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Original Article

PBRM1 Expression Has Subtype-Specific Prognostic Value in Renal Cell Carcinoma

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Abstract : Renal cell carcinoma (RCC) is a heterogeneous malignancy comprising distinct histological subtypes, including clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC), which differ in their molecular and clinical characteristics. Polybromo-1 (PBRM1), a key component of the SWI/SNF chromatin remodeling complex, is frequently altered in RCC. However, the prognostic significance of its transcriptomic expression remains incompletely understood. In this study, transcriptomic and clinical data were obtained from The Cancer Genome Atlas (TCGA), and patients were stratified into high and low PBRM1 expression groups based on median mRNA expression levels. The association between PBRM1 expression and clinicopathological characteristics was analyzed using the chi-square test, and overall survival was evaluated using the Kaplan-Meier method with the log-rank test. PBRM1 expression was not associated with clinicopathological parameters in either ccRCC or pRCC. However, high PBRM1 expression was significantly associated with improved overall survival in ccRCC (HR = 0.72, CI = 0.54~0.97, P = 0.03), whereas no significant survival difference was observed in pRCC (HR = 0.96, CI = 0.53~1.75, P = 0.8). These findings suggest that the prognostic relevance of PBRM1 expression may differ according to RCC subtype, with a favorable association observed in ccRCC but not in pRCC. Our results highlight the importance of considering tumor heterogeneity in biomarker evaluation and support the potential value of PBRM1 expression as a prognostic indicator in ccRCC.

Keywords : PBRM1, Clear cell renal cell carcinoma, Papillary renal cell carcinoma, TCGA

INTRODUCTION

Renal cell carcinoma (RCC) represents the most common type of kidney cancer and is a major cause of cancer-related mortality worldwide [1,2]. Among the various histological subtypes of RCC, clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC) are the two most prevalent forms, exhibiting distinct genetic alterations, clinical behaviors, and therapeutic responses [3,4]. ccRCC is characterized by frequent inactivation of the VHL tumor suppressor gene, leading to aberrant activation of the hypoxia-inducible factor (HIF) pathway, whereas pRCC is a more heterogeneous entity commonly associated with MET proto-oncogene alterations [5,6]. Despite advances in surgical and targeted therapies, the prognosis for advanced RCC remains unfavorable, highlighting the need to identify subtype-specific biomarkers to improve clinical management.

Polybromo-1 (PBRM1) is a tumor suppressor gene loca-

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ted on chromosome 3p21 that encodes a subunit of the SWI/SNF chromatin remodeling complex, specifically the PBAF subtype, and plays a crucial role in regulating gene transcription, DNA repair, and cellular differentiation [7-9]. PBRM1 mutations are among the most frequent genetic alterations in ccRCC, occurring in approximately 40% of cases, and have been implicated in tumor development and progression [10,11]. Previous studies have suggested that PBRM1 status may influence tumor behavior and response to therapy, particularly in the context of immunotherapy [12]. However, the biological and clinical implications of PBRM1 mRNA expression may not necessarily parallel those of genomic alterations, and its prognostic significance at the transcriptomic level remains incompletely understood.

However, the prognostic significance of PBRM1 expression at the transcriptomic level remains controversial and may vary depending on RCC histological subtype [13]. Although several studies have investigated the role of PBRM1 in RCC, most have focused predominantly on ccRCC or have treated RCC as a single disease entity, leaving the prognostic relevance of PBRM1 in other subtypes such as pRCC largely unexplored [13-15]. Given the substantial molecular and clinical disparities between ccRCC and pRCC, a comparative analysis of PBRM1 expression across these subtypes is warranted to better understand its clinical relevance.

In this study, we aimed to evaluate the clinicopathological and prognostic significance of PBRM1 expression in ccRCC and pRCC using transcriptomic and clinical data from The Cancer Genome Atlas (TCGA). Specifically, we compared the association between PBRM1 expression levels and various clinicopathological parameters, as well as overall survival, to explore whether PBRM1 expression demonstrates subtype-specific prognostic relevance in RCC.

MATERIALS AND METHODS

1. Data acquisition and patient stratification

Transcriptomic and clinical data for RCC were obtained from The Cancer Genome Atlas (TCGA) data portal (http://cancergenome.nih.gov/). Gene expression data were downloaded from TCGA-KIRC and TCGA-KIRP cohorts as HTSeq-FPKM values and log2 transformed prior to analysis. Within each histological subtype, patients were categorized into high- and low-expression groups based on the median PBRM1 expression value. The median expression value was selected as the cutoff because it is a widely used and unbiased approach for dichotomizing gene expression data in TCGA-based exploratory studies while maintaining balanced group sizes and minimizing overfitting. Clinical variables with unavailable or missing information were treated as missing data and were excluded only from analyses involving the corresponding variable. Consequently, the number of evaluable cases varied slightly among clinicopathological parameters. All data used in this study were publicly available and complied with TCGA data usage and publication guidelines.

2. Statistical analysis and survival evaluation

All statistical procedures were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The primary endpoint was overall survival, defined as the duration from the date of diagnosis to the date of death or last follow-up. Survival probabilities were estimated using the Kaplan-Meier method, and differences between the curves were assessed using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to estimate the prognostic impact of PBRM1 expression. The association between PBRM1 expression and clinicopathological characteristics was evaluated separately in ccRCC and pRCC. Variables analyzed included age, sex, AJCC stage, T stage, N stage, and M stage. Comparisons between high- and low-expression groups were performed using the chi-square (χ^2) test. In all analyses, a P-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

1. Correlation between PBRM1 expression and clinicopathological features

To evaluate the clinical significance of PBRM1 in RCC, we investigated its association with various clinicopathological characteristics in both ccRCC and pRCC data from TCGA. Patients were classified into high- and low-expression groups according to the median PBRM1 mRNA expression level. This approach has been widely used in exploratory TCGA-based biomarker studies and provides balanced group sizes for survival analysis.

In ccRCC (Table 1), PBRM1 expression levels did not show a statistically significant correlation with most clin-

Table 1. Clinical characteristics of PBRM1 expression in clear cell renal cell carcinoma

	PBRM1 expression		P-value
	High (%, N)	Low (%, N)	
Age			0.152
≤65 years	28.9 (144)	34.9 (174)	
>65 years	14.0 (70)	22.2 (111)	
Sex			0.314
Male	28.7 (143)	35.7 (178)	
Female	14.2 (71)	21.4 (107)	
Stage (AJCC)			0.752
Stage I	21.2 (106)	27.3 (136)	
Stage II	4.8 (24)	5.4 (27)	
Stage III	9.6 (48)	15.0 (75)	
Stage IV	7.2 (36)	9.4 (47)	
M stage			0.761
M0	32.9 (164)	45.9 (229)	
M1	6.8 (34)	8.8 (44)	
N stage			0.252
N0	17.2 (86)	27.7 (138)	
N1	1.6 (8)	1.4 (7)	
T stage			0.081
T1	22.0 (110)	27.4 (137)	
T2	5.6 (28)	7.0 (35)	
T3	13.8 (69)	21.8 (109)	
T4	1.4 (7)	0.8 (4)	

Numbers may not total the cohort size because of missing or unavailable clinicopathological data in the TCGA database.

Table 2. Clinical characteristics of PBRM1 expression in papillary renal cell carcinoma

	PBRM1 expression		P-value
	High (%, N)	Low (%, N)	
Age			0.249
≤65 years	31.8 (88)	30.0 (83)	
>65 years	17.0 (47)	21.3 (59)	
Sex			0.226
Male	34.7 (96)	39.7 (110)	
Female	14.1 (39)	11.6 (32)	
Stage (AJCC)			0.401
Stage I	28.5 (79)	31.4 (87)	
Stage II	3.2 (9)	4.3 (12)	
Stage III	7.9 (22)	9.4 (26)	
Stage IV	2.5 (7)	2.9 (8)	
M stage			0.942
M0	13.7 (38)	18.1 (50)	
M1	1.4 (4)	1.8 (5)	
N stage			0.100
N0	7.9 (22)	9.0 (25)	
N1	2.2 (6)	6.1 (17)	
N2	1.1 (3)	0.4 (1)	
T stage			0.490
T1	32.1 (89)	35.0 (97)	
T2	6.2 (17)	5.0 (14)	
T3	11.1 (31)	9.8 (27)	
T4	0.0 (0)	0.7 (2)	

Numbers may not total the cohort size because of missing or unavailable clinicopathological data in the TCGA database.

ical parameters, including age (P=0.152), biological sex (P=0.314), and AJCC pathological stage (P=0.752). While a marginal trend was observed regarding the T stage (P=0.081), it did not reach the conventional threshold for statistical significance. Similarly, other indicators such as M stage (P=0.761) and N stage (P=0.252) remained non-significant.

A similar pattern was revealed in the pRCC analysis (Table 2). No significant differences were found between PBRM1 expression and clinicopathological factors, such as age (P=0.249), sex (P=0.226), and AJCC stage (P=0.401). Additionally, T stage (P=0.490), N stage (P=0.100), or M stage (P=0.942) showed no distinct association with the mRNA expression of PBRM1.

2. Prognostic significance of PBRM1 expression in ccRCC and pRCC

The prognostic impact of PBRM1 expression on overall survival was analyzed using Kaplan-Meier curves and the log-rank test. Our findings demonstrate a subtype-specific prognostic role for PBRM1. In ccRCC, high PBRM1 expression was significantly associated with improved overall survival compared to low expression (HR=0.72, 95% CI=0.54~0.97, P=0.03) (Fig. 1A). In contrast, in pRCC, no significant difference in overall survival was observed between the high and low PBRM1 expression groups (HR=0.96, 95% CI=0.53~1.75, P=0.8) (Fig. 1B). These findings suggest that the prognostic significance of PBRM1 expression may differ between RCC subtypes, with a significant association observed in ccRCC but not in pRCC.

DISCUSSION

This study demonstrates that PBRM1 expression has a subtype-specific prognostic value in RCC. Specifically, high

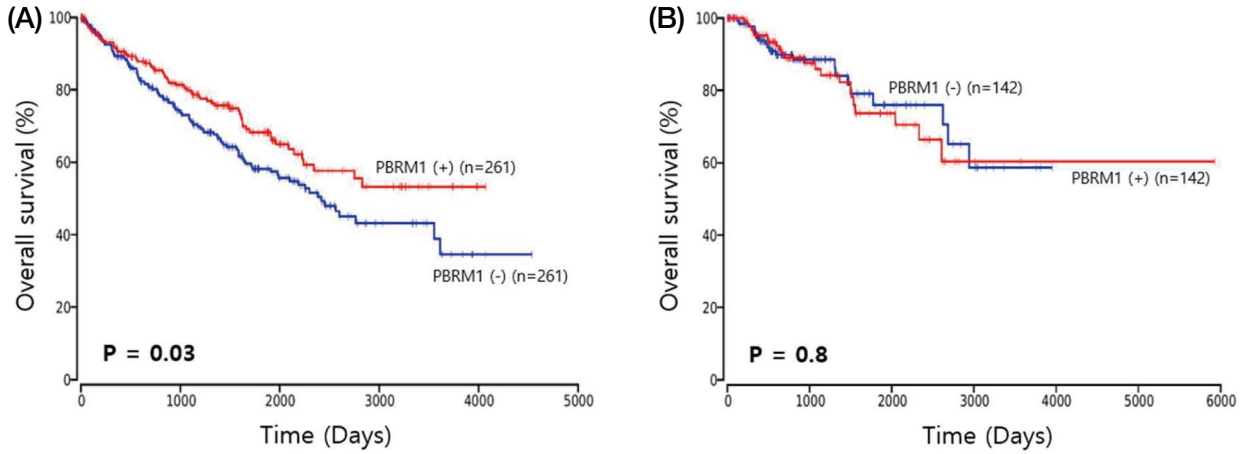

Fig. 1. Overall survival analysis in clear cell renal cell carcinoma (A) and papillary renal cell carcinoma (B) according to PBRM1 expression.

PBRM1 expression was associated with improved overall survival in ccRCC, whereas no such association was observed in pRCC. Additionally, no significant correlation was observed between PBRM1 expression and clinicopathological characteristics in either subtype. PBRM1 is widely recognized as a tumor suppressor gene in ccRCC [16]. Consistent with previous experimental studies demonstrating that loss of PBRM1 promotes tumor progression and impairs genomic stability [17,18], our findings showed that higher PBRM1 expression was associated with improved overall survival. These findings are consistent with the hypothesis that preserved PBRM1 expression may be associated with a less aggressive tumor phenotype in ccRCC.

A key observation of this study is the subtype-specific prognostic relevance of PBRM1 expression. While significant in ccRCC, PBRM1 expression had no prognostic value in pRCC. This discrepancy underscores the profound molecular heterogeneity between ccRCC and pRCC. In ccRCC, which is predominantly driven by VHL inactivation and subsequent HIF pathway activation, PBRM1 represents the second most frequently mutated gene, suggesting its integral role in the molecular pathogenesis of this subtype [19,20]. Unlike ccRCC, pRCC is characterized by distinct genetic drivers such as MET mutations or chromosomal gains of 7 and 17 [5]. The lack of prognostic significance in pRCC suggests that the SWI/SNF complex, or at least the PBRM1 subunit, may play a less central role in the oncogenic progression of the papillary subtype compared to the clear cell subtype [21,22]. From a clinical perspective, ccRCC and pRCC also differ substantially in their natural history and therapeutic landscape. ccRCC is generally associated with a higher metastatic potential and poorer prognosis, whereas pRCC often exhibits a more indolent clinical course, particularly in type 1 tumors [5,23]. Together with their distinct molecular drivers, these differences may contribute to the subtype-specific prognostic impact of PBRM1 observed in the present study. Our findings further support the importance of evaluating prognostic biomarkers within individual RCC subtypes rather than treating RCC as a single disease entity. In addition, consistent with previous reports [24,25], PBRM1 molecular profiling may offer prognostic value complementary to conventional clinicopathological assessment [26].

The present study has several limitations that should be acknowledged. First, this study was based on a retrospective analysis of publicly available TCGA data, which carries inherent limitations. Retrospective designs are susceptible to selection bias, as the patient population may not be fully representative of the broader clinical setting. Moreover, the absence of standardized treatment protocols across patients may confound survival outcomes, making it difficult to isolate the prognostic effect of PBRM1 expression from the influence of variable therapeutic interventions. These limitations preclude definitive causal inferences and underscore the need for prospective validation in well-controlled cohorts. Second, mRNA expression levels do not necessarily reflect protein abundance or functional activity. Accordingly, further validation through protein-based approaches, such as immunohistochemistry, is warranted. Third, the present findings were derived exclusively from the TCGA cohort

and were not validated in an independent external dataset. Therefore, the generalizability and reproducibility of the observed associations require confirmation in additional patient cohorts.

Finally, multivariate analyses, including Cox proportional hazards regression, were not performed in this study. Therefore, whether PBRM1 provides prognostic information beyond established clinicopathological factors remains to be determined. Future prospective studies incorporating larger cohorts, multivariate survival analyses, and functional validation are needed to confirm these findings and elucidate the molecular mechanisms underlying the subtype-specific prognostic role of PBRM1.

CONCLUSION

In conclusion, our study demonstrates that PBRM1 expression has subtype-specific prognostic significance in RCC. High PBRM1 expression was associated with improved overall survival in ccRCC, whereas no significant association was observed in pRCC. Furthermore, PBRM1 expression was not significantly correlated with major clinicopathological parameters, such as age, sex, or TNM stage, in either subtype. These findings suggest that PBRM1 expression may provide prognostic information complementary to conventional clinicopathological assessment in ccRCC. Overall, our results underscore the importance of considering histological heterogeneity when evaluating prognostic biomarkers in RCC. Further prospective studies, external validation and functional investigations are warranted to confirm the clinical utility of PBRM1 and to better understand the biological and clinical relevance of PBRM1 in ccRCC.

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