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Exploring the causal role of pathogen-derived antibodies in major urinary and kidney diseases: Insights from generalized summary data-based Mendelian randomization

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ABSTRACT

Chronic kidney and urinary tract diseases, including glomerulonephritis, nephrotic syndrome, and chronic kidney disease (CKD), present significant global health challenges. Recent studies suggest a complex interplay between infectious pathogens and immune-mediated kidney damage. This study employs Generalized Summary data-based Mendelian Randomization (GSMR) to explore causal relationships between pathogen-derived antibodies and major urinary and kidney diseases. We conducted a two-sample MR analysis using summary statistics from large-scale Genome-Wide Association Studies (GWAS) to assess associations between 46 pathogen-specific antibodies and seven urinary system diseases. We utilized robust statistical methods, including inverse variance weighting, to ascertain causal effects while controlling for potential confounders.Significant associations were identified between several pathogen-specific antibodies and disease risk. Notably, Epstein-Barr virus (EBNA-1) antibody levels were inversely associated with glomerulonephritis and nephrotic syndrome, indicating a potential protective effect. Conversely, Anti-Merkel cell polyomavirus IgG seropositivity was linked to increased risks of CKD and glomerulonephritis. Additionally, immune-mediated mechanisms were highlighted, with certain antibodies exhibiting dual roles as risk factors or protective agents.This study underscores the complex role of pathogen antibodies in the pathogenesis of kidney and urinary tract diseases, revealing significant implications for future research and potential therapeutic strategies. The findings advocate for further investigation into specific pathogen interactions with the immune system, aiming to inform targeted interventions.

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Introduction

Chronic kidney and urinary tract diseases, such as glomerulonephritis, nephrotic syndrome, Interstitial cystitis, and other related conditions, represent a significant burden on global health, contributing to substantial morbidity and mortality [1–4]. In recent years, the interplay between infectious pathogens and immune-mediated kidney damage has gained significant attention in medical research. Many of these diseases are considered multifactorial, with genetic, environmental, and infectious components contributing to their development and progression. Notably, pathogen infections are hypothesized to act as both initiators and exacerbators of immune responses, potentially leading to conditions such as glomerulonephritis, nephropathy, and interstitial cystitis [5–7]. Given the complexity of these diseases, it is essential to explore the causal relationships between pathogen exposure, particularly pathogen-derived antibodies, and the subsequent development of urinary and kidney diseases.

Glomerulonephritis (GN), one of the primary diseases of interest, is characterized by inflammation of the glomeruli and is often linked to prior infections. Several types of glomerulonephritis, such as IgA nephropathy, are associated with the immune system's response to infectious pathogens, such as viruses or bacteria.IgA nephropathy is marked by the deposition of IgA antibodies in the glomeruli, often following mucosal infections like those of the respiratory tract [8]. The immune complexes formed by IgA deposition lead to glomerular inflammation and, ultimately, renal impairment [9]. It is also believed that genetic predispositions play a role in the degree of renal damage experienced by individuals exposed to these infections, making it a highly heterogeneous disease [10].

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Another critical disease, nephrotic syndrome, is a renal disorder characterized by massive proteinuria, hypoalbuminemia, and oedema. The exact aetiology of nephrotic syndrome remains largely unknown, but it is thought to arise from both intrinsic genetic mutations and external triggers, including infections. Several studies have demonstrated that nephrotic syndrome can be precipitated by viral infections, such as hepatitis B, hepatitis C, and HIV [11–13]. These infections stimulate the immune system, leading to alterations in glomerular permeability. Thus, there is growing interest in the study of pathogen-induced antibodies as potential biomarkers and risk factors for developing nephrotic syndrome.

Chronic kidney disease (CKD), a condition characterized by the gradual loss of kidney function over time, is another major public health concern. CKD is associated with multiple aetiologies, including diabetes, hypertension, and infections etc. Infectious pathogens can contribute to CKD through direct renal infection or through immune-mediated mechanisms, where pathogen-specific antibodies lead to chronic inflammation in the renal tissues [14]. The immune responses triggered by pathogen infections may lead to progressive damage to the kidneys, exacerbating the decline in function in susceptible individuals [15]. Research has shown that certain infectious diseases, such as tuberculosis and hepatitis, have significant associations with CKD progression. Therefore, exploring the causal impact of pathogen antibodies on CKD is crucial for understanding the underlying mechanisms of disease progression.

Interstitial cystitis (IC) is a chronic, non-bacterial inflammatory condition of the bladder characterized by bladder pain, urinary frequency, and urgency; however, the majority of patients present without clear evidence of infection [16]. Although the exact cause of IC remains under investigation, it is hypothesized that occult infections and immune dysregulation may play a role. Evidence suggests that microbial content, including bacteria, viruses, and fungi, is significantly higher in the urine of IC patients compared to healthy controls. Additionally, 26% to 70% of IC patients report drug allergies, and many are positive for antinuclear antibodies (ANA), with immunosuppressive therapies showing some efficacy in treating the condition [17]. Therefore, antibody responses to pathogens may provide new insights into potential infectious triggers or contributing factors in the development of IC.

Prostatitis can affect adult males across nearly all age groups and is commonly associated with bacterial infections. However, chronic non-bacterial prostatitis-(CNBP) remains an enigmatic subtype. In the majority of CNBP cases, no bacteria are detected in prostatic secretions, yet a subset of patients experiences significant symptom relief following the administration of immunosuppressive agents. This observation suggests that immune mechanisms may play a crucial role in the pathogenesis of chronic prostatitis [18]. Therefore, investigating the relationship between pathogen-specific antibodies and chronic prostatitis could provide novel insights into its pathophysiology and identify potential therapeutic targets.

Given the growing body of evidence linking infections to immune-mediated kidney and urinary tract diseases, it is crucial to assess the causal relationships between pathogen exposure and these conditions. The use of generalized summary-data-based Mendelian randomization (GSMR) provides a robust approach to exploring these associations [19]. GSMR leverages genetic variants associated with pathogen antibody levels as instrumental variables to determine the causal effects of these antibodies on disease outcomes. By minimizing the confounding factors inherent in traditional observational studies, GSMR allows for more accurate causal inference, making it an invaluable tool for investigating the role of infections in complex diseases.

In this study, we aim to use GSMR to explore the causal relationships between pathogen-derived antibodies and seven major urinary and kidney diseases: glomerulonephritis, nephrotic syndrome, chronic kidney disease, IgA nephropathy, interstitial cystitis, calculus of kidney and ureter, and inflammatory diseases of the prostate. By analysing large-scale genome-wide association studies (GWAS) data on pathogen antibodies and these diseases, we seek to elucidate the potential role of infections in the pathogenesis of these conditions. The results of this analysis could offer novel insights into the mechanisms of immune-mediated kidney and urinary tract diseases, potentially leading to new approaches in diagnosis, prevention, and treatment.

Methods and material

Study design

In this study, we employed a generalized summary-data-based Mendelian randomization (GSMR) approach to explore the causal relationships between pathogen-specific antibodies and a range of urinary and kidney diseases. The workflow of our study is summarized in Figure 1. To enhance the credibility of our findings, we strictly followed the three core assumptions of Mendelian Randomization: (1) the instrumental variables (IVs) must exhibit a strong

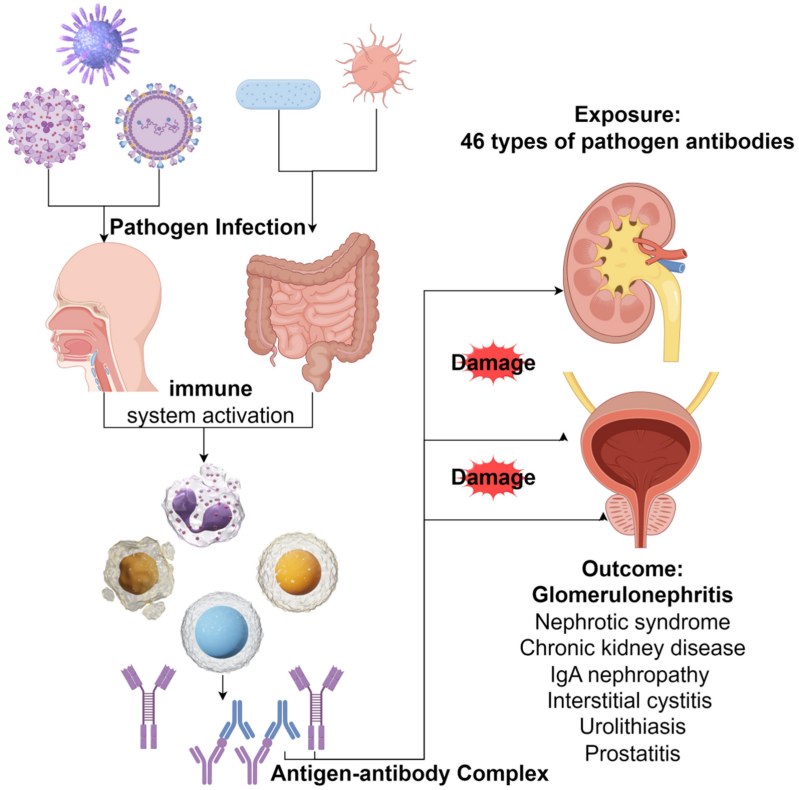

Figure 1. Research workflow.

correlation with the exposure of interest; (2) the IVs should remain unaffected by confounding factors that are not accounted for; and (3) the IVs should impact the outcome solely via their influence on the exposure, with no alternative causal mechanisms playing a role [20].

Data source

Exposure data

We used 46 types of pathogen antibodies data from Butler-Laporte et al, a genome-wide association study (GWAS) [21]. This study included genome-wide serological measurements of antibodies in participants from the UK Biobank cohort, examining their responses to a variety of infectious agents, including viruses, bacteria, and fungi. The dataset includes seropositivity for 13 pathogens and quantitative antibody measurements, with up to 10,000 participants. These data provide crucial insights into the genetic determinants of immune responses, making it an ideal source for investigating the association between pathogen antibodies and diseases of the urinary system. For a comprehensive list of pathogen-specific antibodies and their detailed definitions, please refer to the (Table S1) section of this manuscript.

Outcome data

Outcome data were extracted from publicly available GWAS summary statistics for seven key diseases of the urinary system. These diseases, along with their corresponding phenotypes and sample sizes, are outlined as follows:1.Glomerulonephritis (Phenocode: N14_GLOMER_NEPHRITIS):3,556 cases and 450,177 controls.2. Nephrotic Syndrome (Phenocode: N14_NEPHROTICSYND): 1,008 cases and 446,969 controls.3. Chronic Kidney Disease (Phenocode: N14_CHRONKIDNEYDIS): 11265 cases and 436,208 controls.4.IgA Nephropathy (Phenocode: N14_IGA_NEPHROPATHY):726 cases and 453,007 controls.5.Interstitial Cystitis (Phenocode: INTERSTITIAL_CYSTIT_CHR) :98 cases and 453,635 controls.6.Calculus of Kidney and Ureter (Phenocode: N14_CALCUKIDUR):11,650 cases and 441,039 controls.7.Prostatitis (Phenocode: N14_PROSTATITIS):4,743 cases and 141,300 controls.

Selection of instrumental variable

We selected single-nucleotide polymorphisms (SNPs) significantly linked to antibody levels based on previous research, utilizing a stringent p-value cut-off ($p < 5 \times 10^{-6}$). SNPs with notable linkage disequilibrium (LD) and p-values above this threshold were subsequently

excluded (window size = 10,000 kb, r^2 <0.001). The F-statistic was then computed using the formula F = R^2 (N – k – 1)/k(1 - R^2) to evaluate potential weak instrument bias [22]. In this equation, N refers to the sample size, k to the number of SNPs, and R^2 to the variance explained by the instrument. An F-statistic below 10 suggests the presence of weak instruments in this context.

GSMR analysis

Generalized Summary data – based Mendelian Randomization (GSMR) is an enhancement of traditional two-sample MR, offering the ability to address genetic pleiotropy while identifying and excluding pleiotropic SNPs through the application of the HEIDI (Heterogeneity in Dependent Instruments) test. The HEIDI test helps detect and eliminate SNP heterogeneity caused by pleiotropy, thereby reducing the likelihood of false-positive results. Additionally, the GSMR method effectively handles linkage disequilibrium (LD) between genetic variants by integrating multiple genetic markers, providing more accurate causal inference. When dealing with datasets involving multiple traits with potentially complex associations or the presence of pleiotropy, GSMR is better suited for uncovering intricate causal relationships. By addressing pleiotropy and LD, it minimizes false positives and delivers more robust causal inference outcomes.

Statistical analysis

The data analysis was conducted utilizing R software, version 4.2.3, in accordance with standard Mendelian Randomization procedures. The MR analyses were performed using the "TwoSampleMR" and "MRPRESSO" packages. Odds Ratios (OR), Hazard Ratios (HR), along with their corresponding 95% confidence intervals (CI), were calculated. Statistical significance was defined as a two-sided p-value below 0.05.

Ethical considerations

This study used publicly available summary-level data from genome-wide association studies (GWAS) including the UK Biobank and FinnGen databases. All data used in this analysis were de-identified, and ethical approval for the primary studies was obtained by the respective institutions according to the regulations of each study's governing body. As the data were anonymized and did not involve individual patient interaction, no additional ethical approval was required for the current analysis.

Result

We found significant associations between several pathogen-specific antibodies and the risk of developing glomerulonephritis. Specifically, Anti-Merkel cell polyomavirus IgG seropositivity was associated with an increased risk of glomerulonephritis (OR = 1.116, 95% CI: 1.041–1.198, $p = 0.002$). Conversely, Epstein-Barr virus nuclear antigen-1 (EBNA-1) antibody levels were inversely associated with the risk of glomerulonephritis (OR = 0.864, 95% CI: 0.780–0.958, $p = 0.005$), suggesting a protective effect (Figure 2). Additionally, Anti-BK polyomavirus IgG seropositivity was also negatively associated with the risk of glomerulonephritis (OR = 0.947, 95% CI: 0.906–0.991, $p = 0.019$). Similarly, Epstein-Barr virus early antigen D (EA-D) antibody levels were associated with a reduced risk (OR = 0.832, 95% CI: 0.712–0.973, $p = 0.022$).

Several pathogen-specific antibodies were significantly associated with nephrotic syndrome. Notably, Epstein-Barr virus (EBNA-1) antibody levels were strongly associated with a lower risk of nephrotic syndrome (OR = 0.678, 95% CI: 0.561–0.820, $p = 5.97E–05$). On the other hand, Human herpesvirus 7 U14 protein antibody levels were positively associated with an increased risk of nephrotic syndrome (OR = 1.552, 95% CI: 1.129–2.134, $p = 0.007$). Additionally, Varicella zoster virus glycoproteins E and I antibody levels were significantly associated with a higher risk of nephrotic syndrome (OR = 1.414, 95% CI: 1.093–1.830, $p = 0.008$, Figure 2).

For chronic kidney disease, multiple antibodies demonstrated significant associations. Epstein-Barr virus (EBNA-1) antibody levels showed a protective effect, with a lower risk of CKD (OR = 0.862, 95% CI: 0.813–0.914, $p = 7.86E–07$). In contrast, Anti-Merkel cell polyomavirus IgG seropositivity was associated with an increased risk of CKD (OR = 1.070, 95% CI: 1.028–1.115, $p = 0.001$). Merkel cell polyomavirus VP1 protein antibody levels also demonstrated a significant association with a higher risk of CKD (OR = 1.122, 95% CI: 1.027–1.225, $p = 0.01$). Furthermore, Anti-human herpesvirus 6 IE1B IgG seropositivity was associated with a reduced risk of CKD (OR = 0.940, 95% CI: 0.891–0.991, $p = 0.022$), while Epstein-Barr virus ZEBRA protein antibody levels were positively associated with CKD (OR = 1.073, 95% CI: 1.009–1.142, $p = 0.025$, Figure 2).

Among the pathogen antibodies, Toxoplasma gondii sag1 protein antibody levels were significantly

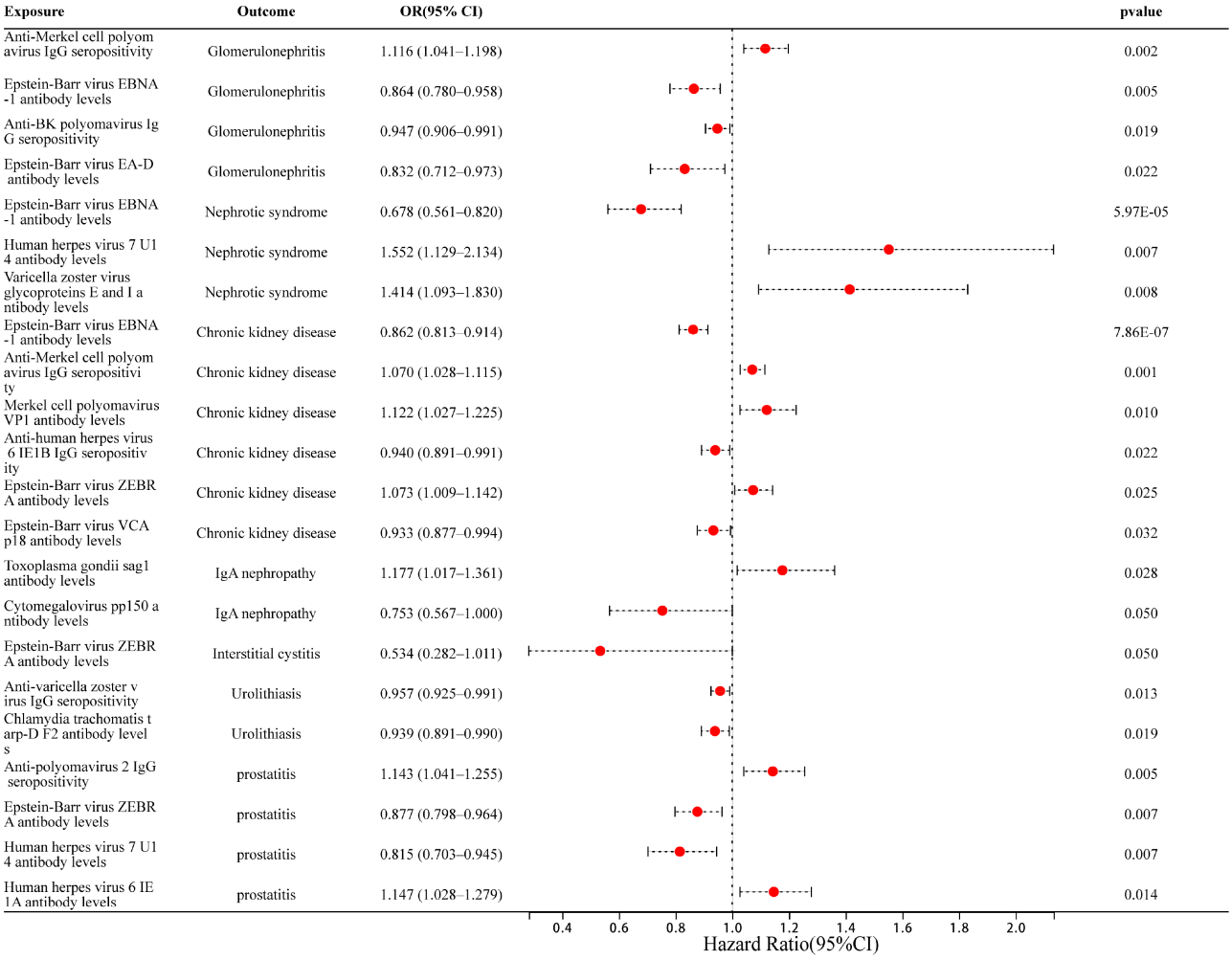

Figure 2. GSMR analysis results of antibody levels and diseases.

associated with an increased risk of IgA nephropathy (OR = 1.177, 95% CI: 1.017–1.361, $p = 0.028$). On the other hand, Cytomegalovirus pp150 protein antibody levels showed a borderline protective effect against IgA nephropathy (OR = 0.753, 95% CI: 0.567–1.000, $p = 0.05$, Figure 2).

For interstitial cystitis, Epstein-Barr virus ZEBRA protein antibody levels demonstrated a suggestive protective effect, although the association did not reach statistical significance (OR = 0.53, 95% CI: 0.28–1.01, $p = 0.05$, Figure 2).

In the case of kidney and ureter stones (urolithiasis), Anti-varicella zoster virus IgG seropositivity was significantly associated with a reduced risk (OR = 0.957, 95% CI: 0.925–0.991, $p = 0.013$). Additionally, Chlamydia trachomatis tarp-D protein F2 subunit antibody levels were also associated with a lower risk of urolithiasis (OR = 0.939, 95% CI: 0.891–0.990, $p = 0.019$, Figure 2).

Regarding prostatitis, several pathogen-specific antibodies showed significant associations. Anti-polyomavirus 2 IgG seropositivity was associated with an increased risk of prostatitis (OR = 1.143, 95% CI: 1.041–1.255, $p = 0.005$), while Epstein-Barr virus ZEBRA antibody levels were associated with a reduced risk of prostatitis (OR = 0.877, 95% CI: 0.798–0.964, $p = 0.007$). Similarly, Human herpesvirus 7 U14 antibody levels were negatively associated with prostatitis (OR = 0.815, 95% CI: 0.703–0.945, $p = 0.007$), whereas Human herpesvirus 6 IE1A antibody levels were positively associated with an increased risk (OR = 1.147, 95% CI: 1.028–1.279, $p = 0.014$, Figure 2).

Through the Sankey plot, we observed a significant correlation between anti-Merkel cell polyomavirus IgG seropositivity and conditions such as glomerulonephritis and chronic kidney disease. Additionally, Epstein-Barr virus EBNA-1 antibody levels were significantly associated with glomerulonephritis, nephrotic syndrome, and chronic kidney disease, while Epstein-Barr virus ZEBRA antibody levels showed significant correlations with chronic kidney disease, interstitial cystitis, and prostatitis (Figure 3).

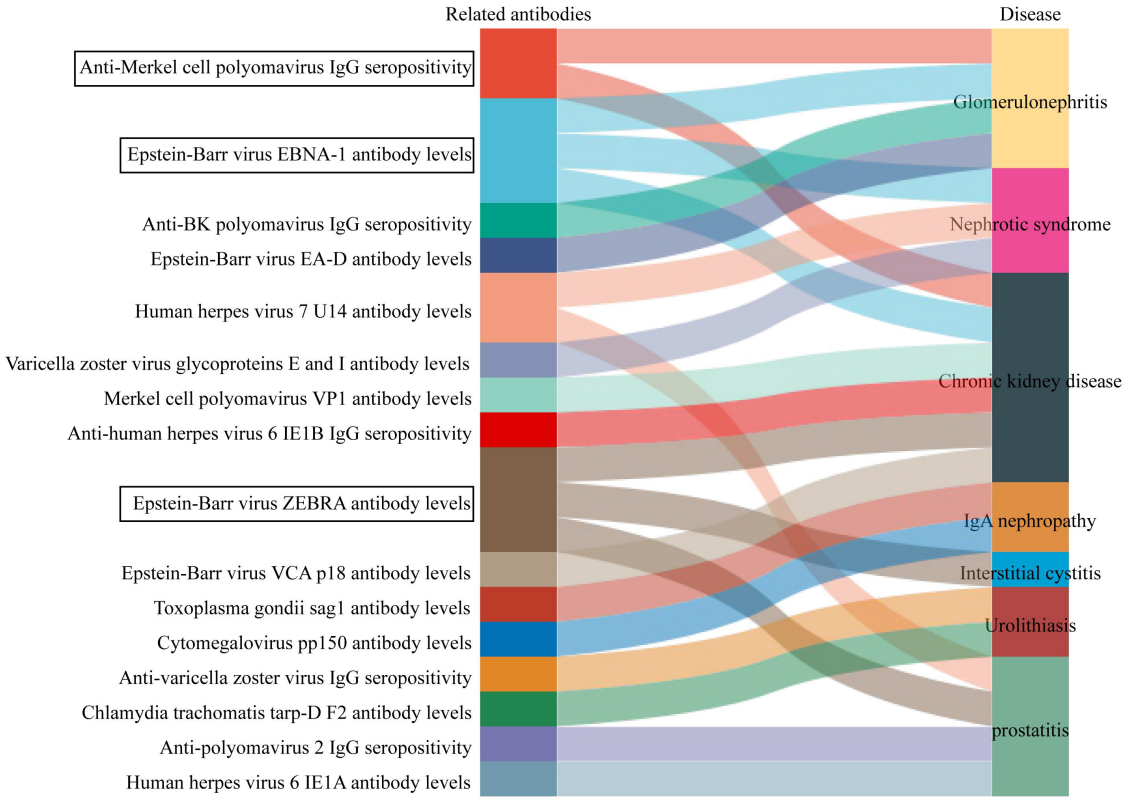

Figure 3. The correspondence between antibodies and diseases significantly associated with them.

Discussion

The pathogenesis of kidney diseases is complex, and over the years, it has been strongly associated with infections by specific pathogens. However, there is limited research investigating whether there is a clear causal relationship between pathogen infections and disease onset, as well as how these infections contribute to disease progression. In this study, we utilized the robust Generalized Summary data – based Mendelian Randomization method, complemented by Mendelian Randomization, to identify pathogen antigens and antibodies that exhibit a strong causal relationship with seven types of urinary system diseases, including glomerulonephritis and nephrotic syndrome, thereby laying a foundation for future research in this area.

Idiopathic nephrotic syndrome (INS) is primarily characterized by significant proteinuria and podocyte foot process effacement [23]. Although the exact mechanism remains unclear, recent studies have found that in approximately 50% of patients experiencing their first episode of INS, EBV replication can be detected in peripheral blood, suggesting that EBV may play an important role in the disease process [24]. Many scholars believe that EBV interacts with the immune system via viral antigens, forming immune complexes that deposit and induce nephritis, ultimately leading to kidney damage. EBV antigens such as EBNA 1, ZEBRA, EA-D, and VCA p18 play central roles in regulating the immune response [25], ultimately resulting in glomerular injury.

EBNA1 is a critical protein for maintaining viral latency and ensuring the survival of EBV in host cells. It is known for its ability to evade immune detection through its glycine-alanine repeat (GAr) domain, which suppresses the presentation of MHC-I peptides on infected cells. This immune evasion strategy allows EBV-infected B cells to persist undetected in the host [26]. In particular, EBNA1 antibodies, directed against an EBV nuclear antigen, have been found to cross-react with podocyte proteins, leading to podocyte injury and proteinuria. This cross-reactivity may be mediated by the neonatal Fc receptor, which internalizes these antibodies into podocytes, triggering a cytoskeletal disruption that results in the loss of foot processes and subsequent proteinuria [27].

ZEBRA (BZLF1), a key transcription factor, regulates the switch from EBV latency to the lytic replication cycle. ZEBRA triggers the activation of viral replication, leading to the production of viral antigens that stimulate immune

responses. During reactivation, ZEBRA expression induces the production of new viral particles and immune complex formation [28]. This reactivation is particularly harmful in individuals with underlying kidney diseases, as it can lead to glomerular injury due to the accumulation of immune complexes and the recruitment of immune cells to the kidneys [29].

EA-D, a viral DNA polymerase processivity factor, plays a crucial role in facilitating lytic replication by interacting with host proteins like poly(ADP-ribose) polymerase 1 (PARP1).PARP1 is a host protein that regulates DNA damage responses and viral replication. In the context of EBV infection, PARP1 suppresses lytic replication by modifying proteins involved in viral transcription, such as ZEBRA [30]. However,EA-D induces the degradation of PARP1 through K29-linked polyubiquitination, promoting the reactivation of the virus by suppressing the inhibitory effects of PARP1 on lytic replication [31].

Notably, Epstein-Barr virus has also been closely associated with interstitial cystitis. A previous study demonstrated that serum samples from all patients with interstitial cystitis included in the study showed evidence of prior EBV infection [32]. According to a more recent study, EBV may play a critical role in the development and progression of interstitial cystitis by inducing the expression of brain-derived neurotrophic factor (BDNF) [33]. Through its interaction with the BDNF receptor, TrkB, EBV promotes heightened neural responsiveness and the occurrence of chronic pain, which are thought to contribute significantly to the pathogenesis of interstitial cystitis.Chronic prostatitis (CP) was previously thought to be associated with certain bacteria, mycoplasma, or Chlamydia trachomatis. Although some researchers have suggested a potential link with viruses, fungi, or parasitic factors, there has been a lack of substantial evidence to support these claims. However, recent studies have indicated that Polyomavirus infections have been implicated in chronic inflammation of the prostate, especially in immunocompromised individuals [34]. Our study identified a positive correlation between polyomavirus antibodies and prostatitis. Additionally, for the first time, the Epstein-Barr virus ZEBRA protein was found to have a causal relationship with chronic prostatitis, a finding that has not been previously reported in the literature.

Merkel cell polyomavirus (MCPyV), a member of the human polyomavirus family, is another pathogen that plays a significant role beyond skin malignancies. MCPyV primarily enters the body through skin lesions, infecting the Merkel cells in the basal layer of the epidermis. These viral particles efficiently integrate their genome into the host cell genome, resulting in persistent infections [35]. Although traditionally associated with Merkel cell carcinoma, recent studies have shown that MCPyV can also affect other skin cell types. Its oncogenic effects, however, are predominantly linked to Merkel cells [36]. In the context of solid organ transplantation (SOT) recipients, MCPyV poses considerable risks due to the immunosuppressive state of these patients. MCPyV infection has been associated with the development of Merkel cell carcinoma, but its potential impact on systemic immune regulation in immunocompromised individuals remains underexplored. The early region proteins of MCPyV, such as the small tumour (sT) antigen, play critical roles in oncogenesis and immune evasion, which could exacerbate complications in SOT patients [37,38]. Notably, infections by other polyomaviruses have a close association with urological diseases [39]. Studies indicate that BK polyomavirus (BKPyV) infection may lead to nephropathy and haemorrhagic cystitis [40], while JC polyomavirus (JCPyV) infection may also result in kidney disease [41]. BKPyV infection is common, with over 80% of adults showing seropositivity by early adulthood. It typically remains asymptomatic, but in immunosuppressed individuals, particularly kidney transplant recipients, it can cause BK virus-associated nephropathy (BKVAN). BKVAN occurs in 1–10% of kidney transplant recipients and accounts for up to 50% of graft failures in affected individuals [42]. Although the primary management strategy for BKVAN involves reducing immunosuppressive therapy, this can increase the risk of graft rejection. Emerging therapies such as intravenous immunoglobulin (IVIG) and monoclonal antibodies like MAU868 offer promise in preventing and treating BKVAN, emphasizing the need for tailored interventions in at-risk populations [43].

Recent advancements in BKPyV research also highlight the clinical importance of neutralizing antibodies in controlling viral replication. Neutralizing antibodies targeting the VP1 protein of BKPyV have demonstrated the ability to inhibit viral entry independently of cell-mediated immunity. Studies have shown that low pre-transplant neutralizing antibody titres against the donor's BKPyV genotype are associated with increased post-transplant viraemia, underscoring the potential role of pre-emptive antibody-based interventions. Given the similarities between MCPyV and BKPyV in immune evasion and persistent infection, further research is needed to understand how these pathogens interact with the host immune system, particularly in immunocompromised individuals. Understanding these dynamics could provide valuable insights into the broader implications of pathogen-derived antibodies in kidney diseases and transplant medicine, and ultimately guide more effective therapeutic interventions. For SOT recipients, regular monitoring of skin lesions, particularly for MCPyV-

related conditions, is essential for early detection and improved outcomes. Furthermore, routine screening for BKPyV replication in kidney transplant recipients is recommended to mitigate the risk of BKVAN. In cases of confirmed polyomavirus infections, reducing immunosuppressive therapy to regain immune control should be carefully considered [44].

The prevalence of common infections, including a range of viral and bacterial pathogens, varies significantly across geographic regions and demographic groups, influencing the interpretation of our findings. For example, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are among the most prevalent, with over 80% of adolescents in Asia testing positive for EBV antibodies, compared to a delayed seroconversion rate in European and North American populations, where primary infection typically occurs in early adulthood. Similarly, CMV seroprevalence ranges from approximately 50%-60% in Scandinavian countries to nearly 90% in parts of sub-Saharan Africa. These variations underscore the need to consider geographic and demographic differences in interpreting antibody-disease associations, particularly when studying the impact of various pathogens across different populations [45–48].

Such differences in seroprevalence can significantly alter the baseline immune landscape. High seroprevalence in certain regions may result in a saturation effect, where most individuals have detectable antibody levels, potentially masking true causal relationships or creating spurious associations. Conversely, in populations with lower seroprevalence, the observed antibody-disease associations may reflect a more direct causal mechanism. This underscores the importance of incorporating population-specific data into causal inference studies.

Additionally, the temporal dynamics of antibody levels in relation to disease onset remain underexplored. Longitudinal studies tracking serological markers over time could provide critical insights into whether antibody level changes precede disease onset or merely reflect an ongoing disease process. Furthermore, the use of stratified analyses across geographic and demographic subgroups would enhance the robustness and generalizability of our findings. For example, extending these analyses to non-European populations could validate the external applicability of our conclusions, given that our current study relies exclusively on European cohorts. These steps are essential for contextualizing the observed relationships and refining the understanding of pathogen-antibody interactions in diverse populations.

This study has several limitations. Firstly, although we performed numerous sensitivity analyses, a thorough assessment of horizontal pleiotropy continues to present difficulties. Secondly, since our data are exclusively sourced from European populations, the generalization of our findings to other racial groups remains ambiguous, thereby restricting the wider relevance of our conclusions. Additionally, the use of aggregated statistical data in place of individual-level data has limited the potential for in-depth subgroup analyses, particularly regarding gender-related variations.

While our Mendelian Randomization analysis provides evidence supporting associations between pathogen-derived antibodies and various kidney diseases, it is important to interpret these findings cautiously. MR is a robust tool for inferring causal relationships using genetic data; however, it is not without its limitations.For example, pleiotropy, where genetic variants influence multiple traits, could lead to spurious associations. Furthermore, the observed inverse association between EBNA1 antibodies and kidney diseases may reflect complex immune regulatory mechanisms rather than a direct protective effect. The proposed mechanism of EBNA1 antibody cross-reactivity with podocyte proteins, while biologically plausible, remains speculative in the absence of direct experimental evidence. Experimental studies, such as in vitro assays to assess cross-reactivity or in vivo models to explore immune-mediated kidney injury, are needed to validate this hypothesis. Similarly, the causal implications of other pathogen-derived antibodies observed in this study require further investigation to elucidate their underlying mechanisms. These limitations underscore the exploratory nature of our findings and highlight the need for complementary studies. Integrating functional validation with longitudinal and population-based analyses would provide a more comprehensive understanding of the complex interplay between pathogen-derived antibodies and immune-mediated kidney diseases.

Conclusion

In conclusion, this study employed the GSMR approach to explore the causal relationships between 46 pathogen-specific antibodies and the development of 7 major urinary and renal diseases. Our findings highlight significant associations between pathogens such as Epstein-Barr virus and polyomaviruses and conditions like glomerulonephritis, nephrotic syndrome, chronic kidney disease, and prostatitis, underscoring the potential role of certain specific pathogens and antigens in immune-mediated renal and urinary tract disorders. This research indicates that specific pathogen antibodies may serve as risk factors for certain diseases while also acting as protective factors for others, providing new insights into their pathogenesis. These results carry significant implications for the development of targeted prevention and treatment strategies.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Authors' contributions

Funding acquisition: DPW,WC; Conceptualization: HXH, BHC; Data curation:HXH; Formal analysis:HXH,BHC,CF; Methodology:HXH; Software:BHC;Validation: HXH,WC; Writing – original draft:HXH,CF; Writing – review & editing:WC; All authors reviewed the manuscript.

Data availability statement

Data derived from public domain resources: The data that support the findings of this study are available in [FinnGen] at [https://www.finngen.fi/en] and [UK Biobank] at [https://www.ukbiobank.ac.uk/]. These data were derived from the following resources available in the public domain: [https://www.finngen.fi/en] and [https://www.ukbiobank.ac.uk/].

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References

[1] Satoskar AA, Parikh SV, Nadasdy T. Epidemiology, pathogenesis, treatment and outcomes of infection-associated glomerulonephritis. Nat Rev Nephrol. 2020;16(1):32–50. doi: 10.1038/s41581-019-0178-8
[2] Romagnani P, Remuzzi G, Glassock R, et al. Chronic kidney disease. Nat Rev Dis Primers. 2017 [cited 2017 Nov 23];3(1):17088. doi: 10.1038/nrdp.2017.88
[3] Homma Y, Akiyama Y, Tomoe H, et al. Clinical guidelines for interstitial cystitis/bladder pain syndrome. Int J Urol. 2020;27(7):578–589. doi: 10.1111/iju.14234
[4] Collins MM, Meigs JB, Barry MJ, et al. Prevalence and correlates of prostatitis in the health professionals follow-up study cohort. J Urol. 2002;167 (3):1363–1366. doi: 10.1016/S0022-5347(05)65301-3
[5] Anders HJ, Kitching AR, Leung N, et al. Glomerulonephritis: immunopathogenesis and immunotherapy. Nat Rev Immunol. 2023;23 (7):453–471. doi: 10.1038/s41577-022-00816-y
[6] Haq A, Mattocks S, Wong L, et al. Incidence of *Helicobacter pylori* in patients with interstitial cystitis. Eur Urol. 2001;40(6):652–654. doi: 10.1159/000049852
[7] Ronco P, Beck L, Debiec H, et al. Membranous nephropathy. Nat Rev Dis Primers. 2021 [cited 2021 Sep 30];7(1):69. doi: 10.1038/s41572-021-00303-z
[8] Gesualdo L, Di Leo V, Coppo R. The mucosal immune system and IgA nephropathy. Semin Immunopathol. 2021;43(5):657–668. doi: 10.1007/s00281-021-00871-y
[9] Tomana M, Novak J, Julian BA, et al. Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-deficient hinge region and antiglycan antibodies. J Clin Invest. 1999;104(1):73–81. doi: 10.1172/JCI5535
[10] Berthoux F, Suzuki H, Thibaudin L, et al. Autoantibodies targeting galactose-deficient IgA1 associate with progression of IgA nephropathy. J Am Soc Nephrol. 2012;23(9):1579–1587. doi: 10.1681/ASN.2012010053
[11] Combes B, Shorey J, Barrera A, et al. Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. Lancet. 1971;2(7718):234–237. doi: 10.1016/s0140-6736(71)92572-4
[12] Johnson RJ, Gretch DR, Couser WG, et al. Hepatitis C virus-associated glomerulonephritis. Effect of alpha-interferon therapy. Kidney Int. 1994;46 (6):1700–1704. doi: 10.1038/ki.1994.471
[13] Rao TK. Human immunodeficiency virus (HIV) associated nephropathy. Annu Rev Med. 1991;42(1):391–401. doi: 10.1146/annurev.me.42.020191.002135
[14] Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. JAMA. 2019;322(13):1294–1304. doi: 10.1001/jama.2019.14745
[15] Henson JB, Sise ME. The association of hepatitis C infection with the onset of CKD and progression into ESRD. Semin Dial. 2019;32(2):108–118. doi: 10.1111/sdi.12759
[16] Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J Urol. 2011;185 (6):2162–2170. doi: 10.1016/j.juro.2011.03.064
[17] Moutzouris DA, Falagas ME. Interstitial cystitis: an unsolved enigma. Clin J Am Soc Nephrol. 2009;4 (11):1844–1857. doi: 10.2215/CJN.02000309
[18] Domingue GJ Sr, Hellstrom WJ. Prostatitis. Clin Microbiol Rev. 1998;11(4):604–613. doi: 10.1128/CMR.11.4.604
[19] Zhu Z, Zheng Z, Zhang F, et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. Nat Commun. 2018 [cited 2018 Jan 15];9(1):224. doi: 10.1038/s41467-017-02317-2
[20] Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. JAMA. 2017;318(19):1925–1926. doi: 10.1001/jama.2017.17219
[21] Butler-Laporte G, Kreuzer D, Nakanishi T, et al. Genetic determinants of antibody-mediated immune responses to infectious diseases agents: a genome-wide and HLA association study. Open Forum Infect Dis. 2020 [cited 2020 Sep 24];7(11): ofaa450. doi: 10.1093/ofid/ofaa450

[22] Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol. 2011;40(3):755–764. doi: 10.1093/ije/dyr036
[23] Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children [published correction appears in lancet. The Lancet. 2018 Jul;28(392):61–74. doi: 10.1016/S0140-6736(18)31608-8] Lancet. 2018;392-(10141): 61–74.
[24] Mestecky J, Julian BA, Raska M. IgA nephropathy: pleiotropic impact of Epstein-Barr virus infection on immunopathogenesis and racial incidence of the disease. Front Immunol. 2023 [cited 2023 Feb 7];14:1085922. doi: 10.3389/fimmu.2023.1085922
[25] Kelleher CA, Dreyfus DH, Jones JF, et al. EBV infection of T cells: potential role in malignant transformation. Semin Cancer Biol. 1996;7 (4):197–207. doi: 10.1006/scbi.1996.0027
[26] Frappier L. EBNA1. Curr Top Microbiol Immunol. 2015;391:3–34. doi: 10.1007/978-3-319-22834-1_1
[27] Dossier C, Jamin A, Deschênes G. Idiopathic nephrotic syndrome: the EBV hypothesis. Pediatr Res. 2017;81 (1–2):233–239. doi: 10.1038/pr.2016.200
[28] Daskalogianni C, Pyndiah S, Apcher S, et al. Epstein-Barr virus-encoded EBNA1 and ZEBRA: targets for therapeutic strategies against EBV-carrying cancers. J Pathol. 2015;235(2):334–341. doi: 10.1002/path.4431
[29] Kupin WL. Viral-associated GN: hepatitis B and Other viral infections. Clin J Am Soc Nephrol. 2017;12 (9):1529–1533. doi: 10.2215/CJN.09180816
[30] Middeldorp JM. Epstein-Barr virus-specific humoral immune responses in health and disease. Curr Top Microbiol Immunol. 2015;391:289–323. doi: 10.1007/978-3-319-22834-1_10
[31] Lee S, Kim J, Chung WC, et al. Epstein-Barr virus viral processivity factor EA-D facilitates virus lytic replication by inducing Poly(ADP-Ribose) polymerase 1 degradation. J Virol. 2022;96(21):e0037122. doi: 10.1128/jvi.00371-22
[32] Painful bladder diseases: interstitial or abacterial cystitis? Lancet. 1988;1(8581):337–338. doi: 10.1016/s0140-6736(88)91127-0
[33] Jhang JF, Liu CD, Hsu YH, et al. EBV infection mediated BDNF expression is associated with bladder inflammation in interstitial cystitis/bladder pain syndrome with Hunner's lesion. J Pathol. 2023;259 (3):276–290. doi: 10.1002/path.6040
[34] Masek-Hammerman K, Brown TP, Bobrowski WF, et al. Polyomavirus-associated prostatitis in wistar han rats following immunosuppression in a chronic toxicity study. Toxicol Pathol. 2017;45(5):589–592. doi: 10.1177/0192623317713320
[35] Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. Nat Rev Dis Primers. 2017 [cited 2017 Oct 26];3(1):17077. doi: 10.1038/nrdp.2017.77
[36] Silling S, Kreuter A, Gambichler T, et al. Epidemiology of Merkel cell polyomavirus infection and Merkel cell carcinoma. Cancers (Basel). 2022 [cited 2022 Dec 14];14(24):6176. doi: 10.3390/cancers14246176
[37] Iyer JG, Afanasiev OK, McClurkan C, et al. Merkel cell polyomavirus-specific $CD8^+$ and $CD4^+$ T-cell responses identified in Merkel cell carcinomas and blood. Clin Cancer Res. 2011;17(21):6671–6680. doi: 10.1158/1078-0432.CCR-11-1513
[38] Ohnezeit D, Huang J, Westerkamp U, et al. Merkel cell polyomavirus small tumor antigen contributes to immune evasion by interfering with type I interferon signaling. PLOS Pathog. 2024 [cited 2024 Aug 7];20(8): e1012426. doi: 10.1371/journal.ppat.1012426
[39] Papadimitriou JC, Randhawa P, Rinaldo CH, et al. BK polyomavirus infection and renourinary tumorigenesis [published correction appears in. Am J Transplant. 2017 Jan;17(1):308. doi: 10.1111/ajt.14098] Am J Transplant. 2016;16(2):398–406. doi:10.1111/ajt.13550.
[40] Olson A, Lin R, Marin D, et al. Third-party BK virus-specific cytotoxic T lymphocyte therapy for hemorrhagic cystitis following allotransplantation [published correction appears in. J Clin Oncol. 2023 Oct;20 (41):4826. doi: 10.1200/JCO.23.01860] J Clin Oncol. 2021;39(24):2710–2719. doi:10.1200/JCO.20.02608.
[41] Bauer J, Gold R, Adams O, et al. Progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome (IRIS). Acta Neuropathol. 2015;130(6):751–764. doi: 10.1007/s00401-015-1471-7
[42] Chong S, Antoni M, Macdonald A, et al. BK virus: current understanding of pathogenicity and clinical disease in transplantation. Rev Med Virol. 2019;29(4): e2044. doi: 10.1002/rmv.2044
[43] Helle F, Aubry A, Morel V, et al. Neutralizing antibodies targeting BK polyomavirus: clinical importance and therapeutic potential for kidney transplant recipients. J Am Soc Nephrol. 2024;35(10):1425–1433. doi: 10.1681/ASN.0000000000000457
[44] Hirsch HH, Babel N, Comoli P, et al. European perspective on human polyomavirus infection, replication and disease in solid organ transplantation. Clin Microbiol Infect. 2014;20(7):74–88. doi: 10.1111/1469-0691.12538
[45] Balfour HH Jr, Sifakis F, Sliman JA, et al. Age-specific prevalence of Epstein-Barr virus infection among individuals aged 6–19 years in the United States and factors affecting its acquisition. J Infect Dis. 2013;208 (8):1286–1293. doi: 10.1093/infdis/jit321
[46] Kuri A, Jacobs BM, Vickaryous N, et al. Epidemiology of Epstein-Barr virus infection and infectious mononucleosis in the United Kingdom. BMC Public Health. 2020 [cited 2020 Jun 12];20(1):912. doi: 10.1186/s12889-020-09049-x
[47] Fourcade G, Germi R, Guerber F, et al. Evolution of EBV seroprevalence and primary infection age in a French hospital and a city laboratory network, 2000–2016. PLOS ONE. 2017 [cited 2017 Apr 17];12 (4):e0175574. doi: 10.1371/journal.pone.0175574
[48] Fowler K, Mucha J, Neumann M, et al. A systematic literature review of the global seroprevalence of cytomegalovirus: possible implications for treatment, screening, and vaccine development. BMC Public Health. 2022 [cited 2022 Sep 1];22(1):1659. doi: 10.1186/s12889-022-13971-7