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OPEN ACCESS Review Paper

Current Insights into Epstein - Barr virus Prevalence and Clinical Impact among Kidney Transplant Recipients in Iraq: An Updated Review

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ABSTRACT

Background: Epstein–Barr virus (EBV) is a major concern in kidney transplantation, contributing to post-transplant lymphoproliferative disorder (PTLD), graft dysfunction, and allograft loss. In Iraq, data on EBV prevalence among kidney transplant recipients (KTRs) are scarce, with most evidence derived from hemodialysis patients.
Objective: To systematically review the prevalence and clinical impact of EBV in Iraqi KTRs and assess associated risk factors, diagnostic approaches, and management strategies.
Methods: A systematic search of PubMed, Scopus, Web of Science, Google Scholar, and Iraqi repositories was conducted. Eligible studies on EBV prevalence and outcomes in KTRs and hemodialysis were screened, appraised, and synthesized following PRISMA guidelines.
Results: Available Iraqi studies indicate variable EBV prevalence in KTRs and hemodialysis, with risk factors including intensive immunosuppression, lymphocyte-depleting therapies, donor and graft characteristics, co-infections, recipient age, and post-transplant timing. Diagnostic strategies reported include donor-recipient serostatus, quantitative EBV PCR, and histopathology. Emerging therapeutic options, particularly EBV-specific adoptive T-cell therapy, show promise in reducing reactivation and preserving graft function.
Conclusion: EBV poses a significant but understudied risk in Iraqi KTRs. Consolidating regional evidence with international insights highlights the urgent need for targeted EBV surveillance and management strategies to improve transplant outcomes in Iraq.

Keywords: Epstein–Barr virus, kidney transplant recipients, PTLD, immunosuppression, Iraq.

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INTRODUCTION

Epstein-Barr virus (EBV), a ubiquitous human herpes virus, poses significant clinical challenges in Immunocompromised populations, particularly kidney transplant recipients (KTRs) [1]. In the context of renal transplantation, the use of immunosuppressive drugs to prevent graft rejection increases the susceptibility of recipients to EBV infection and reactivation, which can trigger serious complications such as post-transplant lymphoproliferative disorder (PTLD) and contribute to graft loss and renal impairment. This makes EBV infection a critical factor influencing long-term outcomes in kidney transplant patients [2–4]. In EBV D+/R− KTRs (donor EBV-seropositive, recipient seronegative), the risk of PTLD is markedly increased. These patients are prone to primary EBV infection after transplantation, often leading to EBV DNAemia and higher rates of graft dysfunction or loss. Mortality can be high in affected cases, although differences from EBV-seropositive recipients are not always statistically significant. Immunosuppressive therapy, while essential for preventing rejection, impairs control of EBV-infected B cells, enabling the unchecked proliferation that drives PTLD [3,5,6].

In Iraq, recent studies have highlighted a notably high seroprevalence of EBV in the general population and among patients with kidney diseases, including transplant recipients and those undergoing hemodialysis. For instance, Redha et al. [7] reported that seroprevalence rates of EBV IgG antibodies among Iraqi blood donors approach nearly 79.8%, with higher rates observed in females and residents of more densely populated areas like Baghdad, suggesting widespread latent infection and potential risks for viral reactivation under immunosuppression. Furthermore, research in Iraqi renal transplant recipients reported that around one-third (33%) had detectable EBV viremia by sensitive molecular assays such as real-time PCR, with viral loads ranging widely, underscoring the virus's active role post-transplant [8].

Management of EBV-related complications in kidney transplant patients involves balancing immunosuppression reduction, antiviral therapies, chemotherapy (such as rituximab), and sometimes surgical or radiation interventions for advanced PTLD. However, antivirals do not have direct anti-oncogenic effects against EBV; instead, therapeutic strategies focus mainly on controlling immune dysregulation. Given these severe sequelae, recent research advocates for improved EBV serostatus matching between donors and recipients and enhanced post-transplant screening strategies to mitigate EBV-associated risks [3,9]. Given the high prevalence and significant clinical impact of EBV infection among KTRs in Iraq, conducting a systematic review to synthesize existing evidence is both timely and essential. This review aims to consolidate current knowledge on EBV prevalence, viral load kinetics, associated clinical outcomes, including the risk of PTLD, and diagnostic strategies within this high-risk population.

METHODS

This study was conducted as a systematic literature review to comprehensively assess the prevalence and clinical impact of Epstein–Barr virus among kidney transplant recipients (KTRs) and hemodialysis patients in Iraq.

Search Strategy

A systematic search was performed across electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, using combinations of keywords and MeSH terms: "Epstein–Barr Virus," "EBV," "kidney transplantation," "renal transplant," "hemodialysis," and "Iraq." To capture locally published studies not indexed in international databases, Iraqi academic repositories and institutional databases were also screened.

Eligibility Criteria

1. **Inclusion:** Studies reporting EBV prevalence, diagnostic methods, clinical outcomes, or associated risk factors among KTRs and hemodialysis patients in Iraq.
2. **Exclusion:** Case reports, editorials, conference abstracts lacking sufficient data, studies not involving KTRs or hemodialysis patients, and studies conducted outside Iraq.

Study Selection and Appraisal

All retrieved records were imported into Mendeley Reference Manager, and duplicates were removed. The methodological quality of included studies was rigorously evaluated using established critical

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appraisal tools, and findings were systematically synthesized following PRISMA guidelines.

Data Extraction and Synthesis

A standardized form was used to extract relevant information, including study characteristics, EBV prevalence rates, diagnostic approaches, clinical outcomes, and reported risk factors among KTRs and hemodialysis patients. In addition, the geographic distribution of studies across Iraqi governorates was visualized on a map to highlight regional coverage and potential gaps in the literature. Due to heterogeneity in study design, diagnostic methods, and outcome measures, the results were synthesized narratively.

RESULTS

Epstein-Barr virus (EBV)

Discovery and Early Research on EBV

Epstein-Barr virus was first discovered in 1964 by Dr. Anthony Epstein's team through electron microscopy of cells from Burkitt's lymphoma biopsies [10]. Early studies linked EBV to tumor development, with elevated antibody levels found in Burkitt's lymphoma and nasopharyngeal carcinoma patients by 1966 [11,12]. EBV was confirmed as the cause of infectious mononucleosis in 1968 [13]. By 1970, EBV DNA was detected directly in tumor cells of Burkitt's lymphoma and nasopharyngeal carcinoma [14,15]. In the 1980s, its association expanded to non-Hodgkin's lymphoma and AIDS-related oral hairy leukoplakia [16,17]. EBV DNA has since been identified in various lymphomas, leukemias, and epithelial cancers, as well as linked to autoimmune diseases like multiple sclerosis [18–21]. The history of EBV discovery is illustrated in
Figure 1.

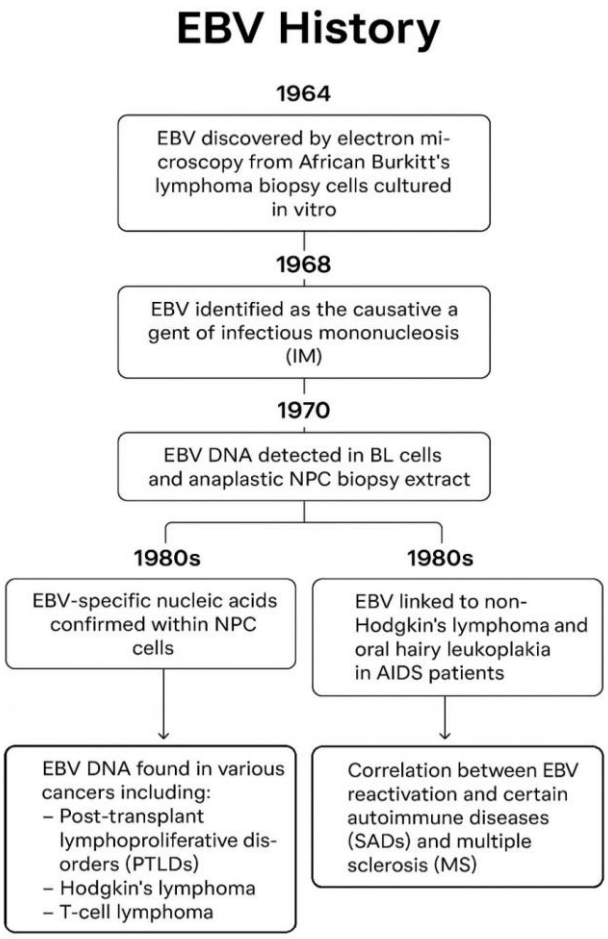

Figure 1: Historical Milestones in EBV Discovery and Disease Associations. Created by the authors.

Genomic and Structural Properties of EBV

Epstein–Barr virus, classified as a gammaherpesvirus, possesses a linear, double-stranded DNA genome measuring approximately 170–185 kb and encoding over 85 genes [22]. At both ends of the genome lie ~0.5 kb terminal direct repeats, while internal repeat sequences divide the genome into distinct long and short domains, each encoding various proteins [23]. The EBV nucleocapsid consists of 162 capsomeres surrounded by a viral envelope derived from host cell membranes. Between the nucleocapsid and envelope lies the tegument layer. The envelope is embedded with surface glycoproteins that form characteristic "spike-like" protrusions (

Figure 2) [24,25]. Viral entry into epithelial cells and lymphocytes is mediated by the interaction of these glycoproteins with specific cellular receptors, enabling direct fusion of the viral envelope with host cell membranes. Once inside the cell, the linear viral DNA circularizes through the joining of terminal direct repeats at both ends. Within the infected cell, the EBV genome persists as an extrachromosomal episome, allowing its stable maintenance during cell replication [26].

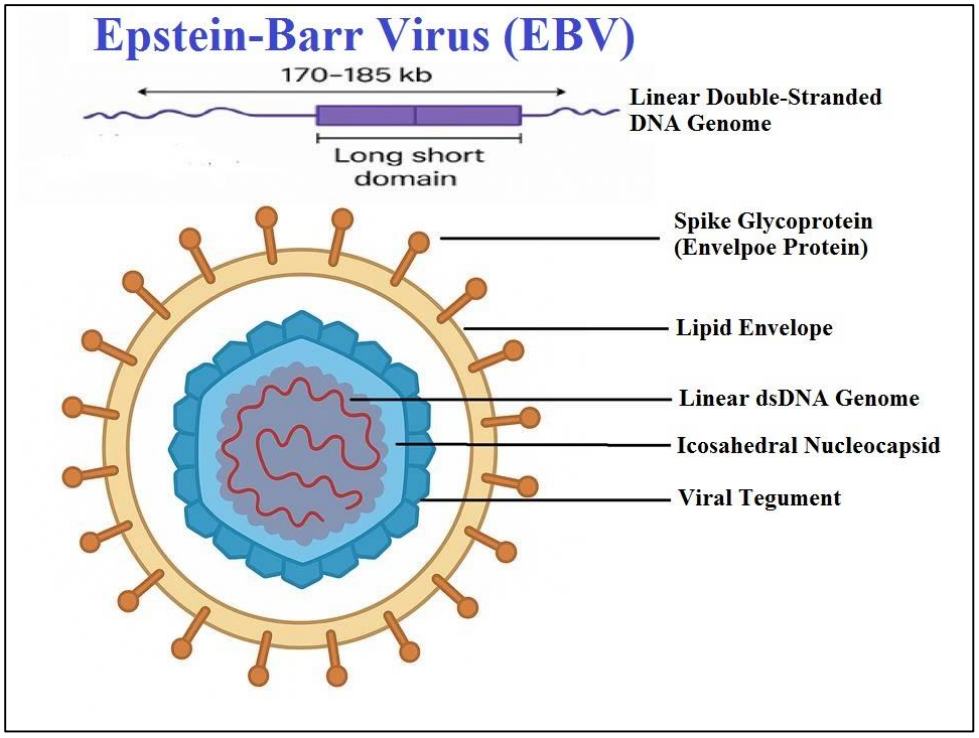

Figure 2: Diagram of the Structural Components of EBV. Created by the authors.

Viral Latency and Replication

EBV Latency

Following primary infection, EBV persists as an episome in memory B cells, maintaining a dynamic balance between latency, replication, and immune surveillance. Latency gene expression involves six nuclear antigens (EBNAs), three latent membrane proteins (LMPs), two non-coding RNAs (EBERs), and numerous microRNAs [27]. Three latency programs are recognized:

- Type III: Full latency gene expression; common in immunocompromised patients with PTLD or certain diffuse large B-cell lymphomas [28].
- Type II: Restricted expression (EBNA1, LMP1, LMP2, EBERs, and miRNAs); observed in Hodgkin lymphoma and nasopharyngeal carcinoma.
- Type I/0: Minimal expression (EBNA1, EBERs, miRNAs); characteristic of Burkitt lymphoma and EBV-associated gastric carcinoma.

EBNA1 is essential for genome maintenance, LMP1 drives oncogenic signaling, and LMP2 regulates reactivation. Non-coding RNAs facilitate immune evasion [29].

EBV Lytic Cycle

The lytic cycle progresses through immediate early, early, and late phases, involving the expression of more than 80 proteins. Immediate early proteins BZLF1 (ZEBRA) and BRLF1 (Rta) initiate the switch from latency to replication, followed by early replication proteins and late structural proteins such as capsid antigens, protease, and glycoproteins [30]. Lytic antigens are targeted by $CD8^+$ and $CD4^+$ T cells, while surface glycoproteins elicit neutralizing

antibodies [31,32]. Evidence indicates that lytic proteins contribute to oncogenesis [33, 34].

Kidney Transplantation and Immunosuppression

Transplantation has revolutionized the treatment of end-stage organ failure, providing life-saving options for patients who would otherwise have limited alternatives. For those with end-stage kidney disease (ESKD), kidney transplantation offers improved survival and quality of life compared with long-term dialysis [35–37]. The first successful kidney transplant, performed between identical twins in December 1954 by Dr. Joseph Murray and colleagues, represented a landmark achievement in medical history [38]. The primary challenge in transplantation medicine is the recipient's immune system rejecting the transplanted organ. The immune system distinguishes between self and foreign tissue, leading to immune-mediated injury and potential graft failure. Such rejection may occur in different forms: hyperacute, developing within minutes after the transplant; acute, arising days to months post-transplant; or chronic, which can progress over several years [39]. While advances in surgical techniques and organ preservation have greatly contributed to transplant success [40], the management of the recipient's immune response remains the primary determinant of outcomes. As a result, widespread adoption of kidney transplantation did not accelerate until decades later. The 1980s marked a turning point with the introduction of the calcineurin inhibitor cyclosporine [41, 42]. The use of calcineurin inhibitors (CnIs) and antimetabolite-based immunosuppressive regimens significantly reduced acute rejection rates, improving short-term graft survival. However, long-term graft outcomes have seen more modest gains, partly due to the nephrotoxic and metabolic side effects associated with prolonged immunosuppression. Chronic CnI exposure can cause arteriolar hyalinosis, tubular injury, and interstitial fibrosis [43, 44], while long-term corticosteroid use has been linked to cardiovascular complications and increased mortality. To address these challenges, recent research has focused on optimizing immunosuppressive strategies, including CnI- and steroid-sparing regimens, to enhance long-term graft survival [45].

Induction immunosuppression remains a critical initial phase following kidney transplantation, aimed at reducing the risk of early graft rejection. Commonly used agents include interleukin-2 receptor antagonists (IL2Ra) and rabbit antithymocyte globulin (r-ATG). Recent evidence suggests that IL2Ra induction may offer superior long-term survival compared to r-ATG without increasing graft loss, highlighting ongoing efforts to refine induction protocols for improved outcomes [46]. Immunosuppressive strategies have also been adapted for special populations, such as pediatric patients and individuals with autoimmune disorders like lupus nephritis, where careful balancing of immune suppression and disease control is essential. Despite these advances, progress has been limited by the scarcity of new drug approvals, underscoring the need for continued innovation through collaboration between clinical research and pharmaceutical development [47, 48]. Emerging approaches aim to achieve operational tolerance, allowing recipients to maintain graft function with minimal or no immunosuppression. Techniques such as transient mixed allogeneic chimerism, although still experimental, hold the potential to transform kidney transplantation by reducing or even eliminating lifelong immunosuppressive therapy [49]. Parallel improvements in donor-recipient matching, including precision strategies like eplet matching via registries, have further enhanced transplant outcomes. These methods are associated with reduced formation of donor-specific antibodies, lower graft failure rates, and opportunities for immunosuppression minimization, representing an important adjunct in optimizing both graft longevity and patient safety.

Prevalence of EBV Infection in Kidney Transplant Recipients

Global context: EBV Prevalence in Kidney Transplant Populations Worldwide

Epstein–Barr virus infection is highly prevalent worldwide among kidney transplant populations, carrying significant implications for transplant outcomes. Multiple studies confirm that EBV is frequently detected both before and after kidney transplantation, with prevalence influenced by geographic, genetic, and clinical factors. Globally, pre-transplant EBV exposure is widespread, with EBV IgG seropositivity in kidney transplant candidates often exceeding 90%. Among hemodialysis (HD) patients, the main group awaiting transplantation, rates reflect the near-universal exposure to EBV in the general population. In the Middle East, EBV prevalence is similarly high. In Iran, anti-EBV (VCA) IgG seropositivity among HD patients is reported at 96.42%, with EBV DNA detected in 8.33% of cases [50]. Another Iranian study reported 100% EBV IgG positivity among adult potential kidney donors and recipients [51]. Among renal transplant recipients, EBV infection has been documented in 15.5% of patients [52]. Nikoobakht et al. observed EBV DNA positivity in 44.1% of pre-transplant saliva samples, increasing to 67.6% after transplantation [53]. In Europe, similarly high pre-transplant EBV exposure rates are observed. In Croatia, 98% of HD patients were EBV IgG positive [54], while in Cyprus, the prevalence was 94% [55]. In the United Kingdom, a sero-epidemiological survey of 2,325 individuals aged 0–25 years found 85.3% seropositivity, with higher rates among females during adolescence (ages 10–15) [56]. Regarding post-transplant EBV reactivation, Italy reported 24.8% of kidney transplant recipients (KTRs) testing positive for EBV DNA within the first year [57], while Germany observed EBV reactivation in 18.4% of recipients during the same period, with pre-transplant EBV shedding and male sex identified as risk factors; importantly, reactivation was not associated with severe complication [58]. In North America, particularly the United States, Verghese et al. [59] detected EBV DNA in 34% (32/95) of pre-transplant patients. A large retrospective cohort study involving 962 KTRs found EBV infection in 11.3%, with most cases developing more than three years post-transplant [60]. Furthermore, recipients with donor-positive/recipient-negative (D+/R−) serostatus demonstrated a 22.1% cumulative incidence of post-transplant lymphoproliferative disorder (PTLD), with 48.1% of these recipients developing EBV DNAemia after transplantation [3]. The variation in EBV prevalence and DNAemia rates across these regions reflects differences in host genetic background, immunosuppressive regimens, diagnostic approaches, and local epidemiology. Post-transplant immunosuppression facilitates EBV reactivation or primary infection, which can increase the risk of PTLD, a potentially fatal malignancy. Although often asymptomatic, EBV reactivation can accelerate graft dysfunction, reduce estimated glomerular filtration rate (eGFR), and raise the likelihood of acute rejection. Co-infection with other viruses such as cytomegalovirus (CMV) can further worsen patient outcomes. Consequently, routine EBV DNA monitoring using sensitive PCR-based methods is recommended worldwide to support early detection, guide clinical decision-making, and mitigate EBV-related complications in KTRs [8,60].

Regional/Local data: EBV Prevalence among Hemodialysis and Kidney Transplant Patients in Iraq

Epstein-Barr virus poses a significant health concern among immunocompromised patients, particularly those undergoing kidney transplantation or hemodialysis. EBV can establish lifelong latency and reactivate under immunosuppressed conditions, increasing the risk of complications such as PTLD and potential graft dysfunction or loss. In Iraq, where kidney transplantation programs have been developing since the early 1973s [61], limited studies have examined the prevalence of EBV among transplant patients (
Figure 3). A study in Baghdad reported that 33% of renal transplant recipients exhibited EBV viremia, highlighting the potential role of EBV in post-transplant renal dysfunction and the utility of real-time PCR as a sensitive diagnostic tool [8]. Given the limited transplant-focused data, regional research has increasingly evaluated EBV prevalence in hemodialysis and chronic kidney disease (CKD) populations, who share similar immunological risks. In Al-Najaf, multiple studies reported EBV prevalence among hemodialysis patients. One study found 36%

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positivity by RT-qPCR and 22% by EBNA2 IgG, with higher prevalence in younger patients (17–26 years) and no infection detected in healthy controls [62]. Another study in the same region found 41.4% IgM positivity, 57.6% IgG positivity, and 44.9% PCR positivity among 118 patients, indicating a substantial EBV burden, slightly higher in males [63]. Further, co-occurrence of EBV and systemic lupus erythematosus (SLE) was observed in 36% of patients, with elevated IL-10 and IL-18 levels, suggesting a link between EBV infection and inflammatory responses [64]. In Kirkuk, studies reported 42.8% IgG and 7.6% IgM positivity among hemodialysis patients, with acute EBV infection (IgM) significantly associated with longer dialysis duration and higher weekly dialysis frequency ($p = 0.015$) [65]. Another study from the same city reported 43.7% IgM positivity compared to 9.1% in healthy controls, confirming the heightened susceptibility of hemodialysis patients to acute EBV infection [66]. Furthermore, patients with acute EBV infection had significantly elevated IL-8 and IL-10 levels, indicating that EBV may promote pro-inflammatory cytokine production in this population [67]. In Erbil, ABO blood group was shown to influence EBV susceptibility, with hemodialysis patients carrying blood group A+ being more prone to infection compared to other groups [68]. Collectively, these findings demonstrate that EBV infection is highly prevalent among kidney transplant and hemodialysis patients across different Iraqi cities, with younger age, longer dialysis duration, and specific blood groups increasing susceptibility. Real-time PCR and serological assays remain essential tools for accurate detection and monitoring of EBV in this high-risk population, and the virus may contribute to immune dysregulation, inflammatory responses, and potential post-transplant complications.

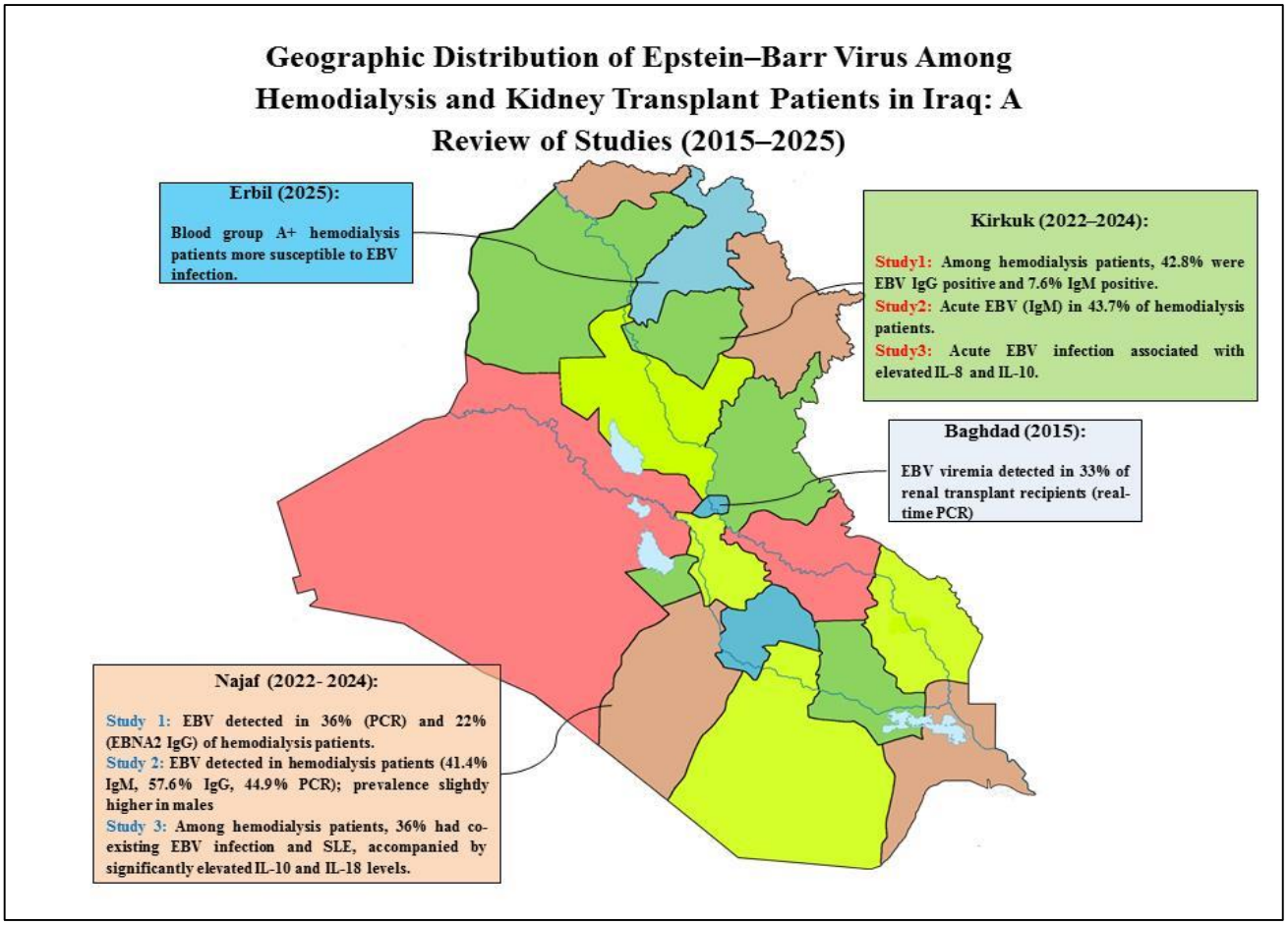

Figure 3: Map of Iraq illustrating EBV prevalence and key findings among hemodialysis and kidney transplant patients across different cities. Created by the authors.

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Emerging Risk Factors for EBV Infection in Kidney Transplant Recipients

Epstein-Barr virus infection remains a critical challenge in kidney transplantation, particularly due to the immunosuppressed state of recipients, which favors both primary infection and viral reactivation. These infections can precipitate serious complications, most notably PTLD. Recent studies (2020–2025) have refined our understanding of risk factors, highlighting novel insights into patient susceptibility and viral dynamics (Figure 4)

Donor-Recipient EBV Serostatus Mismatch

The highest risk occurs in EBV-seronegative recipients receiving kidneys from EBV-seropositive donors. Recent cohort studies indicate that up to 22% of these high-risk recipients develop PTLD within three years, with aggressive disease and significant mortality in a subset [3]. Seropositive recipients prior to transplantation show markedly reduced PTLD risk, suggesting that pre-existing immunity is a protective factor [3, 69].

Age and Developmental Factors

Pediatric and young adult transplant recipients remain disproportionately susceptible to primary EBV infection [70, 71]. Data indicate that EBV-naïve children receiving EBV-positive donor organs exhibit the highest incidence of PTLD, emphasizing the continued importance of age-stratified risk assessment in clinical protocols [72, 73].

Intensified and Targeted Immunosuppression

Modern immunosuppressive strategies have nuanced effects on EBV risk [72]. Intensive therapy within the first year post-transplant or following acute rejection impairs T-cell surveillance, increasing EBV reactivation and PTLD risk. Lymphocyte-depleting agents, such as thymoglobulin, and elevated tacrolimus trough levels further amplify susceptibility [69]. Emerging biologics, including belatacept, slightly elevate PTLD risk in EBV-seropositive adults but may offer overall safety advantages compared to conventional regimens [74–76].

Coinfections and Immune-Modulating Factors

Concurrent viral infections, particularly active cytomegalovirus (CMV), are increasingly recognized as amplifiers of EBV DNAemia and immune perturbation [77].

Graft Source, Donor Characteristics, and Microenvironment

Organs from deceased donors and grafts rich in lymphoid tissue are linked to higher EBV risk, particularly in pediatric and immunologically naive recipients [78–80]. Current research is exploring how donor-specific viral microenvironments within the graft may influence EBV replication dynamics post-transplant.

Post-Transplant Timeline

EBV reactivation and PTLD predominantly occur within the first 1–2 years, but late-onset complications are increasingly reported, underscoring the need for long-term surveillance in high-risk recipients [72].

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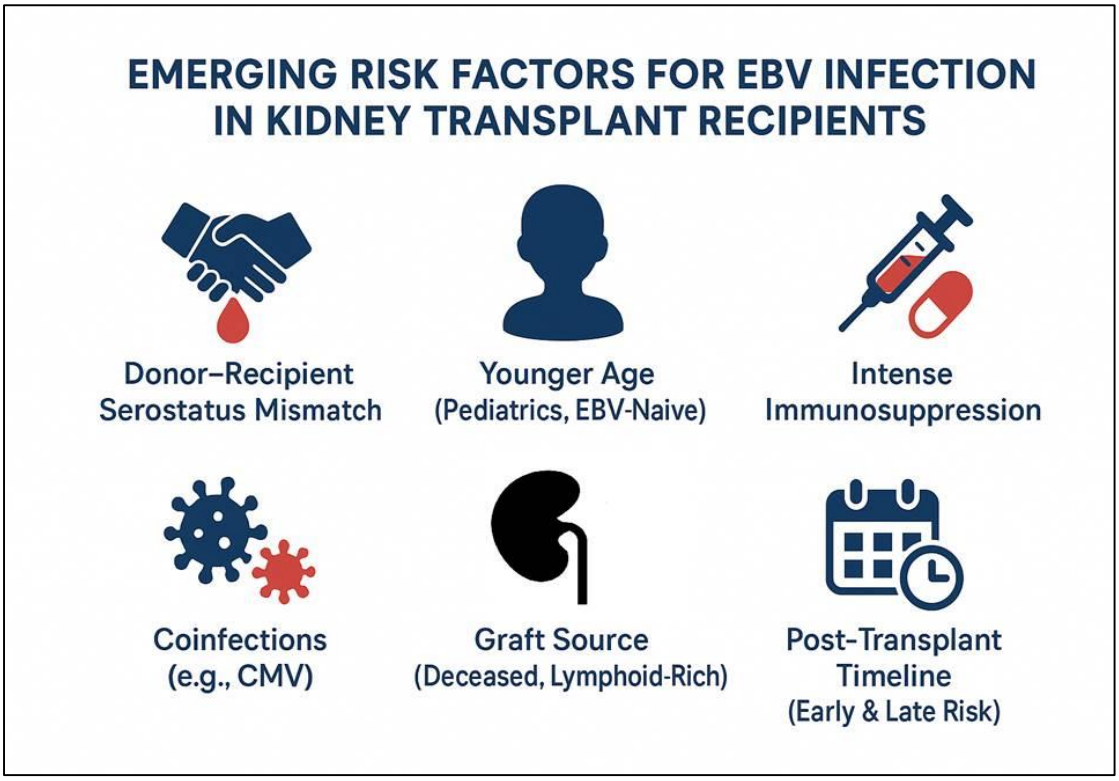

Figure 4: Risk Factors for EBV Infection in Kidney Transplant Recipients. Created by the authors.

Clinical Impact of EBV in Kidney Transplant Recipients

In kidney transplant recipients (KTRs), Epstein–Barr virus manifests along a continuum from asymptomatic DNAemia to infectious mononucleosis–like illness, graft-involving disease, and post-transplant lymphoproliferative disorders (PTLD). Contemporary syntheses place the cumulative incidence of PTLD in adult renal recipients around 0.6–2.5%, far lower than thoracic/intestinal grafts but still clinically consequential because 60–70% of PTLD is EBV-related and mortality remains substantial [81–84]. Recent registry and cohort work underscores how donor–recipient serostatus dominates risk: early-onset PTLD in EBV-seronegative recipients of seropositive donor kidneys (D^+/R^-) is markedly enriched; one recent adult cohort estimated a 22.1% cumulative incidence of early PTLD in D^+/R^- pairs [3]. PTLD remains associated with substantial mortality beyond the first posttransplant year. Evidence from multiple cohorts indicates that patient survival is adversely affected by PTLD, even in cases where graft survival rates are not consistently reduced [5]. Immunosuppressive therapy compromises EBV-specific T-cell surveillance, leading to unchecked B-cell proliferation, viral reactivation, and, in a subset of cases, malignant transformation. Evidence from reviews and consensus guidelines supports a graded, exposure-dependent risk model: T-cell–depleting induction regimens (such as antithymocyte globulin [ATG] or alemtuzumab) and augmented therapy for rejection confer a markedly higher risk of EBV DNAemia and PTLD compared with non–depleting induction agents (such as basiliximab). This association was reinforced by a large multicenter study, which demonstrated a significantly greater incidence of PTLD with ATG or alemtuzumab relative to basiliximab, even after comprehensive multivariable adjustment [69].

Children and young adults are more susceptible to early EBV infection after transplantation, partly because of their younger age and often being EBV-naïve (not previously exposed to the virus) [5, 85]. Coinfections, especially CMV, are frequent and can heighten viral loads and immune dysregulation, reinforcing the value of coordinated surveillance for herpesviruses in high-risk KTRs [86]. EBV DNAemia and PTLD are associated with increased

hospitalization, intensified immunosuppression, and higher mortality, even when graft survival is maintained in some cases. Contemporary studies in solid-organ transplant cohorts report PTLD-related mortality between 30 and 60%, depending on histology and treatment response [81, 87]. Iraqi studies further confirm that opportunistic viral infections, particularly Epstein-Barr virus (EBV), represent a significant threat to renal transplant recipients, especially under contemporary immunosuppressive regimens. EBV reactivation can result in graft dysfunction and loss if not promptly detected and managed. Gaining insight into EBV prevalence, associated risk factors, and its clinical impact is essential for optimizing outcomes in KTRs in Iraq [8, 88].

Diagnosis and Management of EBV among Kidney Transplant Recipients

Diagnosis

Accurate diagnosis of clinically significant Epstein–Barr virus infection in kidney transplant recipients (KTRs) rests on three pillars: 1) pre-transplant risk stratification (donor/recipient serostatus), 2) molecular surveillance by quantitative EBV PCR, and 3) tissue diagnosis when invasive disease or PTLD is suspected. Pre-transplant EBV serology remains essential to identify high-risk D^+/R^- pairs who require intensified post-transplant monitoring because primary infection in a naïve recipient carries the highest early PTLD risk. Guidelines and registry analyses therefore recommend documenting donor and recipient EBV IgG prior to transplantation and flagging seronegative recipients for more intensive follow-up [80, 89, 90]. Quantitative nucleic-acid testing (qPCR) of blood remains the cornerstone of EBV diagnosis and monitoring. Whole blood provides greater sensitivity for low-level, cell-associated EBV DNA, while plasma more accurately reflects free viral DNA indicative of lytic replication and active disease. Adoption of the WHO International Standard has enhanced assay harmonization across laboratories. Nevertheless, qPCR demonstrates a high negative predictive value but a limited positive predictive value, making it more reliable for ruling out EBV disease than for confirming it [91–93].

Serological testing for EBV, most commonly by measuring viral capsid antigen (VCA) IgG/IgM, EBV nuclear antigen (EBNA-1) IgG, and occasionally early antigen (EA), is primarily used pre-transplant to determine the EBV serostatus of both donor and recipient. This stratification (D^+/R^-, D^+/R^+, D^-/R^+, D^-/R^-) identifies recipients at greatest risk for primary EBV infection and subsequent PTLD, particularly in D^+/R^- pairs. Post-transplant, however, serology is of limited diagnostic value: antibody responses may be blunted by immunosuppression, and interpretation is complicated by donor-derived antibodies or passive transfer via transfusion or IVIG. Thus, while serology remains crucial for risk assessment and baseline classification, molecular assays (EBV PCR) are the preferred tool for monitoring active infection or reactivation after transplantation [94–96]. In Iraq, most studies on EBV among KTRs have employed diagnostic strategies comparable to those used globally, primarily relying on serological assays and molecular techniques such as PCR to detect infection.

Surveillance Strategies

Surveillance strategies should be risk-adapted. Most expert reviews and society guidance recommend frequent EBV PCR during the early post-transplant period (for example, weekly to biweekly for the first 1–3 months in high-risk D^+/R^- recipients, then gradually spacing to monthly through 6–12 months), with lower intensity or no routine monitoring for low-risk adult D^+/R^+ or D^-/R^- pairs depending on center practice. Because evidence for exact schedules and thresholds is imperfect, many centers adopt programmatic algorithms that combine serostatus, age (pediatric vs. adult), induction regimen, and clinical events (e.g., rejection) to decide frequency and action thresholds [97, 98].

Initial management (first-line: reduce net immunosuppression ± rituximab)

The universally recommended first step for significant EBV DNAemia or early EBV-driven disease is reduction of immunosuppression (RIS) to restore EBV-specific T-cell surveillance, balanced against rejection risk. RIS typically involves stepwise reduction or withdrawal of anti-proliferative agents (mycophenolate) and lowering calcineurin inhibitor exposure. For EBV-positive PTLD or persistent/high-level DNAemia despite RIS, rituximab (anti-CD20), often given as weekly infusions, is the standard next intervention for B-cell PTLD (polymorphic or early

lesions) and increasingly used preemptively in high-risk scenarios; combination with RIS improves response rates compared with RIS alone in many series [75, 99–101]. Antiviral agents (acyclovir, ganciclovir) have limited efficacy against latent EBV and are not reliable as stand-alone therapies for EBV DNAemia or established PTLD; they may have a role in specific settings with lytic replication but are not substitutes for RIS/rituximab or cellular therapy in established disease. Intravenous immunoglobulin (IVIG) is occasionally used adjunctively but lacks definitive evidence as primary therapy [102, 103].

Emerging and Advanced Therapies

For rituximab-refractory, relapsed, or high-risk EBV-positive PTLD, EBV-specific adoptive T-cell therapy has rapidly advanced from case series to regulatory approvals in some jurisdictions. The allogeneic, partially HLA-matched product tabelecleucel (brand name Ebvallo™/Tab-cel) received conditional marketing authorization in the European Union (2022) and in several other countries for relapsed/refractory EBV-positive PTLD after failure of at least one prior therapy, and real-world and trial data show meaningful durable responses with acceptable safety. The product's U.S. regulatory path has been active, with recent submissions and regulatory interactions reflecting manufacturing and inspection issues rather than lack of clinical effect; therefore, availability remains region-dependent and evolving. Adoptive therapy using donor-derived or third-party EBV-specific cytotoxic T lymphocytes in specialized centers also demonstrates high response rates and is increasingly included in algorithms for refractory disease [104].

Research Gap

Despite the recognized global importance of the Epstein–Barr virus in organ transplantation, there is a striking scarcity of local studies in Iraq, particularly among transplant recipients. Most available research focuses on EBV prevalence in hemodialysis patients, while data on kidney transplant recipients remain limited. Geographic representation is uneven, with significant variation between governorates, and there is substantial inconsistency in diagnostic approaches across studies. Notably, there are no long-term studies examining post-transplant complications such as post-transplant lymphoproliferative disorder (PTLD) or graft dysfunction. Furthermore, the role of EBV in donor status, whether positive or negative, has not been investigated. Addressing these gaps is crucial to better understand the epidemiology, risk factors, and clinical impact of EBV in Iraq and to align local knowledge with global evidence.

CONCLUSION

The impact of Epstein–Barr virus on kidney transplant outcomes in Iraq remains an underexplored yet critical area of study. Evidence from regional hemodialysis and transplant populations indicates that EBV infection contributes substantially to post-transplant complications, including PTLD and graft dysfunction. Recognizing and addressing the multifactorial risk factors, such as immunosuppressive regimens, donor-recipient characteristics, and co-infections, is essential to optimize patient care. Implementation of systematic EBV monitoring, adoption of sensitive molecular diagnostics, and integration of emerging therapies, including EBV-specific adoptive T-cell strategies, could transform management and improve long-term graft survival. Future research should focus on expanding national surveillance, clarifying EBV epidemiology in transplant recipients, and evaluating innovative prevention and treatment approaches to mitigate the virus's clinical burden.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Authors' Contribution

All authors contributed to the conception and design of the study. Safaa Shehab Ahmed conducted the literature search, data extraction, and synthesis. Anfal Kadhim Abed prepared the figures, including the map of study locations, and assisted in data analysis. Shahad Saad Alwan drafted the manuscript, and all authors critically revised the content for intellectual accuracy. All authors have read and approved the final version of the manuscript.

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