Prostate International 12 (2024) 167–177

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Research Article

Insights from immunomics and metabolomics on the associations between prostatic diseases and coronavirus disease 2019

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A R T I C L E I N F O

Article history:
Received 10 June 2024
Received in revised form
12 July 2024
Accepted 22 July 2024
Available online 25 July 2024

Keywords:
COVID-19
Immunity
Metabolites
Mendelian randomization
Prostatic diseases
Prostatitis

A B S T R A C T

Background: The causal associations and potential mechanisms between prostatic diseases, the predominant male urological disorders, and the course of COVID-19 remain unclear.
Methods: A two-sample Mendelian randomization (MR) analysis was performed to evaluate causal associations between prostate cancer, benign prostatic hyperplasia, and prostatitis and different COVID-19 outcomes (SARS-CoV-2 infection, hospitalized COVID-19, and severe COVID-19). Reverse MR, linkage disequilibrium score regression, and Bayesian colocalization analyses were subsequently performed to strengthen the identified causal relationships. Furthermore, immunome- and metabolome-wide MR analysis was conducted to prioritize COVID-19-associated immune characteristics and metabolites. Two-step MR analysis was performed to evaluate the mediating effects of the immunome and metabolome on the associations between prostatic diseases and COVID-19.
Results: Genetically predicted prostatic diseases were not causally associated with severe COVID-19, while prostatitis was suggested to be an independent risk factor for SARS-CoV-2 infection (odds ratio (OR) = 1.11, 95% confidence interval (CI) 1.01 to 1.23; $P = 0.03$). Multiple sensitivity tests verified the reliability of the established causal relationships. Dozens of blood immune and metabolic features were identified to reveal the immune and metabolic profiles of different COVID-19 courses. Moreover, PDL-1 on monocyte was found to mediate the interaction between prostatitis and SARS-CoV-2 infection, with a mediation proportion of 9.2%.
Conclusion: Our study identified the causal relationships of prostatic diseases with COVID-19 and suggested pathways explaining these associations through alterations in the blood immunome and metabolome.

1. Introduction

Since the onset of the COVID-19 pandemic in 2019, it has posed a significant public health threat nationwide. The emergence of continuous mutant strains of COVID-19 has heightened concerns regarding viral reinfection and transmission.[1] Researchers have identified ACE2 as the receptor for SARS-CoV-2, which mediates viral entry into host cells.[2] The infection of organs by viruses depends on the co-expression of ACE2 and TMPRSS2.[2] While the virus predominantly targets the lungs, co-expressing ACE2 and TMPRSS2 has also been detected in other organs, including the prostate.[3] Interestingly, there are gender disparities in the morbidity and

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https://doi.org/10.1016/j.prnil.2024.07.003
p2287-8882 e2287-903X/

mortality rates of severe COVID-19, with males exhibiting a greater likelihood of severe illness.[4] Prostatic diseases, including prostate cancer, benign prostatic hyperplasia (BPH), and prostatitis, are prevalent urological conditions among men. The co-occurrence of these high-prevalence prostatic diseases with the COVID-19 pandemic has raised concerns among urologists regarding the potential impact of prostatic diseases on the severity of COVID-19.

Patients with prostate diseases exhibit alterations in immune responses, metabolism, microbiome, and other micro-environments,[5–8] which may pose risk conditions for COVID-19. Recent studies have investigated the links between COVID-19 and prostate cancer, revealing that individuals recently diagnosed with prostate cancer were more susceptible to COVID-19 and had a poorer prognosis.[9] Furthermore, research examining various cancer types, including prostate cancer, has reported higher 30-day mortality rates in cancer patients infected with COVID-19.[10] Notably, chronic prostatitis is the most common urinary tract disease in men under 50 years of age, with over half of Chinese males estimated to be afflicted with this condition.[11] On the other hand, BPH is prevalent in men over 50, affecting 70% of males over 60 and rising to 90% among those over 80.[12] Despite the high prevalence of BPH and prostatitis, their associations with COVID-19 have not been extensively explored.

To assess the causal relationships between prostatic diseases and COVID-19, this study employed Mendelian randomization (MR). MR was a robust approach that enabled the determination of diseases causality unbiased by environmental confounders, leveraging genetic variants assigned at birth.[13] Specifically, two-sample MR analysis was utilized to investigate the causal associations between prostatic diseases and susceptibility, hospitalization, and severity of COVID-19. Furthermore, potential mechanisms underlying the interaction between prostatic disease and COVID-19 mediated by immune characteristics and the blood metabolome were explored using two-step MR analysis.

2. Methods

As with other statistical methods, Mendelian randomization analysis follows three major assumptions (correlation, independence, and exclusion restriction assumption) (Supplementary Fig. 1). These assumptions allow genetic variants to serve as proxies for modifiable exposures, facilitating the estimation of causal effects on outcomes. The details of the study design were displayed in Fig. 1, and more specific method description was presented in Supplementary Materials.

2.1. GWAS data sources

2.1.1. Data sources for prostatic diseases and comorbid factors

For prostate cancer, we obtained GWAS data from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome consortium[14] with a sample size of 140,254 individuals. Patient inclusion criteria were based on pathological or self-reported diagnoses within the PRACTICAL consortium and the ICD-10 C61 code. To minimize the impact of sample randomness, we chose two independent GWASs for BPH and prostatitis. The GWAS data for BPH and prostatitis were extracted from the UK Biobank and FinnGen consortium, with sample sizes ranging from 134,299 to 183,888 individuals. Inclusion criteria for UK Biobank participants included ICD-10 N40 code or surveys by the Office of Population and Censuses for BPH, and diagnosis of chronic or acute bacterial prostatitis for prostatitis; FinnGen used ICD-10 N40 for BPH and N41 for prostatitis. A genome-wide meta-analysis was performed for two independent GWASs of BPH and prostatitis using a fixed effects model through METAL software.[15]

We searched for the major comorbid factors of prostate cancer, including smoking, alcohol consumption, diabetes status, obesity, hypertension, and a high-fat diet, based on previous meta-analysis studies (Supplementary Table 1). The detailed sources of GWAS data for comorbid factors can be found in Table 1.

2.1.2. Data sources for three different COVID-19 outcomes

Three largest GWAS datasets from the COVID-19 Host Genetics Initiative Consortium[16] were chosen for the outcome of SARS-CoV-2 infection, hospitalized COVID-19, and severe COVID-19, with sample sizes of 2,297,856, 2,095,324 and 1,086,211 individuals, respectively. SARS-CoV-2 infection was defined through laboratory testing, clinical confirmation, or self-reported diagnosis. Hospitalized COVID-19 were defined as patients admitted to the hospital with COVID-19 symptoms. Severe COVID-19 were defined as patients with severe respiratory failure secondary to COVID-19.

2.2. Statistical analyses

A threshold *P*-value less than 5×10^{-8} and a linkage disequilibrium threshold of an r2 cutoff of 0.001 within a 10 Mb window were applied. A larger threshold of 5×10^{-6} was introduced to achieve enough genetic variants for immune characteristics and the blood metabolome. The strength of association of the genetic variants for prostatic diseases and comorbid factors was quantified by the *F*-statistic, and all SNPs with *F*-statistics less than 10 were removed to ensure statistical strength. To minimize pleiotropy caused by potential confounders, the SNPs associated with potential confounders identified through previous meta-analysis studies were removed using the PhenoScanner database (Supplementary Tables 1 and 2).

As the primary method of MR analysis, we used inverse variance weighted (IVW) to separately assess the causal effects. Heterogeneity was quantified through Cochran's Q test. For results with heterogeneity, we employed the IVW method with a random effects model, while a fixed effects model was used for results without heterogeneity. To ensure robust results, three additional methods, MR Egger, the weighted median, and the weighted mode, were carried out for sensitivity testing.

The relationships estimated by MR analysis could be interpreted as follows: 1) causal association; 2) reverse causation; 3) biased by horizontal pleiotropy; and 4) interference by genetic correlation or linkage disequilibrium (LD). To determine the causal inference linking prostatic diseases with COVID-19, we extended our investigation through several sensitivity analyses. 1) To exclude reverse causality, we conducted reverse MR analysis to evaluate the causal effects of COVID-19 on prostatic diseases. 2) To assess pleiotropy, MR Egger regression was calculated. The MR pleiotropy residual sum and outlier (MR-PRESSO) test was performed to further remove outliers causing pleiotropy. 3) To mitigate the impact of overall genetic correlation, we employed linkage disequilibrium score regression (LDSC) analysis to evaluate comprehensive genetic correlation.[17] 4) To account for linkage disequilibrium, we adopted Bayesian colocalization analysis to investigate whether the identified causality could be driven by LD among shared genetic loci.[18] Two-step MR analysis was conducted to evaluate the potential mediating effects of COVID-19-related immune characteristics and circulating metabolism on the causal associations between prostatitis and SARS-CoV-2 infection. As in previous studies, only immune characteristics and metabolites with consistent total and mediation effects were included in the mediation analyses.[19]

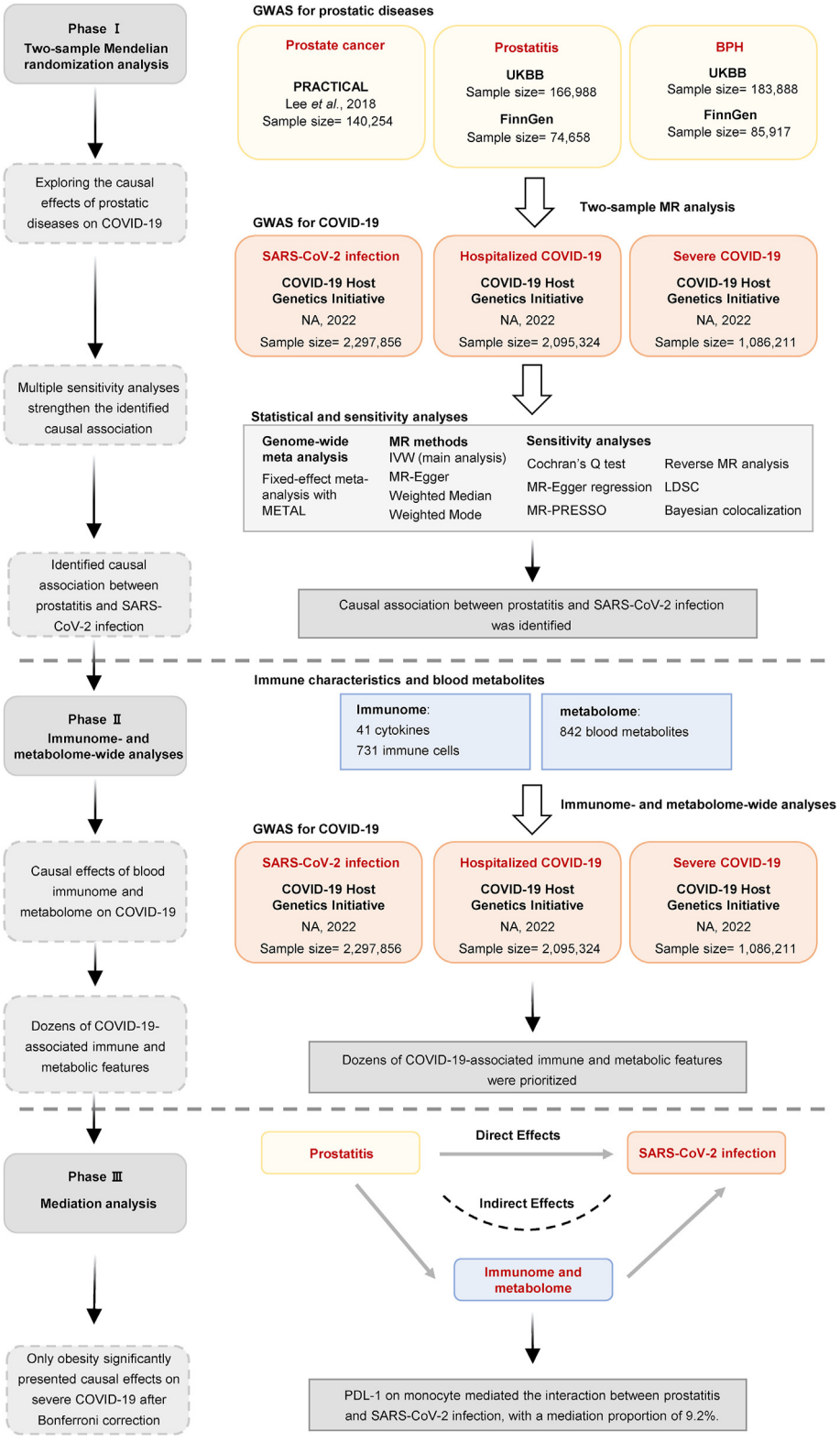

Fig. 1. Overall study design.

Table 1
Detailed information on used studies

Phenotypes		Data source (Consortium)	Sexes	Sample size	Author, published year	PMID
Prostatic diseases						
Prostate cancer		PRACTICAL	males	140,254	Schumacher et al., 2018	29892016
Benign prostatic hyperplasia		UKBB	males	183,888	NA, 2018	NA
		FinnGen	males	163,095	NA, 2023	NA
Prostatitis		UKBB	males	166,988	NA, 2018	NA
		FinnGen	males	134,299	NA, 2023	NA
Comorbid factors for prostate cancer[a)]						
Smoking	Current tobacco smoking	UKBB	combined	462,434	NA, 2018	NA
	Ever smoked	UKBB	combined	461,066	NA, 2018	NA
	Cigarettes smoked per day	GSCAN	combined	249,752	Liu et al., 2019	30643251
Alcohol	Alcohol intake frequency	UKBB	combined	462,346	NA, 2018	NA
Diabetes	Type 2 diabetes	NA	combined	655,666	Xue et al., 2018	30054458
	Fasting glucose	NA	combined	200,622	Chen et al., 2021	34059833
	Fasting insulin	NA	combined	151,013	Chen et al., 2021	34059833
Hypertension	Diastolic blood pressure	International Consortium of Blood Pressure	combined	757,601	Evangelou et al., 2018	30224653
	Systolic blood pressure	International Consortium of Blood Pressure	combined	757,601	Evangelou et al., 2018	30224653
Obesity	Hip circumference	GIANT	combined	224,459	Shungin et al., 2015	25673412
	Waist circumference	GIANT	combined	232,101	Shungin et al., 2015	25673412
	Body mass index	GIANT	combined	339,224	Shungin et al., 2015	25673412
	Waist-to-hip ratio	GIANT	combined	212,244	Shungin et al., 2015	25673412
High-fat diet	Saturated fatty acids	NA	combined	114,999	Borges et al., 2020	NA
	Total fatty acids	NA	combined	114,999	Borges et al., 2020	NA
	Monounsaturated fatty acids	NA	combined	114,999	Borges et al., 2020	NA
	Polyunsaturated fatty acids	NA	combined	114,999	Borges et al., 2020	NA
COVID-19						
SARS-CoV-2 infection		COVID-19 Host Genetics Initiative	combined	2,597,856	NA, 2022	NA
Hospitalized COVID-19		COVID-19 Host Genetics Initiative	combined	2,095,324	NA, 2022	NA
Severe COVID-19		COVID-19 Host Genetics Initiative	combined	1,086,211	NA, 2022	NA
Immune characters and blood metabolome						
Circulating cytokines and growth factors		-	combined	8,290	Ahola-Olli et al., 2017	27989323
Immune cells		-	combined	3,757	Orrù et al., 2020	32929287
Human blood metabolites		-	combined	7,824	Shin et al., 2014	24816252
Circulating metabolites		-	combined	24,925	Kettunen et al., 2016	27005778
Metabolic biomarkers		UKBB	combined	115,078	NA, 2018	NA

GIANT, Genetic Investigation of ANthropometric Traits; GSCAN, GWAS & Sequencing Consortium of Alcohol and Nicotine use; PRACTICAL, Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; UKBB, UK Biobank.
UKBB: http://www.nealelab.is/uk-biobank.
FinnGen: https://www.finngen.fi/fi.
COVID-19 Host Genetics Initiative: https://www.covid19hg.org/results/r7/.
[a)] Major comorbid factors of prostate cancer, including smoking, alcohol consumption, diabetes status, obesity, hypertension, and a high-fat diet, based on previous meta-analysis studies.

3. Results

3.1. Causal effects of genetically predicted prostatitis on SARS-CoV-2 infection

After removing SNPs associated with confounding factors through the PhenoScanner database, a total of 131, 21, and 6 SNPs were extracted as genetic instrumental variants for prostate cancer, BPH, and prostatitis, respectively, while 13, 29, and 26 SNPs were filtered as instruments for SARS-CoV-2 infection, Hospitalized COVID-19, and Severe COVID-19, respectively (Supplementary Tables 3 and 4). All the instrumental variables were of sufficient strength to achieve *F*-statistics greater than 10.

MR analysis suggested that prostatitis, rather than prostate cancer, was genetically associated with COVID-19. The causal effects of prostate cancer and BPH on SARS-CoV-2 infection, hospitalized COVID-19, and severe COVID-19 were not significant ($P < 0.05$). Genetically predicted prostatitis was causally associated with increased susceptibility to SARS-CoV-2, with odds ratios (ORs) of 1.11 (95% confidence intervals (CIs) 1.01 to 1.23, $P = 0.03$), despite no associations with hospitalization or severity of COVID-19 (Fig. 2). These findings were consistent across the IVW, MR Egger, weighted median, and weighted mode methods, as presented in Supplementary Table 5.

3.2. Results from reverse MR, genetic correlation, and colocalization analyses

To reinforce the identified causation between prostatitis and SARS-CoV-2 infection, multiple additional sensitivity analyses were also conducted (Supplementary Tables 6–9). Reverse MR results revealed noncausal effects of COVID-19 on prostatic diseases, suggesting that reverse causation would not interfere with the causal associations (Fig. 3a). Mild pleiotropy was observed in the associations between hospitalized patients and severe COVID-19 and BPH patients. The removal of outliers by MR-PRESSO corrected for pleiotropy, although the significance of the causal effect did not change after removal of these outliers (Supplementary Table 7). LDSC analysis revealed genetic correlations among the three COVID-19 outcomes and among each of the three prostatic diseases, as expected. Moreover, significant genetic correlations were found between BPH and hospitalized COVID-19, as well as between prostatitis and severe COVID-19. Interestingly, no genetic correlation was detected between prostatitis and SARS-CoV-2 infection, suggesting that the causal

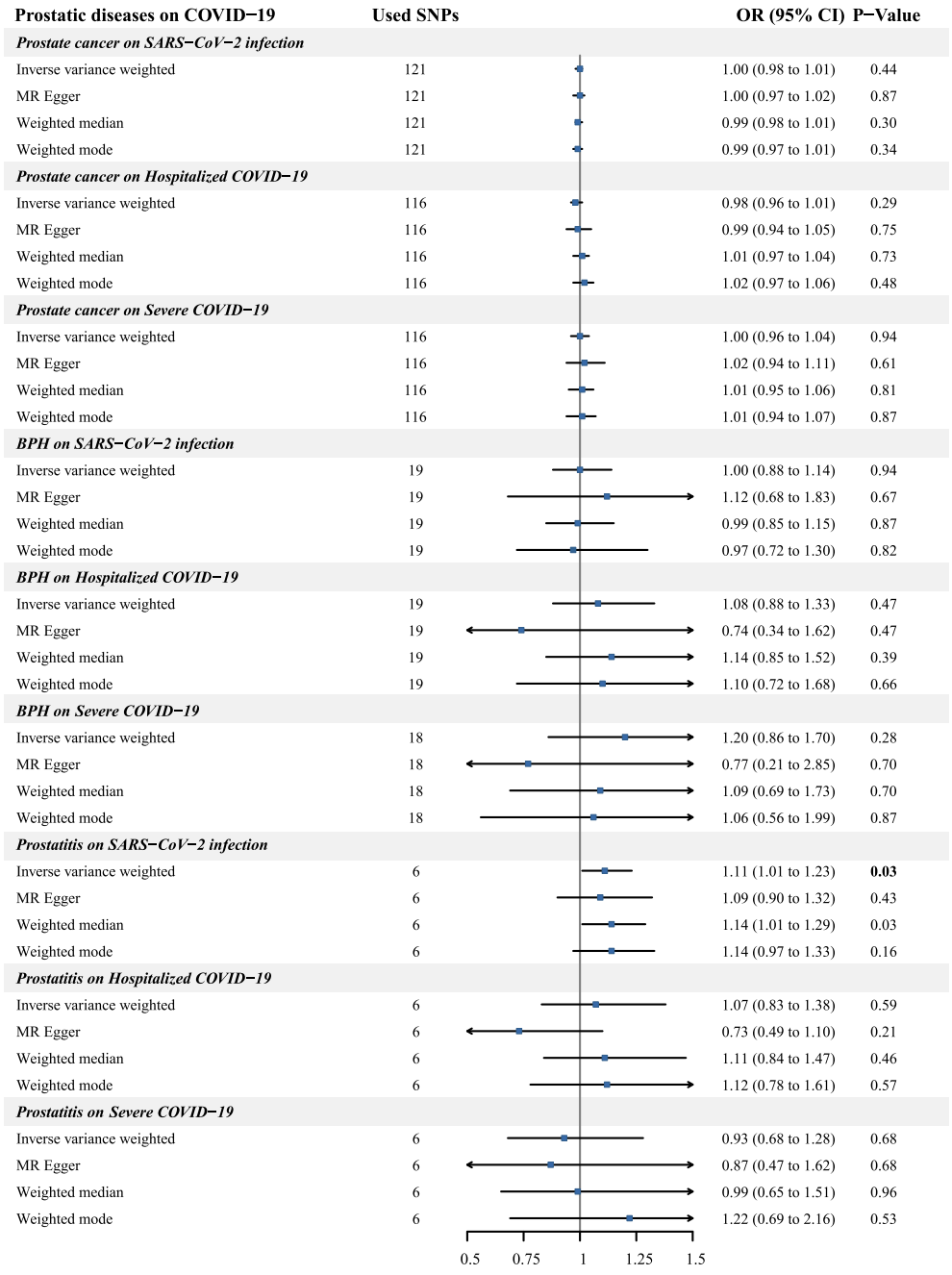

Fig. 2. Forest plot for the causal associations between prostatic diseases with COVID-19. Inverse variance weighted, MR-Egger, weighted median, and weighted mode presented different MR models, and inverse variance weighted was considered the primary analysis method. Statistically significant results ($P < 0.05$) were indicated in bold font.

association was not disturbed (Fig. 3b). Bayesian colocalization analysis indicated that the probability of sharing the same genetic locus between prostatitis and SARS-CoV-2 infection or of having linkage disequilibrium among their major SNPs was low, eliminating the disturbance of linkage disequilibrium (Fig. 3c).

3.3. Causal associations between comorbid factors of prostate cancer and COVID-19

We further explored the causal associations between prostate cancer-related comorbid factors and COVID-19. The 17 major comorbid factors of prostatic diseases were extracted from previous meta-analysis studies and are presented in Table 1. The MR results suggested that genetically predicted Body mass index (BMI), hip circumference (HC), waist circumference (WC), waist-to-hip ratio (WHR), smoking per day, and systolic blood pressure (SBP) were causally associated with the three different COVID-19 outcomes. To control for the incidence of type I errors, we used the Bonferroni-corrected *P*-value ($P = 9.8 \times 10^{-4}$, $\alpha = 0.05/51$) as the significance threshold. We found that only BMI, HC, and WC had significant effects on SARS-CoV-2 infection, hospitalized COVID-19, and severe COVID-19 after the adjusted threshold was applied (Fig. 4 and Supplementary Table 10).

3.4. Results from immunome- and metabolome-wide MR analysis of COVID-19

Immunome- and metabolome-wide MR analyses, which included 772 immune characteristics and 842 blood metabolites, were also conducted to explore the COVID-19-associated blood

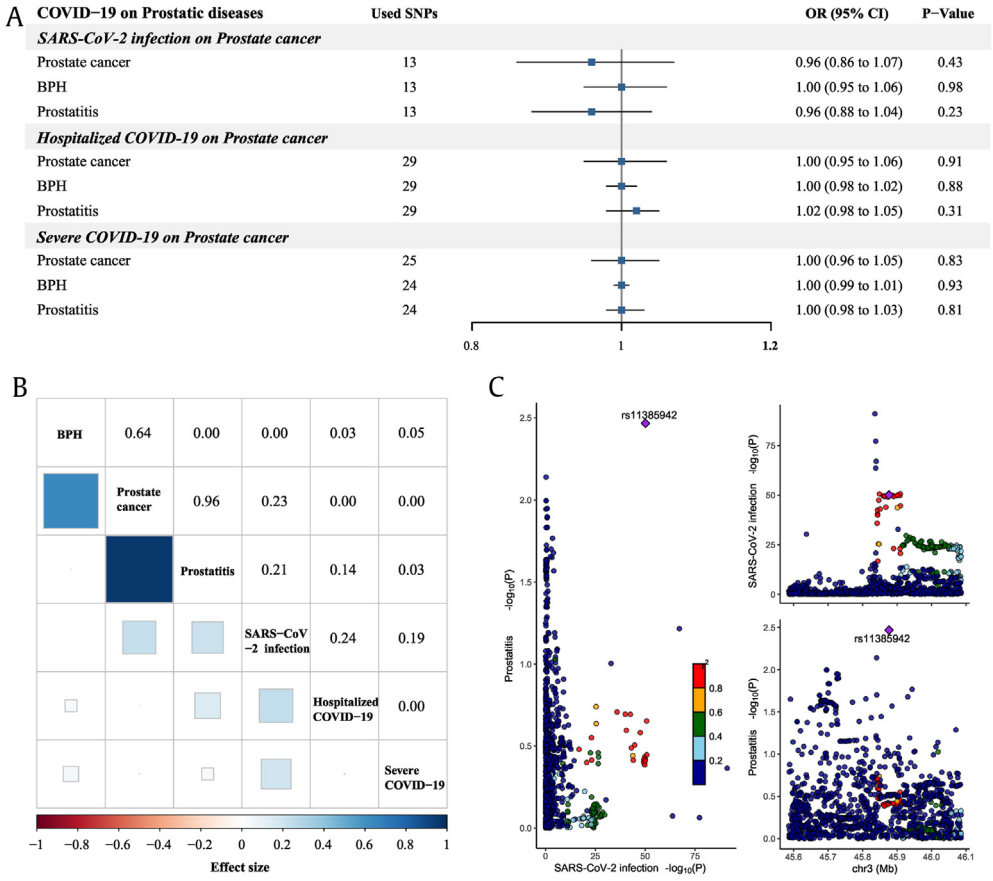

Fig. 3. Sensitivity and additional analyses. **A**, forest plot of reverse MR results for prostatic disease on COVID-19. **B**, Heatmap for LDSC analysis between prostatic diseases and COVID-19. The size of the squares represented the magnitude of the effect size of genetic correlation. **C**, Regional LocusZoom Plots of colocalization between prostatitis and SARS-CoV-2 infection within 250 kb.

biomarkers. Notably, no phenotypes survived to Bonferroni correction ($P = 3.1 \times 10^{-5}$, $\alpha = 0.05/1614$); therefore, the significance threshold was set at 0.05.

We identified 22 immune and 33 metabolic characteristics which were associated with SARS-CoV-2 infection. The imbalances in the immune system, especially regulatory T (Treg) cell, were associated with susceptibility of SARS-CoV-2. Additionally, the activation of adaptive immunity and the involvement of innate immunity such as central memory CD4-CD8- T cell %CD4-CD8- T cell (OR = 0.98, $P = 0.04$), IgD + CD24+ B cell AC (OR = 0.97, $P = 0.01$), and PDL-1 on monocyte (OR = 0.98, $P = 0.04$), were identified as protective immune characteristics for SARS-CoV-2 infection, as we expected (Fig. 5 and Supplementary Table 11). The lipid and amino acid levels in the blood metabolome had also been identified as risk factors for SARS-CoV-2 infection. Lipid-related metabolites, including linoleate (18:2n6), 1-stearoyl glycerophocholine (OR = 1.34, $P = 0.03$), and linolenate [alpha or gamma; (18:3n3 or 6)] (OR = 1.72, $P = 9.8 \times 10^{-5}$), were causally associated with increased susceptibility to COVID-19, while docosapentaenoate (n3 DPA; 22:5n3) (OR = 0.78, $P = 0.02$) and total lipids in large VLDL (OR = 0.97, $P = 0.04$) were associated with decreased susceptibility to COVID-19. Moreover, there were results indicating the relationships between SARS-CoV-2 infection and alterations in blood amino acid levels, including phenylalanine, isoleucine, valine, and total concentration of branched-chain amino acids (leucine + isoleucine + valine) (Fig. 5 and Supplementary Table 11).

Dozens of immune and metabolic characteristics were identified as hospitalized COVID-19 and severe COVID-19-related blood biomarkers. Similarly, dysregulation of Treg cell subpopulations among T cells was associated with more advanced COVID-19 outcomes, particularly in hospitalized COVID-19. The presence of specific subgroups of B cells, such as IgD + CD24+ and IgD + CD38+, were identified as the protective features for COVID-19. Moreover, higher macrophage inflammatory protein 1b levels were thought to be protective against progression to both hospitalized and severe COVID-19, and higher interleukin-1beta levels were only recognized to mitigate severe COVID-19 risk (Supplementary Figs. 2 and 3, Supplementary Tables 12 and 13). We also highlighted novel metabolic features associated with the risk of hospitalization and severe COVID-19 outcomes. In addition to unidentified metabolites, the metabolic pathways included energy (lactate), cofactors (bilirubin [E,Z or Z,E*]), carbohydrates (1,6-anhydroglucose), lipids (palmitoleate [16:1n7]), peptides (albumin), and amino acids (valine)). Some metabolites displayed similar effects on disease courses in hospitalized and severe COVID-19. 3-hydroxybutyrate (BHBA), bilirubin (E,Z or Z,E)*, and myristoleate (14:1n5), exemplify well, known to be associated with a greater risk of these more advanced COVID-19 outcomes. Nonetheless, metabolites exhibited different metabolic profiles between hospitalized COVID-19 and severe COVID-19, with lipid-related metabolites being more frequently associated with severe COVID-19; interestingly, creatinine levels were also correlated exclusively with it (Supplementary Figs. 2 and 3, Supplementary Tables 12 and 13).

3.5. PDL-1 on monocyte partially mediated the effect of prostatitis on the risk of SARS-CoV-2 infection

To explore the mediating mechanisms by which prostatitis increased the risk of SARS-CoV-2 infection, we further evaluated

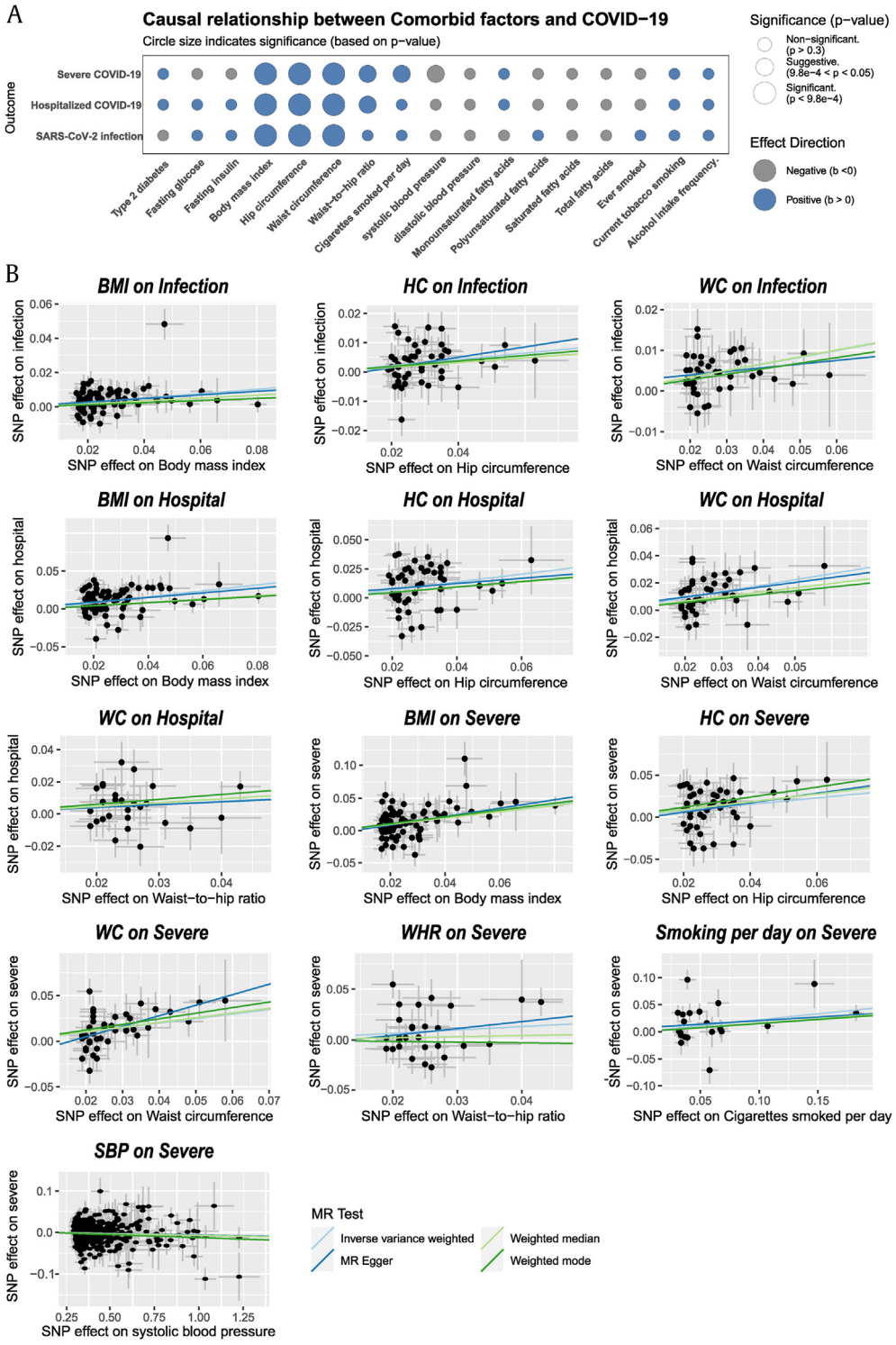

Fig. 4. Causal associations between comorbid factors of prostate cancer and COVID-19. A, bubble chart for the causal associations between comorbid factors of prostate cancer and COVID-19. The Bonferroni-corrected *P*-value ($P = 9.8 \times 10^{-4}$) was set as the significance threshold. B, scatterplot of associations with suggestive evidence ($P < 0.05$). BMI: body mass index; HC: hip circumference; WC: waist circumference; WHR: waist-to-hip ratio; SBP: systolic blood pressure.

the alterations of 55 immune and metabolic characteristics associated with SARS-CoV-2 infection. After the exclusion of inconsistent direction between total effects and mediation effects, only PDL-1 on monocyte was identified as the potential mediator between prostatitis and SARS-CoV-2 infection, with a 9.2% mediation proportion (Table 2, Fig. 6). Patients with prostatitis appear to be associated with lower levels of PDL-1 on monocyte, which could increase the risk of SARS-CoV-2 infection. Blood metabolites, on the other hand, did not mediate the causal relationship between prostatitis and SARS-CoV-2 infection (Supplementary Table 14).

4. Discussion

In this study, we conducted an MR analysis to identify the causal relationships between prostatic diseases and three different COVID-19 outcomes utilizing the largest scale of GWAS data.

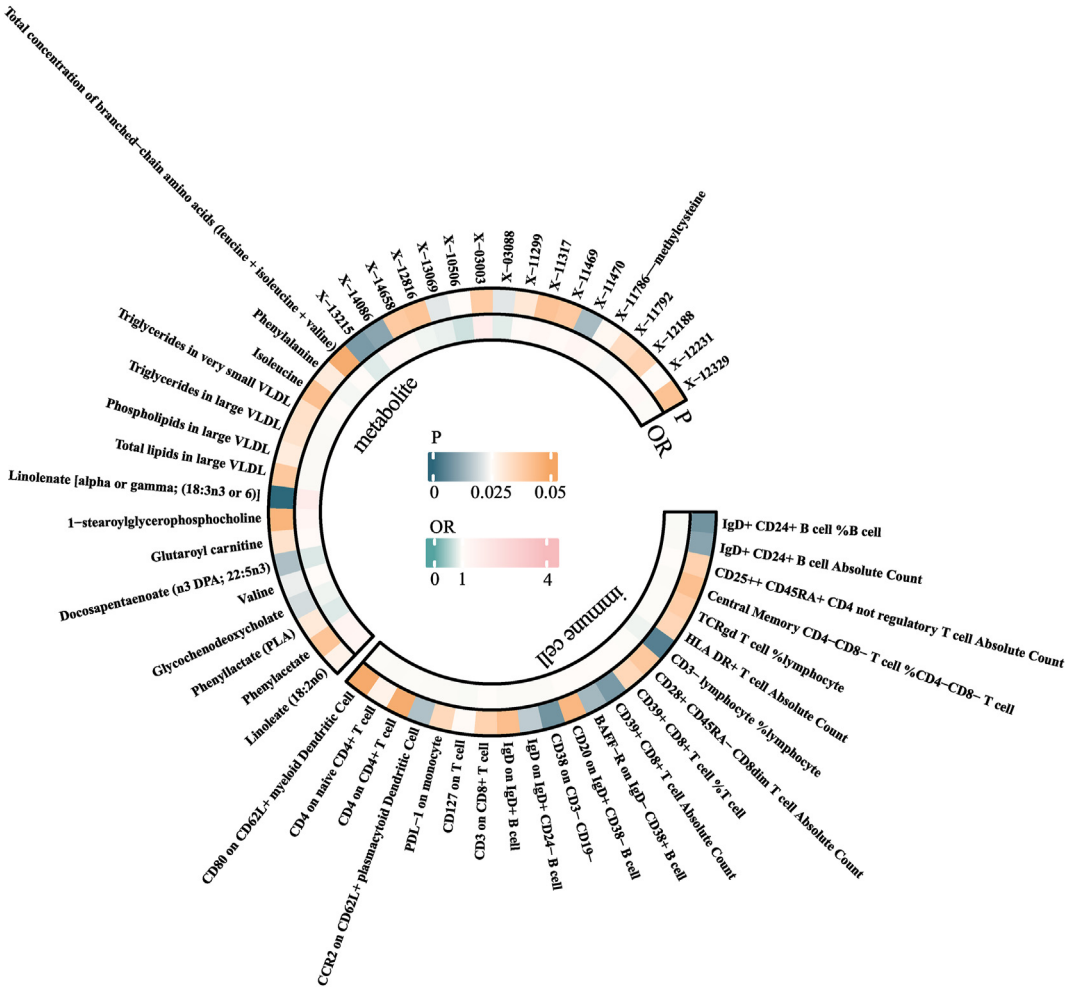

Fig. 5. Heatmap for immune and metabolic features associated risk of SARS-CoV-2 infection. This figure showed the MR results in the inverse variance weighted method, and effect size of causal association was indicated with OR.

Prostatitis, not prostate cancer, was identified as a risk factor for SARS-CoV-2 infection, and this causal relationship was verified by multiple sensitivity tests. Additionally, comprehensive immunomic and metabolomic-wide MR analyses prioritized dozens of COVID-19-associated immune and metabolic features, especially imbalances in specific subgroups for Treg and B cells and alterations in lipid-, energy-, and amino acid-related metabolite levels. Through further two-step MR analysis, PDL-1 on monocyte was identified as a potential mediator between prostatitis and SARS-CoV-2 infection, with 9.2% of the effect being mediated.

Previous studies have focused on the associations between prostate cancer and COVID-19,[9,10] neglecting the two highly prevalent diseases, prostatitis and BPH. We obtained the largest GWAS dataset for prostatic diseases by genome-wide meta-analysis, systematically evaluating the causal relationships between prostatic diseases and three different COVID-19 outcomes. Only prostatitis was identified as a risk factor for SARS-CoV-2 infection, while prostate cancer was not. Our findings demonstrated that only obesity (including BMI, HC and WC) among the prostate cancer-associated comorbid factors was significantly associated with severe COVID-19 after Bonferroni correction. This result aligns with previous MR studies examining severe COVID-19.[20] Obesity is a shared risk factor for both prostate cancer and COVID-19, with shared mechanisms such as inflammation and immune dysregulation, and metabolic disturbances[21,22] potentially confounding associations between prostate cancer and COVID-19 identified in previous studies. Additionally, prostatitis had been identified as an independent risk factor for SARS-CoV-2 infection; however, it did not increase the risk of developing advanced COVID-19 outcomes requiring hospitalization or intensive care. This observation could

Table 2
Mediation effects between prostatitis, PDL-1 on monocyte, and SARS-CoV-2 infection

Mediator	Exposure	Outcome	Total effect	Mediation effect A	Mediation effect B	Mediation effect	Mediation proportion (%)
PDL-1 on monocyte	Prostatitis	SARS-CoV-2 infection	0.108 (0.010 to 0.206)	−0.486 (−0.897 to −0.080)	−0.021 (−0.040 to −0.001)	0.010 (−0.003 to 0.022)	9.2 (−5.0 to 23.4)

Mediation effect A, effect of exposure on mediator; mediation effect B, effect of mediator on outcome; mediation effect, calculated by "coefficient product method" that mediation effect equaled to mediation effect A multiplied by mediation effect B; mediation proportion (%), the proportion of mediation effect on total effect; Total effect, effect of exposure on outcome.

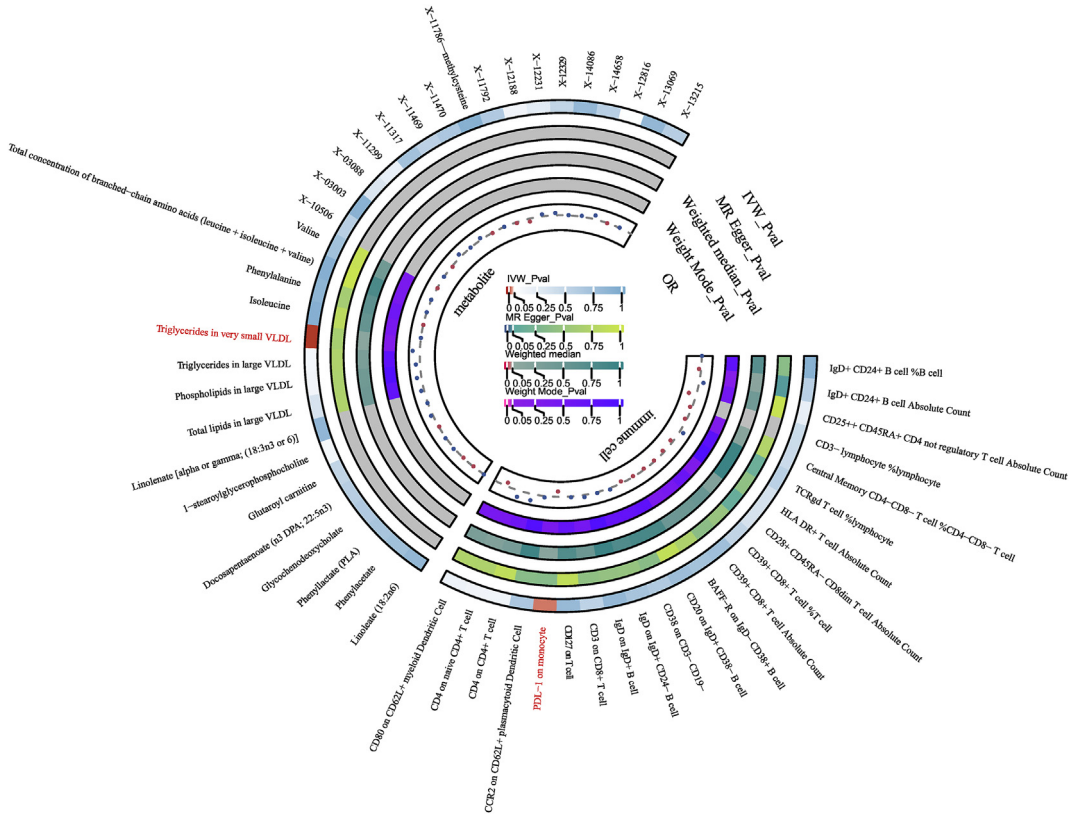

Fig. 6. Heatmap for causal effects of prostatitis on SARS-CoV-2 infection-related immune and metabolic features. Inverse variance weighted, MR-Egger, weighted median, and weighted mode presented different MR models, and inverse variance weighted was considered the primary analysis method. Significant results ($P < 0.05$) in IVW method were identified in red.

be attributed to the demographic typically affected by prostatitis, predominantly comprising young to middle-aged adults[11] who generally exhibit robust physiological resilience against severe outcomes of COVID-19.

We performed comprehensive immunome- and metabolome-wide analyses to reveal the immune and metabolic profiles of different COVID-19 courses. Our findings underscored the complex role of specific immune cell subpopulations, particularly Tregs, in influencing COVID-19 outcomes. Previous studies have come to contradictory conclusions about altered concentrations of Treg cells and interactions with COVID-19,[23,24] which we found may be due to the different roles of specific Treg subgroups. Our study showed that enriched CD28+ CD45RA- CD8dim Tregs were associated with a reduced risk of COVID-19 in both the mild and severe stages, which may be attributed to enhanced T cell activation, proliferation, and memory formation.[25] Additionally, our analysis indicated that the presence of an enriched CD39+ Treg population correlated with a higher risk of COVID-19, whereas this phenomenon was consistent with the findings of Simsek et al.[26] The role of the CD39+ Treg subpopulation, known for suppressing immunity and inflammation,[27] in determining COVID-19 severity further exemplified the complex interplay between immune regulation and disease outcome.

Our study corroborated findings from Shi et al., who linked metabolites such as phenylalanine, serine, and cholesterol significantly with COVID-19.[28] Despite some discrepancies in the direction of metabolite impacts,[28] suggesting variability, our comprehensive examination offered a broader perspective on the metabolic disruption caused by COVID-19. By conducting a comprehensive metabolomic analysis, we identified key alterations across various pathways, including those involved in energy production, lipid regulation, and amino acid balance, echoing and expanding upon previous research.[29,30] This extended analysis highlighted the complex metabolic reprogramming that occurred in response to COVID-19 and the potential for targeted therapeutic interventions.

Our findings suggested that PDL-1 levels on monocyte mediated causal effect of prostatitis on SARS-CoV-2 infection and that lower PDL-1 levels on monocyte following prostatitis may contribute to increased COVID-19 risk. However, these findings contrast with the commonly observed correlation between lower PDL-1 levels and greater T cell activation,[31] which typically correlates with an increased risk of virus infection. Nevertheless, excessive T cell activation can also lead to immune-mediated damage to host tissues. In the context of COVID-19, excessive T cell activation is implicated in systemic inflammatory responses in severe cases.[32] Furthermore, conflicting reports exist regarding changes in monocyte PDL-1 levels following COVID-19 infection, with some studies indicating an increase in PD-L1, while others suggest a decrease.[33–35] These discrepancies underscore the complex interplay between immune regulation and disease pathogenesis, highlighting the need for further research to elucidate the precise role of PDL-1.

Nonetheless, this study has several limitations. First, the GWAS data utilized in this study were obtained solely from individuals of European ancestry, thereby restricting the generalizability of the findings to other populations. Second, while efforts were made to minimize potential bias by matching the corresponding sex-specific GWAS data for prostatic diseases, the lack of sex-specific data for COVID-19 and other mediators may have affected the

results. Third, despite the use of the largest GWAS dataset for prostatic diseases and the combination of estimated results from two independent datasets, the restricted sample size may limit the accuracy of the statistical findings. Fourth, the *P*-values from the immunome- and metabolome-wide analyses did not survive multiple corrections; thus, a more lenient significance threshold was employed, potentially increasing the probability of type I errors.

In conclusion, our study evaluated the causal relationships between prostatic diseases and different COVID-19 outcomes and explained these associations through alterations in the blood immunome and metabolome. These findings emphasized the importance of considering both local and systemic factors in disease management. Our research contributed to understanding the implications of COVID-19 for individuals with prostatic conditions, informing clinical and public health interventions.

Availability of data and material

GWAS data for COVID-19 was derived from COVID-19 Host Genetics Initiative (https://www.covid19hg.org/results/r7/); GWAS data for prostate cancer was derived from Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome consortium (PRACTICAL) (http://practical.icr.ac.uk/); GWAS data from UK Biobank could be obtained from http://www.nealelab.is/uk-biobank; GWAS data from FinnGen consortium could be obtained from https://www.finngen.fi/. The original contributions from the study are contained in the article/supplementary materials; further inquiries should be addressed to the corresponding authors.

Ethical statement

This study utilized data from previously conducted GWAS analyses that had received ethical approval. As such, no additional ethical statements were deemed necessary for the current investigation.

Funding

This work was supported by National Natural Science Foundation (Grant Number: 82200860; 82170787); Natural Science Research min Colleges and Universities of Anhui Province (Grant Number: 2022AH051133); Natural Science Foundation of Anhui Province (Grant Number: 2208085QH239); College Students' Innovation and Entrepreneurship Training Program of Anhui Medical University (Grant Number: X202310366062); Early scientific training program of Anhui Medical University (Grant Number: 2022-ZQKY-194).

Author contributions

Feixiang Yang: conceptualization, data curation, formal analysis, investigation, project administration, visualization, writing – original draft. **Peng Guo**: conceptualization, data curation, investigation, project administration, visualization, writing – review & editing. **Kun Wang**: formal analysis, methodology, software, validation, writing – review & editing. **Xiangyu Zhang**: conceptualization, data curation, formal analysis, methodology, project administration, software, validation, writing – original draft. **Zhehao Hu**: data curation, investigation, methodology, software, validation, visualization, writing – review & editing. **Qiyue Lou**: investigation, methodology, software, validation, writing – review & editing. **Qintao Ge**: investigation, methodology, software, validation, writing – review & editing. **Yiding Chen**: formal analysis, software, validation, writing – review & editing. **Chaozhao Liang**: conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, writing – review & editing. **Jialin Meng**: conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, writing – review & editing.

Consent for publication

Not applicable.

Conflicts of interest

The authors declared no competing interests.

Acknowledgments

We acknowledge the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome consortium (PRACTICAL) for providing GWAS data on prostate cancer. We thank the Mathematical Medicine Integration Innovation Training Program for Undergraduate Students (MITUS) for providing valuable guidance, support, research opportunities, and resources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2024.07.003.

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