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Age-related clinical and serological spectrum of Epstein-Barr virus infection: primary infection predominates in children and reactivation in adults—a retrospective study of 290 hospitalized patients

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Abstract

Background

Epstein-Barr virus (EBV) infection manifestations vary by age; however, the serological basis for this age-related difference remains incompletely understood in hospitalized cohorts. We aimed to compare the clinical and serological features of pediatric versus adult EBV infection.

Methods

We retrospectively reviewed 342 hospitalizations with an EBV-related diagnosis at a tertiary teaching hospital between January 2019 and June 2026. After excluding 52 hospitalizations (duplicate admissions, incomplete data, isolated VCA-IgG positivity without evidence of active infection, and other confirmed infections), 290 hospitalizations (from 290 patients) with confirmed active EBV infection (VCA-IgM positive and/or detectable EBV DNA) were included; each patient contributed one hospitalization. Patients were stratified into pediatric (< 18 years, n = 197) and adult (≥ 18 years, n = 93) groups. EBV serology, EBV DNA viral load, clinical manifestations, laboratory findings, and length of hospital stay were compared using the Mann-Whitney U test and Fisher's exact test.

Results

Pediatric patients had higher VCA-IgM positivity (87.1% vs 39.7%, $P < 0.001$, among tested patients) and lower EBNA-IgG positivity (9.7% vs 81.5%, $P < 0.001$, among tested patients), consistent with primary infection in children and reactivation in adults. Pediatric EBV infection was predominantly characterized by infectious mononucleosis (85.8%), followed by myocarditis (10.7%) and pneumonia (4.6%); these categories were not mutually exclusive. Adult EBV infection was predominantly characterized by hepatitis (31.2%), gastrointestinal involvement (9.7%), and chronic/invasive EBV disease, including CAEBV (4.3%), LPD (4.3%), and HLH (5.4%). Adults had a longer length of hospital stay (13 vs 7 days; $P < 0.001$).

Conclusions

Pediatric EBV infection is predominantly primary infection, often with lymphoproliferative manifestations; adult EBV infection is more often associated with reactivation, organ injury, and chronic/invasive potential. Age-stratified evaluation may improve diagnostic yield.

Background

Epstein-Barr virus (EBV) infects over 90% of adults worldwide and establishes lifelong latency[1]. Primary infection in young children is often asymptomatic, whereas in adolescents and young adults it typically

causes infectious mononucleosis (IM) [2, 3]. Beyond IM, EBV is associated with a broad spectrum of diseases, including hepatitis, pneumonitis, myocarditis, gastrointestinal involvement, neurologic disease, chronic active EBV infection (CAEBV), EBV-associated lymphoproliferative disorders (LPD), and hemophagocytic lymphohistiocytosis (HLH) [4–6]. Clinical observations suggest that age strongly influences EBV manifestations: children tend to develop acute lymphoproliferative manifestations, whereas adults more often develop hepatic complications or chronic disease[7]. However, this age-related pattern has been inferred from clinical presentations rather than confirmed by serological evidence distinguishing primary infection from viral reactivation. We therefore aimed to compare serological markers (VCA-IgM, VCA-IgG, EBNA-IgG, EA-IgG) and clinical manifestations between pediatric and adult hospitalized patients with EBV infection.

Methods

Study design and population

This single-center retrospective study was conducted at The First Affiliated Hospital of Chongqing College of Traditional Chinese Medicine from January 2019 to June 2026. We initially identified 342 hospitalizations with an EBV-related diagnosis in the electronic medical record system using ICD codes or text searches for “EBV,” “Epstein-Barr,” or “infectious mononucleosis.”

Exclusion criteria were: (1) duplicate admissions of the same patient during the study period (n = 18); (2) incomplete EBV laboratory data without serological confirmation or EBV DNA results (n = 15); (3) isolated VCA-IgG positivity with negative VCA-IgM and undetectable EBV DNA, consistent with remote past infection without active disease (n = 12); and (4) co-infection with other confirmed pathogens (e.g., hepatitis B virus, hepatitis C virus, or cytomegalovirus) or bacterial sepsis (n = 7). After exclusions, 290 hospitalizations from 290 unique patients with confirmed active EBV infection were included; each patient contributed one hospitalization (Fig. 1).

Active EBV infection was defined as detectable EBV DNA by quantitative PCR and/or positive VCA-IgM in a patient with clinical features compatible with active EBV infection. The study was approved by the Institutional Ethics Committee (approval No. 2025-KY-HY-18); this retrospective study was covered by the ethics approval for review of previously collected medical records, and informed consent was waived due to the retrospective design.

Data collection

Data were extracted from electronic medical records: demographics (age, sex), symptoms and signs, EBV disease classification (per attending physician diagnosis; categories are not mutually exclusive), EBV serology (VCA-IgG/IgM, early antigen IgG, EBNA-IgG), EBV DNA quantitative PCR, complete blood count, C-reactive protein (CRP), liver and renal function, electrolytes, lactate dehydrogenase (LDH), creatine kinase (CK), creatine kinase-MB (CK-MB), and length of hospital stay.

Definitions

Pediatric was defined as age < 18 years; adult as ≥ 18 years. VCA-IgM positivity with EBNA-IgG negativity was interpreted as acute/primary infection. VCA-IgG positivity with EBNA-IgG positivity and negative VCA-IgM was interpreted as past infection. In adults, reactivation was considered when clinical manifestations were present together with detectable EBV DNA and/or positive EA-IgG, regardless of VCA-IgM status; EBNA-IgG was usually positive but was not required for classification. Adults with VCA-IgM positivity and EBNA-IgG negativity were classified as primary infection. In children, primary infection was defined as VCA-IgM positivity with EBNA-IgG negativity. Disease diagnoses were based on attending physician assessment using standard clinical criteria: infectious mononucleosis (fever, pharyngitis, cervical lymphadenopathy with atypical lymphocytes on peripheral smear); EBV hepatitis (ALT > 2× upper limit of normal with positive EBV serology/DNA and exclusion of other causes); EBV myocarditis (cardiac troponin elevation with ECG and/or echocardiographic abnormalities, after exclusion of coronary artery disease); EBV pneumonia (respiratory symptoms with chest imaging showing pulmonary infiltrates, after exclusion of other causes); CAEBV (persistent IM-like symptoms > 3 months with elevated EBV DNA and exclusion of other causes); EBV-LPD and HLH were diagnosed per standard histological and clinical criteria.

Statistical analysis

Continuous variables are presented as median (IQR) and compared using the Mann-Whitney U test. Categorical variables are presented as n (%) and compared using Fisher's exact test. Given the exploratory, hypothesis-generating nature of this study, *P* values are presented without correction for multiple comparisons.

Results

Study population

Of 342 initially identified hospitalizations, 52 were excluded, leaving 290 hospitalizations from 290 unique patients for analysis (Fig. 1). Of these, 197 (67.9%) were pediatric patients (median age 5 years, IQR 3–7) and 93 (32.1%) were adult patients (median age 57 years, IQR 34–69). Male patients accounted for 51.8% of children and 46.2% of adults ($P = 0.45$). Median length of hospital stay was 7 days in pediatric patients versus 13 days in adults ($P < 0.001$) (Table 1).

Disease manifestations

Pediatric infection was predominantly characterized by infectious mononucleosis (IM) (169/197, 85.8%), followed by myocarditis (21/197, 10.7%) and pneumonia (9/197, 4.6%). Adult infection was predominantly characterized by hepatitis (29/93, 31.2%), gastrointestinal involvement (9/93, 9.7%), and mucocutaneous lesions (6/93, 6.5%). Chronic/invasive manifestations, including CAEBV (4/93), LPD

(4/93), and HLH (5/93), were observed exclusively in adults (Table 1, Fig. 2). No pancreatitis was observed in either group. Disease categories were not mutually exclusive.

Physical findings and symptoms

Hepatosplenomegaly was more common in children (60.8% vs 31.3%, $P < 0.001$), as was lymphadenopathy (92.3% vs 35.7%, $P < 0.001$). Fever (70.1% vs 50.5%, $P = 0.002$) and cervical mass (11.7% vs 3.2%, $P = 0.026$) were also more prevalent in children (Table 1).

Laboratory findings

Children had higher lymphocyte counts (median 7.1, IQR 4.6–9.9 vs 1.3, IQR 0.8–2.1 $\times 10^9$/L; $P < 0.001$), LDH levels (478, IQR 393–576 vs 294, IQR 213–397 U/L; $P < 0.001$), CK-MB levels (21.0, IQR 17.5–29.0 vs 13.5, IQR 9.2–20.9 U/L; $P < 0.001$), white blood cell (WBC) counts (10.5, IQR 7.0–14.2 vs 7.4, IQR 4.5–12.1 $\times 10^9$/L; $P < 0.001$), and platelet counts (221.5, IQR 173.5–258.8 vs 163.0, IQR 106.0–248.0 $\times 10^9$/L; $P < 0.001$). Adults had higher CRP levels (17.0, IQR 4.1–75.0 vs 6.6, IQR 2.3–19.3 mg/L; $P < 0.001$), total bilirubin (11.7, IQR 8.1–16.1 vs 5.1, IQR 3.9–6.9 μmol/L; $P < 0.001$), direct bilirubin (4.0, IQR 2.7–9.3 vs 1.5, IQR 1.1–2.4 μmol/L; $P < 0.001$), and creatinine (58, IQR 48.5–76.8 vs 34, IQR 29.8–41.0 μmol/L; $P < 0.001$), but lower albumin levels (35.3, IQR 31.1–39.6 vs 39.2, IQR 37.2–41.6 g/L; $P < 0.001$). Some laboratory differences may partly reflect age-related normal reference ranges (Table 1).

Serological findings

VCA-IgM was tested in 94 patients (children: n = 31, positive n = 27; adults: n = 63, positive n = 25). Positivity was 87.1% in children versus 39.7% in adults ($P < 0.001$). VCA-IgG was tested in 89 patients (children: n = 31, positive n = 9; adults: n = 58, positive n = 53). Positivity was 29.0% in children versus 91.4% in adults ($P < 0.001$). EBNA-IgG was tested in 85 patients (children: n = 31, positive n = 3; adults: n = 54, positive n = 44). Positivity was 9.7% in children versus 81.5% in adults ($P < 0.001$). EA-IgG was tested in 83 patients (children: n = 31, positive n = 14; adults: n = 52, positive n = 22). Positivity was similar between groups (45.2% vs 42.3%, $P = 0.82$). EBV DNA was quantified in 141 patients (children: n = 122, median 3,500, IQR 1,322–15,532 copies/mL; adults: n = 19, median 1,820, IQR 1,190–14,225 copies/mL; $P = 0.35$) (Table 2, Fig. 3).

Discussion

In this single-center cohort of 290 hospitalized patients with EBV infection, we observed a striking age-related disease spectrum supported by serological findings. Pediatric patients predominantly presented with primary infection (mostly VCA-IgM positive and EBNA-IgG negative), manifesting as acute manifestations including infectious mononucleosis (IM) and myocarditis. In contrast, adult patients predominantly presented with features consistent with reactivation of latent infection (mostly EBNA-IgG positive; VCA-IgM may be positive or negative), manifesting as organ-specific injury such as hepatitis

and chronic/invasive EBV disease and severe complications, including CAEBV, LPD, and HLH; these categories may overlap.

Our findings align with and extend previous reports. The high rate of IM in children (85.8%) is consistent with prior Chinese pediatric series, which report IM as the dominant presentation in young children[8]. The high rate of hepatitis in adults (31.2%) is likewise consistent with literature describing EBV hepatitis as an important cause of hepatic viral infection in adults[9]. However, most prior studies focused on either pediatric or adult populations in isolation. To our knowledge, this is among the first studies to directly compare serological profiles across age groups in a hospitalized cohort, providing an immunological basis for the observed clinical divergence.

The reciprocal serological pattern—higher VCA-IgM positivity with lower EBNA-IgG positivity in children, and lower VCA-IgM positivity with higher EBNA-IgG positivity in adults—is the key finding of this study. In immunologically naive children, primary EBV infection triggers a vigorous polyclonal B-cell expansion with atypical lymphocytosis, splenomegaly, and hepatic involvement, consistent with the IM syndrome[2, 10, 11]. The elevated LDH (478 vs 294 U/L) and lymphocyte counts (7.1 vs 1.3 $\times 10^9$/L) in children further support this lymphoproliferative state. In adults, by contrast, pre-existing EBV-specific T-cell immunity controls latent virus and limits reactivation, and clinical disease occurs when latent virus reactivates under immune perturbation, leading to organ-specific injury rather than diffuse lymphoproliferation[12, 13]. The higher CRP and bilirubin with lower albumin in adults are consistent with a more inflammatory/organ-injury pattern rather than systemic B-cell proliferation.

The 10.7% myocarditis rate in children deserves attention. While EBV myocarditis is uncommon in the general population, its recognition is important because it can present as arrhythmia[14], conduction block[15], or even heart failure[16]. Our data suggest that cardiac evaluation should be considered in pediatric EBV patients, particularly those with elevated CK-MB. Conversely, the absence of myocarditis in adults should not be interpreted as true absence; rather, cardiac workup was likely underperformed in adult patients presenting with hepatitis-dominant illness.

The exclusively adult occurrence of CAEBV, LPD, and HLH (14% combined; categories may overlap) has important prognostic implications. These conditions represent severe EBV-associated lymphoproliferative or immune dysregulatory disorders that require hematology referral and may be life-threatening[17]. Clinicians should have a low threshold for EBV DNA quantification and hematologic workup in adults with persistent fever, cytopenias, or organ dysfunction.

The longer hospital stay in adults (13 vs 7 days) likely reflects both greater diagnostic complexity (workup of chronic/invasive complications) and potentially greater disease severity, as evidenced by higher CRP and bilirubin and lower albumin.

Clinically, our findings suggest an age-stratified approach: in pediatric EBV patients, focus on cardiac monitoring (ECG, troponin, echocardiography) given the 10.7% myocarditis rate; in adult EBV patients,

prioritize hepatic evaluation (liver enzymes, bilirubin, coagulation) and consider hematologic referral for CAEBV/LPD/HLH.

Limitations

This study has several limitations. First, this was a single-center retrospective study with a pediatric-to-adult ratio of 2:1, reflecting our center's referral pattern; the findings may not be generalizable to other settings. Second, disease diagnoses were based on attending physician diagnoses documented in the medical record rather than standardized adjudication, which may introduce classification bias. Third, EBV DNA was measured in 141 patients (48.6%), but complete serological panels (VCA-IgM, VCA-IgG, EBNA-IgG, and EA-IgG) were available in only 83–94 patients (29–32%), with preferential testing in diagnostically unclear cases; this selection bias likely biased results toward the null. Fourth, some laboratory differences (lymphocyte count, LDH, WBC, and creatinine) may partly reflect age-related normal reference ranges rather than EBV-specific effects. Fifth, cardiac and hepatic workups were not systematically performed in all patients, so the true prevalence of subclinical myocarditis or hepatitis may be underestimated. Sixth, we lacked data on adult comorbidities and immune status, which might influence reactivation. Seventh, P values were not corrected for multiple comparisons given the exploratory nature of this study. Eighth, we lacked treatment and long-term outcome data, so the prognostic implications of age-related manifestation patterns remain unclear.

Conclusions

Pediatric EBV hospitalizations predominantly represent primary infection, with manifestations including IM and myocarditis, whereas adult EBV hospitalizations are more often associated with reactivation, organ injury such as hepatitis, and severe complications including CAEBV, LPD, and HLH. Age-stratified evaluation—cardiac assessment in children and liver/hematologic evaluation in adults—may improve diagnostic yield.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and its later amendments. The study was approved by the Institutional Ethics Committee of The First Affiliated Hospital of Chongqing College of Traditional Chinese Medicine (approval No. 2025-KY-HY-18). As this was a retrospective study involving the review of previously collected medical records, the requirement for informed consent was waived by the Institutional Ethics Committee, and the study was covered by the ethics approval for review of previously collected medical records.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are available from the corresponding authors on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YC and JY contributed equally to this work and share first authorship. YC conceived and designed the study, collected and analyzed the data, and drafted the manuscript. JY assisted with data collection and statistical analysis. QC, JZ, JC, and LS assisted with data collection. CW and YR contributed equally as co-corresponding authors, supervised the study, and critically revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

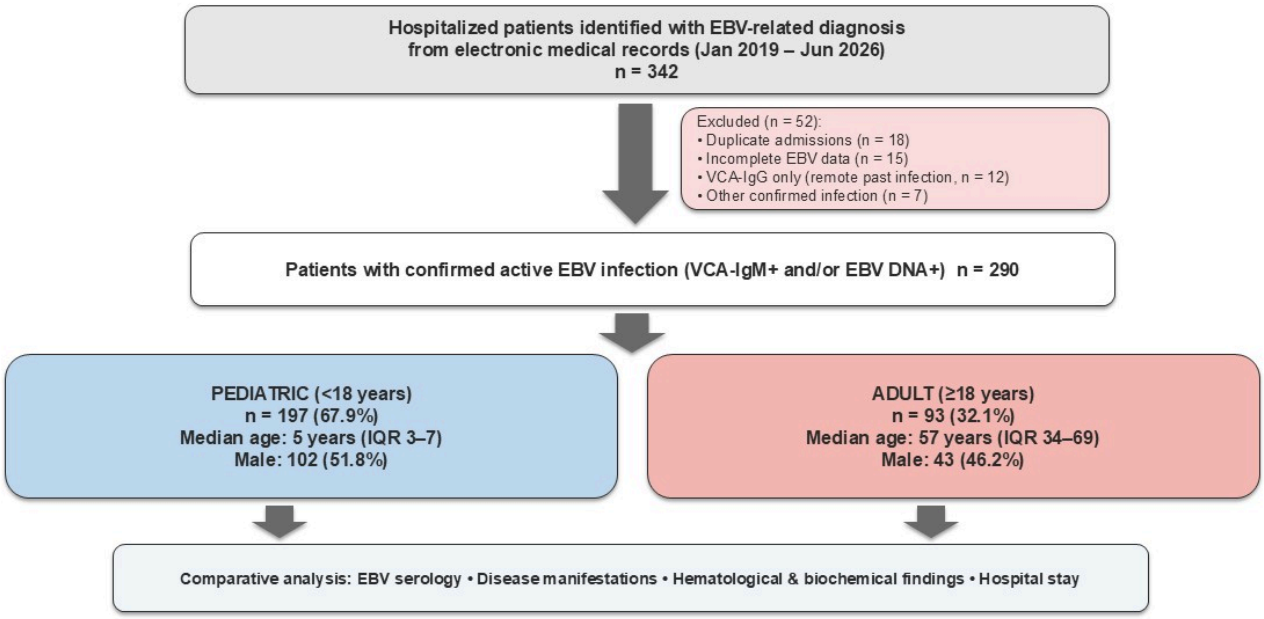


Figure 1

Flow diagram of patient selection. Of 342 hospitalizations initially identified with an EBV-related diagnosis in electronic medical records, 52 were excluded: 18 duplicate admissions, 15 with incomplete EBV data, 12 with isolated VCA-IgG positivity (remote past infection without active disease), and 7 with other confirmed infections. The remaining 290 patients with confirmed active EBV infection (VCA-IgM positive and/or detectable EBV DNA) were included and stratified into pediatric (<18 years, n = 197) and adult (≥18 years, n = 93). Abbreviations: EBV = Epstein-Barr virus; VCA = viral capsid antigen; IgM = immunoglobulin M; IgG = immunoglobulin G.

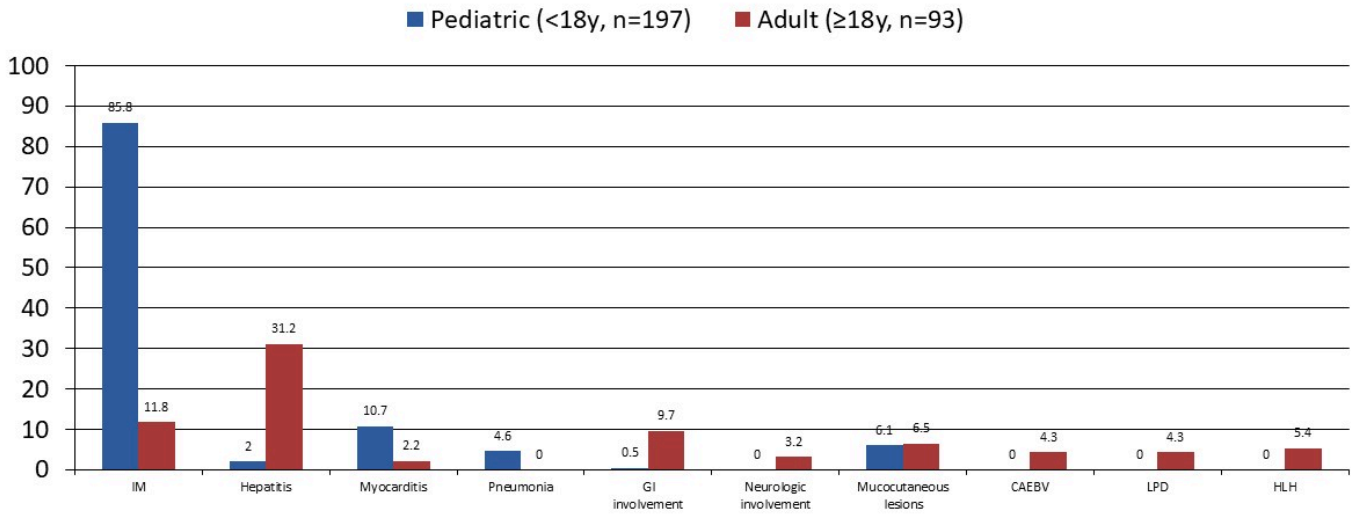


Figure 2

EBV disease manifestations by age group. Pediatric infection (blue) is dominated by infectious mononucleosis (IM, 85.8%) and myocarditis (10.7%). Adult infection (red) is dominated by hepatitis (31.2%) and chronic/invasive conditions (CAEBV 4.3%, LPD 4.3%, HLH 5.4%). Fisher's exact test showed significant differences between pediatric and adult groups ($P < 0.05$) for IM, hepatitis, myocarditis, GI involvement, neurologic involvement, CAEBV, LPD, and HLH. Categories are not mutually exclusive. No pancreatitis cases were observed in either group. Abbreviations: EBV = Epstein-Barr virus; IM = infectious mononucleosis; GI = gastrointestinal; CAEBV = chronic active EBV infection; LPD = EBV-associated lymphoproliferative disorders; HLH = hemophagocytic lymphohistiocytosis.

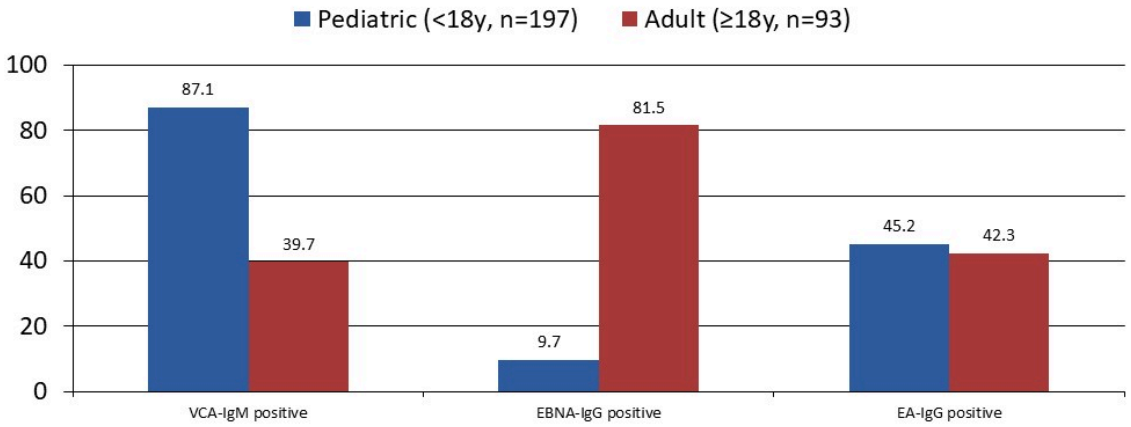


Figure 3

Comparison of EBV serological markers between pediatric and adult patients. Among tested patients, VCA-IgM positivity was higher in children (87.1% vs 39.7%, P < 0.001), consistent with acute/primary infection. EBNA-IgG positivity was higher in adults (81.5% vs 9.7%, P < 0.001), consistent with past infection or, in the appropriate clinical context, reactivation. EA-IgG positivity was similar between groups (45.2% vs 42.3%, P = 0.82). The reciprocal pattern is consistent with primary infection in children and reactivation in adults. Abbreviations: EBV = Epstein-Barr virus; VCA = viral capsid antigen; EBNA = EBV nuclear antigen; EA = early antigen; IgM = immunoglobulin M; IgG = immunoglobulin G.

Supplementary Files

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- Tables.xlsx