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High *BIRC7* Expression Might Be an Independent Prognostic Indicator of Poor Recurrence-Free Survival in Patients With Prostate Cancer

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Abstract

Background: *BIRC7*, which encodes Baculoviral inhibitor of apoptosis (IAP) repeat-containing protein 7, is an oncogene in multiple types of cancer. In this study, we examined the association between *BIRC7* expression and the clinicopathological characteristics of prostate cancer, the independent prognostic value of *BIRC7* in terms of recurrence-free survival, and the molecular mechanisms of its dysregulation. **Methods:** Data mining was performed using data from The Cancer Genome Atlas. The patients were divided into high and low *BIRC7* expression groups according to the Youden index determined by receiver operating characteristic curves for recurrence. Subgroup analysis was performed according to T stages and Gleason score. **Results:** *BIRC7* was significantly upregulated in prostate cancer tissues (N = 497) than in normal prostate tissues (N = 52). High *BIRC7* expression group had lower ratios of overall response rate and medium-grade (Gleason score 6-7) tumors and higher proportions of nodal invasion and recurrence after surgery. Although Kaplan-Meier curves showed that high *BIRC7* expression was generally associated with poor recurrence-free survival, the following subgroup analysis only confirmed the association in T3/T4 and medium-grade tumors. Multivariate analysis showed that *BIRC7* expression was not an independent indicator of recurrence-free survival in T2 or high-grade tumors, but was independently associated with poor recurrence-free survival in T3/T4 tumors (hazard ratio: 4.249, 95% confidence interval: 1.563-11.546, $P = .005$) and in medium-grade tumors (hazard ratio: 6.041, 95% confidence interval: 1.763-20.703, $P = .004$). DNA amplification was associated with significantly upregulated *BIRC7* expression. There was also a weak negative correlation between *BIRC7* expression and its DNA methylation (Pearson $r = -0.23$). **Conclusion:** Based on these findings, we infer that *BIRC7* upregulation might serve as a valuable biomarker of increased recurrence risk in advanced T stages and medium-grade prostate cancer. Its expression is at least regulated by both copy number alteration and DNA methylation.

Keywords

BIRC7, prognosis, recurrence-free survival, prostate cancer

Abbreviations

BCR, biochemical recurrence; BIR, Baculoviral IAP repeat; CI, confidence interval; HR, hazard ratio; NF, nuclear factor; OS, overall survival; PSA, prostate-specific antigen; RFS, recurrence-free survival; SEM, standard error of the mean; TCGA, The Cancer Genome Atlas.

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Introduction

Baculoviral inhibitor of apoptosis (IAP) repeat (BIR)-containing protein 7, which is also called Livin, is a protein encoded by the *BIRC7* gene in human.[1] *BIRC7* encodes 2 splicing variants of Livin, termed Livin-α and Livin-β. Both proteins have a single copy of BIR and a Really Interesting New Gene (RING) -type zinc finger domain.[2] The BIR domain has a well-characterized role in interacting with caspases and inhibiting apoptosis, while

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the RING-type zinc finger domain has a putative E3 ubiquitin ligase activity and may enhance its antiapoptotic activity.[1,3]

A series of previous studies showed that aberrant *BIRC7* expression is associated with tumorigenesis, development, and progression in a variety of human malignancies, such as melanoma,[4] non-small cell lung cancer,[5] malignant pleural mesothelioma,[6] gallbladder cancer,[7] breast cancer,[8] and prostate cancer.[9] In prostate cancer, upregulated Livin-α can promote cell proliferation by enhancing G1-S cell cycle transition[9] and enhance prostate cancer cell invasion via nuclear factor κB (NF-κB) signaling, and the downstream Fibronectin (FN) and C-X-C chemokine receptor type 4 (CXCR4) pathway.[10,11] Knockdown of endogenous Livin could significantly inhibit prostate cancer cell proliferation and enhance apoptosis.[12] Another recent study based on 43 paraffin-embedded prostate cancer tissues found that Livin expression was positively correlated to the pathological grading of prostate cancer.[13] These findings suggest that *BIRC7* also acts as an oncogene that modulates cancer cell proliferation and invasion and might be related to differentiation of prostate cancer.

Currently, radical prostatectomy remains a first-line therapeutic option for most patients with localized prostate cancer.[14] Biochemical recurrence (BCR), which is defined as detectable prostate-specific antigen (PSA) level after radical prostatectomy, or an increasing PSA level following radiation therapy, may signify local or metastatic recurrence.[15] Around 20% to 40% of the patients suffer BCR by 10 years after surgery.[16] In fact, the median overall survival (OS) of the patients after radical prostatectomy is usually over 15 years.[17] In comparison, the median OS was 14.7 years for men who had 1 BCR after surgery and further dropped to 13.6 years in patients who had 2 BCRs.[14] However, patients with BCR may have different clinical courses: some may suffer rapid disease progression and increased risk of prostate cancer-specific mortality, but some may have indolent course, which had little adverse influence on their survival.[18] Therefore, besides the use of PSA as an indicator, it is meaningful to explore other biomarkers for early prediction of recurrence.

In this study, we examined the association between *BIRC7* expression and the clinicopathological characteristics and the independent prognostic value of *BIRC7* in terms of recurrence-free survival (RFS).

Materials and Methods

Data Mining in The Cancer Genome Atlas

Data mining was performed in The Cancer Genome Atlas-prostate cancer (TCGA-PRAD), in which biopsy specimen of 497 prostate cancer tissues and 52 normal prostate tissues have *BIRC7* expression measured by RNAseq (IlluminaHiSeq). *BIRC7* expression data (log2 [normalized count+1]), gene-level thresholded GISTIC2-processed copy-number alteration (−2: homozygous deletion; −1: heterozygous loss, 0: copy-neutral; +1: low-level copy gain; +2: high-level amplification), DNA methylation (measured by Infinium Human Methylation 450K BeadChip) and relevant clinical data were downloaded by using the UCSC Xena browser (https://xenabrowser.net/).

Kaplan-Meier Curves of RFS

Kaplan-Meier curves of RFS after primary therapy were generated by GraphPad Prism v6.0. Receiver operating characteristic curves for recurrence was constructed and the optimal cutoff values of *BIRC7* expression were determined based on Youden index. Subgroup analysis was performed according to T stages and tumor grade.

Statistical Analysis

Statistical analysis was performed using SPSS 19.0 and GraphPad Prism v6.0. Continuous variables were reported as means ± standard error of the mean. The group difference was compared by 2-tailed Student *t* test or analysis of vairance with Student-Newman-Keuls test as a post hoc test. The association between *BIRC7* expression and the clinicopathological parameters was assessed by using χ^2 tests. The difference between the RFS curves was compared using the log-rank test. Univariate and multivariate Cox regression models were used to evaluate the independent prognostic values of *BIRC7* expression in terms of RFS. Pearson goodness of fit test was performed to assess the correlation between *BIRC7* expression and its DNA methylation. $P < .05$ was considered statistically significant.

Results

BIRC7 Expression Is Upregulated in Prostate Cancer and Is Associated With Malignant Tumor Behaviors

By using RNA-seq data in TCGA-PRAD, we found 497 prostate cancer tissues had *BIRC7* RNA expression measured. *BIRC7* expression was significantly higher in prostate cancer tissues than in normal prostate tissues (N = 52; Figure 1A) and showed a trend of increase in advanced T stages (Figure 1B). In addition, we also observed substantially higher *BIRC7* expression in nodal positive (N1) cases than in nodal negative (N0) cases (Figure 1C) and in high-grade tumors (Gleason score 8-10) than in medium-grade tumors (Gleason score 6-7; Figure 1D). Then, we compared the clinicopathological parameters in the patients with RFS data recorded (N = 436). The patients were divided into high and low *BIRC7* expression groups according to the optimal cutoff value (Table 1). Results showed that the high *BIRC7* expression group had older ages (61.58 ± 0.42 vs 59.96 ± 0.54, $P = .018$), a higher proportion of nodal positive cases (47/235, 20.0% vs 15/135, 11.1%, $P = .028$), lower proportions of overall response rate (215/249, 86.3% vs 140/150, 93.3%, $P = .031$), R0 cases (163/254, 64.2% vs 118/155, 76.1%, $P = .011$) and medium-grade (Gleason score 6-7) tumors (144/273, 52.7% vs 118/163, 72.4%, $P < .0001$), and a higher risk of recurrence (44/273, 16.1% vs 8/163, 4.9%, $P = .0005$; Table 1). *PTEN* deletion has been considered as an important marker of RFS in prostate cancer.[19,20] In TCGA-

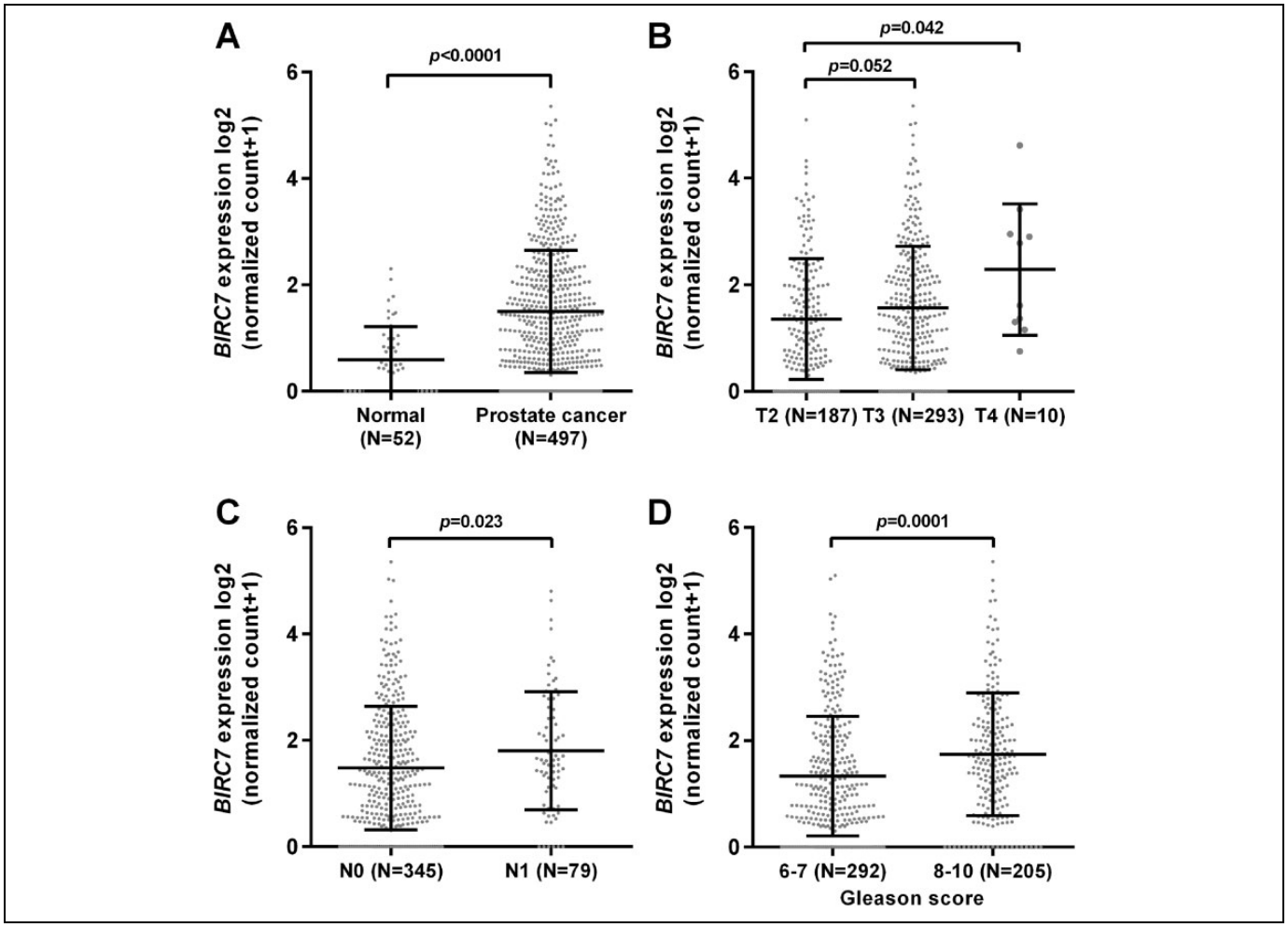

Figure 1. BIRC7 expression is upregulated in prostate cancer and is associated with malignant tumor behaviors. Comparison of *BIRC7* expression between prostate cancer tissues (N = 497) and normal prostate tissues (N = 52) (A), among T2/T3/T4 stage tumors (B), between nodal positive (N = 79) and negative (N = 345) tumors (C), and between high-grade (Gleason score 8-10; (N = 205) and medium-grade tumors (Gleason score 6-7; (N = 292).

PRAD, we also observed a high frequency of *PTEN* deletion (heterozygous loss and homozygous deletion/all tumor cases with copy number alteration data: 159/491) and associated decreased *PTEN* expression (Supplemental Figure 1A and B). However, no difference in *BIRC7* expression was observed in these groups (Supplemental Figure 1C). In addition, between the high and low *BIRC7* expression groups, we did not find any significant difference in *PTEN* copy number alterations (Table 1). These results suggest that *BIRC7* expression is irrelevant to *PTEN* in prostate cancer.

BIRC7 *Upregulation Is Associated With Poor RFS in Prostate Cancer*

By generating Kaplan-Meier curves of RFS, we found that high *BIRC7* expression was associated with unfavorable RFS in prostate cancer ($P = .0003$; Figure 2). To verify the robustness of the association, we performed subgroup analysis according to T stages and tumor grades. By using the Youden Index as the cutoff (>1.285 vs $\leq$ 1.285), we found that *BIRC7* expression was not related to RFS in patients with T2 tumors ($P = .080$; Figure 3A). However, high *BIRC7* expression (> 0.92, N = 166) was significantly associated with poor RFS in T3/T4 tumors ($P = .0007$; Figure 3B). To explore the independent prognostic value of *BIRC7* in these subgroups, we then conducted univariate and multivariate analysis with Cox regression model. Results showed that *BIRC7* expression was not an independent indicator of RFS in T2 tumors, but was independently associated with poor RFS in T3/T4 tumors (hazard ratio [HR]: 4.249, 95% confidence interval [CI]: 1.563-11.546, $P = .005$; Table 2).

In subgroup analysis according to the Gleason score, we found that high *BIRC7* expression (>2.00, N = 67) was significantly associated with poor RFS in medium-grade tumors (Gleason score 6-7; $P = .0003$; Figure 4A), but not in high-grade tumors (> 0.90, N = 129; Gleason score 8-10; $P = .10$; Figure 4B). Univariate and multivariate analysis showed that *BIRC7* expression was independently associated with

Table 1. The Association Between *BIRC7* Expression and the Clinical Parameters in Patients With Prostate Cancer.

Parameters		*BIRC7* Expression		χ^2	*P* Value
		High (N = 273)	Low (N = 163)		
Age (Mean ± SEM)		61.58 ± 0.42	59.96 ± 0.54		.018
PSA value (Mean ± SEM)		1.945 ± 1.354	0.685 ± 0.319		.37
T stages	T2	102	73	2.21	.14
	T3/T4	166	88		
	Null	5	2		
N stages	N0	188	120	4.86	.028
	N1	47	15		
	Null	38	28		
Primary therapy outcome	CR+PR	215	140	4.66	.031
	SD+PD	34	10		
	Discrepancy + null	24	13		
Radiation therapy	No	222	141	3.36	.067
	Yes	40	14		
	Discrepancy + null	11	8		
Residual tumor	R0	163	118	6.40	.011
	R1+R2	91	37		
	RX + null	19	8		
Gleason score	6/7	144	118	16.43	<.001
	8/9/10	129	45		
PTEN CNAs	Amplification	4	0	2.42	.30
	Copy neutral	179	109		
	Deletion	87	53		
	Null	3	1		
Recurrence	No	229	155	12.21	<.001
	Yes	44	8		

Abbreviations: CNAs, copy number alterations; CR, complete remission; PD, progressive disease; PR, partial remission; PSA, prostate-specific antigen; R0, No residual tumor; R1, Microscopic residual tumor; R2, Macroscopic residual tumor; RX, the presence of residual tumor cannot be assessed; SD, stable disease; SEM, standard error of the mean; null, no data.

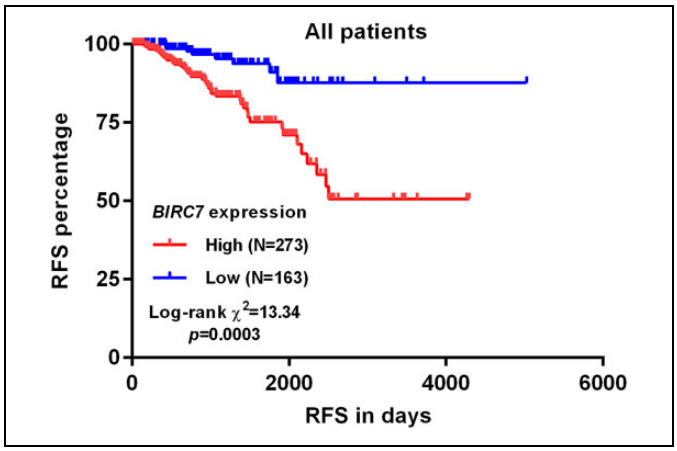

Figure 2. Kaplan-Meier curves of RFS in prostate cancer. RFS indicates recurrence-free survival.

unfavorable RFS in medium-grade tumors (HR: 6.041, 95% CI: 1.763-20.703, $P = .004$), but not in high-grade tumors (Table 3).

BIRC7 *Dysregulation Is Related to Both Copy Number Alteration and Methylation*

To explore the mechanisms of *BIRC7* dysregulation in prostate cancer, we examined the correlation between its RNA expression and DNA copy number alteration/methylation by using deep-sequencing data in TCGA-PRAD (Figure 5A). *BIRC7* copy number alteration was quantified in 492 out of 498 patients with primary prostate cancer. Forty patients (8.13%) had DNA amplification (+1/+2; Figure 5A), which was associated with significantly upregulated *BIRC7* expression ($P = .0033$; Figure 5B). The results of regression analysis showed a weak negative correlation between *BIRC7* expression and its DNA methylation (Pearson $r = -0.23$; Figure 5C). These findings suggest that the expression of *BIRC7* in prostate cancer is at least regulated by both copy number alteration and DNA methylation.

Discussion

In this study, we observed that *BIRC7* expression was significantly upregulated in prostate cancer tissues than in normal prostate tissues. In addition, by comparing the clinical parameters between high and low *BIRC7* expression groups, we observed that the high *BIRC7* expression group had lower ratios of overall response rate and medium-grade (Gleason score 6-7) tumors and higher proportions of nodal invasion and recurrence after surgery. Previous studies showed that Livin acts as a caspase inhibitor, which blocks caspase activation and further inhibits apoptosis.[21] In prostate cancer, upregulated

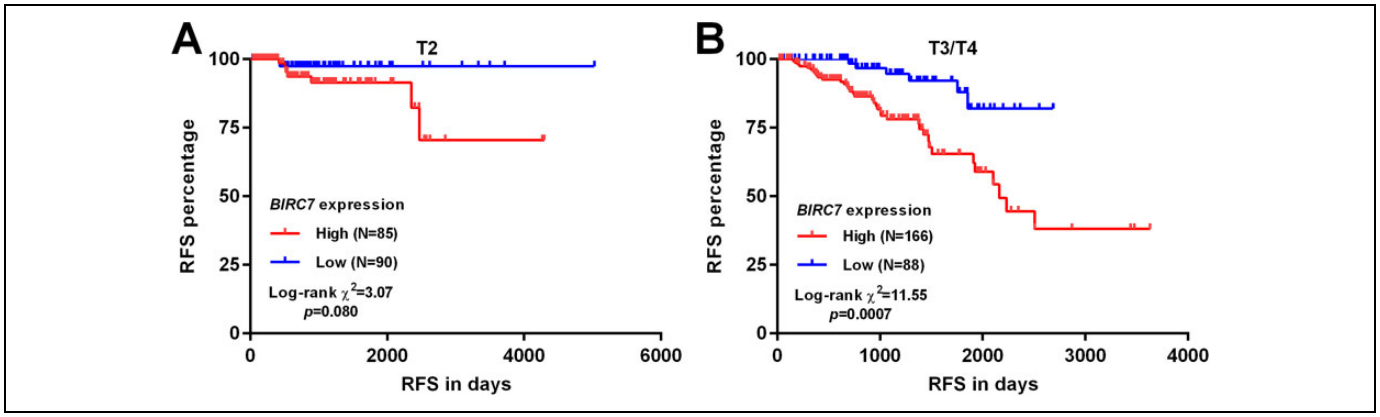

Figure 3. Kaplan-Meier curves of RFS in T2 (A) and T3/T4 (B) tumors. RFS indicates recurrence-free survival.

Table 2. Univariate and Multivariate Analysis of RFS in T2 and in T3/T4 Tumors.

	Univariate Model				Multivariate Model			
			95% CI				95% CI	
Parameters	*P*	HR	(Lower/Upper)		*P*	HR	(Lower/Upper)	
T2								
Age (continuous)	.386	1.041	0.951	1.140				
N status: N0 vs N1	.109	0.170	0.020	1.482				
Primary therapy outcome: SD/PD vs CR/PR	.006	10.114	1.949	52.486				
PSA value (continuous)	.134	1.230	0.938	1.613				
Radiation therapy: No vs Yes								
Residual tumor: R1+R2 vs R0	.410	1.938	0.401	9.370				
Gleason score:8/9/10 vs 6/7	.039	4.002	1.070	14.975				
BIRC7 expression: High vs low	.102	3.716	0.770	17.935				
T3/T4								
Age (continuous)	.568	0.986	0.940	1.034				
N status: N0 vs N1	.820	0.923	0.461	1.845				
Primary therapy outcome: SD/PD vs CR/PR	.011	2.276	1.203	4.308	.358	1.394	0.686	2.832
PSA value (continuous)	.027	1.043	1.005	1.082	.014	1.057	1.011	1.105
Radiation therapy: No vs Yes	.339	0.695	0.330	1.464				
Residual tumor: R1+R2 vs R0	.012	2.214	1.187	4.129	.136	1.692	0.848	3.376
Gleason score: 8/9/10 vs 6/7	<.001	4.505	2.004	10.128	.027	2.634	1.118	6.205
BIRC7 expression: High vs Low	.002	3.999	1.685	9.490	.005	4.249	1.563	11.546

Abbreviations: CI, confidence interval; CR, complete remission; HR, hazard ratio; PD, progressive disease; PR, partial remission; PSA, prostate-specific antigen; RFS, recurrence-free survival.

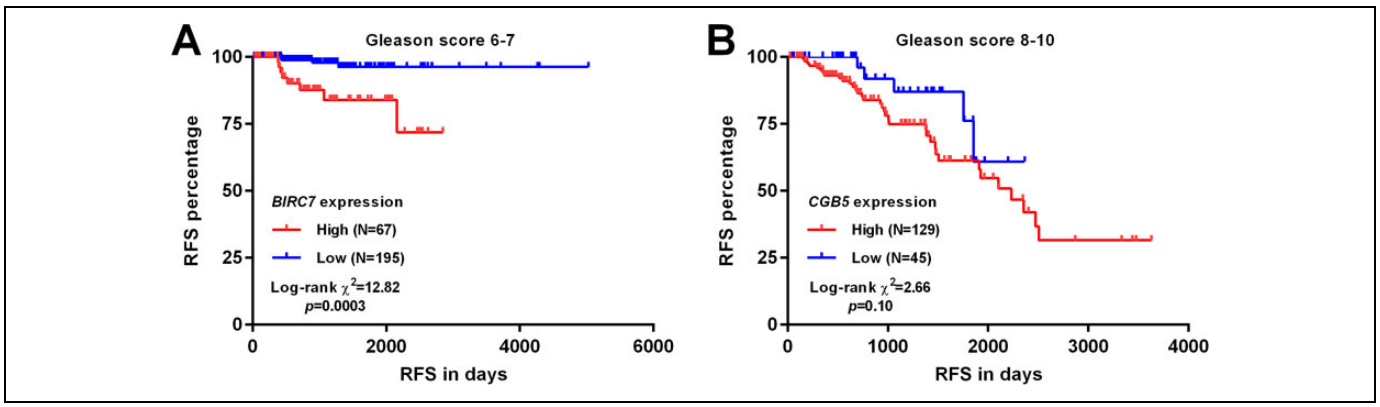

Figure 4. Kaplan-Meier curves of RFS in medium-grade (A) and high-grade (B) tumors. RFS indicates recurrence-free survival.

Table 3. Univariate and Multivariate Analysis of RFS in Medium-Grade and High-Grade Tumors.

	Univariate Model				Multivariate Model			
			95% CI					
Parameters	*P*	HR	(Lower/Upper)		*P*	HR	95% CI (Lower/Upper)	
Gleason score 6/7								
Age (continuous)	.277	1.048	0.963	1.140				
T stages: T3/T4 vs T2	.366	1.701	0.538	5.380				
N status: N0 vs N1	.388	0.403	0.051	3.180				
Primary therapy outcome: D/PD vs CR/PR	.015	6.682	1.447	30.863	.110	3.595	0.749	17.264
PSA value (continuous)	.983	1.006	0.582	1.740				
Radiation therapy: No vs Yes	.390	0.404	0.051	3.181				
Residual tumor: R1+R2 vs R0	.273	1.959	0.589	6.522				
BIRC7 expression: High vs Low	.002	6.716	2.015	22.381	.004	6.041	1.763	20.703
Gleason score 8/9/10								
Age (continuous)	.399	0.980	0.936	1.027				
T stages: T3/T4 vs T2	.184	2.020	0.715	5.707				
N status: N0 vs N1	.508	1.271	0.626	2.581				
Primary therapy outcome: SD/PD vs CR/PR	.211	1.518	0.789	2.920				
PSA value (continuous)	.085	1.034	0.995	1.073				
Radiation therapy: No vs Yes	.855	0.934	0.452	1.932				
Residual tumor: R1+R2 vs R0	.025	2.123	1.099	4.099				
BIRC7 expression: High vs Low	.111	2.154	0.838	5.538				

Abbreviations: CI, confidence interval; CR, complete remission; HR, hazard ratio; PD, progressive disease; PSA, prostate-specific antigen; RFS, recurrence-free survival; SD, stable disease.

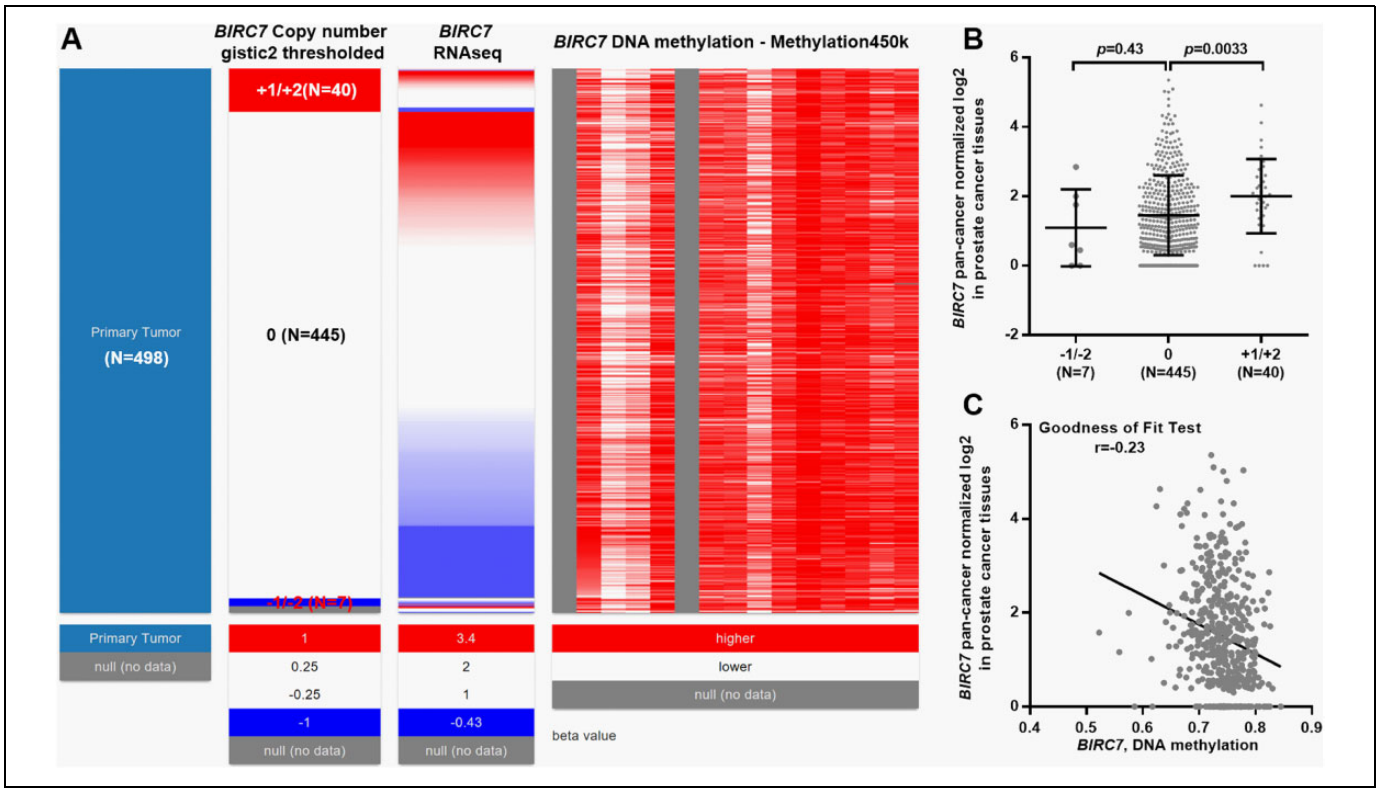

Figure 5. The association between *BIRC7* expression and its DNA copy number alteration/methylation. A, Heat map showing the correlation between *BIRC7* expression and its DNA copy number alteration/methylation; −2: homozygous deletion; −1: heterozygous Loss, 0: copy-neutral; +1: low-level copy gain; +2: high-level amplification. B, Comparison of *BIRC7* expression in groups with different *BIRC7* copy number alteration. C, Regression analysis of the correlation between *BIRC7* expression and its DNA methylation.

Livin-α can facilitate S phase entry in prostate cancer cells and subsequently enhance their proliferation and survival.[9] It can also enhance prostate cancer cell invasion via NF-κB signaling, and the downstream FN and CXCR4 pathway.[10,11] These mechanisms help to explain the oncogenic properties of *BIRC7* in prostate cancer.

As an oncogene, the independent prognostic value of *BIRC7* was also observed in several cancers. In patients with rectal cancer, Livin expression was associated with unfavorable OS independent of TNM stage, local and distant recurrence, grade of differentiation, gender, and age.[22] In squamous cell/adenosquamous carcinomas and adenocarcinoma of gallbladder, *BIRC7* expression was an independent poor prognostic factor in terms of postoperative survival.[7] Although the oncogenic effects of *BIRC7* have been reported in prostate cancer, its prognostic value has not been explored. In fact, current prognostic tools such as clinicopathological parameters lack sufficient accuracy to effectively predict recurrence in prostate cancer.[23] For example, PSA is one of the most important screening tools for prostate cancer. But its prognostic value is debated controversially due to limited specificity and imprecise prediction of tumor aggressiveness.[24] Therefore, it is necessary to explore other potential prognostic biomarkers for both early predictions and proactive use of adjuvant therapeutic options before frank recurrence. In this study, we further assessed the independent prognostic value of *BIRC7* in terms of RFS. Although Kaplan-Meier curves of RFS showed that high *BIRC7* expression was generally associated with poor RFS, the following subgroup analysis only confirmed the association in T3/T4 and in medium-grade tumors. Multivariate analysis showed that *BIRC7* expression was not an independent indicator of RFS in T2 or in high-grade tumors, even under the best cutoff model. In comparison, high *BIRC7* expression was independently associated with poor RFS in T3/T4 tumors (HR: 4.249, 95% CI: 1.563-11.546, $P = .005$) and in medium-grade tumors (HR: 6.041, 95% CI: 1.763-20.703, $P = .004$). These findings suggest that *BIRC7* expression might serve as a valuable biomarker of recurrence risk in advanced T stages and medium-grade prostate cancer. However, due to insufficiency data of OS in TCGA-PRAD, we failed to evaluate the prognostic value of *BIRC7* in terms of OS.

Previous studies suggest that Livin is a potential therapeutic target in some cancers.[2] Some therapeutic strategies for its inhibition, such as antisense oligonucleotides, small-molecule inhibitors, and immune-mediated approaches have been tested in *in vitro* cell models and *in vivo* animal models and showed certain therapeutic values.[2,25] In this study, we found that high *BIRC7* expression was associated with poor therapeutic responses in prostate cancer. In addition, some previous studies found that Livin inhibition could also significantly inhibit prostate cancer cell proliferation and enhance apoptosis.[9,12] Therefore, it is meaningful to further explore the potential of Livin inhibition as a therapeutic option in prostate cancer in the future. Although we found that the expression of *BIRC7* in prostate cancer is at least regulated by both copy number alteration and DNA methylation, we could not exclude other genetic or epigenetic mechanisms influencing its transcription and translations. Thus, it is also necessary to investigate other potential mechanisms underlying its dysregulation in prostate cancer.

Conclusion

BIRC7 upregulation might serve as a valuable biomarker of increased recurrence risk in advanced T stages and medium-grade prostate cancer, which is at least regulated by both copy number alteration and DNA methylation.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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