies have demonstrated that TP53 mutations are associated with more aggressive disease forms [39]. The combined effects of these processes collectively provide a robust defense against malignant transformation. Extensive research has underscored the central role of p53 in maintaining cellular homeostasis and its significant impact on cancer biology. These findings highlight the potential for investigating the interplay between PITPNC1 expression and TP53 mutations

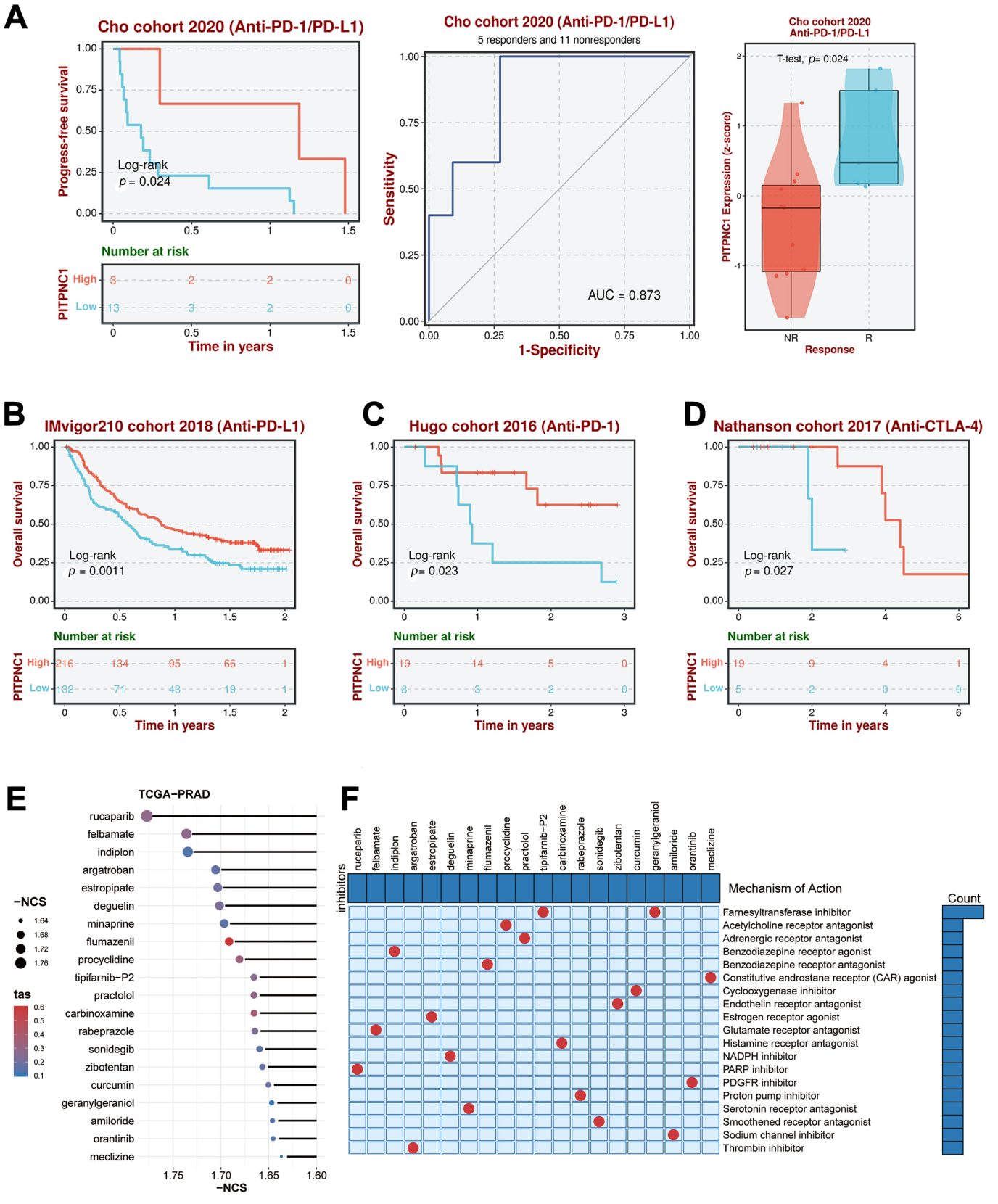

FIGURE 7. PITPNC1 and therapy response. (A–D) Survival analysis Prognosis across PITPNC1 expression within multiple immunotherapy cohorts. (E) Bubble plot representing the CMap analysis. (F) Drug-related signaling pathways derived from CMap analysis. CMap: Connectivity Map.

as a promising avenue for identifying new therapeutic targets in PCa.

The efficacy of immunotherapy has received significant attention in recent years. Despite PCa traditionally being considered a "cold tumor", our functional enrichment analysis revealed its association with several immune pathways. This discovery prompted us to investigate PITPNC1's potential as a biomarker for immunotherapy response. Across four cohorts treated with Anti-PD-1/PD-L1 and anti-CTLA-4 therapies, we consistently found that patients with low PITPNC1 expression had poorer outcomes. However, studies specifically focusing on immunotherapy in PCa are lacking, necessitating further investigation into PITPNC1's role in PCa immunotherapy. Additionally, our drug prediction analysis identified rucaparib as potentially more effective for patients with high PITPNC1 expression. This finding suggests that rucaparib, Food and Drug Administration-approved (FDA-approved) for later-line treatment of PCa, could benefit from targeting appropriate patient subgroups based on PITPNC1 expression levels.

Our main objective in this paper was to preliminarily identify and validate the role of PITPNC1 in PCa through multi-center data mining. Therefore, this study still has some limitations. After validating the clinical significance of PITPNC1 in PCa using an in-house cohort, the *in vivo* and *in vitro* phenotypes of PITPNC1 have not been verified due to time constraints. Although our functional enrichment analysis indicated that PITPNC1 is associated with cell adhesion and immune signaling, we lack mechanistic experimental data to support these findings. We plan to further investigate the role of PITPNC1 in PCa in future studies.

5. Conclusions

Our study identifies PITPNC1 as a novel prognostic marker in primary PCa, with lower expression correlating with earlier BCR and reduced survival rates. The activation of cell adhesion and immune receptor pathways by PITPNC1, along with its interaction with TP53 mutations, highlights its distinct role in PCa progression. Importantly, our findings suggest that low PITPNC1 expression predicts poorer outcomes in immunotherapy, supporting its potential as a biomarker for risk stratification in clinical practice.

AVAILABILITY OF DATA AND MATERIALS

The datasets employed in this study are comprehensively detailed in the Materials and Methods section. For additional information, please contact the corresponding author.

AUTHOR CONTRIBUTIONS

RJM and ZGC—they were instrumental in securing funding and designing the study. JML, YZF, JXL, RXZ and LZ—the collection and analysis of public datasets were meticulously performed. JML and RXZ—immunohistochemistry and cell assays were carried out. JML, YZF and JXL—prepared the initial manuscript draft. CC, RJM and ZGC—The manuscript was revised. All authors made substantial contributions to the article and approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The acquisition of clinical samples was ethically approved by the Ethics Committee of Shanghai Outdo Biotech Company (Approval No. YBM-05-02). All patients signed informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/files/article/1862398951251951616/attachment/Supplementary%20material.xlsx.

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