Original Article

Epstein-Barr virus seroprevalence among inflammatory bowel disease patients in Saudi Arabia

Badr Al-Bawardy[1,2,3], Abdulaziz F. Alfadley[1], Mohammed Almousallam[1], Saad AlShathri[1], Mohamed Aboueissa[1], Abdulrahman Alsulaiman[1], Mashary Attamimi[2], Abdulelah AlMutairdi[1,2]

[1]College of Medicine, Alfaisal University, Riyadh, Saudi Arabia, [2]Department of Internal Medicine, Division of Gastroenterology and Hepatology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [3]Department of Internal Medicine, Section of Digestive Diseases, Yale School of Medicine, New Haven, CT, USA

Abstract

Background: Seroprevalence of Epstein-Barr virus (EBV) in patients with inflammatory bowel disease (IBD) is variable based on geographic distribution. There are no published data on the seroprevalence of EBV in patients with IBD in Saudi Arabia. This study aims to assess the seroprevalence of EBV in patients with IBD in a tertiary center in Saudi Arabia.

Methods: This is a retrospective chart review of patients ≥14 years of age with a confirmed diagnosis of IBD and known EBV status at our institution from January 1, 2018, to January 1, 2023. The primary outcome was the seroprevalence of EBV in IBD. Secondary outcomes included factors associated with EBV seropositivity and rates of EBV seroconversion in originally negative patients.

Results: A total of 150 patients were included (74.7% with Crohn's disease, median age 28 years [interquartile range 21-36.3]). EBV non-exposure was noted in 16.8% ($n = 25$). The mean age was significantly lower in the EBV-naïve group at 26 ± 8.5 years compared to the EBV-exposed group at 31.2 ± 12.9 years ($P = 0.02$). Seroprevalence of EBV was highest in patients >40 years of age (92.9%) and lowest in patients 14-25 years of age (78.2%). The rate of seroconversion in EBV-naïve patients was 16.7% after a mean follow-up time of 47.9 ± 46.3 months.

Conclusion: In our cohort of IBD patients, 16.8% were naïve to EBV, and young age was a significant predictor of EBV non-exposure. Our data supports the practice of assessing EBV before initiating thiopurine therapy since EBV seroprevalence is not universal in our population.

Keywords: Crohn's disease, EBV, IBD, seroprevalence, ulcerative colitis

Address for correspondence: Dr. Badr Al-Bawardy, Consultant Gastroenterologist, Department of Internal Medicine, Division of Gastroenterology and Hepatology, King Faisal Specialist Hospital and Research Center, P. O. Box - 3354, 11121, Riyadh, Saudi Arabia.
E-mail: badr.albawardy@yale.edu

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INTRODUCTION

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) result in relapsing and remitting chronic intestinal inflammation. Thiopurine agents such as azathioprine and mercaptopurine are maintenance treatment options that can be utilized as monotherapy or in combination with anti-tumor necrosis factor agents (anti-TNF) in the management of IBD.[1]

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Thiopurine agents are associated with an increased risk of lymphoproliferative disorders, particularly Epstein-Barr virus (EBV)-related disorders.[2-6] EBV is a common human herpesvirus that causes infectious mononucleosis. A risk factor for the development of lymphoproliferative disorders in IBD patients on thiopurine therapy is the development of primary infection during treatment.[3,4] In patients with IBD who developed lymphomas, approximately 40%-75% were EBV-positive tumors.[3,5] The European Crohn's and Colitis Organization (ECCO) guidelines recommend assessing EBV status before commencing thiopurine therapy in patients with IBD.[7] In IBD patients who are EBV-negative, avoidance of thiopurine therapy should be considered.

The population prevalence of EBV in adults is estimated to be high at >90%.[8,9] However, there's potential variability in the rate of EBV exposure according to age. For example, in the pediatric IBD population, the seropositivity of EBV has ranged from 37.8% to 64%.[10-12] The rate of EBV seroprevalence in patients with IBD also varies from one demographic area to another. A study in the United States conducted in 2007 included 79 IBD patients and 25 control subjects and showed a higher incidence of EBV seropositivity in the IBD group compared to the control subjects at 49% vs 32%.[13] A study in Iraq evaluated EBV serologies (anti-viral capsid antigen IgM, IgG, and IgA subtypes) of 180 patients with CD and UC.[14] The study concluded that the prevalence of EBV infection was 96.67% in both subtypes, which is relatively higher than in the controls involved in this study. Another study conducted in Canada included 243 IBD patients who underwent serological testing for EBV seropositivity.[9] It showed that the IBD population aged 18-25 years had similar seronegativity to the general population, and the population aged above 25 years had a 100% seropositivity rate.[9]

The incidence and prevalence of IBD continue to increase in Saudi Arabia.[15] There are currently no data on the prevalence of EBV seropositivity among patients with IBD in Saudi Arabia. This information has clinical implications as it can help identify patterns and importance of EBV screening in IBD patients planning on commencing thiopurine therapy. Therefore, this study aims to evaluate the seroprevalence of EBV in a cohort of patients with IBD in a tertiary referral center.

PATIENTS AND METHODS

We conducted a single-center retrospective study at our institution from January 1, 2018, to January 1, 2023. We included patients aged ≥14 years with a confirmed diagnosis of IBD and who had their EBV status evaluated. Exclusion criteria were age <14, no confirmed diagnosis of IBD, and lack of assessment of EBV status. The study protocol was approved by our Institutional Review Board (IRB#2231156) on August 13, 2023.

Data collected included patient demographic characteristics such as age, sex, baseline body mass index (BMI), and smoking status. Disease-related variables included duration of IBD, IBD subtype, disease location, disease phenotype, and extraintestinal manifestations. Treatment-related variables included all current and prior medical and surgical therapies for IBD, use of thiopurines and other medications such as mesalamine, methotrexate, infliximab, adalimumab, vedolizumab, ustekinumab, certolizumab, tofacitinib, and upadacitinib. EBV status was assessed utilizing a combination of serologies including EBV viral capsid antigen (VCA) IgM/IgG, EBV early antigen IgG, EBV nuclear antigen (EBNA) IgG. A patient would be considered EBV seronegative if all the abovementioned serologies were negative. EBV seropositivity was defined as previous infection (+VCA-IgG/+EBNA-IgG) or history of serologies indicating active infection or reactivation.[16]

The primary outcome was the seroprevalence of EBV in IBD. Secondary outcomes included factors associated with EBV seropositivity and rates of EBV seroconversion in originally negative patients. We utilized JMP® (SAS Institute Inc., Cary, North Carolina, United States) statistical software for data analysis. Unpaired student's *t*-test was used for continuous variables. Pearson's Chi-square test was used to analyze categorical variables. A *P*- value <0.05 was considered statistically significant.

RESULTS

A total of 150 patients were included in the study. The median age was 28 years [interquartile range (IQR) 21-36.3 years] and 54.7% were male. The median disease duration was 4 years (IQR: 1.5-9.0 years). CD was the most frequent diagnosis at 74.7% (n = 112), followed by UC at 25.3% (n = 38) [Table 1]. The patients' medical therapy included mesalamine in 24.7%, methotrexate in 2%, thiopurines in 41.3%, and advanced therapies in 86.0% (this included some patients who were also on mesalamine and thiopurines).

A total of 25 patients (16.8%) were not previously exposed to EBV (EBV naïve). There were no significant differences between the EBV naïve and exposed groups in terms of disease type (Crohn's vs. UC), presence of perianal disease

Table 1: Baseline characteristics

Variable	Value
Age (years), median (IQR)	28 (21-36.3)
Male, *n* (%)	82 (54.7)
BMI, median (IQR)	24.3 (19.1-28.5)
Disease duration (years), median (IQR)	4 (1.5-9.0)
Follow-up time (months), median (IQR)	45 (5.8-86.0)
IBD subtype	
Crohn's disease, *n* (%)	112 (74.7)
L1	11 (9.8)
L2	18 (16.1)
L3	83 (74.1)
L4	16 (14.3)
B1	19 (17.0)
B2	24 (21.4)
B3	69 (61.6)
Perianal disease, *n* (%)	44 (39.3)
Ulcerative colitis, *n* (%)	38 (25.3)
Proctitis	5 (13.2)
Left-sided colitis	12 (31.6)
Pancolitis	21 (55.2)
Prior bowel resection, *n* (%)	81 (54.0)
Current smoker, *n* (%)	18 (12.0)
Extraintestinal manifestation, *n* (%)	43 (28.7)

IQR: Interquartile range; BMI: Body mass index

or stricturing/penetrating phenotype [Table 2]. Patients in the EBV naïve group were significantly younger, with a mean age of 26 ± 8.5 years compared to 31.2 ± 12.9 years in the EBV-exposed group ($P = 0.02$).

EBV seroprevalence was 92.9% ($n = 26$) in patients over 40 years of age compared to 80.8% ($n = 97$) in patients between the ages of 14 and 40. In individuals below the age of 20, the EBV seroprevalence was 83.3% ($n = 25$) compared to 89.7% ($n = 61$) in patients 30 years of age or older. EBV seroprevalence was 78.2% ($n = 43$) in patients <25 years old, 82.7% ($n = 43$) in patients between 25 and 35 years of age, and 90.7% ($n = 39$) in patients >35 years of age.

Table 2: Comparison of characteristics between EBV-Naïve and EBV-exposed patients with IBD

Patient characteristics	EBV-Naïve (*n*=25)	EBV-exposed (*n*=125)	*P*
Baseline characteristics			
Age (years), mean (SD)	26 (8.49)	31.2 (12.9)	0.02
Age groups, *n* (%)			0.17
<14 years of age	0	2 (1.6)	
14-40 years of age	23 (92)	97 (77.6)	
>40 years of age	2 (8)	26 (20.8)	
Male sex, *n* (%)	12 (48)	70 (56)	0.46
Follow-up (months), mean (SD)	47.9 (46.3)	52.8 (51.3)	0.64
Disease characteristics			
Disease type, *n* (%)			0.74
Crohn's disease	18 (72)	94 (75.2)	
Ulcerative colitis	7 (28)	31 (24.8)	
Bowel resection, *n* (%)	11 (44)	70 (56)	0.27
Presence of extraintestinal manifestations, *n* (%)	7 (28)	36 (28.8)	0.94
Stricturing/Penetrating Crohn's disease, *n* (%)	15 (83.3)	78 (82.9)	0.97
Perianal Crohn's disease, *n* (%)	6 (33.3)	38 (40.4)	0.57

EBV: Epstein-Barr virus; SD: Standard deviation

A total of 62 patients were on thiopurines. In these patients, 87.1% ($n = 54$) had previously been exposed to EBV, compared to 12.9% ($n = 8$) who had not. There were no cases of lymphoproliferative disorders in the whole cohort after a mean follow-up time of 54.0 ± 47.1 months. The mean follow-up time was similar between the EBV-naïve group at 47.9 ± 46.3 months and 52.8 ± 51.3 months in the EBV-exposed group ($P = 0.64$).

Only 6 of the 25 EBV-naïve patients had repeat EBV serologies evaluation. Repeat EBV serologies were negative in five patients and positive in only one patient, giving an overall rate of EBV seroconversion of 16.7%. The patient had colonic CD and was treated with ustekinumab monotherapy at the time of EBV-seroconversion. The patient did not experience any adverse infectious or neoplastic events.

DISCUSSION

The findings of this study contribute valuable insights into the prevalence of EBV seropositivity among patients with IBD in Saudi Arabia. The data suggests that EBV seroprevalence varies with age, particularly older patients being more likely to be EBV seropositive. In addition, we found that EBV seroprevalence is not universal in our adult population with IBD as compared to Western populations. For example, 17.3% of patients between the age of 25-35 years were EBV-naïve, and 9.3% of patients >35 years of age were EBV-naïve. This highlights the importance of evaluating EBV status before commencing thiopurine therapy in adult patients with IBD in Saudi Arabia.

The prevalence of EBV seropositivity in the general population may vary depending on geographic location. In a cross-sectional study of more than 700 participants in England, the prevalence of EBV seropositivity was 93% in young adults (ages 22-24 years).[17] In a cross-sectional sampling study of over 1200 participants in Iran, EBV seropositivity was noted in 92.2% of participants aged between 20 and 29 years.[18] A multinational study of over 500 participants demonstrated a significantly higher prevalence of EBV seropositivity (anti-EBV VCA) in participants from Mexico compared to Israel and the Netherlands ($P < 0.05$).[19]

The prevalence of EBV seropositivity among patients with IBD has been evaluated in a few studies. In a single-center

study of 1483 patients with IBD in Spain, the overall EBV seropositivity rate was 97.4%, with a 98.4% rate in those who were >30 years of age.[20] In a Canadian study of 243 patients, the overall EBV seropositivity rate was around 93%.[9] In the >40 years of age group of the aforementioned study, only 3% were seronegative for EBV while 100% were seropositive for EBV in the 26-40 years age groups.[9] The observed EBV seroprevalence rates in this Saudi Arabian cohort are lower than what has been reported in the previous studies. We demonstrated a lower EBV seroprevalence rate of 82.7% in IBD patients between the ages of 25-35 and 90.7% among patients >35 years of age. This highlights the importance of investigating and understanding EBV status as it pertains to geographic location.

In our study, we have demonstrated that older age is significantly associated with EBV seroprevalence. This pattern of age-related EBV exposure has been demonstrated by multiple studies from different geographic regions.[9,18,20] We have also demonstrated that the EBV seropositivity rates across our cohort were similar in CD (83.9%) and UC (81.6%), which aligns with findings from previous studies.[9,10] We have also found that EBV exposure, or the lack thereof was not necessarily associated with aggressive CD phenotypes such as stricturing or penetrating complications. However, this observation is limited by the small sample size of EBV-negative individuals in our cohort.

Evaluating EBV serologic status before the commencement of immunosuppressive therapy, particularly thiopurines, is recommended by the ECCO guidelines on the prevention, diagnosis, and management of infections in IBD.[7] The primary reason is that primary EBV infection during immunosuppression is associated with an increased risk of lymphoproliferative disorders, as demonstrated in post-transplant populations.[21] In populations with IBD, Afif *et al*.[5] demonstrated that 75% of lymphomas were positive for EBV. A prospective observational cohort of over 19,000 patients with IBD found that over 40% of lymphomas were EBV-positive and that thiopurines increased the risk of lymphoproliferative disorders.[5] In our cohort, only eight patients who were EBV seronegative commenced on thiopurine therapy, and none developed lymphoproliferative disorders. The absolute risk of lymphoproliferative disorders in patients with IBD on thiopurines remains low compared to the relative risk. Therefore, our study is not adequately powered to evaluate the risk of lymphoproliferative disorders in this subset of patients. We would still recommend caution with the use of thiopurines in EBV naïve patients.

Our study is the first to report on the prevalence of EBV seropositivity among patients with IBD in Saudi Arabia. We have demonstrated that EBV seropositivity in this population is slightly lower than what has been reported in Western populations. Although EBV seropositivity increases with age, we demonstrated that almost 10% of patients with IBD over the age of 35 remain EBV naïve.

The study's findings highlight the need to assess EBV status before initiating thiopurine therapy, as recommended by guidelines from the ECCO. This cautious approach aims to reduce the risk of EBV-related complications, especially in patients who are EBV-negative. This study adds to the body of evidence supporting the importance of EBV status assessment before initiating thiopurine treatment in IBD patients. Our study is limited by the relatively small sample size and retrospective study design. The sample size precluded doing sensitivity or subgroup analyses looking at factors such as geographic distribution and socioeconomic status of these patients within Saudi Arabia.

In conclusion, this study provides crucial information about the prevalence of EBV seropositivity among IBD patients in Saudi Arabia. The data supports the practice of assessing EBV status in adult patients with IBD before initiating thiopurine therapy, especially considering the potential risks associated with EBV-related lymphoproliferative disorders. Further research with longer follow-up times and larger sample sizes could help corroborate the observed findings in this study and provide a more comprehensive understanding of the impact of EBV seropositivity on IBD patients' outcomes.

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Nil.

Conflicts of interest

- Dr. Badr Al-Bawardy: Speaker fees: AbbVie, Takeda, Bristol-Myers Squibb, Janssen Pharmaceuticals. Advisory board: Bristol-Myers Squibb, Pfizer.
- Dr. Abdulelah AlMutairdi: Speaker fees: AbbVie, Takeda, Bristol-Myers Squibb. Advisory board: AbbVie, Takeda, Bristol-Myers Squibb, Pfizer.

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