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PAPER

Blood Protein Ratios Reveal New Diagnostic Biomarkers for Prostate Cancer: A Study from the Perspective of Mendelian Randomization

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ABSTRACT

Prostate cancer (PCa) is a leading malignancy affecting men globally, contributing significantly to cancer-related morbidity and mortality. Our study aims to explore causal relationships between blood protein ratios (BPR) and PCa using a Mendelian randomization (MR) approach, potentially identifying new diagnostic and therapeutic targets. Methods: A two-sample MR method was employed, utilizing genetic variants as instrumental variables (IVs) to infer causality between circulating BPR and PCa. Data on BPR were obtained from a proteomics study of the UK Biobank, while PCa data were sourced from FinnGen, the PRACTICLE Consortium, and the GWAS Catalog. Stringent criteria were applied for IV selection, and statistical analyses included the inverse-variance weighted (IVW) method with sensitivity analyses to address pleiotropy and heterogeneity. Results: Significant causal associations were identified between several BPR and PCa. Notably, the ratios of CEBPB/PXN, APBB1IP/NCF2, APP/EGF, and CRKL/EGF were found to be protective against PCa, while the ratios of ARHGAP1/RAD23B, EGF/TNFSF14, and GOLM2/STC1 were identified as risk factors. Reverse MR analysis suggested that PCa might act as a protective factor for the GOLM2/STC1 ratio. Sensitivity analyses confirmed the robustness of these findings. Conclusions: This study elucidates significant causal relationships between 7 BPR and PCa, offering new insights for diagnosis, treatment evaluation, and personalized therapeutic strategies. Future research should focus on validating these findings and exploring the underlying biological mechanisms to improve PCa management.

KEYWORDS

prostate cancer (PCa), blood protein ratios (BPR), Mendelian randomization (MR), genetic variants, diagnosis, treatment, biomarkers

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1 BACKGROUND

Prostate cancer (PCa) significantly contributes to cancer-related morbidity and mortality worldwide [1]. PCa is the most frequently diagnosed cancer among men in Europe, representing a significant public health concern [2]. Factors such as age, family history, and genetic predisposition play crucial roles in its development [3]. Epidemiological studies have shown that lifestyle and environmental factors also affect the risk of PCa, highlighting the complex interplay of genetic and non-genetic factors in its pathogenesis [4].

The study of blood protein ratios (BPR) has become increasingly important in the diagnosis and early screening of PCa [5]. Traditional diagnostic methods, such as prostate-specific antigen (PSA) testing, have significant limitations, including low specificity and sensitivity, which can lead to overdiagnosis and overtreatment of non-aggressive cancers [6]. Recent literature emphasizes the utility of additional biomarkers like %p2PSA and the Prostate Health Index, which combine different PSA isoforms and their ratios to improve diagnostic accuracy [7, 8]. A meta-analysis verified that these biomarkers are more effective in distinguishing aggressive PCa from indolent forms, thus helping to reduce unnecessary biopsies and treatments [9]. Certain BPR can also predict cancer prognosis, such as the C-reactive protein (CRP) to albumin ratio [10]. These advancements highlight the potential of BPR not only to detect cancer early but also to provide insights into tumor behavior, aiding in the stratification of patients based on risk and guiding clinical decision-making.

Moreover, ongoing research has highlighted the importance of specific proteins, such as CHRM1 and JUN, in the progression and treatment resistance of PCa. For instance, the CHRM1 protein has been identified as a key factor in the resistance of PCa cells to chemotherapy, underscoring the potential of targeting specific protein pathways to overcome treatment resistance [11]. Additionally, new therapeutic approaches, including bispecific antibodies targeting PD-L1 and PD-L2, are being explored for their potential to enhance the immune response against PCa, further emphasizing the role of protein interactions in the development of innovative treatments [12]. These studies have underscored the importance of understanding how BPR interacts with various PCa subtypes and how these interactions can be leveraged to improve clinical outcomes.

Understanding BPR is also crucial for developing targeted therapies. The heterogeneity of PCa means that treatments effective for one patient might not be suitable for another [13]. By studying BPR, researchers can identify specific molecular pathways involved in cancer progression, leading to the development of precision medicine approaches. Furthermore, the characterization of BPR can aid in monitoring treatment efficacy and adjusting therapeutic strategies accordingly [14]. Proteomic analyses can reveal changes in protein expression and ratios in response to treatments, providing biomarkers for treatment response and resistance. This dynamic monitoring capability is particularly important for managing metastatic and recurrent PCa, where treatment resistance is a common challenge. In recent years, traditional Chinese medicine has developed rapidly. Correlating the study of BPR in the blood with existing traditional Chinese medicine targets will also help discover new therapeutic targets and blood monitoring indicators for PCa. However, there are currently few articles investigating causal relationships between BPR and PCa. Two-sample Mendelian randomization (MR) effectively reduces confounding bias by using genetic variants as instrumental variables (IVs) to infer causality. Additionally, it enhances statistical power and reliability by employing separate datasets for the exposure and the outcome, allowing for more robust and accurate causal estimates [15]. This study conducts a two-sample MR approach to

explore the causal association between BPR and PCa, aiming to identify new targets for the diagnosis and personalized treatment of prostate cancer.

2 METHODS

2.1 Study design

This study leverages a two-sample MR method to investigate potential causal links between BPR and PCa using data from existing genome-wide association studies (GWAS). Reverse causality was also evaluated. MR utilizes genetic variants as IVs to infer causality between BPR and PCa [16]. For valid causal inference, three conditions must be met: 1) The IVs must be strongly related to the exposure (circulating BPR); 2) They must be independent of confounders; and 3) They should affect the outcome (PCa) solely through the exposure [17, 18]. The workflow for the MR analysis is depicted in Figure 1.

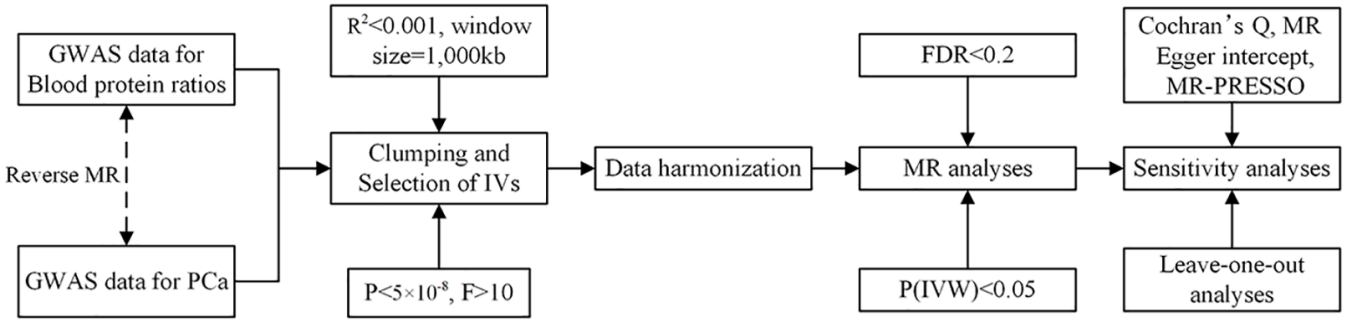

Fig. 1. Mendelian randomization workflow chart to study the relationship between blood pressure ratio and prostate cancer

2.2 Data sources

For data on circulating BPR, we referred to the latest authoritative studies. We utilized GWAS data on BPR from a recent study examining protein quantitative trait loci (pQTLs) [19]. This study employed Olink proteomics to measure 1,463 proteins in over 54,000 UK Biobank samples, resulting in data for 2,821 BPR, all from European populations (Table 1). Initially, individual protein levels were analyzed through a GWAS data, identifying over 10,000 pQTLs. Ratios between partially correlated protein pairs were then calculated and tested for genetic associations. These GWAS data on BPR are available on the GWAS Catalog website (https://www.ebi.ac.uk/gwas/).

We obtained GWAS data on PCa from the FinnGen database (https://www.finngen.fi/), the IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/), and the GWAS Catalog website (https://www.ebi.ac.uk/gwas/). Specifically, we utilized data from the FinnGen R11 cohort (C3_PROSTATE_EXALLC) [20], the PRACTICLE Consortium dataset (ieu-b-85), and the GWAS Catalog dataset (GCST90018905) [21]. The FinnGen R11 cohort includes 17,258 European PCa patients and 143,624 controls. The ieu-b-85 dataset comprises 79,148 PCa patients and 61,106 controls, while the GCST90018905 dataset includes 11,599 PCa patients and 199,628 controls, all from European populations. For detailed information on the sources of these data, refer to Table 1.

Table 1. Sources of data for Mendelian randomization analyses

Trait	Data Source	Ethnicity	Details
BPR	UK Biobank	European	2821 BPR
Prostate Cancer	FinnGen R11 cohort (C3_PROSTATE_EXALLC)	European	17,258 PCa patients and 143,624 controls
	PRACTICLE Consortium dataset (ieu-b-85)	European	79,148 PCa patients and 61,106 controls
	GWAS Catalog dataset (GCST90018905)	European	11,599 PCa patients and 199,628 controls

2.3 Instrumental variable selection

We conducted a stringent screening process to identify suitable IVs. IVs significantly associated with BPR at a genome-wide significance level ($p < 5 \times 10^{-8}$) were selected [22]. This rigorous standard ensures that the associations are robust and minimizes the risk of false positives due to multiple testing in GWAS. The R^2 value, indicating the proportion of variance in the exposure explained by these genetic variants, was calculated using the formula $R^2 = 2\beta^2/(2N \times SE^2 + 2\beta^2)$, where β is the regression coefficient, SE is the standard error, and N is the sample size [23]. To prevent confounding due to linkage disequilibrium (LD), we pruned single nucleotide polymorphisms (SNPs) using a clumping approach with an R^2 threshold of 0.001 within a window of 10,000 kb, ensuring independence among selected IVs [24]. The Two Sample MR package was utilized for SNP clumping. Weak IVs, identified by an F-statistic < 10, were excluded to avoid bias. The F-statistic is calculated using the formula: $F = ((N - k - 1) \times R^2)/((1 - R^2) \times k)$, where N is the sample size, R^2 is the proportion of variance explained by the IV, and k is the number of IVs [25]. The same criteria were applied for IV selection in reverse MR analysis.

2.4 Statistical analysis

This study utilized a two-sample MR method to examine the causal relationship between circulating BPR and PCa. The inverse-variance weighted (IVW) approach was used as a primary method for MR analysis, which combines the effect estimates of the IVs, weighted by the inverse of their variance, to produce an overall causal estimate [26]. To address multiple testing, the false discovery rate (FDR) correction was introduced using the Benjamini-Hochberg calculation method, ensuring that the significant results were not false positives [27]. Sensitivity analyses, containing MR-Egger, weighted median method, MR-PRESSO global test, and Cochran's Q statistic, were performed to detect and correct for pleiotropy and heterogeneity [28]. Leave-one-out analyses were also conducted to ensure robustness. All data analyses were performed using R programming software (version 4.4.0). In summary, the criteria for establishing a causal relationship included: 1) an IVW method p-value < 0.05 and an FDR < 0.2 [29]; 2) consistent directions across five MR analyses (MR-Egger, weighted median, IVW, simple mode, weighted mode) methods; and 3) no horizontal pleiotropy or heterogeneity evidence were detected. The same statistical methods were applied in the reverse MR analysis.

3 RESULTS

3.1 Causal relationship between blood pressure ratio and prostate cancer

By addressing LD and setting a stringent threshold ($p < 5 \times 10^{-8}$), we refined the dataset of 2,821 circulating blood proteins. This process also involved removing

duplicate SNPs and ensuring an F-statistic greater than 10 for robustness. These steps culminated in the selection of 44,499 SNPs to be used as the exposure data in our analysis, as detailed in Supplementary Table S1. This comprehensive filtration ensures that the SNPs employed are independent, significant, and strong instruments for subsequent analyses. Using BPR as the exposure, we conducted MR analyses with the three aforementioned PCa datasets as the outcomes. The results were obtained using five different MR methods. We used the results from the IVW method as the chief basis for determining the causal relationship between the exposure and the outcome. Using the FinnGen R11 cohort (C3_PROSTATE_EXALLC) as the outcome data, we discovered a strong causal association between the protein ratio of CEBPB/PXN and PCa (OR = 0.866346, 95% CI: 0.807979 – 0.928929, $p = 5.54 \times 10^{-5}$). The analysis of the MRC-IEU Consortium dataset (ieu-b-85) as outcome data also reveals a strong causal relationship between the APBB1IP/NCF2 protein ratio and PCa (OR = 0.856495, 95% CI: 0.794654 – 0.923148, $p = 5.09 \times 10^{-5}$). The GWAS Catalog dataset (GCST90018905) yielded the most extensive array of causal associations. Our findings indicate that the BPR of APP/EGF (OR=0.829465, 95% CI: 0.757549 – 0.908208, $p = 5.33 \times 10^{-5}$), ARHGAP1/RAD23B (OR = 1.282499, 95% CI: 1.127521 – 1.458779, p = 0.000153), CRKL/EGF (OR = 0.845028, 95% CI: 0.785432 – 0.909147, $p = 6.40 \times 10^{-6}$), EGF/TNFSF14 (OR = 1.154972, 95% CI: 1.083415 – 1.231254, $p = 1.01 \times 10^{-5}$), and GOLM2/STC1 (OR = 1.208384, 95% CI: 1.09025 – 1.339317, p = 0.000311) exhibit robust causal relationships with PCa, underscoring their potential as significant biomarkers for PCa (Supplementary Tables S2–S4). The results indicate that the BPR CEBPB/PXN, APBB1IP/NCF2, APP/EGF, and CRKL/EGF serve as protective factors against PCa. However, the BPR ARHGAP1/RAD23B, EGF/TNFSF14, and GOLM2/STC1 are identified as risk factors for PCa. The scatter plots depicting the causal relationships between each BPR and PCa are presented in Figure 2. Figure 3 presents a forest plot illustrating the causal relationships between BPR and PCa.

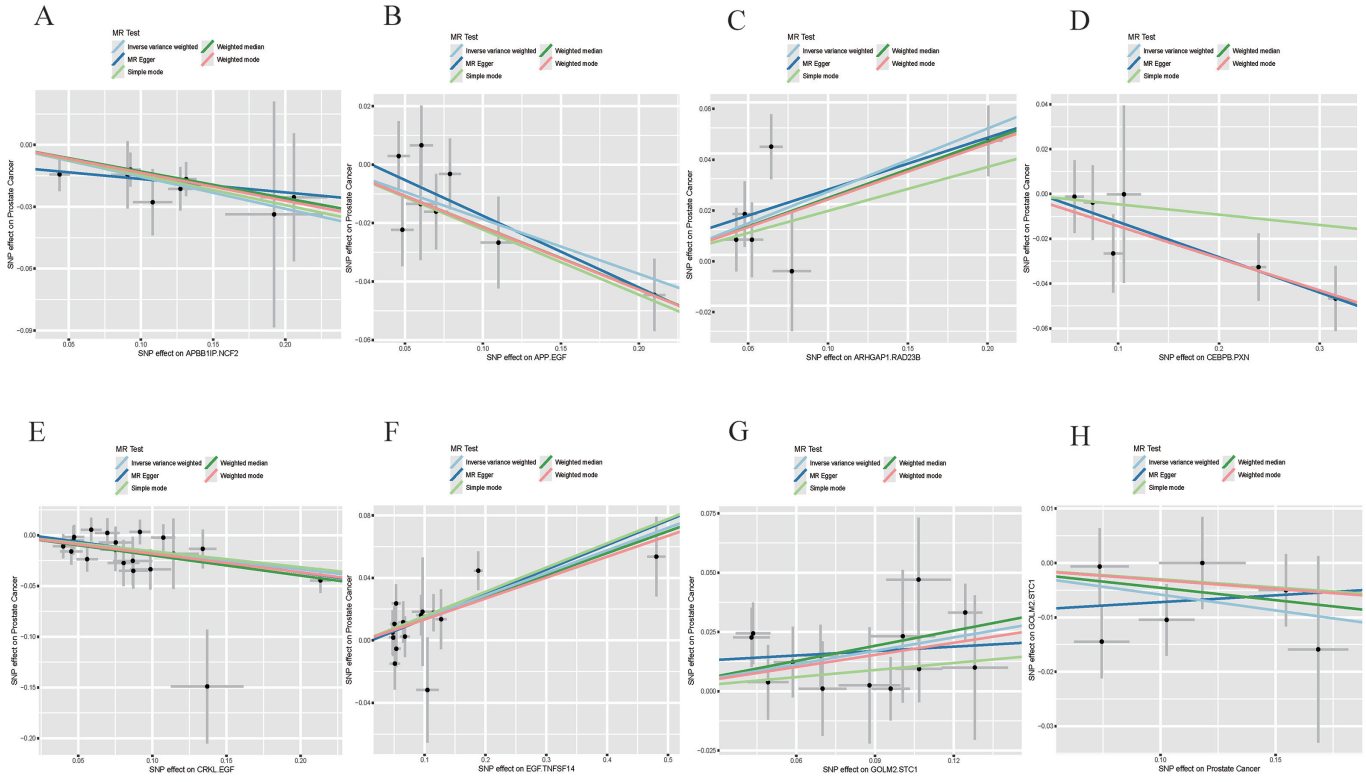

Fig. 2. Scatter plots show relationships between blood protein ratios and prostate cancer

Figure 2 illustrates the linear regression results of five MR methods, showing the causal relationships for the following BPR with PCa: (A) APBB1IP/NCF2, (B) APP/EGF, (C) ARHGAP1/RAD23B, (D) CEBPB/PXN, (E) CRKL/EGF, (F) EGF/TNFSF14, and (G) GOLM2/STC1. Additionally, it presents the reverse MR result (H), demonstrating the causal association between PCa and the GOLM2/STC1 protein ratio.

Exposure ID	nsnp	Method	pval	OR(95% CI)
GCST90313299	8	MR Egger	0.572	0.937 (0.758 to 1.159)
	8	Weighted median	**0.006**	0.879 (0.802 to 0.964)
	8	Inverse variance weighted	**<0.001**	0.856 (0.795 to 0.923)
	8	Simple mode	0.051	0.864 (0.765 to 0.976)
	8	Weighted mode	**0.042**	0.873 (0.785 to 0.972)
GCST90313322	8	MR Egger	**0.032**	0.783 (0.659 to 0.930)
	8	Weighted median	**<0.001**	0.808 (0.727 to 0.898)
	8	Inverse variance weighted	**<0.001**	0.829 (0.758 to 0.908)
	8	Simple mode	0.050	0.800 (0.666 to 0.962)
	8	Weighted mode	**0.005**	0.807 (0.727 to 0.897)
GCST90313343	6	MR Egger	0.173	1.227 (0.963 to 1.562)
	6	Weighted median	**0.001**	1.252 (1.093 to 1.433)
	6	Inverse variance weighted	**<0.001**	1.282 (1.128 to 1.459)
	6	Simple mode	0.276	1.189 (0.901 to 1.569)
	6	Weighted mode	**0.024**	1.244 (1.088 to 1.423)
GCST90314008	6	MR Egger	0.078	0.854 (0.749 to 0.974)
	6	Weighted median	**<0.001**	0.866 (0.803 to 0.934)
	6	Inverse variance weighted	**<0.001**	0.866 (0.808 to 0.929)
	6	Simple mode	0.504	0.955 (0.842 to 1.083)
	6	Weighted mode	**0.013**	0.866 (0.804 to 0.934)
GCST90314265	19	MR Egger	**0.017**	0.818 (0.704 to 0.950)
	19	Weighted median	**<0.001**	0.820 (0.742 to 0.905)
	19	Inverse variance weighted	**<0.001**	0.845 (0.785 to 0.909)
	19	Simple mode	0.124	0.854 (0.706 to 1.034)
	19	Weighted mode	**0.005**	0.833 (0.744 to 0.933)
GCST90314615	15	MR Egger	**0.010**	1.171 (1.057 to 1.296)
	15	Weighted median	**0.002**	1.150 (1.054 to 1.255)
	15	Inverse variance weighted	**<0.001**	1.155 (1.083 to 1.231)
	15	Simple mode	**0.040**	1.168 (1.021 to 1.337)
	15	Weighted mode	**0.010**	1.143 (1.047 to 1.248)
GCST90314952	13	MR Egger	0.684	1.064 (0.796 to 1.421)
	13	Weighted median	**0.003**	1.237 (1.076 to 1.423)
	13	Inverse variance weighted	**<0.001**	1.208 (1.090 to 1.339)
	13	Simple mode	0.446	1.105 (0.863 to 1.414)
	13	Weighted mode	0.099	1.186 (0.984 to 1.429)

Fig. 3. Forest plot showing the relationship between blood protein ratios and prostate cancer

CI: confidence interval; nsnp: numbers of SNP used in each MR analysis; pval: p value; GCST90313299: APBB1IP to NCF2 ratio; GCST90313322: APP to EGF ratio; GCST90313343: ARHGAP1 to RAD23B ratio; GCST90314008: CEBPB to PXN ratio; GCST90314265: CRKL to EGF ratio; GCST90314615: EGF to TNFSF14 ratio; GCST90314952: GOLM2 to STC1 ratio.

3.2 Reverse Mendelian randomization analyses

Furthermore, we utilized the three PCa GWAS datasets as exposure variables and the original data of the seven BPR, which exhibited forward causal relationships, as outcome variables to conduct reverse MR analyses. This approach aimed to further investigate whether PCa influences BPR. Each of the three PCa datasets was

meticulously adjusted to exclude LD ($p < 5 \times 10^{-8}$, $r^2 < 0.001$, window size = 1000 kb), ensuring the robustness and accuracy of our findings (Supplementary Tables S5–S7). Based on the results of forward MR, we reversed the positions of the exposure and outcome and conducted seven sets of reverse MR analyses. We continued to use the IVW method as the dominant indicator for determining the presence of a causal relationship. The results revealed a causal relationship only between PCa and the GOLM2/STC1 protein ratio (OR = 0.94349, 95% CI: 0.893645 – 0.996115, p = 0.035679), suggesting that PCa may act as a protective factor for the GOLM2/STC1 ratio (Supplementary Table S8).

3.3 Sensitivity analyses

We conducted extensive sensitivity analyses to validate the causal relationship between circulating blood proteins and PCa. Results of Cochran's Q test showed no significant heterogeneity among IVs for all circulating blood proteins ($p > 0.05$), as detailed in Supplementary Table S9. The funnel plot displayed no noticeable asymmetry, indicating an absence of significant heterogeneity among the SNPs used as IVs (Supplementary Figure 1). Furthermore, p-values of MR-Egger intercept tests and MR-PRESSO global tests were greater than 0.05, suggesting no evidence of horizontal pleiotropy affecting the MR results (Supplementary Tables S10 and S11). Additionally, leave-one-out analyses confirmed the robustness of our findings, demonstrating that no single IV disproportionately influenced the results (Supplementary Figure 2). These comprehensive analyses reinforce the reliability of our conclusions regarding the causal association between circulating blood proteins and PCa. The results of the sensitivity analysis for the reverse MR between PCa and the GOLM2/STC1 protein ratio did not detect any horizontal pleiotropy or heterogeneity, demonstrating the robustness of the findings (Supplementary Tables S12–S14).

4 DISCUSSION

This pioneering MR study, investigating the causal relationship between BPR and PCa, offers significant advancements in oncology. By minimizing confounding factors, it provides robust causal inferences that deepen our understanding of PCa pathophysiology. The identification of specific BPR linked to PCa risk reveals new biological pathways, suggesting novel biomarkers for early detection and prognosis. These insights facilitate the development of targeted therapeutic strategies, offering potential for personalized treatments and improved patient outcomes. Additionally, this research sets a precedent for future studies, encouraging the exploration of genetic and proteomic data to discover further cancer-related biomarkers, thereby enhancing diagnostics, treatment, and our comprehensive understanding of cancer biology.

CEBPB is a transcription factor involved in regulating various cellular activities, including differentiation, proliferation, and apoptosis. Its expression patterns and functional roles can vary significantly depending on the cellular context. CEBPB can stimulate autophagy in PCa cells by inducing the formation of autolysosomes [30]. PXN (Paxillin), on the other hand, is a cytoskeletal protein associated with focal adhesions and is involved in cell motility. High PXN expression has been linked to cancer progression and metastasis in various cancer types, including PCa. It facilitates the interaction between the cytoskeleton and the extracellular matrix, which is crucial

for cell movement and invasion [31]. The CEBPB/PXN protein ratio may exert a protective effect in PCa by modulating these critical pathways. High levels of CEBPB could potentially counteract the pro-tumorigenic effects of PXN by promoting cellular differentiation and apoptosis while inhibiting proliferation and migration. Research has indicated that inhibiting the androgen receptor (AR) can trigger a swift increase in CEBPB expression [32]. This balance might prevent the aggressive behavior of cancer cells, thereby inhibiting tumor growth and metastasis. Additionally, the anti-inflammatory effects of CEBPB might reduce the inflammatory milieu that often supports tumor progression.

APBB1IP, also known as the Rap1-GTP-interacting adaptor molecule, is involved in integrin activation and cell adhesion. It plays a critical role in the regulation of immune cell function. Enhanced expression of APBB1IP has been linked to improved immune surveillance and anti-tumor responses by facilitating the proper functioning of immune cells, for instance, T-cells and neutrophils [33]. NCF2, a component of the NADPH oxidase complex, is essential for the production of reactive oxygen species (ROS) in phagocytes. While ROS are crucial for microbial killing and inflammation, excessive ROS can promote tumor progression by inducing DNA damage and supporting a pro-tumorigenic environment. However, NCF2's role in cancer is context-dependent, and its overexpression has been associated with various malignancies, including PCa [34, 35]. The APBB1IP/NCF2 protein ratio might act as a protective factor against PCa through several mechanisms. High levels of APBB1IP could enhance immune cell adhesion and migration, boosting anti-tumor immunity and facilitating the destruction of cancer cells. Conversely, lower levels of NCF2 might reduce ROS production, minimizing DNA damage and the pro-tumorigenic effects of chronic inflammation. This balance could prevent the initiation and progression of PCa by maintaining effective immune responses while limiting harmful oxidative stress.

Amyloid beta precursor protein (APP) is known primarily for its role in the nervous system, particularly in Alzheimer's disease. However, recent research has suggested that APP might also play a role in cancer biology. In PCa, APP has been shown to interact with various cellular pathways that regulate cell growth, differentiation, and apoptosis [36]. CRKL (CRK Like Proto-Oncogene) is an adaptor protein that participated in several critical signaling pathways that regulate cell proliferation, survival, and migration. It functions by linking receptor tyrosine kinases to downstream signaling molecules, thus playing a pivotal role in cellular communication and response to external stimuli. Overexpression of CRKL has been associated with various cancers, including PCa, where it contributes to tumor growth and metastasis by enhancing signaling pathways such as RAS/RAF/MEK/ERK and PI3K/AKT [37]. EGF and its receptor, EGFR, are critical in the regulation of cell growth, survival, and differentiation. The overexpression and activation of EGFR have been strongly associated with the progression and metastasis of various malignancies, including PCa. EGFR promotes oncogenic signaling through pathways such as PI3K/AKT and MAPK, leading to increased tumor cell survival, proliferation, and invasion [38, 39]. Despite the elevated expression of APP and CRKL that could promote cancer growth, low levels of EGF would result in reduced activation of EGFR, thereby diminishing its pro-tumorigenic effects [40]. Thus, the APP/EGF and CRKL/EGF protein ratios may act as protective factors against PCa through the mechanisms described above.

TNFSF14, also known as LIGHT, is a member of the TNF superfamily involved in immune responses and inflammation. LIGHT interacts with receptors like HVEM and LTβR [41], which are expressed on various immune cells. Its role in cancer is complex. It can enhance anti-tumor immune responses by promoting the recruitment and

activation of immune cells within the tumor microenvironment. However, LIGHT's function can be context-dependent and may also contribute to tumor progression by influencing the tumor immune microenvironment [42]. The EGF/TNFSF14 protein ratio could act as a risk factor for PCa through several mechanisms. High levels of EGF may enhance tumorigenic signaling pathways, leading to increased cell proliferation, survival, and metastasis [43]. Conversely, low levels of TNFSF14 might reduce anti-tumor immune responses, allowing the tumor to evade immune surveillance and grow unchecked. This imbalance could create a tumor microenvironment conducive to cancer progression, making the EGF/TNFSF14 protein ratio a potential biomarker for PCa risk.

ARHGAP1 is a member of the RhoGAP family, which plays a critical role in regulating the Rho family of GTPases. These GTPases are involved in various cellular processes, including cell morphology, migration, and cell cycle progression. In cancer, dysregulation of Rho GTPase signaling has been implicated in promoting metastasis and tumor progression by affecting the cytoskeletal organization and cellular adhesion properties. Overexpression of ARHGAP1 has been associated with enhanced cell migration and invasion [44], potentially contributing to the aggressive behavior of PCa cells. RAD23B is a key protein involved in the nucleotide excision repair (NER) pathway, which is crucial for repairing DNA damage caused by UV radiation and other genotoxic stresses. Proper functioning of the NER pathway is essential for maintaining genomic stability. Deficiencies in RAD23B have been linked to increased susceptibility to various cancers due to impaired DNA repair mechanisms leading to genomic instability and accumulation of mutations [45]. The ARHGAP1/RAD23B protein ratio might act as a risk factor for PCa through its combined impact on cellular signaling and DNA repair mechanisms. High levels of ARHGAP1 could enhance cellular motility and invasive potential, while low levels of RAD23B might compromise DNA repair capacity, leading to increased mutation rates and tumor progression.

Golgi membrane protein 2 (GOLM2), a protein involved in the processing and transport of proteins within the Golgi apparatus, has been implicated in various cellular functions, including protein glycosylation and trafficking. In the context of cancer, alterations in glycosylation patterns are known to affect tumor cell behavior, including growth, adhesion, and metastasis. Overexpression of GOLM2 has been observed in several cancers, where it may enhance tumor progression by facilitating the secretion and function of oncogenic factors [46]. STC1 (Stanniocalcin 1), a glycoprotein involved in calcium and phosphate homeostasis, has been associated with the regulation of cell proliferation, apoptosis, and angiogenesis. Increased expression of STC1 has been linked to the progression of various malignancies, including PCa. STC1 is believed to promote tumor growth and metastasis by enhancing cell survival and resistance to apoptosis, as well as by stimulating angiogenesis, which provides the necessary blood supply for tumor expansion [47]. The GOLM2/STC1 protein ratio could act as a risk factor for PCa through several mechanisms. Elevated levels of GOLM2 might enhance the processing and secretion of STC1, and the quantity of GOLM2 secreted may be significantly greater than that of STC1, thereby amplifying its pro-tumorigenic effects. This interplay could lead to increased tumor cell proliferation, survival, and metastatic potential. Additionally, the GOLM2-mediated alterations in glycosylation patterns might further enhance the functional capabilities of STC1, contributing to a more aggressive cancer phenotype. Additionally, reverse MR indicates that PCa acts as a protective factor for the GOLM2/STC1 protein ratio. Possible mechanisms are as follows: First, in response to tumor growth, the body may attempt to regulate and mitigate the cancer's effects. The high

GOLM2/STC1 ratio seen in aggressive tumors might trigger feedback mechanisms that inhibit further proliferation or activate immune responses. Second, treatments targeting PCa can alter the expression of these proteins. For instance, therapies that reduce GOLM2 or STC1 expression can lead to tumor regression. Post-treatment changes in these protein levels might reflect the body's protective adaptation to reduce cancer recurrence.

The results of this study align with and expand upon previous research that has explored the role of proteomic biomarkers in PCa. For instance, earlier studies have identified several proteins, including PSA, as key biomarkers in PCa detection and monitoring. However, the current study's use of MR provides a novel approach by establishing causal links between specific BPR and PCa risk, which adds a deeper level of understanding to these associations. This approach differs from traditional observational studies, which often struggle with confounding factors and reverse causality. Comparisons with other recent studies, such as those employing high-throughput proteomics, reveal a consistent identification of key proteins involved in PCa progression but also highlight the need for further validation in diverse populations and across different stages of the disease. These comparisons underscore the potential of BPR as robust biomarkers that could enhance current diagnostic and prognostic tools in clinical practice [5, 12, 48].

The findings of this study have significant implications for both future research and clinical practice in the field of PCa. By establishing causal relationships between specific BPR and PCa risk through MR, this study paves the way for the development of more precise diagnostic tools and targeted therapies. These results suggest that BPR could serve as reliable biomarkers not only for early detection but also for predicting disease progression and patient response to treatment. This is particularly relevant in the era of personalized medicine, where understanding the molecular underpinnings of cancer at an individual level can lead to tailored therapeutic strategies.

Future research should focus on validating these findings in diverse populations and exploring the underlying mechanisms by which these proteins influence PCa development and progression. Additionally, integrating these biomarkers into clinical practice could enhance current screening protocols, potentially reducing reliance on invasive procedures like biopsies. The application of such biomarkers in routine clinical settings could lead to earlier detection, better prognosis, and more effective management of PCa, ultimately improving patient outcomes. Furthermore, these insights could stimulate research into other cancers, where similar proteomic approaches might unveil novel diagnostic and therapeutic targets [49].

Our study offers several significant advantages. Primarily, we are the first to employ MR to investigate the causal relationship between BPR and PCa. MR leverages genetic variants as IVs, which are randomly allocated at conception, effectively mimicking the randomization in a randomized controlled trial (RCT). This design minimizes confounding factors typically encountered in observational studies. Moreover, genetic variants are measured with a high degree of precision, avoiding the measurement errors common in self-reported exposures, thereby providing a robust method for causal inference. Additionally, genetic variants are stable across populations, enhancing the generalizability and reproducibility of our MR findings across various cohorts and settings. Despite these strengths, our study also faces certain limitations and challenges. Firstly, the GWAS data on BPR predominantly originates from European populations, potentially limiting the generalizability of our findings to other ethnic groups due to genetic and environmental differences. Secondly, the GWAS data does not capture patients at various pathological stages of PCa, hindering our ability to assess dynamic changes in BPR throughout disease

progression. Lastly, while we have identified causal relationships between seven protein ratios and PCa and proposed potential molecular and pathological mechanisms, these findings require validation through further laboratory research. Additionally, unknown mechanisms may not have been accounted for in our study. Addressing these limitations in future research will enhance the robustness and applicability of our results, providing a deeper understanding of PCa pathophysiology and aiding in the development of targeted diagnostic and therapeutic strategies.

5 CONCLUSION

This study has provided valuable insights into the role of BPR in the diagnosis and management of PCa, particularly through the use of MR to establish causal relationships. The identification of specific BPR as potential biomarkers could significantly enhance early detection and personalized treatment strategies, ultimately improving patient outcomes. However, there are limitations that must be acknowledged. The study primarily utilized data from European populations, which may limit the generalizability of the findings to other ethnic groups. Additionally, the reliance on publicly available genetic data may introduce biases related to data quality and completeness. Future research should focus on validating these findings in more diverse populations and employing larger, more comprehensive datasets. Further investigation into the biological mechanisms underlying these associations is also necessary to fully understand the role of BPR in PCa progression and to translate these findings into clinical practice.

5.1 Conflict of interest

The author declares that this study was conducted without any potential conflicts of interest.

5.2 Contributions of authors

ZJ: Writing–original draft, supervision, software, formal analysis, conceptualization. JS: Writing–review & editing, software, formal analysis, data curation. YZ: Software, formal analysis, data curation. YH: Writing–review & editing, investigation, conceptualization.

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5.5 Data availability statement

All data and their sources used in this study can be found in detail in the main text and supplementary materials (https://tinyurl.com/454fm66a). If you need more information, please contact the corresponding author of this article.

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