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THE ROLE OF EPSTEIN-BARR VIRUS IN HAEMATOLOGICAL MALIGNANCIES

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ABSTRACT

The majority of adults worldwide are infected with the Epstein-Barr virus (EBV). It was the first human virus to be linked to cancers and is now considered a causative factor in the development of a broad group of B-cell, T-cell and NK-cell neoplasms. This narrative review summarises the role of EBV in haematological malignancies. A structured search of PubMed/MEDLINE, Scopus, and Web of Science was conducted for English-language publications available up to October 2026, supplemented by current guidance from international health authorities. It covers pathogenesis, the clinical features and prognostic meaning of EBV in eight entities, diagnosis and prevention. EBV acts through latent proteins such as LMP1, LMP2A and EBNA2, through viral microRNAs, and through changes in host signalling, antigen presentation, immune checkpoints and the tumour microenvironment. Deletions and variants of the viral genome add a further layer. EBV is found in nearly all endemic Burkitt lymphoma, extranodal NK/T cell lymphoma, in a minority of sporadic Burkitt lymphoma and diffuse large B-cell lymphoma. Prognostic meaning differs between entities. The presence of an EBV infection was associated with a poorer prognosis in diffuse large B-cell lymphoma, NK/T cell lymphoma and, in a meta-analysis, Hodgkin lymphoma. In plasmablastic lymphoma the largest cohort found lower survival rate in EBV-negative disease. Epstein-Barr virus-encoded RNA (EBER) in situ hybridisation remains the diagnostic standard. Plasma EBV DNA adds prognostic and monitoring value, but assays and cut-offs are not standardised. Rituximab prophylaxis and DNA surveillance lower the risk of post-transplant lymphoproliferative disorder in selected groups. Due to the high complexity of the EBV virus, no vaccine has yet been developed against it.

KEYWORDS

EBV, Lymphoma, Burkitt lymphoma, Hodgkin lymphoma, Vaccine, Carcinogenesis

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1. Introduction

Epstein-Barr virus (EBV) is a gammaherpesvirus with a linear double-stranded DNA genome. More than 90% of adults are carriers of the virus, and for most of them the infection remains asymptomatic for their entire lives. Epstein and Barr first discovered the virus in Burkitt lymphoma (BL) cells in 1964. The International Agency for Research on Cancer placed EBV in group 1 of human carcinogens in 1997 (Xiao et al., 2025; Wong et al., 2022).

This occurrence is a significant challenge. Wong et al. (2022) estimated 239,700 to 357,900 new EBV-related cancers and 137,900 to 208,700 deaths in 2020, which is 1.3% to 1.9% of all cancers. A subsequent review reported about 170,000 EBV-attributable cases in 2022, with 120,000 of them in Asia (Xiao et al., 2025). An National Institutes of Health (NIH) position paper listed about 84,000 gastric cancers, 78,000 nasopharyngeal carcinomas, 28,000 Hodgkin lymphomas and more than 6,000 Burkitt's lymphomas each year (Cohen et al., 2013). Lymphomas account for part of this burden. Wong et al. (2022) put the number of EBV-related Hodgkin lymphoma cases at 34,300 to 52,400.

The EBV virus does not occur with the same frequency in all types of lymphoma. The proportion of classical Hodgkin lymphoma (cHL) attributable to EBV ranges from 74% in Africa and 60% in Latin America to 36% in Europe and 32% in North America (Wong et al., 2022). In a non-selective French series comprising 756 cases of lymphoma, 7.7% were cases strongly associated with the EBV virus (Donzel et al., 2022). A paediatric centre in Argentina observed a fall in EBER positivity in cHL from 69.2% before 2020 to 41.2% afterwards (Amarillo et al., 2025). As the classification system changes, so also does the clinical picture. The 2022 International Consensus Classification (ICC) includes the addition of EBV-positive polymorphic B-cell lymphoproliferative disorder, not otherwise specified, and a provisional entity of primary nodal EBV-positive T/NK cell lymphoma (Quintanilla-Martinez et al., 2023). The cut-off values for classifying a lymphoma as EBV-positive still differ between studies (Malpica et al., 2024; Frontzek et al., 2023).

The following two questions arise from these facts. The first concerns how the EBV virus contributes to malignant transformation in each of these conditions. The second relates to how a clinician can utilize these findings in the context of diagnosis, prognosis and prevention. At present there is no approved vaccine or antiviral drug for the treatment of cancers caused by the EBV virus (Wong et al., 2022). Recent genomic work suggests that EBV is more than just a "passenger virus" - it acts as a co-factor that influences the genetic changes in a tumour (Frontzek et al., 2023).

This review covers the pathogenesis of EBV-associated lymphomas, the clinical features and the prognostic significance of EBV in eight haematological units, diagnostic methods and prevention.

2. Methods

This paper is a narrative review. PubMed/MEDLINE, Scopus, and Web of Science were searched for publications available up to October 2026, using combinations of search terms related for the pathogen (Epstein-Barr virus, EBV, EBNA), the clinical entities under review, and preventive strategies. It is based on a defined set of 39 full-text publications selected for their relevance to EBV in haematological malignancies. No separate systematic database search was conducted specifically for this review, and no protocol was registered. Publications were eligible if they addressed EBV in relation to haematological malignancies with preference given to meta-analyses, randomized controlled trials, systematic reviews and cohort studies. The resulting evidence base comprised 43 publications dating from 2012 to 2026. Estimates are presented as reported by the original authors, and where discrepancies between sources were identified, the reported range is provided instead of a pooled estimate, given the heterogeneity in EBV detection methods across studies.

3. Results

3.1. Pathogenesis

3.1.1. Entry and persistence

The EBV enters B cells through interaction of glycoprotein gp350 with CD21 receptor. Subsequently, glycoprotein gp42 binds to HLA class II, facilitating the interactions of the gH/gL complex, which activates glycoprotein B (gB), causing membrane fusion and viral entry. Epithelial cells are infected through interactions involving integrins and the ephrin receptor A2 (Xiao et al., 2025). Following primary infection the virus persists in memory B cells without expressing viral antigens. This latency programme 0 allows the virus to evade recognition by T cells. The virus can periodically enter the lytic cycle (Xiao et al., 2025). Reactivation in a subset of carriers is associated with B-cell immortalisation and lymphoma development (Frontzek et al., 2023).

3.1.2. Latency programmes

The EBV utilises four latency programmes (0, I, II and III) characterised by an increasing number of viral genes. Latency programme I involves the EBNA1 protein and the EBER RNA. Latency programme II adds LMP1 and LMP2. In latency programme III, the EBNA2 and EBNA3 proteins appear (Xiao et al., 2025). The programme observed in a tumour depends on the type of tumour and the host's immune response. EBV-positive diffuse large B-cell lymphoma (DLBCL) typically exhibits latency programme III, with the presence of LMP1 in approximately 90% of cases and EBNA2 in approximately 30% (Malpica et al., 2024). EBV-positive post-transplant lymphoproliferative disorder (PTLD) also shows latency programme III (Quintanilla-Martinez et al., 2023). In the case of plasmablastic lymphoma (PBL) the programme is most commonly 0 or I, so staining for the presence of LMP1 has little diagnostic value (Bailly et al., 2022). In one review, cHL and extranodal natural killer/T-cell lymphoma (ENKTCL) were classified as latency II, whilst BL was classified as latency I or I and II (Xiao et al., 2025). The same review labels EBV-positive DLBCL as latency II and III in one instance, whilst in another it associates latency III with DLBCL in immunocompromised patients; therefore, these classifications should be regarded as approximate (Xiao et al., 2025).

3.1.3. Viral proteins and RNAs

EBNA2 promotes B-cell immortality and increases c-Myc expression. LMP1 mimics CD40 and activates NF-kB. It also binds to JAK3 and activates JAK/STAT, PI3K/AKT/mTOR and MAPK signalling pathways, as well as increasing PD-L1 levels (Xiao et al., 2025; Frontzek et al., 2023). LMP2A acts as a B-cell receptor mimetic, keeping B cells alive when they have lost their receptor. This process depends on SYK and BTK (Malpica et al., 2024). EBNA1 maintains the viral genome. EBNA3A blocks terminal differentiation. EBER RNAs are associated with resistance to apoptosis and with autocrine IL-10 in BL. The EBV virus also encodes more than 40 microRNAs. Members of the BART family inhibit antigen presentation, reduce caspase-3 levels and increase PD-L1 levels (Xiao et al., 2025).

3.1.4. Host genetic changes in EBV-positive large B-cell lymphoma

The most detailed profile comes from a study of 60 EBV-positive DLBCL cases from Germany (Malpica et al., 2024). SOCS1 was the most frequently mutated gene (24%), and 30% of cases harboured a mutation in the JAK/STAT pathway. NOTCH1 or NOTCH2 mutations occurred in 22% of cases, and were mutually exclusive. Chromatin modifier genes were mutated in 52% of cases, most commonly KMT2D (22%) and KMT2C (17%). CD58 and B2M were each mutated in 11% of cases, again with no overlap, suggesting impaired antigen presentation. Copy number analysis revealed amplification of 9p24.1 (PD-L1, PD-L2 and JAK2) in 20% of cases, of 6p25.3 involving IRF4 in 35%, and of 1q24.3 involving FASLG in 22%. Eight of nine cases with PD-L1 gain or amplification expressed the protein. Mutations typically associated with NF-kB-driven DLBCL, such as MYD88 and CD79B, were rare. The authors attributed this finding to NF-kB activation by LMP1. Only 17.4% of cases fitted a LymphGen cluster, compared with 36.6% of DLBCL cases not otherwise specified ($p = 0.007$). Because only some tumours still express EBNA2, NOTCH mutations may compensate for the loss of EBNA2 signalling. The authors concluded that EBV shapes the genetic landscape of the tumour and acts as a cofactor (Frontzek et al., 2023). A second review reported that EBV-positive DLBCL exhibits more copy number alternations than EBV-negative disease, especially involving PD-L1 and JAK2 (Malpica et al., 2024).

3.1.5. Hodgkin lymphoma

In EBV-related cHL the NF-kB inhibitors, such as TNFAIP3 and NFKBIA are frequently mutated, whilst the LMP1 protein stimulates the NF-kB and JAK/STAT signalling pathways in Hodgkin's and Reed-Sternberg cells (Xiao et al. 2025). In 64 Egyptian patients, the JAK2, STAT1, PD-L1, COX-2 and Bcl-xL genes showed higher expression in EBV-positive tumors (Alabiad et al., 2024). It has been reported that 9p24.1 amplification and the presence of the EBV are mutually exclusive in cHL (Frontzek et al., 2023).

3.1.6. Burkitt lymphoma

BL is defined by a MYC gene translocation. EBNA2 causes an increase in c-Myc levels, and latent EBV, in combination with c-Myc overexpression induces BL-like lymphoma in mice. EBV-related BL exhibits overall DNA hypomethylation with a number of hypermethylated CpG islands. Among 162 sporadic cases of BL, a mutation in the ID3 gene was found in 65% and a mutation in the ID3/TCF3/CCND3 axis in 86%. In EBV-positive cases, fewer mutations were observed in the ID3 gene, whilst more mutations were found in the FOXO1 and GNA13 genes. EBV-positive cases were also over-represented amongst those with a gene expression profile classified as "intermediate" ($p = 0.0024$) (Xiao et al., 2025; Richter et al., 2022).

3.1.7. T-cell and NK-cell neoplasms

ENKTCL harbours mutations in STAT3, STAT5B, JAK3, BCOR, KMT2D, ARID1A, EP300, TP53, MGA and DDX3X (Quintanilla-Martinez et al., 2023). In an international cohort of 260 patients, alterations in PD-L1 were found in 38% of cases, while mutations in DDX3X occured 17%, KMT2D in 16%, STAT3 in 15% to 16% and BCOR in 13% (Lim et al., 2022). EBV-positive nodal T/NK cell lymphoma harboured TET2 mutations in 68% cases and DNMT3A mutations in 32%. Clonal haematopoiesis was identified in three of four patients for whom blood-rich tissue samples were available (Kato et al., 2024). In hydroa vacciniforme-like lymphoproliferative disorder (HVLPD), exome sequencing identified mutations in STAT3, IKBKB, ELF3, CHD7 and KMT2D (Xie et al., 2020). In classic hydroa vacciniforme, 57% to 68% of the EBER-positive cells were gamma-delta T cells (Hirai et al., 2012).

3.1.8. Variation of the viral genome

Khine et al. (2025) analysed 990 EBV genomes and identified 22,319 variants. EBV type 2 has been linked to B-cell diseases. In one cluster, comprising 91 of 366 samples, a region with an increased frequency of mutations was detected at amino acid positions 195 to 203 of the EBNA3B protein. Intragenic deletions were concentrated in the BART region and occurred more frequently in lymphomas than in healthy carriers. This prevalence was 46% in DLBCL (18 of 39), 37% in ENKTCL and 30% in chronic active Epstein-Barr virus disease (CAEBV). In Hodgkin lymphoma, the frequency was 22%, in BL 20%, in PTLD 7% and in healthy carriers 5%. Cell lines deficient in EBNA3B exhibited 3,776 genes with altered expression, with lower levels of PTEN and RB1. The authors suggest that EBNA3B acts as a tumour suppressor (Khine et al., 2025). In the case of EBV-positive nodal T/NK cell lymphoma, structural variants of the viral genome were found in 63% of cases, compared with 43% in ENKTCL and 35% in CAEBV. In one tumour, the viral genome contained a DOCK8/PD-L1 fusion (Kato et al., 2024).

Both EBV type and variant matter in BL. In Kenya, EBV type 1 was detected in 74.5% of 58 cases of endemic BL and 47.5% of 40 controls (odds ratio 3.24). In 130 EBV-positive BL genomes, the LMP1 variants H101Q and I152L were associated with poorer survival, with adjusted hazard ratios of 10.9 and 2.43. In cHL cases from Croatia, all 46 EBV-positive cases carried EBV type 1, and the LMP1 variants (B95-8 type in 24 cases, Mediterranean deletion type in 13) were not associated with survival (Kaymaz et al., 2020; Kim et al., 2025; Begic et al., 2022).

3.1.9. Immune evasion and microenvironment

EBV-positive non-Hodgkin lymphoma has higher numbers of CD8-positive cells, regulatory T cells and M2 macrophages than EBV-negative form (Xiao et al., 2025). In 433 cases of DLBCL, EBV-positive tumours exhibited higher levels of PD-L1, LAG3, CD163 and B2M, and a CD163/CD68 ratio above 0.75 was predicted to have a worse outcome (Keane et al., 2019). In the case of PTLD, a 189-gene signature enabled the distinction between EBV-positive and EBV-negative form. EBV-positive tumours contained more CD163-positive monocytes and fewer T cells. Knocking out the CD300a gene restricted tumour growth and the volume of the xenograft (Toh et al., 2024; Bednarska et al., 2024).

3.1.10. Immune control as a precondition

PBLs testing positive for EBV were more common in immunocompromised individuals (72% compared with 43%) (Di Ciaccio et al., 2024). People living with Human Immunodeficiency Virus (HIV) are 23 times more likely to develop non-Hodgkin lymphoma (Xiao et al., 2025). Impaired T-cell control is a common risk factor for both PTLD and HIV-related lymphomas.

In summary, the data suggest that the EBV virus does not act alone. Viral proteins provide early survival and growth signals. Subsequently, host mutations arise within the same pathways, and the clone establishes itself by evading the immune response. The order of these events remains unclear in most entities (Xiao et al., 2025, Di Ciaccio et al., 2024; Sausen et al., 2023).

3.2 EBV-associated haematological malignancies

In this review, the EBV virus is associated with eight clinical entities. These differ in terms of the prevalence of the virus, the host's condition, and the impact of EBV status on treatment outcomes. Table 1 shows the prevalence of EBV in each of these disease entities, based on data from the included studies. The following sections describe each of these disease entities in turn.

Table 1. Frequency of EBV in the eight entities. The 60% to 80% figure for PTLD is derived from the statement that 20% to 40% of PTLD are EBV-negative.

Entity	EBV positivity reported	Typical setting
Burkitt lymphoma	Endemic 81% to 100%, sporadic 10% to 15%, HIV-associated 30% to 40%	Children in equatorial Africa for endemic disease, children and adults for sporadic disease
Classical Hodgkin lymphoma	29% to 74% of cases attributable to EBV, depending on region	Children, older adults and people with HIV
EBV-positive DLBCL	About 5% in the West, 10% to 15% in Asia, Eastern Europe and South America	Older adults, no known immunodeficiency
Post-transplant lymphoproliferative disorder	60% to 80% of cases	Solid organ and stem cell transplant recipients
Plasmablastic lymphoma	57% to 70%	HIV and other immunodeficiency
Lymphomatoid granulomatosis	EBV-positive B cells define the disease	Lung, immune dysregulation or immunosuppression
Extranodal NK/T cell lymphoma	Nearly all cases	East and Southeast Asia, Latin America
Hydroa vacciniforme-like lymphoproliferative disorder	17 of 19 cases by EBER in one series	Children and adults, reported mainly from East Asia

Note. DLBCL - diffuse large B-cell lymphoma, EBER - Epstein-Barr virus-encoded small RNAs, EBV - Epstein-Barr Virus, HIV - Human Immunodeficiency Virus, NK - Natural Killer cell. Adapted from Wong et al. (2025), Quintanilla-Martinez et al. (2023), Malpica et al. (2024), Hu et al. (2022), Bailly et al. (2022), Xie et al. (2020), Di Ciaccio et al. (2024), Loghavi et al. (2015) and Huang et al. (2017).

3.2.1 Burkitt lymphoma

BL is the tumour in which EBV was first detected. Three clinical forms of this disease are recognised. Endemic BL occurs in children in equatorial Africa and in 81% to 100% of cases the EBV virus is present.. Sporadic BL shows the presence of the EBV virus in 10% to 15% of cases. HIV-associated BL shows the presence of the EBVvirus in 30% to 40% (Wong et al., 2022). Another review reported a wider range for the sporadic form (15% to 30%) and for the immunodeficiency-related form (25% to 40%) (Xiao et al., 2025). It is estimated that in 2018, EBV caused 6,600 new cases of BL, mainly in children aged between 5 and 10 years (Xiao et al., 2025). Other estimates suggest over 6,000 cases of BL each year (Cohen et al., 2013). Approximately 85% of BL cases in Africa tests positive for EBV, compared with about 15% in the United States (Cohen et al., 2015).

In sporadic BL, EBV status depends on age. Among 162 patients, the EBER test was positive in 6% of children (5 of 89) and 20% of adults (13 of 65) ($p = 0.0097$) (Richter et al., 2022). EBV-positive sporadic BL more closely resembled endemic BL, characterised by fewer ID3 mutations and a greater number of mutations in the FOXO1 and GNA13 genes. The authors were unable to determine whether this pattern was due to age or the presence of EBV, as these two factors are closely linked in central Europe (Richter et al., 2022). In a French case series none of three cases of BL tasted positive for EBV (Donzel et al., 2022), which shows how rarely sporadic BL is associated with the presence of this virus.

The prognostic significance of the EBV virus in BL has not been conclusively established. In a study involving 130 EBV-positive BL genomes, the virus type had no prognostic significance, whereas variants of the LMP1 gene did have prognostic importance. Hte H101Q variant was associated with an adjusted hazard ratio for death of 10.9, whilst the I152L variant was associated with a hazard ratio of 2.43. Income level was the strongest single prognostic factor. The concordance index increased from 0.56 for income alone to 0.72 for viral variants and 0.76 for the complete model; furthermore, three prognostic subgroups were defined (Kim et al., 2025). This finding indicates that the outcomes of treatment in endemic BL depend on both viral and socio-economic factors. In Kenya, EBV type 1 was more prevalent in endemic BL than in the control group (74.5% compared with 47.5%). The viruses in plasma and tumour samples were identical in six paired samples (Kaymaz et al., 2020). Viral genomes may also undergo integration. All four cases of integration detected as part of a large-scale genomic study were associated with the endemic form of BL (Khine et al., 2025).

BL is a highly invasive disease, but one that is sensitive to chemotherapy. In HIV-infected patients, the addiction of rituximab to CODOX-M/IVAC scheme improves survival without increasing toxicity (Xiao et al., 2025). Conducting a clinical trial of the vaccine in sub-Saharan Africa would be feasible, but would need to be carried out on a large scale. Early administration of a multi-dose schedule would be necessary, as about half of children in this region become infected before their first birthday (Cohen et al., 2015).

3.2.2 Hodgkin lymphoma

EBV is found in the Hodgkin and Reed-Sternberg cells in a variable proportion of cHL. This proportion depends on region, age, histological subtype and HIV status. Wong et al. (2022) estimated the EBV-attributable fraction at 74% in Africa, 60% in Latin America, 56% in Asia, 36% in Europe, 32% in North America and 29% in Oceania. In HIV-associated Hodgkin lymphoma, 80% to 100% of cases are EBV-positive. Another review reported a prevalence of approximately 30% for Western cHL and 40% worldwide (Xiao et al., 2025). In developed countries, EBV is detected in approximately 75% of mixed cellularity and lymphocyte-depleted cHL cases, and in 10- 25% of nodular sclerosis cHL cases (Begic et al., 2022). EBV-positive infectious mononucleosis is associated with an increased risk of Hodgkin lymphoma, which subsequently develops one in 800 patients (Cohen et al., 2015). In Egypt, 34 of 64 patients (53.1%) were EBV-positive by EBNA1 PCR (Alabiad et al., 2024). In an Argentine paediatric series, 68 of 112 cases (60.7%) were EBER-positive. This proportion decreased from 69.2% before 2020 to 41.2% thereafter ($p = 0.006$) (Amarillo et al., 2025). In the French series, 31% of cHL were EBV-positive (Donzel et al., 2022).

The prognostic value of EBV has been extensively investigated. A meta-analysis of 42 studies and 9,570 patients found poorer overall survival in EBV-positive disease (HR 1.443, 95% CI 1.250 to 1.666). Disease-specific survival was also poorer (HR 2.312, 95% CI 1.799 to 2.972). No significant differences were observed in failure-free, progression-free or event-free survival (Hu et al., 2022). The effect varied by age. In older adults, the hazard ratio for overall survival was 1.905. In children and adolescents there was a non-significant trend towards better survival (HR 0.296, $p = 0.056$). The association was more pronounced when EBV status was defined by EBER (HR 2.024) than when EBER and LMP1 were combined (Hu et al., 2022). A single-centre Egyptian cohort showed a similar pattern. Relapse occurred in 55.9% of EBV-positive patients and 23.3 % of EBV-negative patients. Five-year disease-free survival was 44.1% versus 76.7%, while five-year overall survival was 47.1% versus 76.7% (Alabaid et al., 2024). The French series also linked EBER positivity to relapse in cHL (Donzel et al., 2022). In contrast, viral variants were not prognostic in the Croatian cohort. Among 46 EBV-positive patients, none of the LMP1 variants was associated with survival (Begic et al., 2022).

None of the included sources describes a standard EBV-specific treatment for cHL. First-line chemotherapy achieves remission in 75-80% of patients, while relapsed or refractory disease remains associated with a poor prognosis. Brentuximab vedotin, PD-1 inhibitors and EBV-specific T cells have been investigated. LMP1-specific cytotoxic T cells represent a potential treatment option for EBV-positive cHL (Xiao et al., 2025).

3.2.3 Diffuse large B-cell lymphoma

EBV-positive DLBCL, not otherwise specified (NOS), was first described by Oyama et al. (2024) in 2003 as a disease affecting the elderly. It was included in the revised 4th edition of the World Health Organisation (WHO) classification in 2016. The provisional classification from 2008 was limited to patients over 50 years of age without a recognised immunodeficiency (Malpica et al., 2024). The actual prevalence of this disease is unknown. Case series report about 5% of DLBCL cases in Western countries and 10% to 15% in Asia, Eastern Europe and South America (Malpica et al., 2024). In a pooled analysis, using an EBER cut-off value of 20%, 7.2% of cases were identified in East and Southeast Asia, 15.2% in Latin America and 4% in the rest of the world (Wong et al., 2022). In the French series, 11 out of 223 cases of DLBCL (4.9%) were EBV-positive (Donzel et al., 2022). In an Australian cohort comprising 433 cases of DLBCL, 6.9% were EBV-positive (Keane et al., 2019).

Patients are older and more likely to have the extranodal form of the disease than patients with EBV-negative DLBCL. The most common sites of involvement are the intestines, the skin and the bone marrow. LDH levels are higher, the disease is at a more advanced stage, and necrosis is common. About 70% of cases are polymorphic, whilst 30% are monomorphic. In a French cohort, 14% of patients developed haemophagocytic lymphohistiocytosis, and the median survival was just one month. CD30 is expressed in 43% of EBV-positive and 16% of EBV-negative DLBCL cases, which was associated with poorer survival. The

tumours are usually of the activated B-cell type. In the German series, 43% were ABC-type, 27% were GCB-type and 30% were unclassified (Malpica et al., 2024; Frontzek et al., 2023).

According to the 2022 ICC classification, EBV-positive DLBCL NOS is defined as the presence of EBER in more than 80% of tumour cells. A new entity has also been introduced: EBV-positive polymorphic B-cell lymphoproliferative disorder NOS (Quintanilla-Martinez et al., 2023). Previous studies have used cut-offs values ranging from 10% to 50%, which makes it difficult to compare survival data (Malpica et al., 2024). The German case series even included 9 cases with EBER in only 10% to 40% of cells, as no cut-off value was adopted (Frontzek et al., 2023).

Most studies found poorer outcomes in cases with EBV infection. In Japan, the five-year overall survival rate following chemotherapy was 25%, compared with 65%. In Peru, the median survival was 7 months compared with 47 months. In some studies, rituximab reduced this difference, but did not eliminate it. In Korea, the three-year survival rate was 57% compared with 60%. In the large Australian cohort, the five-year survival rate in the group treated with R-CHOP was 65% compared with 82%, and EBV infection status remained an independent factor influencing overall survival in a multivariable model ($p = 0.045$). A French study found shorter survival exclusively in patients aged over 50. The Oyama score (age and B symptoms) enabled the identification of groups with median survival of 56, 25 and 9 months. The GELL score, developed on the basis of data from 154 Latin American patients, showed hazard ratios of 4.9 for the intermediate-risk group and 12.5 for the high-risk group. In the Australian cohort, a CD163/CD68 ratio above 0.75 predicted a poorer treatment outcome, which links prognosis to the microenvironment (Malpica et al., 2024; Keane et al., 2019).

R-CHOP is the standard treatment scheme, and no prospective comparative studies have been conducted on EBV-positive forms of the disease. It is expected that polatuzumab vedotin in combination with R-CHP will become the preferred regimen, as the POLARIX trial specifically included these patients. However, this still requires confirmation. Nanatinostat in combination with valganciclovir induces a lytic cycle and resulted in an overall response in four of six patients with EBV-positive DLBCL, and a complete response in two. A preliminary report indicates that nivolumab induced a complete response in two out of four patients with EBV-positive DLBCL NOS. The genetic data suggest other therapeutic targets, such as JAK/STAT, NOTCH and PD-1/PD-L1. No EBV-directed drug is approved for use in this condition (Malpica et al., 2024; Frontzek et al., 2023; Kong et al., 2024).

3.2.4 Post-transplant lymphoproliferative disorder

PTLD arises when immunosuppression weakens T-cell control of EBV-infected B cells (Cohen et al., 2015). Most cases are EBV-positive, although approximately 20-40% are EBV-negative. EBV-positive PTLD is associated with latency III programme. The spectrum includes polymorphic, monomorphic and classic Hodgkin lymphoma-type PTLD. In one study, two-year survival was 1.00 for Hodgkin lymphoma-type, 0.62 for monomorphic B-cell and 0.69 for polymorphic PTLD. EBV-positive mucocutaneous ulcer is a distinct, indolent lesion in which EBV DNA levels in the blood are not elevated (Quintanilla-Martinez et al., 2023).

The risk depends on EBV serostatus and on the transplanted organ. Seronegative recipients have a 25- to 30-fold higher risk of PTLD than seropositive recipients (Cohen et al., 2015). In a prospective study of 872 children, 34 (3.9%) developed EBV-positive PTLD. The subdistribution hazard ratio was 2.68 (95% CI 1.29 to 5.55) for EBV-positive donors and negative recipients, and 5.31 for intestinal transplants. Of the 21 monomorphic or polymorphic cases, 13 (62%) occurred within the first year (Tajima et al., 2024). Among 509 adult kidney transplant recipients, eight developed EBV-associated PTLD, all of whom eight were in the donor-positive, recipient-negative group. The cumulative incidence in this group was 20.0%, and the median time to diagnosis was 7.3 months (Ludvigsen et al., 2026). Among 229 seropositive adult lung recipients, 6 developed PTLD (2.6%) (Mah et al., 2025). After allogeneic stem cell transplantation in 276 children, PTLD occurred in 13.0% of those who did not receive rituximab prophylaxis and 3.3% of those who did. Anti-thymocyte globulin use was the main driver of these events. A peak EBV load of at least 10^5 copies/mL was followed by PTLD in 75.0% of children, compared with 5.9% of those with lower levels. Seventeen of 24 PTLD cases resolved (Marsjanska et al., 2024).

The tumour biology differs from that of EBV-negative ePTLD. A multimodal study identified a 189-gene signature that distinguished EBV-positive from EBV-negative PTLD. EBV-positive tumours had many CD163-positive monocytes and few T cells, while the myeloid receptor CD300a supported tumour growth (Toh et al., 2024). These findings suggest that EBV-positive and EBV-negative PTLD differ in their underlying biology.

First-line treatment for EBV-PTLD consists of rituximab and reduction of immunosuppression. Second-line options include EBV-specific T cells and chemotherapy, with or without rituximab (Xiao et al., 2025). Tabelecleucel is an off-the-shelf EBV-specific T-cell product. In the phase 3 ALLELE study, the response rate was 52% in patients who had undergone solid organ transplant and in 50% in those who had undergone stem cell transplantation. It received EU authorisation under exceptional circumstances in December 2022 (Malpica et al., 2024). EBV DNA monitoring is discussed in Section 3.3, and prophylaxis in Section 3.4.

3.2.5 Plasmablastic lymphoma

PBL is an aggressive lymphoma of plasmablasts. It was first described in the oral cavity of individuals with HIV and occurs predominatly in adults with HIV or iatrogenic immunosuppression. Males account for up to 75% of cases. The widespread use of antiretroviral therapy has not reduced the incidence of HIV-associated PBL. Pooled data showed EBER positivity in 70.4% of cases (176 of 250). In the MD Anderson series of 61 patients, 40 of 57 (70%) were EBER-positive, including 19 of 19 with HIV and 15 of 29 (52%) without HIV. In an international cohort of 281 patients, 160 (57%) were EBV-positive, 73 were EBV-negative and 48 status were unknown. EBV positivity was more frequent with immunodeficiency than among those without it (72% versus 43%) (Bailly et al., 2022; Di Ciaccio et al., 2024; Loghan et al., 2015).

Most PBL cases exhibit a restricted latency programme, mainly latency 0 or I. LMP1 staining is therefore not useful for diagnosis. Latency programmes II and III have been reported in post-transplant and HIV-associated cases. MYC is involved in most cases. In the MD Anderson series, MYC was rearranged in 10 of 15 tested cases and overexpressed in all 13 cases tested. Among 110 cases of HIV-associated PBL, 62% of mutations affected the JAK/STAT pathway. MYC overexpression and PRDM1 mutations are more frequent in EBV-positive PBL (Bailly et al., 2022; Loghan et al., 2015).

Presentation typically involves an extranodal mass in the oral cavity or gastrointestinal tract, and many patients have advanced-stage diseases. Median survival is less than 12 months regardless of immune status (Bailly et al., 2022). In the international cohort, the five-year overall survival was 36% and the median overall survival was 1.72 years. The prognostic role of EBV is the area where the studies finding differ. In the international cohort of 281 patients, EBV-negative disease was associated with worse outcomes than EBV-positive disease (subdistribution hazard ratio 1.57, 95% CI 1.03 to 2.39). Disease stage, an ECOG performance score above 1 and bone marrow involvement were also independent prognostic factors, whereas HIV status was not (Di Ciaccio et al., 2024). At MD Anderson, EBV-positive patients had better event-free survival ($p = 0.047$) but not better overall survival, and age was the only independent prognostic factor (Loghan et al., 2015). The review suggests that the better outcomes observed in EBV-positive HIV-associated PBL may partly reflect HIV control through antiretroviral therapy (Bailly et al., 2022). EBV status therefore does not appear to be consistent prognostic marker in PBL and its prognostic significance may depend on immune status and the degree of HIV control.

Treatment outcomes remain poor. More intensive regimens and proteasome inhibitors did not improve outcomes in the international cohort. Thirty-five percent of responders experienced relapse, and median survival after relapse was 5.3 months (Di Ciaccio et al., 2024).

3.2.6 Lymphomatoid granulomatosis

LYG is an angiocentric and angiodestructive EBV-positive B-cell lymphoproliferative disorder that primarily affects the lungs. According to the 2022 ICC classification, it requires the presence of lesions in the lungs. The stage is assessed on the basis of the number of large EBV-positive cells in a single high-power field of view. Stage 1 comprises fewer than 5 cells, whilst stage 3 comprises more than 50. The stage determines the choice of treatment (Quintanilla-Martinez et al., 2023; Malpica et al., 2024).

The clinical picture is based mainly on a case report and a review of the literature. Lung are affected in about 70% of cases, the central nervous system in 40%, skin in 34%, kidney in 19% and liver in 17%. Multiple lung nodules are present in about 80% of cases, whilst a solitary nodule is rare. The case involved a woman around 60 who had been taking methotrexate for 18 years for rheumatoid arthritis. Hodgkin-like cells were identified in the excised pulmonary nodular lesion; these were CD30-positive and LMP1-positive, with more than 50 EBV-positive cells per high-power field, corresponding to stage 3 of the disease. Approximately 40% to 70% of methotrexate-associated lymphoproliferative disorders resolve after withdrawal of the drug; therefore, the first step is to discontinue methotrexate. In this patient, the disease persisted after withdrawal of the drug, and R-CHOP therapy was discontinued after two cycles due to poor response and myelosuppression. The patient subsequently received 20 cycles of brentuximab vedotin, and after four years no recurrence of the

disease was detected in the lungs. In other series, about three quarters of patients responded to rituximab-based therapy. DA-EPOCH-R scheme achieved a response rate of 77% in cases of high-grade disease (Fujiwara-Kuroda et al., 2021).

One case report described a case of EBV-positive LYG, which occurred after teeth extractions in a 69-year-old man taking methotrexate. The patient presented with oral ulcers, pulmonary nodules and splenomegaly. The final diagnosis was an EBV-associated lymphoproliferative disorder resulting from methotrexate use. The condition resolved after discontinuation of methotrexate. No lung or spleen biopsies were performed, so LYG was not confirmed (Derbyshire et al., 2023). This case demonstrates that diagnosis can be difficult, and the initial diagnosis may differ from the final one.

Evidence for the presence of LYG in the sources revieved is limited. It is based on classification reviews and two isolated cases. It is not possible to conclude from this evidence that the EBV plays any prognostic role in LYG.

3.2.7 Extranodal NK/T cell lymphoma

ENKTCL is closely associated with EBV. All 141 cases in a Chinese series were EBER-positive (Huang et al., 2017). Most cases exhibit latency II, characterised by the expression of EBNA1, BART RNAs, LMP1, LMP2A and LMP2B (Xiao et al., 2025). The disease is rare outside Asia and Latin America. It accounts for 6.5% of non-Hodgkin lymphoma in East and Southeast Asia, 2.9% in Latin America and 0.2% elsewhere (Wong et al., 2022). In the French series, 25% of NK/T-cell lymphomas were EBV-positive, and all four ENKTCL were EBER-positive (Donzel et al., 2022).

Outcomes vary by region and treatment. In an international cohort of 260 patients, median progression-free survival was 13.2 months and median overall survival 26.6 months. Median overall survival was 62.6 months in China and 11.4 months in Singapore, although the log-rank test showed no statistically significant differences across regions ($p = 0.086$) (Lim et al., 2022). In one analysis, adding radiotherapy to chemotherapy increased five-year survival from 24% to 58% (Wong et al., 2022). Genomic features also have prognostic significance. PD-L1 was altered in 38% of cases, while mutations in DDX3X, KMT2D, STAT3, and BCOR occurred in 17%, 16%, 15–16%, and 13% of cases, respectively. A 13-gene model yields hazard ratios of 3.73 for progression-free survival and 5.23 for overall survival (Lim et al., 2022). PD-L1 is expressed in 39- 100% of cases, and approximately 70% overexpress CD30 (Xiao et al., 2025).

Blood EBV markers have prognostic value. In 141 patients, serum EA-IgA at a titre of at least 1 in 10 predicted a three-year survival of 20%, compared with 70% in patients with lower titres. It was an independent adverse prognostic factor for overall survival (relative risk 2.276, 95% CI 1.240 to 4.178), and was associated with a lower complete response rate (34.8% versus 70.6%). EA-IgA was positive in 18.4% of patients, VCA-IgA in 41.1% and plasma DNA in 35 of 57 tested patients (61.4%) (Huang et al., 2017). In 60 Korean patients, plasma EBV DNA was an independently prognostic factor (hazard ratio 4.22 for progression-free survival and 8.39 for overall survival), whereas whole-blood DNA was not (Ha et al., 2020). In the international cohort, serum EBV titres were positive in 56 of 97 tested patients (57.7%) but were not retained as an independent in the multivariable model (Lim et al., 2022). Assays were not standardised across these studies.

Two related entities warrant mention. EBV-positive nodal T/NK cell lymphoma is a provisional entity in the ICC (Quintanilla-Martinez et al., 2023). Median survival ranges from 2.5 to 8.0 months, and no standard treatment has been established (Kato et al., 2024). TET2 mutations were associated with shorter survival ($p = 0.004$) (Kato et al., 2024). Among 262 patients with peripheral T-cell lymphomas, 30 were EBER-positive and had poorer overall survival ($p = 0.047$) and progression-free survival ($p = 0.009$). Plasma EBV DNA levels above 6,750 copies/mL after four treatment cycles were an independent adverse prognostic factor (HR 5.16) (Chen et al., 2024).

Regarding treatment, panobinostat combined with bortezomib showed benefit in relapsed ENKTCL and reduced EBV copy numbers. Histone deacetylase (HDAC) inhibitors such as romidepsin can reactivate EBV, making viral load monitoring necessary. Brentuximab vedotin, PD-1 antibodies and EBV-specific T cells are under investigation (Xiao et al., 2025).

3.2.8 Hydroa vacciniforme-like lymphoproliferative disorder

HVLPD is a rare EBV-associated T-cell or NK-cell skin disease. In the WHO classification, its name was changed from “hydroa vacciniforme-like lymphoma” due to its association with chronic active EBV infection and a broad spectrum of clinical symptoms (Han et al., 2020). The International Classification Commission (ICC) divides this disease into a classical form and a systemic form (Quintanilla-Martinez et al.,

2023). The disease is classified as the cutaneous form of chronic active EBV disease of the T/NK-cell type (Han et al., 2020). It is more common in Asia and Latin America than in the United States and Europe (Xie et al., 2020). The skin lesions consist of recurrent papulovesicles in sun-exposed areas, which heal leaving scars. In the systemic form, additional symptoms include fever, lymph node swelling, liver damage and haemophagocytic syndrome (Hirai et al., 2012; Oh et al., 2021).

The infected cells are usually T cells. EBV-positive T cells were detected in 31 out of 33 lesions of the hydroa vacciniforme type. In 10 out of 11 patients, gamma-delta T cells accounted for more than 5% of circulating cells, and in 3 cases, gamma-delta T cells accounted for 57% to 68% of EBER-positive cells. In case of hypersensitivity to mosquito bites, the main infected cell type is the NK cell (Hirai et al., 2012). Among 24 Chinese patients, the infected cell was a T cell in 18 individuals and an NK cell in 6. In all cases, the EBER test result was strongly positive, and TCR rearrangement was monoclonal in 15 out of 19 individuals tested (78.9%) (Wang et al., 2021). In another Chinese series comprising 19 patients, the EBER test was positive in 17 (89%) and TCR rearrangement was monoclonal in 12 (63%) (Xie et al., 2020).

Prognosis ranges from benign to fatal. Of 11 Korean patients, 6 were diagnosed with the classic form of the disease, with a favourable treatment outcome, whilst 5 were diagnosed with the systemic form. All 4 deaths were recorded in the group with the systemic form (Oh et al., 2021). In the case series from Seoul National University, 14 out of 26 patients (53.8%) developed lymphoma; 19 out of 26 were diagnosed in adulthood, and 6 died as a result of the disease. No significant differences were found between adults and children in terms of disease progression or mortality (Han et al., 2020). In a group of 24 patients from Zhengzhou, overall survival was 95.0%, 68.6% and 55.4% at one, two and three years, respectively (Wang et al., 2021). In the group of 19 patients from Chengdu, all 6 who died had facial oedema, and were older (mean age 34.0 years compared with 13.0 years). Facial oedema, deep ulcers, necrosis, involvement of sun-protected skin and advanced age were therefore warning signs (Xie et al., 2020; Oh et al., 2021).

The role of EBV DNA is a matter of debate. In Korea, the presence of DNA in whole blood was detected in all 6 patients studied. The median was 2,290 copies/microlitre in the

3 patients who died, and 186.62 in the 3 who survived. In Japan, DNA was detected in peripheral blood mononuclear cells (PBMCs) in all 29 patients with a typical course of disease (an average 18,500 copies per microgram of DNA) and its level was higher in cases of severe disease (Hirai et al., 2012). In two Chinese case series, DNA levels did not predict survival. DNA levels correlated with disease activity. They rose with the appearance of new blisters and fell during antiviral treatment, and in one patient became undetectable following a stem cell transplantation (Xie et al., 2020; Oh et al., 2021; Wang et al., (2021).

Treatment is not standardised. The classic form of the disease can be managed conservatively. Chemotherapy is of limited efficacy in the systemic form. The authors of the Chinese case series recommend allogeneic stem cell transplantation in case of relapsed or treatment resistance; in 2 patients who developed lymphoma, the procedure led to remission (Wang et al., 2021).

3.3 Diagnosis of changes associated with EBV infection in haematological malignancies

3.3.1. Tissue testing

In situ hybridisation for EBV-encoded RNA (EBER) is the standard method for detecting EBV in tissue. The results depend on the cut-off used. Earlier DLBCL studies defined possitivity as EBER expression in a 10%, 20%, 30% or 50% of cells,limiting comparability. The 2022 ICC requires EBER positivity in more than 80% of malignant cells for EBV-positive DLBCL, NOS. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HAEM5) requires positivity in the majority of tumour cells but specifies no threshold (Malpica et al., 2024). In peripheral T-cell lymphoma, one group defined positive cases as those with more than 50 densely EBER-positive cells per high-power field and classified cases with partial positivity as negative (Chen et al., 2024). Digital counting may provide more objective results. In DLBCL, a EBER count of 500 using NanoString showed 10% sensitivity and 94% specificity compared with standard testing (Keane et al., 2019). The identity of the EBV-infected cells is also important. A recent report found that small EBV-positive bystander lymphocytes, rather than large tumour cells, were associated with a poor prognosis (Malpica et al., 2024).

Immunohistochemistry provides additional information on latency. LMP1 is positive in approximately 90% of EBV-positive DLBCL cases and EBNA2 in approximately 30% (Malpica et al., 2024). In PBL both are usually absent, and LMP1 staining should not be used for diagnosis (Bailly et al., 2022). In LYG, LMP1 and CD30 were positive in the large atypical cells (Fujiwara-Kuroda et al., 2021).

3.3.2. Differential diagnosis

EBV-positive tumors exhibit morphological similarities. PBL expresses CD38 and CD138 and lacks most B-cell markers. BL is CD10-positive, and a Ki-67 index is close to 100%. CD200 helps to distinguish cHL from EBV-positive DLBCL, as partial or weak staining is more characteristic of DLBCL (Malpica et al., 2024). A lymphoproliferative disorder resembling hydroa vacciniforme is often misdiagnosed as an inflammatory skin disease (Xie et al., 2020). In elderly patients with systemic disease, it must be distinguished from ENKTCL, as both are EBER-positive (Oh et al., 2021). A solitary pulmonary nodule in a patient receiving methotrexate should raise the suspicion of LYG (Fujiwara-Kuroda et al., 2021). An EBV-positive mucocutaneous ulcer is a benign lesion, and serum EBV DNA levels are not elevated in this condition. T/NK-cell CAEBV requires the presence of symptoms lasting at least three months and a high viral load (Quintanilla-Martinez et al., 2023; Volaric et al., 2025).

3.3.3. Molecular and genomic testing

Molecular classifiers perform poorly in EBV-positive disease. Only 17.4% of EBV-positive DLBCL cases could be assigned to a LymphGen cluster (Frontzek et al., 2023). In sporadic BL, EBV-positive cases were more frequently classified as “intermediate” by a gene-expression classifier, suggesting that these classifiers may require adjustment (Richter et al., 2022). Viral genome sequencing, including typing and variant calling, remains a research tool. It suggests potential prognostic value in BL (Kim et al., 2025) and an association between deletions and disease (Khine et al., 2025).

3.3.4. Blood tests

The presence of EBV DNA in the blood may indicate a tumour burden or viral reactivation. The type of sample influences the result. In 60 patients with ENKTCL, the EBV DNA test result prior to the start of treatment was positive in 61.7% of whole blood samples and 38.3% of plasma samples. Only plasma DNA was an independent prognostic factor (Ha et al., 2020). In the case of HVLPD, the concentration in whole blood reflected the clinical course (Oh et al., 2021)], whilst a Japanese research group used PBMC, reporting results in micrograms of DNA (Hirai et al., 2012). In the case of peripheral T-cell lymphoma, the agreement between EBER and baseline plasma DNA concentration was low (kappa 0.254). The baseline DNA value showed a sensitivity of 68.4% and a specificity of 75.0% compared with the EBER test (Chen et al., 2024). DNA from blood cannot, therefore, replace tissue-based testing.

Units of measurement and assay methods vary considerably between studies. Publications report the number of copies per microlitre, per millilitre, per microgram of DNA, and international units per millilitre. Only in the study on transplants carried out in Norway and Denmark were all assay methods calibrated in accordance with the WHO International Standard (NIBSC 09/260) (Ludvigsen et al., 2026). Threshold values from different studies should not be compared directly.

In transplant medicine, DNA level monitoring has been tested as a tool for the early detection of PTLD. In 229 EBV-seropositive lung transplant recipients, a level in whole-blood of at least 2,840 IU/mL yielded a sensitivity of 83.3% and a specificity of 87.0%. The positive predictive value was 14.7% and the negative predictive value 99.5%. Diagnostic investigations in these patients were initiated on the basis of symptoms rather than DNA concentration (Mah et al., 2025). In kidney recipients where the donor was seropositive for EBV and the recipient seronegative,

a threefold increase in plasma DNA concentration between consecutive samples had a positive predictive value of 88.9%. A fixed plasma concentration threshold of 2,500 IU/mL proved to be too high, as in out of 8 PTLD patients the concentration remained below this value (Ludvigsen et al., 2026). In children following stem cell transplantation, a peak load of at least 10^5 copies/mL was followed by PTLD in 75.0% of cases (Marjanska et al., 2024). The virus replicates rapidly, with a doubling time ranging from 7 hours to 3 days, which argues in favour of frequent sampling intervals. Nevertheless, viral load alone is not a sufficient indicator, as the kinetics of primary infection may resemble those of PTLD. Pre-transplant serological status is a key risk indicator (Cohen et al., 2015; Tajima et al., 2024; Ludvigsen et al., 2026; Mah et al., 2025).

3.3.5. Serology

Anti-EBV antibodies are useful in ENKTCL. EA-IgA was positive in 18.4% of patients and VCA-IgA in 41.1% of 141 patients, and an EA-IgA titre of at least 1 in 10 predicted poorer survival (Huang et al., 2017). In the international cohort, serum EBV antibodies were positive in 57.7% of tested patients but were not an independent prognostic factor (Lim et al., 2022). Clonality testing is a useful additional diagnostic step in T-cell and NK-cell disease. TCR rearrangement was monoclonal in 63% of cases in one HVLPD series, 78.9% in a second and 30.8% in a third (Xie et al., 2020; Han et al., 2020; Wang et al., 2021).

Table 2. Main tests used to detect and monitor EBV in haematological malignancies.

Method	Main use	Findings and limits
EBER in situ hybridisation	Standard detection of EBV in tissue	ICC 2022 requires for more than 80% positive cells in EBV-positive DLBCL NOS, earlier studies used thresholds of 10-50%
Digital EBER count	Objective quantification	A count of 500 showed 100% sensitivity and 94% specificity
LMP1 and EBNA2 staining	Assessment of latency programme	LMP1 in 90% and EBNA2 in 30% of EBV-positive DLBCL, not useful in PBL
Plasma EBV DNA	Prognosis and monitoring	Independent prognostic factor in ENKTCL, poor agreement with EBER in T-cell lymphoma
Whole-blood EBV DNA	Transplant surveillance, HVLPD	A level of 2,840 IU/mL yielded a PPV of only 14.7% in lung transplant recipients
PBMC EBV DNA	Hydroa vacciniforme	Reported per microgram of DNA
EA-IgA and VCA-IgA	ENKTCL risk stratifications	EA-IgA at least 1 in 10 predicted poorer survival
TCR clonality	T-cell and NK-cell disorders	Monoclonal TCR rearrangement in 30.8-78.9% of HVLPD cases

Note. DNA – deoxyribonucleic acid; DLBCL – diffuse large B-cell lymphoma; EA – early antigen; EBER – Epstein–Barr virus-encoded RNA; EBNA – Epstein–Barr virus nuclear antigen; EBV – Epstein–Barr virus; ENKTCL – extranodal natural killer/T-cell lymphoma; HVLPD – hydroa vacciniforme-like lymphoproliferative disorder; LMP1 – latent membrane protein 1; NK – natural killer; NOS – not otherwise specified; PBMC – peripheral blood mononuclear cells; PPV - positive predictive value; TCR – T-cell receptor; VCA – viral capsid antigen. Adapted from Malpica et al. (2024), Bailly et al. (2022), Xie et al. (2020), Hirai et al. (2012), Keane et al. (2019), Huang et al. (2017), Mah et al. (2025), Ha et al. (2020), Chen et al. (2024), Han et al. (2020) and Wang et al. (2021).

3.4. Prevention of EBV-related infections

3.4.1. Vaccines against primary infection

No prophylactic or therapeutic EBV vaccine is licensed, and no antiviral agent is approved for EBV-driven cancers (Xiao et al., 2025; Wong et al., 2022). The most advanced candidate is recombinant gp350, the main target of neutralising antibodies. In a phase 2 trial involving 181 seronegative students, gp350 with alum and MPL reduced the incidence of infectious mononucleosis by 78% but did not prevent infection (Cohen et al., 2015). A later review reported an average efficacy of 78.0% against mononucleosis across two gp350 trials, again without preventing asymptomatic infection (Xiao et al., 2025). Among 16 seronegative children awaiting kidney transplantation, only 4 of 13 developed neutralising antibodies, and one child developed PTLD (Cohen et al., 2015). This small trial ilustrates the challenges of vaccination in patients with organ disease (Cohen et al., 2013). In animal models, gp350 protected cotton-top tamarins against lymphoma, while soluble gp350 provided the greatest protection against infection and the lowest viral load in the rhesus model (Cohen et al., 2015).

Whether a vaccine must prevent infection to prevent cancer remains unknown. A vaccine that lowers the viral set point might reduce cancer risk, as blood viral load predicts PTLD (Cohen et al., 2015). The NIH working group identified several barriers, including the lack of surrogate markers and immune correlates, the long interval between infection and cancer, limited animal models and an unclear economic case. It

recommended a phase 3 trial of gp350, further research into correlates of protection and trials in seronegative transplant candidates (Cohen et al., 2013). A vaccine against endemic BL would need to be administered in infancy, as approximately half of African children are infected before one year of age (COHEN ET AL., 2015).

Newer vaccine designs incorporate additional antigens. Neutralising antibody titres were higher with gH/gL dimers or trimers, trimeric gB or gp350 polymers than with monomeric gp350 (Xiao et al., 2025). A virus-like particle displaying three conserved gp350 peptides induced neutralising antibodies in mice, and two of five peptide orders performed well (Zhang et al., 2020). A pentavalent particle carrying gp350, gB, gp42, gH and gL induced serum IgG with an IC50 of 2.85 μg/mL against epithelial cells and 3.71 μg/mL against B cells, outperforming soluble gp350. Responses to gp42 and gH/gL were weak (Escalante et al., 2020). Neither study assessed protection following challenges. An mRNA vaccine, mRNA-1189, has completed a trial in healthy adults aged 18-30 years, with results pending (Malpica et al., 2024). A therapeutic mRNA vaccine is in early-stage trials in EBV-positive solid tumours (Xiao et al., 2025).

3.4.2. Prevention of PTLD in transplant recipients

The best opportunity arises in the context of organ transplantation, as the risk group is known in advance. The risk is greater when an EBV-positive donor passes an organ to a seronegative recipient (Tajima et al., 2024; Ludvigsen et al., 2026). For this group, there is evidence confirming the effectiveness of three measures.

The first of these is prophylaxis with rituximab. In 276 children following allogeneic stem cell transplantation, administration of rituximab at a dose of 150 mg/m2 on day +5 reduced the incidence of clinically significant EBV-DNAemia from 37.0% to 18.0% and PTLD from 13.0% to 3.3% (HR 0.23). This was not associated with hypogammaglobulinaemia or an increased incidence of CMV infection (Marjanska et al., 2024). In kidney recipients, rituximab induction was associated with a lower incidence of EBV-DNAemia in whole blood (adjusted HR 0.2) (Ludvigsen et al., 2026).

The second strategy is a lower risk of T-cell depletion. Antithymocyte globulin was the main factor contributing to EBV-related complications following stem cell transplantation (Marjanska et al., 2024) and increased the risk of persistent plasma DNA in kidney recipients (HR 4.5) (Ludvigsen et al., 2026).

The third approach is targeted follow-up. In a study conducted in Norway and Denmark, the authors advocate DNA monitoring for up to two years in recipients whose donors were seropositive for EBV and who were themselves negative. However they advise against routine monitoring of seropositive recipients (Ludvigsen et al., 2026). This is confirmed by the results of a study on lung transplant recipients, as monitoring was of limited value in seropositive adults (Mah et al., 2025). For children, weekly testing is recommended prior to hospital discharge, followed by testing every two weeks or monthly for six months (Tajima et al., 2024). If DNA levels rise, the standard approach is to reduce immunosuppression with rituximab (Xiao et al., 2025). EBV-specific T cells have proven effective in both treatment and prevention in patients with PTLD (Malpica et al., 2024).

3.4.3. Other measures

Routine antiviral therapy is not recommended for EBV-related lymphomas. Some anti-cancer drugs can reactivate EBV. HDAC inhibitors such as romidepsin, are one example, and monitoring for reactivation is advised (Xiao et al., 2025). In HIV-associated disease, antiretroviral therapy has not reduced the incidence of PBL. A long-term decline in EBV-positive paediatric cHL has been reported in Brazil and Korea, while a decrease was observed following the COVID-19 pandemic in Argentina. The authors attribute these changes to later EBV exposure, but present this explanation only as a hypothesis (Amarillo et al., 2025; Bailly et al., 2022).

4. Discussion

4.1. Interpretation of the Findings

The studies analyzed support a gradual approach to the EBV virus. In some cases, the virus is present in nearly every instance and appears to be an early driver of tumor development. This applies to endemic BL and ENKTCL (Wong et al., 2022; Huang et al., 2017). In other cases the virus is present only in a minority of patients, and the tumour has its own genetic drivers. This applies to sporadic BL and to DLBCL (Malpica et al., 2024; Richter et al., 2022). In these entities, EBV appears to act as a co-factor. In EBV-positive DLBCL the viral oncoprotein LMP1 may replace mutations in the NF-kB pathway, and the tumour is less frequently classified into the standard genetic cluster (Frontzek et al., 2023). The same logic applies to sporadic BL, where EBV-positive cases are characterised by fewer mutations in the ID3 gene (Richter et al., 2022). Two interpretations are possible, and the data do not allow for distinguishing between them. Either the EBV virus provides signals that the tumor would otherwise have to acquire through mutations, or EBV-positive and EBV-negative tumors arise from different cells under different immunological conditions.

Changes in the viral genome represent an additional factor. Deletions in the BART region were found in 46% of patients with DLBCL and in 63% of patients with T/NK-cell lymphoma in the lymph nodes, compared with 5% in healthy carriers. One interpretation is that the loss of viral microRNAs, which inhibit the lytic cycle, promotes reactivation, which in turn promotes the development of lymphomagenesis. It also challenges the view that these neoplasms arise solely from a latent state (Kato et al., 2024; Khine et al., 2025).

The prognostic significance of EBV presence varies depending on the type of tumor, and the direction of this association is not always the same. A positive EBV test result was linked to poorer survival in DLBCL and, in the meta-analysis, in cHL, while EBV markers in the blood predicted poorer survival in ENKTCL (Hu et al., 2022; Keane et al., 2019; Huang et al., 2017). In the case of PBL, the largest cohort showed an inverse relationship - poorer survival in EBV-negative cases (Di Ciaccio et al., 2024). Several factors partially explain this. Age influences this effect in cHL, resulting in an adverse impact in older individuals and a statistically nonsignificant trend toward a benefit in children (Hu et al., 2022). Rituximab reduced this difference in DLBCL in some cohorts but not in others (Malpica et al., 2024). In PBL, EBV status is associated with HIV and control of HIV infection (Bailly et al., 2022). EBER cutoff values vary across studies. The pooled hazard ratio in cHL was more pronounced when EBV was defined solely based on EBER than when LMP1 was included (Hu et al., 2022). In summary, EBV status is best interpreted as a marker of host and tumour context rather than as a standalone, stable prognostic factor.

A common feature of all these conditions is impaired immune control. PTLD, HIV-associated lymphomas, methotrexate-associated disorders and DLBCL in elderly are all characterized by reduced T-cell surveillance (Malpica et al., 2024; Bailly et al., 2022; Cohen et al., 2015; Fujiwara-Kuroda et al., 2021). At the molecular level, common features include PD-L1 and 9p24.1 amplification, loss of antigen presentation, M2-type macrophages and CD163-positive monocytes (Frontzek et al., 2023; Keane et al., 2019; Toh et al., 2024). These features justify teh use of immune checkpoint inhibitors, CD30-targeted therapy and EBV-specific T cells. They also suggest that the microenvironment may provide prognostic information to the same extent as viral status (Keane et al., 2019).

In terms of diagnosis, the main problem is a lack of standardization. Cut-off values for tissue samples vary; DNA tests differ in terms of sample type and units of measurement; and threshold values from one study cannot be applied to another (Malpica et al., 2024; Ludvigsen et al., 2026). Regarding prevention, data on transplants indicate that the risk can be reduced in a specific group. Prophylaxis with rituximab reduced the incidence of PTLD in children after stem cell transplantation, and surveillance proved most useful in patients with a donor-positive and recipient-negative result (Ludvigsen et al., 2026; Marjanska et al., 2024). For the general population, no vaccine exists, and the only Phase II efficacy trial demonstrated protection against mononucleosis, not against infection (Cohen et al., 2015).

4.2. Limitations

This review has several limits that readers should consider. It is a narrative review of 43 selected publications rather than a systematic review; therefore selection bias is possible, and comprehensive coverage of the literature cannot be claimed.. The evidence is uneven. Rare entities such as LYG and HVLPD are represented by individual cases or series of 11-26 patients. Most clinical studies are retrospective and conducted at single centres or within single regions. Regional differences in EBV prevalence and treatment make pooling difficult (Wong et al., 2022; Lim et al., 2022; Fujiwara-Kuroda et al., 2021; Derbyshire et al., 2023; Han et al., 2020; Oh et al., 2021).

Several sources contained internal inconsistencies, including differences between abstracts and results, or between text and tables. Examples include deletion rates in the viral genome study, the rates of EBV-DNAemia in the paediatric transplant study, and the latency classification in one review (Xiao et al., 2025; Khine et al., 2025; Marjanska et al., 2024). Values reported in the results and tables were used. The Ludvigsen study was available as an online-ahead-of-print version (Ludvigsen et al., 2026). Animal and laboratory vaccine studies do not demonstrate protection in humans (Zhang et al., 2020; Escalante et al., 2020). Finally, no formal risk-of-bias assessment was performed.

4.3. Directions for Future Research

Several priorities emerge for future research. First, standardised EBER positivity thresholds and EBV DNA assays are needed to improve diagnostic consistency and establish disease-specific testing strategies. Second, prospective trials should assess the clinical utility of EBV DNA-guided treatment and monitoring. Third, longitudinal and single-cell studies are needed to clarify the sequence of events driving lymphomagenesis. Fourth, EBV status should be incorporated into clinical trial stratification to facilitate the evaluation of targeted therapies in EBV-positive lymphomas. Fifth, international registries are needed to strengthen the evidence base for rare entities, while randomised studies should establish the benefits and risks of surveillance and rituximab prophylaxis. Sixth, multi-antigen vaccines warrant further evaluation in preclinical and clinical studies. Finally, the contribution of socioeconomic factors to clinical outcomes requires investigation across diverse populations.

5. Summary

EBV contributes to the development of many haematological malignancies, but its role varies between entities. It is almost invariably present in endemic Burkitt lymphoma and extranodal NK/T cell lymphoma. It occurs in a minority of sporadic Burkitt lymphoma and DLBCL cases, in a variable proportion of Hodgkin lymphoma cases, and in most post-transplant lymphoproliferative disorders. The virus acts through latent proteins, viral microRNAs and viral genome alterations. It also interacts with host mutations affecting the NF-kB, JAK/STAT and NOTCH pathways and promotes immune evasion through PD-L1 expression, impaired antigen presentation, and a tolerogenic microenvironment.

The prognostic significance of EBV is entity-specific and depends on age, immune status and the cut-off used. EBER in situ hybridisation remains the diagnostic standard, while plasma EBV DNA provides additional prognostic information in NK/T cell lymphoma and supports transplant monitoring. However standardised thresholds and assays are still lacking. In transplantation, rituximab prophylaxis and targeted surveillance can reduce the risk of PTLD in high-risk groups. No vaccine is licensed, and future research should focus on standardisation, prospective trials, registries for rare entities and multi-antigen vaccines.

Conflicts of Interest

No conflicts of interest to declare.

Ethics Approval

This article is a review of previously published literature. It did not involve research on human participants or animal subjects, and ethics committee approval was therefore not required.

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