Original Article

Comprehensive analyses of *PBRM1* in multiple cancer types and its association with clinical response to immunotherapy and immune infiltrates

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Background: The prognostic value of polybromo 1 (*PBRM1*) gene mutations in clear cell renal carcinoma (CCRCC) with anti-programmed death-ligand 1 (PD-L1) therapy remains controversial, and few studies have reported the impact of *PBRM1* mutations in other cancer types.

Methods: The patient information was obtained from cBioPortal and the Tumor Immune Estimation Resource (TIMER) databases. Mann-Whitney U test were used for correlation analysis. For survival analyses, Kaplan-Meier survival curves were used and compared using the log-rank test. Cox's regression model was used to perform univariable and multivariable analyses

Results: Our study, for the first time, performed comprehensive analyses of *PBRM1* mutation frequency, *PBRM1* expression, relationship of *PBRM1* mutations with clinical benefit from immunotherapy, and *PBRM1* expression with immune infiltrates in diverse cancer types. The results showed that the expression of *PBRM1* was significantly lower in diverse cancer types compared with normal tissues. Based on multivariable analysis, *PBRM1* mutations trended towards worse clinical outcomes from anti-PD-L1 in CCRCC, lung adenocarcinoma (LUAD), bladder urothelial carcinoma (BLCA), and skin cutaneous melanoma (SKCM), and a significant association was observed in LUAD and BLCA. *PBRM1* mutations were associated with higher TMB in diverse cancer types and significant associations were observed in LUAD and BLCA. The expression of PBRM1 was found to positively correlate with immune infiltrates in diverse cancer types.

Conclusions: Our findings suggested caution in starting immunotherapy alone in *PBRM1* mutant patients. Further studies are needed to improve treatment for *PBRM1* mutant patients.

Keywords: *PBRM1* mutations; *PBRM1* expression; immunotherapy; immune infiltrates; multiple cancer types

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Introduction

Immune checkpoint inhibitor (ICI) drugs have revolutionized the treatment landscapes in multiple cancer types (1,2). The use of ICIs against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1) has been approved for treating a variety of malignancies (3-5). Patients with biomarkers such as PD-L1, tumor mutational burden (TMB), and high microsatellite instability (MSI-H), may have a survival advantage with the use of ICIs (6-9). Nevertheless, these biomarkers not enough for clinicians to precisely distinguish responders to immunotherapy. Patient intrinsic factors, tumor intrinsic factors, and environmental factors may impact the efficacy of ICIs (10,11). There is an urgent need to identify specific predictive molecular biomarkers for immunotherapy to facilitate precision of treatment.

The *PBRM1* gene encodes the bromodomain-containing protein BAF180, which is a subtype of the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex and the second most commonly mutated gene in clear cell renal carcinomas (CCRCC) after *VHL* (Vov Hippel-Lindau) (12-15). Approximately 80% of *PBRM1* somatic mutations may result in loss of function of the protein (16). Mutations in *PBRM1* have also been found in other cancer types including pancreatic, gastric, renal, and biliary cancers (17,18). Decreased expression of *PBRM1* has been reported to correlate with poor prognosis and advanced clinicopathological features in CCRCC (19-21).

Different studies have tried to analyze the impact of *PBRM1* status on response to immunotherapy in CCRCC but the results have seemed controversial. Miao *et al.* reported that in patients with metastatic CCRCC who received prior treatment (largely with inhibitors of vascular endothelial growth factor (VEGF), *PBRM1* mutations were associated with increased progression free survival (PFS) with anti-PD-L1 therapy, but the association was not observed in patients who underwent first-line anti-PD-(L)-1 therapy (22). A further study validated the relationship between *PBRM1* truncating mutations and improved response to nivolumab (anti-PD-1) in participants who received prior antiangiogenic therapy (23). In treatment-naive metastatic RCC, *PBRM1* mutant patients had a trend towards better PFS in the sunitinib (anti-VEGF) arm *vs.* both atezolizumab (anti-PD-L1) and atezolizumab + bevacizumab (anti-VEGF) treatment arms (both HR <1) (24). In brief, no evidence has demonstrated *PBRM1* mutant patients have better clinical outcomes with first-line immunotherapy. Some other studies have suggested that *PBRM1* mutations may benefit from antiangiogenic therapy in CCRCC (25,26). Furthermore, a comprehensive analysis of *PBRM1* frequency and *PBRM1* expression, as well as their predictive value for ICIs on clinical outcome in other cancer types has not yet been reported.

In this study, we investigated *PBRM1* mutation frequency and *PBRM1* expression across different cancer types. The correlation between *PBRM1* mutations and clinical outcomes from anti-PD-L1 treatment and TMB was analyzed in CCRCC, lung adenocarcinoma (LUAD), bladder urothelial carcinoma (BLCA), and skin cutaneous melanoma (SKCM). We further evaluated the association of *PBRM1* expression with immune infiltrates in a total of 32 cancer types.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/atm-21-289).

Methods

Participants

The publicly available databases CbioPortal (https://www.cbioportal.org/) and Tumor Immune Estimation Resource (TIMER, https://cistrome.shinyapps.io/timer/) were used in this study. All *PBRM1* genetic mutations and related clinical data were downloaded from three datasets in the cBioPortal database. A dataset with 10,945 samples was used to analyze the frequency of *PBRM1* mutations across different cancer types (27). A dataset containing 1,661 patients was used to analyze the association of *PBRM1* mutations with the overall survival (OS) in CCRCC, LUAD, BLCA, and SKCM with immunotherapy (28). A dataset containing 240 non-small cell lung cancer (NSCLC) patients was used to analyze the association of *PBRM1* mutations with PFS and durable clinical benefit (DCB) in LUAD with immunotherapy (29). The TIMER database that includes 10,897 samples across 32 cancer types from The Cancer Genome Atlas (TCGA) was used to analyze the expression of *PBRM1* and its relationship with immune infiltration levels (30).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

For survival analyses, Kaplan-Meier survival curves were used and compared using the log-rank test. Cox's regression model

was used to perform univariable and multivariable analyses. For testing the association of TMB with *PBRM1* mutation, the Mann-Whitney U test was used. The association between *PBRM1* expression and immune infiltrates was analyzed via the TIMER database. We analyzed the *PBRM1* expression in 32 cancer types via the "DiffExp" module, and the correlation of *PBRM1* expression with the abundance of immune infiltrates, including B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells, via the "gene" module. All reported P values are 2-sided.

Results

PBRM1 mutation frequency and PBRM1 expression in different cancer types

We assessed the frequency of *PBRM1* gene alterations in a cBioPortal dataset of 10,336 patients with different cancer types (27). The frequency of *PBRM1* mutations was 3.8% across all cancer types. Truncating mutations were the most common type of mutation. We further analyzed the *PBRM1* mutation frequency in detailed cancer types, and the cancer types with a sample size less than 100 patients or *PBRM1* mutant patients less than 5 were filtered out. The highest level of *PBRM1* mutations was seen in CCRCC, with a frequency of 45%. The results showed 13 cancer types with a *PBRM1* mutation frequency of more than 1.3% (*Figure 1A*).

The expression of *PBRM1* was examined using the RNA-seq data of multiple cancer types in the TIMER database (*Figure 1B*). It is worth noting that *PBRM1* expression was significantly lower in almost all cancer types that had matched normal tissues, except kidney chromophobe (KICH) and stomach adenocarcinoma (STAD).

Association of PBRM1 mutations with OS in CCRCC, LUAD, BLCA, and SKCM treated with anti-PD-L1

To investigate the association between *PBRM1* mutations and OS in cancers with anti-PD-L1 treatment, the dataset containing 1,661 advanced cancer patients with ICI treatment from the cBioPortal was used (28). The OS was defined as the time of the first ICI treatment to the time of death or most recent follow-up. In this dataset, 139 patients had *PBRM1* mutations, 55 in CCRCC, 16 in SKCM, 14 in LUAD, 6 in BLCA, and 48 in other cancer types. The study included patients who received PD-1 or PD-L1 therapy. Given the varying *PBRM1* mutation frequency and clinical outcomes of immunotherapy across cancer types, we performed analysis of the association of *PBRM1* mutations with OS in patients with CCRCC, SKCM, LUAD, and BLCA treated with anti-PD-L1, respectively.

As shown in *Figure 2*, patients with *PBRM1* mutations showed a shorter median OS (mOS) in all four cancer types. The OS was significantly worse in *PBRM1*-mutant BLCA versus *PBRM1*-wildtype BLCA treated with ICIs.

To further test the independent prognostic value in terms of OS within each cancer type, univariable and multivariable analyses based on the Cox proportional hazards regression model were conducted (*Table 1*). Univariable analysis showed that only in LUAD, high TMB was positively correlated with OS with immunotherapy, while in CCRCC and SKCM, high TMB tended to respond poorly to immunotherapy [hazard ratio (HR) >1]. The impact of *PBRM1* mutations on OS did not reach statistical significance in any of the 4 cancer types, but the numerical trend of poor OS (HR >1) was observed in the univariable analysis. Multivariable analysis with adjustment for age, gender, *PBRM1* status, and TMB in the four cancer types, respectively, indicated that *PBRM1* mutations were an independent biomarker for poor prognosis in LUAD and BLCA, while TMB in these two cancer types was an independently improved prognostic biomarker for ICIs therapy. In multivariable analysis of CCRCC and SKCM patients, no factors were found to be significantly correlated with OS, but the trends of *PBRM1*-mutant patients towards a worse survival (HR >1) and high TMB towards clinical benefit from immunotherapy in CCRCC and SKCM (HR <1) were observed.

Association of PBRM1 mutations with TMB in CCRCC, LUAD, BLCA, and SKCM

We assessed the association between *PBRM1* mutation and TMB in the above four cancer types. The results indicated a trend of *PBRM1* mutants towards higher TMB in all the four cancer types (*Figure 3*). In LUAD and BLCA, *PBRM1* mutations were significantly associated with higher TMB (P<0.0001 and P<0.0023, respectively). The effect in BLCA and SKCM did not reach statistical significance, which may have been due to the small sample size.

Association of PBRM1 mutations with PFS and DCB in LUAD treated with anti-PD-L1

In cBioPortal, we also identified another dataset comprising 240 advanced NSCLC patients. Most sample IDs in this

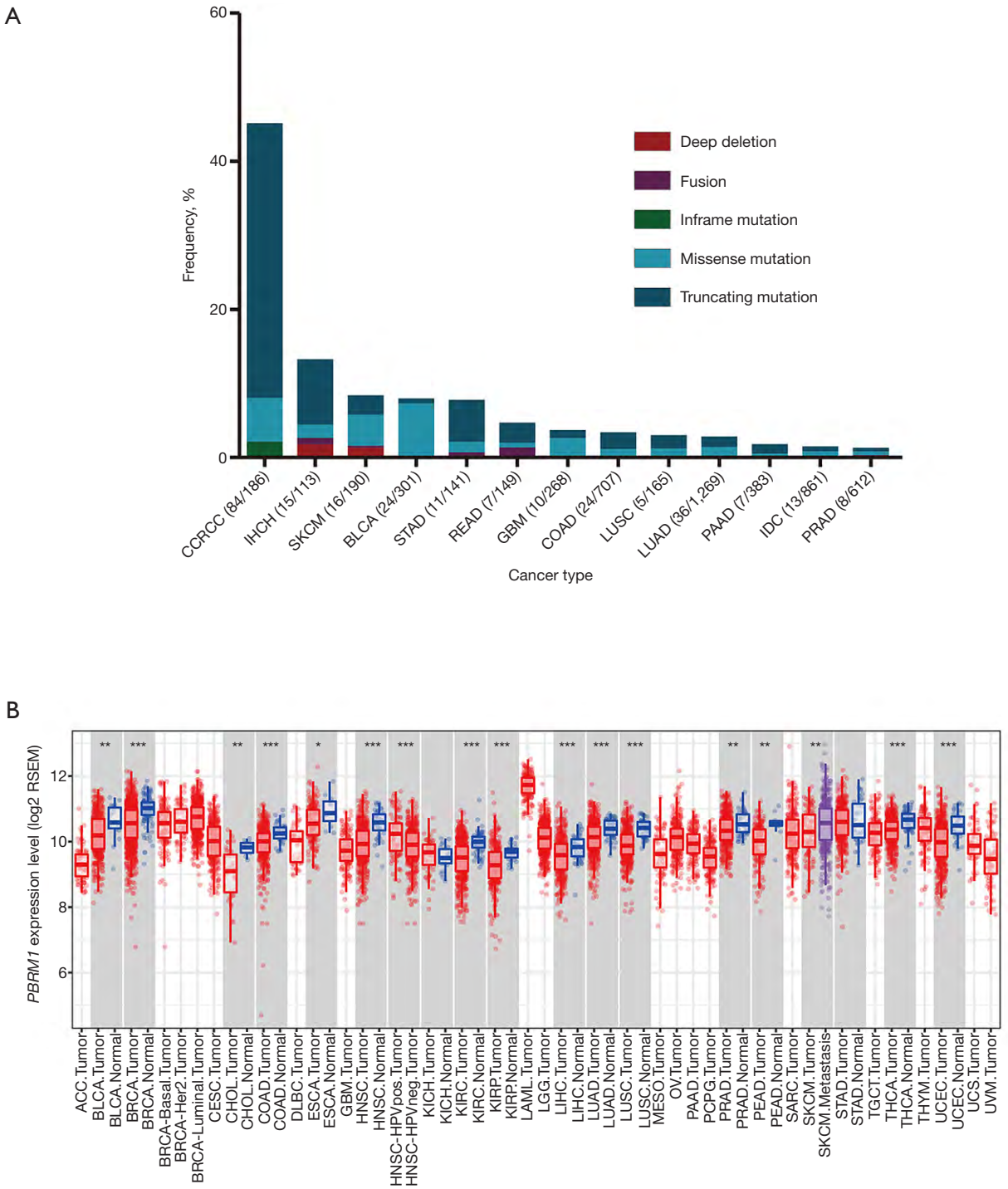

Figure 1 *PBRM1* mutation frequency and *PBRM1* expression pattern in different cancer types. (A) Frequency of *PBRM1* mutations across different cancer types; (B) *PBRM1* expression levels in diverse cancer types determined by TIMER. *, P<0.05; **, P<0.01; ***, P<0.001. PBRM1, polybromo 1; TIMER, Tumor Immune Estimation Resource.

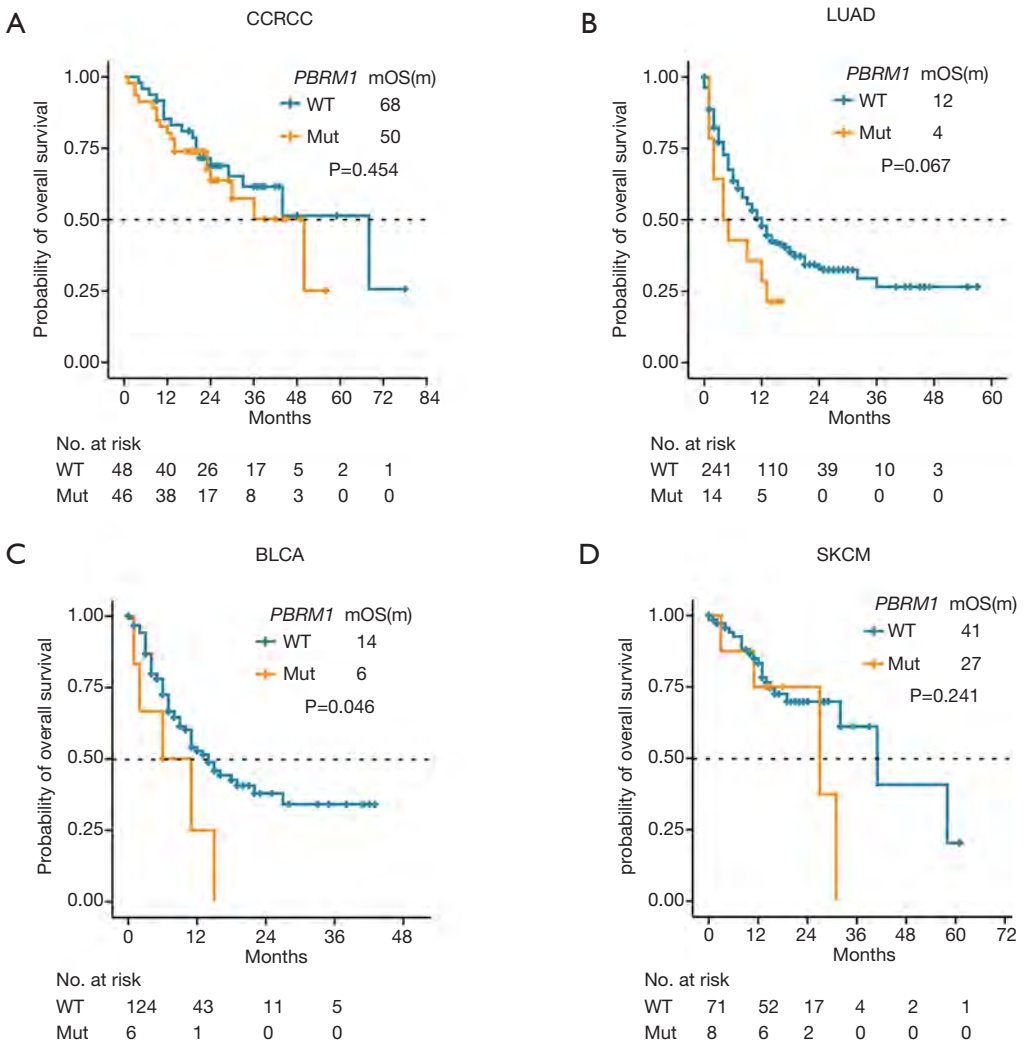

Figure 2 Association between *PBRM1* mutations and OS in 4 cancer types treated with anti-PD-(L)-1. Kaplan-Meier plots of OS in *PBRM1* mutant *vs*. non-mutant patients with (A) CCRCC, (B) LUAD, (C) BLCA and (D) SKCM. Censored data are indicated by vertical tick marks. P values of log-rank test are indicated. Median survival time in each group is indicated. PBRM1, polybromo 1; OS, overall survival; CCRCC, renal clear cell carcinoma; LUAD, lung adenocarcinoma; BLCA, bladder urothelial carcinoma; SKCM, skin cutaneous melanoma.

dataset were included in a dataset of 1,661 patients. The PFS and DCB of patients were available in this dataset (29). We analyzed the association between *PBRM1* mutations, PFS, and DCB. A total of 159 LUAD patients treated with anti-PD-(L)-1 monotherapy in the dataset were included in our study. Although not statistically significant, *PBRM1* mutant LUAD tended to have a worse PFS (HR: 1.601; 95% CI: 0.743 to 3.450) (*Figure 4*). None of the 7 *PBRM1* mutant patients had DCB from ICI, while 41 out of 146 *PBRM1* wild-type patients had DCB. The trends of PFS and DCB in this dataset were consistent with OS in the dataset with 1,661 patients.

Association of PBRM1 expression with immune infiltrates

We then attempted to assess if *PBRM1* expression correlated with immune infiltrates in the 32 cancer types via the TIMER database (Figure S1). A trend of *PBRM1* expression towards higher immune infiltrates was observed in many cancer types, including breast (BRCA), colon

Table 1 Univariate and multivariate analysis of factors associated with OS in CCRCC, LUAD, BLCA, and SKCM

Category	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
CCRCC				
Age (>60 *vs.* ≤60)	1.782 (0.897–3.541)	0.099	1.744 (0.862–3.528)	0.122
Gender (male *vs.* female)	0.85 (0.407–1.777)	0.667	0.903 (0.428–1.903)	0.789
PBRM1 (Mut *vs.* Wt)	1.287 (0.661–2.506)	0.458	1.229 (0.61–2.476)	0.563
TMB (continuous)	1.455 (0.746–2.836)	0.271	0.971 (0.858–1.098)	0.634
LUAD				
Age (>60 *vs.* ≤60)	1.167 (0.828–1.645)	0.378	1.075 (0.76–1.52)	0.683
Gender (male *vs.* female)	1.188 (0.87–1.622)	0.278	1.208 (0.88–1.658)	0.242
PBRM1 (Mut *vs.* Wt)	1.736 (0.938–3.213)	0.079	2.369 (1.243–4.517)	0.009
TMB (continuous)	0.967 (0.948–0.987)	0.001	0.962 (0.942–0.982)	0.000
BLCA				
Age (>60 *vs.* ≤60)	0.929 (0.532–1.622)	0.796	1.086 (0.617–1.912)	0.776
Gender (male *vs.* female)	0.986 (0.501–1.943)	0.968	1.009 (0.511–1.993)	0.980
PBRM1 (Mut *vs.* Wt)	2.41 (0.964–6.03)	0.060	3.877 (1.462–10.283)	0.006
TMB (continuous)	0.793 (0.464–1.354)	0.395	0.972 (0.947–0.997)	0.030
SKCM				
Age (>60 *vs.* ≤60)	2.721 (0.922–8.026)	0.070	2.894 (0.928–9.029)	0.067
Gender (male *vs.* female)	1.394 (0.516–3.761)	0.512	1.601 (0.584–4.389)	0.360
PBRM1 (Mut *vs.* Wt)	1.886 (0.638–5.579)	0.251	1.561 (0.507–4.806)	0.437
TMB (continuous)	1.004 (0.991–1.017)	0.550	0.998 (0.983–1.012)	0.753

OS, overall survival; CCRCC, renal clear cell carcinoma; LUAD, lung adenocarcinoma; BLCA, bladder urothelial carcinoma; SKCM, skin cutaneous melanoma; HR, hazard ratio; CI, confidence interval; TMB, tumor mutational burden; Mut, mutation type; Wt, wild type.

adenocarcinoma (COAD), head and neck squamous cell carcinoma (HNSC), KICH, kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), low-grade glioma (LGG), liver hepatocellular carcinoma (LIHC), LUAD, lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PAAD), prostate adenocarcinoma (PRAD), rectum adenocarcinoma (READ), SKCM, and thymoma (THYM). The results of relationship of *PBRM1* expression with immune infiltrates in the four cancer types is shown in *Figure 5*. In KIRC and LUAD, the expression of *PBRM1* was positively correlated with infiltration of B cells, CD8+ cells, CD4+ cells, macrophages, neutrophils, and dendritic cells. In BLCA, *PBRM1* expression was positively correlated with B cells and macrophages, negatively correlated with CD4+ T cells and dendritic cells, and no significance was observed with CD8+ cells and neutrophils. In SKCM, there was a positive association of *PBRM1* expression with infiltration levels of CD8+ T cells, macrophages, and neutrophils, and no significant correlation with B cells, CD4+ T cells, and dendritic cells was observed.

Discussion

Previous studies have revealed that the mutation frequency of SWI/SNF complexes in all human tumors was about 20%, similar to that of *TP53*, *KRAS*, and *PTEN* (31,32). Our work showed that *PBRM1* mutation frequency was 3.8% across all cancer types and that *PBRM1* expression was significantly decreased in most cancer types. This may

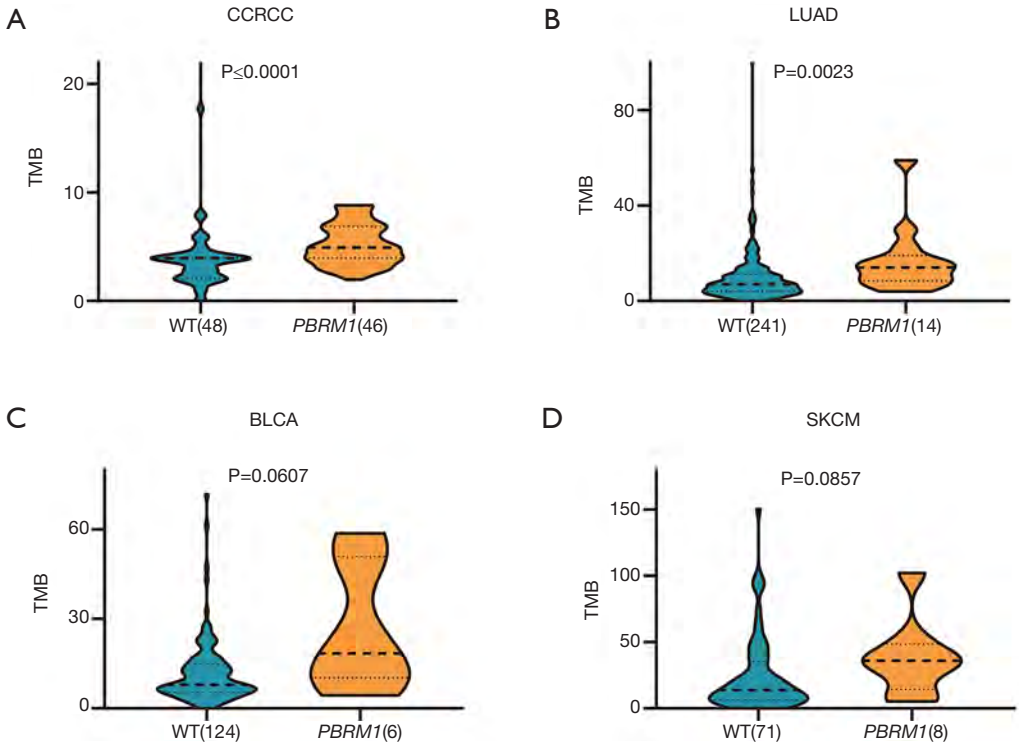

Figure 3 Association between *PBRM1* mutations and TMB in CCRCC, LUAD, BLCA, and SKCM. TMB in *PBRM1* mutant *vs.* non-mutant patients with (A) CCRCC, (B) LUAD, (C) BLCA and (D) SKCM. P values of Mann-Whitney U test are indicated. PBRM1, polybromo 1; TMB, tumor mutational burden; CCRCC, renal clear cell carcinoma; LUAD, lung adenocarcinoma; BLCA, bladder urothelial carcinoma; SKCM, skin cutaneous melanoma.

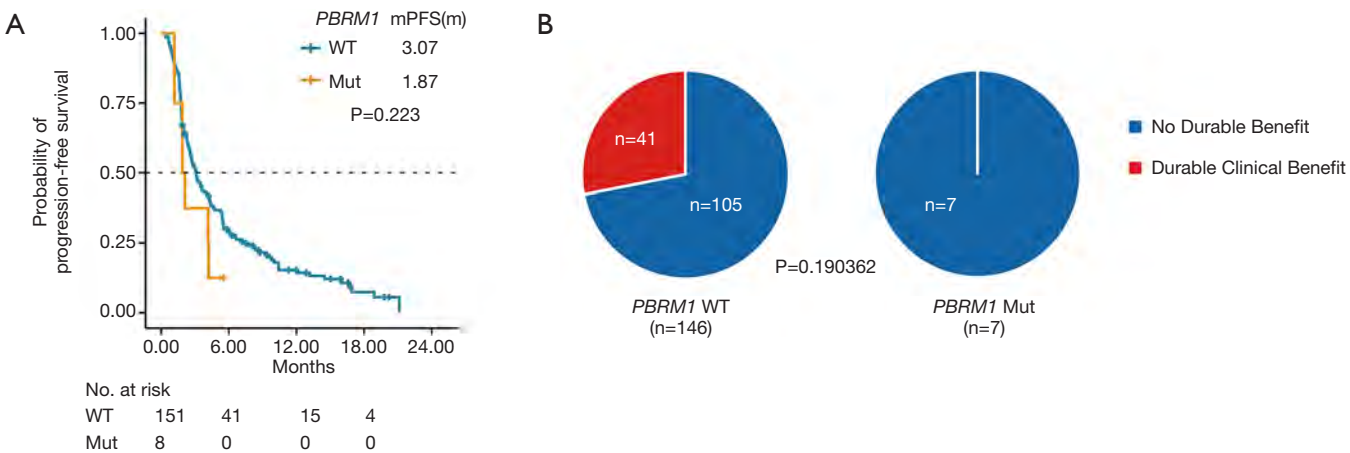

Figure 4 Association between *PBRM1* mutations, PFS, and DCB in LUAD treated with anti-PD-(L)-1. (A) Kaplan-Meier plots of PFS in *PBRM1* mutant *vs.* non-mutant patients with LUAD. Censored data are indicated by vertical tick marks. P value of log-rank test is indicated. Median survival time in each group is indicated. (B) Pie charts of the proportion of patients with durable clinical benefits with or without *PBRM1* mutation in LUAD. P value of Fisher's exact test is indicated. PBRM1, polybromo 1; PFS, progression-free survival; DCB, durable clinical benefit; LUAD, lung adenocarcinoma.

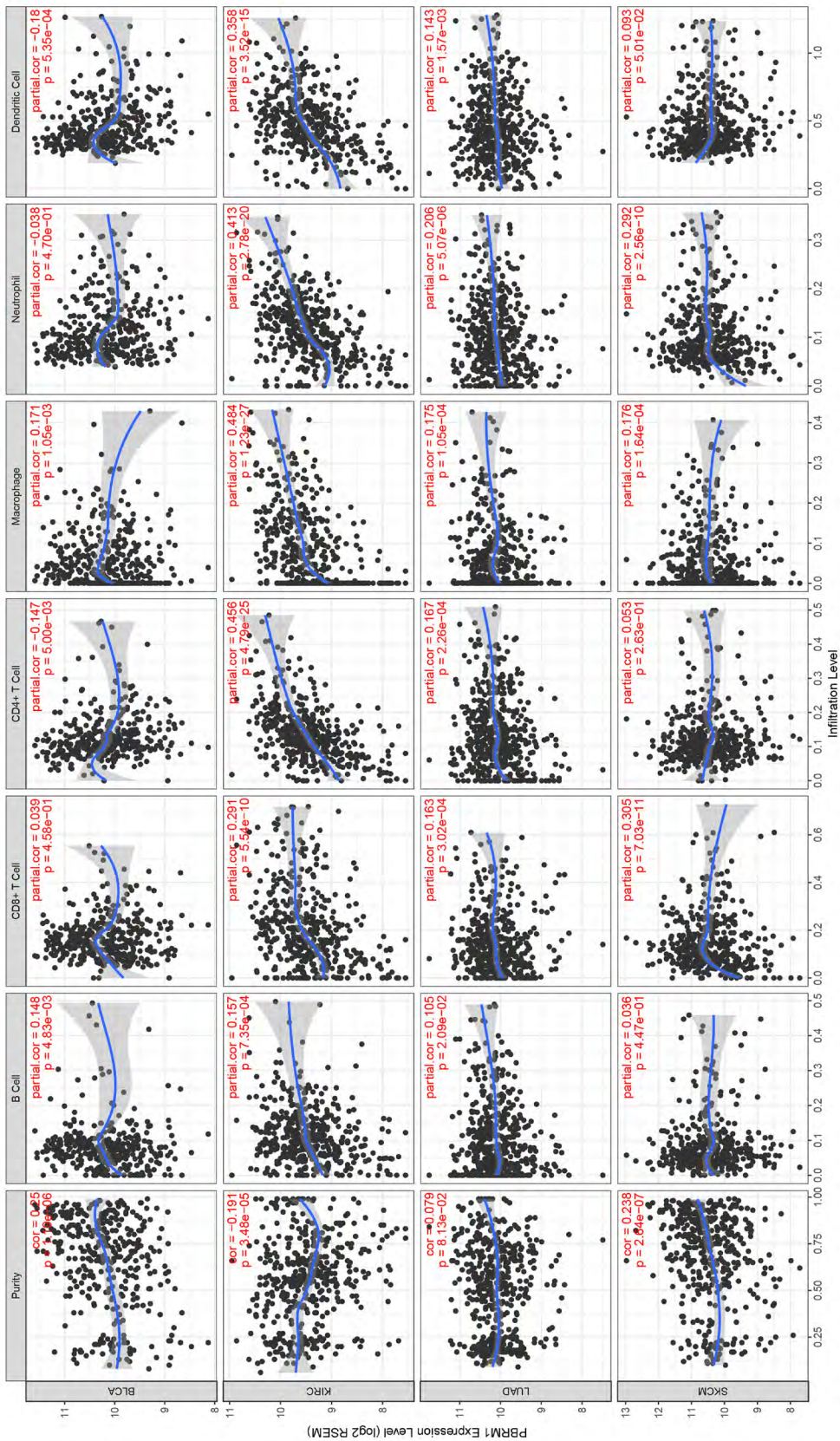

Figure 5 Association between *PBRM1* expression and immune infiltrates in KIRC, LUAD, BLCA, and SKCM. "Gene" module in TIMER was used to determine the association. PBRM1, polybromo 1; KIRC, kidney renal clear cell carcinoma; LUAD, lung adenocarcinoma; BLCA, bladder urothelial carcinoma; SKCM, skin cutaneous melanoma; TIMER, Tumor Immune Estimation Resource.

imply that PRBM1 plays an important role in tumorigenesis in many cancer types.

To our knowledge, studies about the predictive value of PBRM1 were mainly reported in CCRCC. Our study did not observe a positive correlation between *PBRM1* mutations and clinical benefit from anti-PD-L1 therapy. The *PBRM1* mutant patients tended to respond poorly to the therapy in CCRCC, LUAD, BLCA, and SKCM based on multivariable analysis, especially so in LUAD and BLCA. These findings are consistent with the results from IMmotion150 (24).

The TMB was demonstrated as a predictor of superior OS with ICI treatment (33). However, some patients do not show DCB from ICIs even with high TMB (28,34). It is worth noting that in our study LUAD or BLCA patients with *PBRM1* mutations tended to have higher TMB, yet these people responded poorly to anti-PD-L1 based on the log-rank test. Moreover, univariable analysis revealed that TMB tended to correlate with poor response to immunotherapy in CCRCC and SKCM (HR >1). After adjusting for *PBRM1* mutations, age, and gender, the trend of TMB towards clinical benefit was similar across the four cancer types. These findings further suggested that TMB was not sufficient for predicting clinical benefit from immunotherapy response. The identification biomarker is needed as a complement to the existing methods.

Immune cell infiltrations have been suggested as a critical factor for ICIs treatment in recent studies (34-38). Our study revealed that *PBRM1* expression correlated with immune infiltrates in many cancer types. Miao *et al.* reported tumors harboring *PBRM1* mutations showed a lower expression of immune inhibitory ligands than those with intact *PBRM1* (22). Kamal *et al.* reported inactivating mutations in *PBRM1* was independently associated with reduced senescence enrichment in CCRCC, while high tumor senescence activity associates with clinical benefit from checkpoint blockade therapy (39). These mechanisms may contribute to poor clinical outcomes from immunotherapy in patients with immunotherapy.

The *PBRM1* mutant CCRCC patients were reported to have high angiogenesis and respond well to anti-angiogenic therapy (24). The Food and Drug Administration (FDA) has approved anti-angiogenic drugs, such as bevacizumab, sorafenib, and sunitinib, for the treatment of several solid tumors (40). Anti-angiogenic inhibitors were believed to be important players not only in tumor angiogenesis but also in promoting immune cell infiltration (41-43). Further research is required to establish whether *PBRM1* mutant patients with LUAD or BLCA or other cancers can get benefit from anti-angiogenic therapy or not.

This study was limited by the sample size and medical history of the patients. Further studies are needed to verify our findings. Our results may provide an impetus for studies and prospective clinical trials based on *PBRM1* mutations.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at http://dx.doi.org/10.21037/atm-21-289

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-289). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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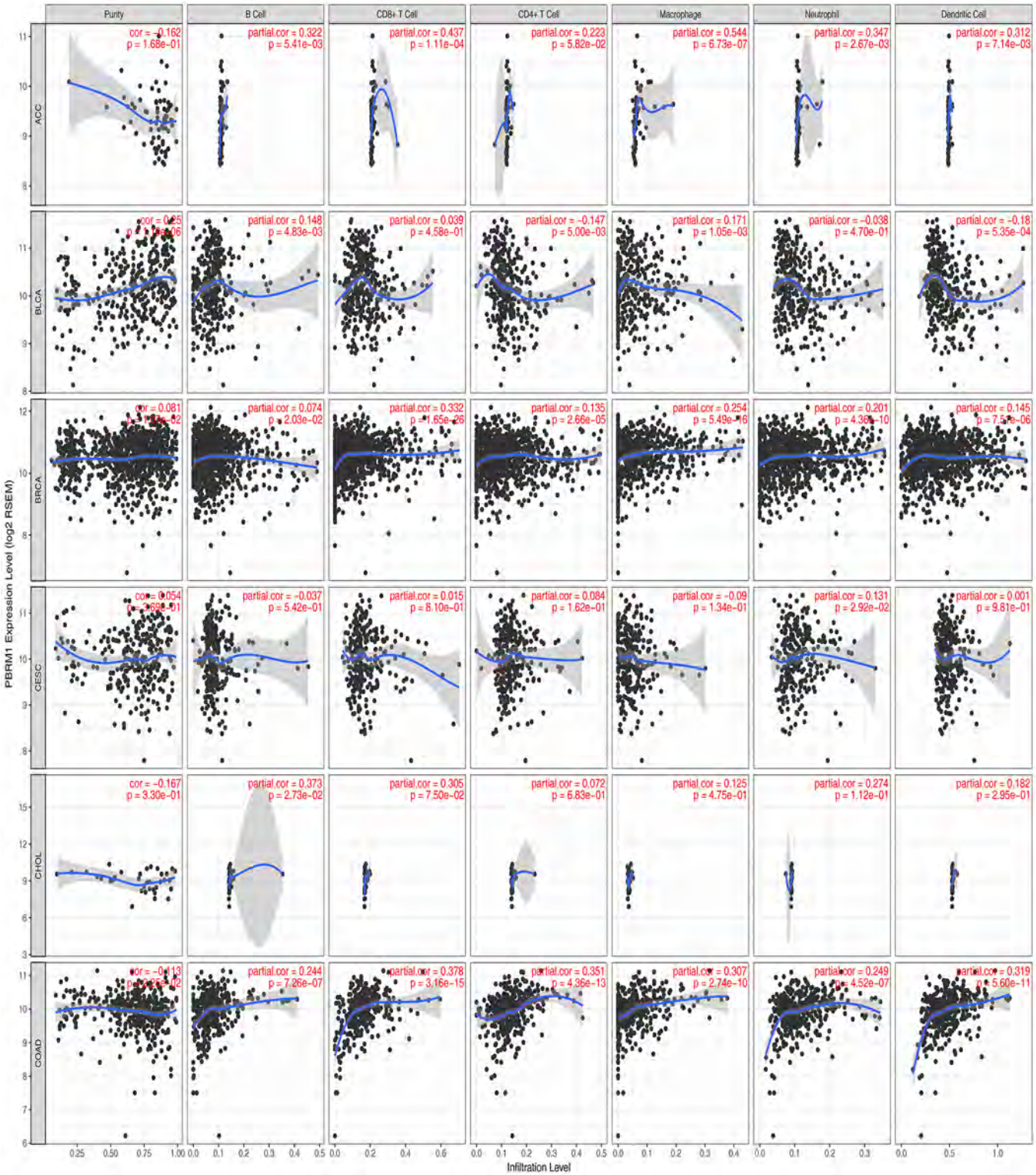
Supplementary



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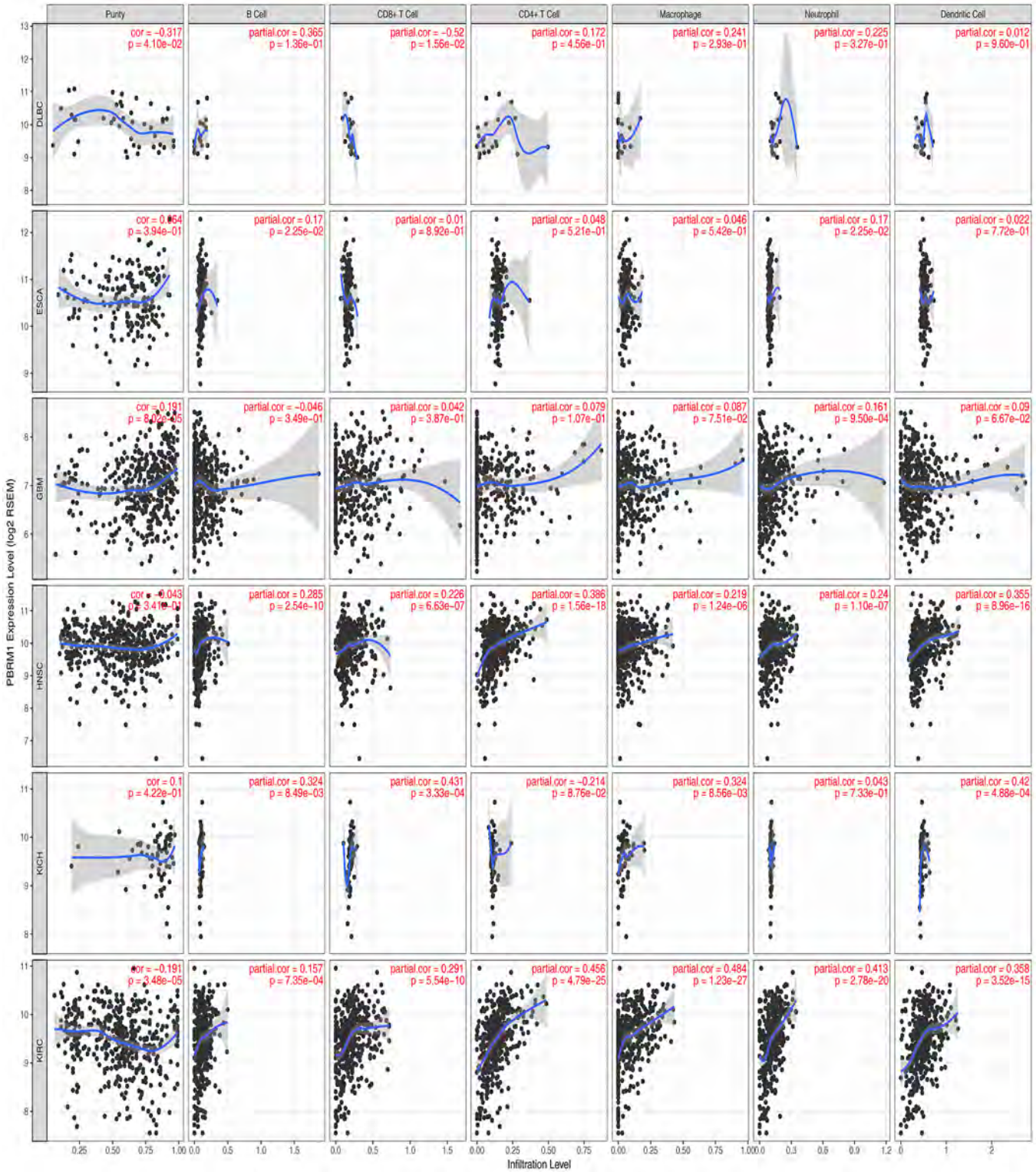

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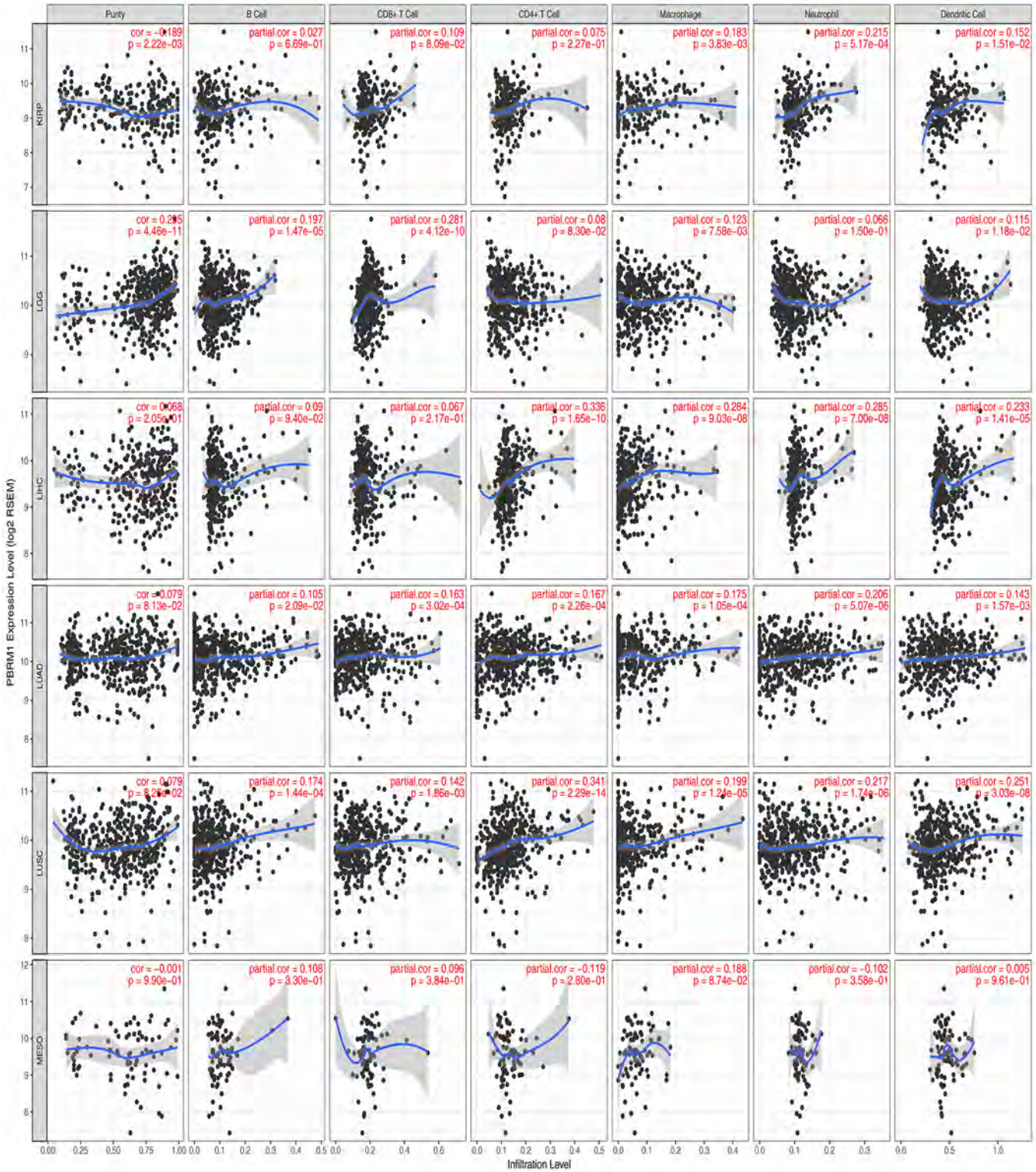

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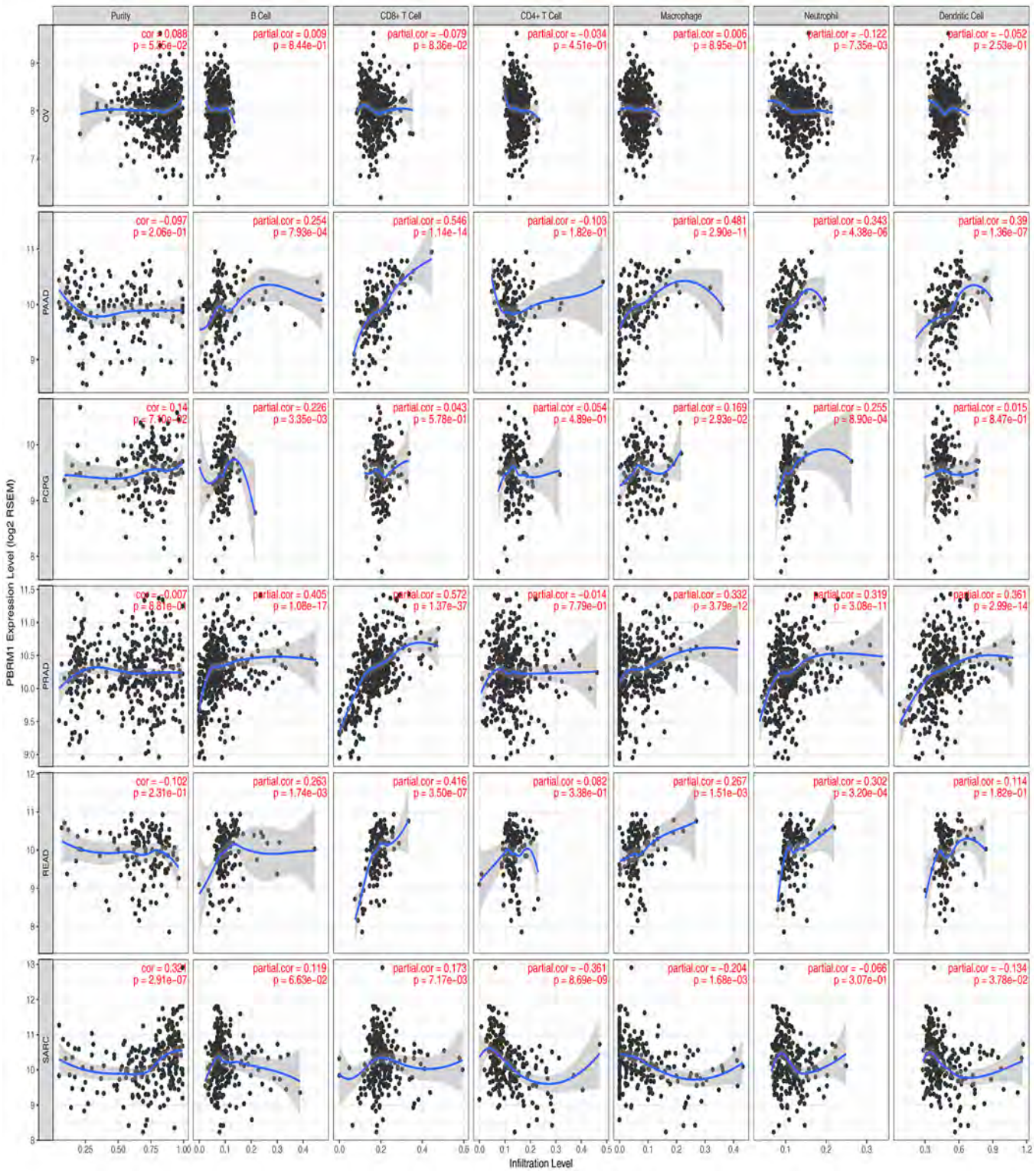

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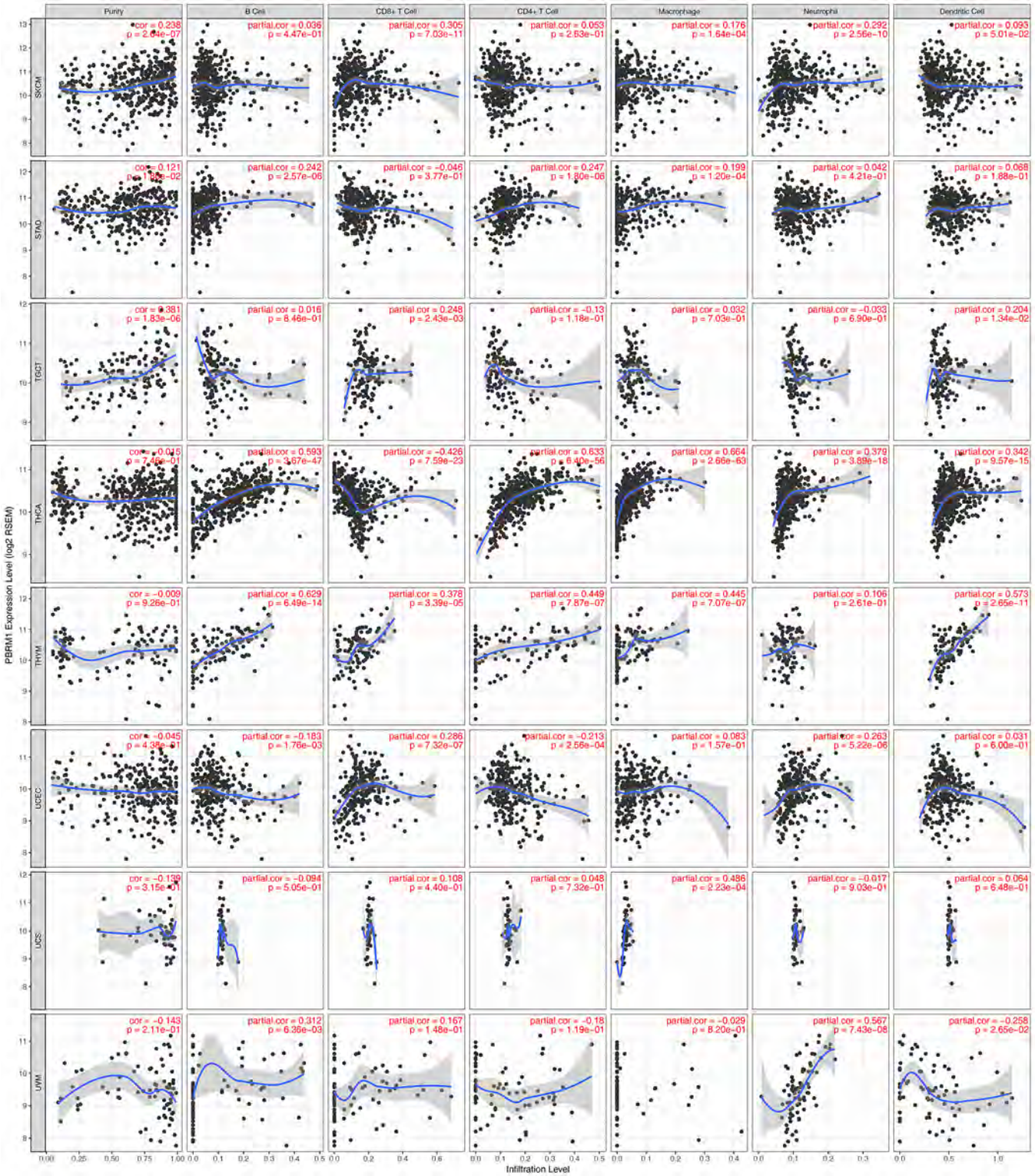

Figure S1 Association between *PBRM1* expression and immune infiltrates in 32 cancer types. "Gene" module in TIMER was used to determine the association. *PBRM1*, polybromo 1; TIMER, Tumor Immune Estimation Resource.

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