Available online at *www.ujpronline.com*
Universal Journal of Pharmaceutical Research
An International Peer Reviewed Journal
ISSN: 2831-5235 (Print); 2456-8058 (Electronic)

RESEARCH ARTICLE

ASSOCIATION OF EPSTEIN-BARR VIRUS WITH SYSTEMIC LUPUS ERYTHEMATOSUS BY LIMITED MATERIALS: PATIENT CHARACTERISTICS AND CLINICAL MANIFESTATIONS IN YEMEN

Mohammed Ismail Al-Mansor[1], Khaled Abdul-Karim A Al-Moyed[1], Mohammed Mohammed Al-Shehari[2], Hassan Abdulwahab Al-Shamahy[1,3], Eshrak Adulmalik Al-gunaid[4], Ahmed Mohamed Al-Haddad[5]

[1]*Medical Microbiology and Clinical Immunology Department, Faculty of Medicine and Health Sciences, Sana'a University.*
[2]*General surgery Department, Faculty of Medicine and Health Sciences, Sana'a University.*
[3]*Medical Microbiology department, Faculty of Medicine, Genius University for Sciences and Technology, Dhamar city.*
[4]*The National Center of Public Health Laboratories (NCPHL), Sana'a, Yemen.*
[5]*Department of Medical Microbiology, Faculty of Medicine and Health Sciences, Hadhramout University, Republic of Yemen.*

Article Info:

Article History:
Received: 5 August 2023
Reviewed: 11 September 2023
Accepted: 19 October 2023
Published: 15 November 2023

Cite this article:
Al-Mansor MI, Al-Moyed KAA, Al-Shehari MM, Al-Shamahy HA, Al-gunaid EA, Al-Haddad AM. Association of epstein-barr virus with systemic lupus erythematosus by limited materials: Patient characteristics and clinical manifestations in yemen. Universal Journal of Pharmaceutical Research 2022; 7(5):49-56.
https://doi.org/10.22270/ujpr.v7i5.839

***Address for Correspondence:**
Dr. Hassan A. Al-Shamahy, Faculty of Medicine and Heath Sciences, Sana'a University, Faculty of Medicine, Genius University for Sciences and Technology, Dhamar/Sana'a, Yemen, The Eye Consultation Center, Sana'a city, Yemen. Tel- +967-1-239551.
E-mail: *shmahe@yemen.net.ye*

Abstract

Background and aims: Systemic lupus erythematosus (SLE) is an autoimmune chronic inflammatory disease with damage to many organs due to the production of auto-antibodies, including auto-antibodies to renal antigen, vascular tissue antigens, brain antigens, ribosomes, nuclear antigens, and phospholipids. This study was conducted to determine patient characteristics and clinical manifestations of systemic lupus erythematosus and to find out the association of positive IgG with high titer of EBV-VCA with clinical features of SLE patients.
Materials and Methods: In this cross-sectional study, 142 patients with SLE diagnosed based on American College of Rheumatology criteria were selected. All were included in the study after obtaining informed consent for participation. Whole blood samples were taken and serum was separated to determine anti-EBV IgG antibodies using the ELISA method and assessment with the SLE.
Results: Female represent 81% of the total patients, while male represent only 19%, with ratio male: female equal to 1: 4.3, most of the patients were adults over 20 years old, with mean age ± SD was 35.8 ± 13.7 years. The most common signs were joint pain (95.1%), fever (92.3%), persistent fatigue (83.8%), followed by joint swelling (69.7%), photosensitivity (54.4%), renal involvement (52.8%), weigh loss (49.3%) and alopecia (49.3%), while other SLE signs were less frequent.
Conclusion: EBV may have an important role in SLE pathogenesis and activity, SLE male: female ratio equals 1:4.3, most patients were adults over 20 years of age, and the most common signs of SLE were joint pain, fever and persistent fatigue.
Keywords: Elevated titer antibody, Epstein-Barr virus, IgG EBV antibody, Systemic Lupus Erythematosus (SLE), Viral Capsid Antigen (VCA).

INTRODUCTION

SLE is an autoimmune illness with no apparent pathogenesis. This illness is described by polyclonal B-cell initiation and distorted T-cell function with the occurrence of multiple auto-antibodies and damaged cellular immunity. It is supposed that both environmental and genetic factors be part of the cause to development of the disease[1,2]. Infection with bacteria and viruses are important environmental factors that can initiate and participate in the pathogenesis of SLE. The Epstein-Barr virus (EBV) is one of the most important causes. This is because Epstein-Barr is homologous to some proteins that produce an autoimmune humoral response[3,4]. These molecular mimics may play a vital role in the antibody induction by EBV infection in SLE patients. More recently, Harley *et al*.,[5] accounted that approximately 50% of the SLE risk sites are occupied by the EBNA-2 protein and numerous co-clusteres with factors of transcription, presenting a fundamental new perception on the pathogenesis mechanism of SLE. In 1971 the first positive association connecting EBV infection with SLE was found[6]. From the time when numerous

researchers have used different angles to explore the option of this association. Though, preceding studies failed to reveal a consistent association. The earliest and single systematic review updated regarding the association between SLE and sero-positivity for distinct EBV antibodies was that of Hanlon *et al*.,[7]. The authors discovered a statistically significant higher seroprevalence of viral capsid antigen (VCA) IgG but not EBNA1 in the cases contrasted to the controls. Meta-analysis of early antigen (EA)/D IgG and VCA IgA also showed significantly higher ORs in the cases group compared to the control group. Numerous studies have since been available and may assist in more completely estimation the association. Additionally, a number of authors assumed that the rise in antibodies in SLE was caused by generalized immune hyper-reactivity in lupus rather than by any specific possessions of the EBV. It was afterward thought that the most excellent way to elucidate this question would be at the DNA level[8-11]. SLE can involve persons of all ages, both sexes, and all ethnic groups. Nevertheless, more than 90% of latest patients presenting with SLE are women in their childbearing years[12,13]. SLE is a disease that affects multiple systems and its symptoms vary widely. Several studies have from the time when published and may assist to completely estimate the association. In addition, several authors hypothesized that the increase in auto-antibodies in SLE is due to generalized immune hyper-reactivity in SLE more readily than to any specific characteristic of EBV. It was later they thought that the best way to make clear this question would be at the DNA level[8-11]. SLE can involve people of genders, all ethnic groups, and all ages. In spite of this, more than 90% of new patients with SLE are women in their reproductive ages[12,13]. This also reinforces the idea that hormonal differences due to physiological development can exacerbate disease symptoms. Lupus is a multisystem disease with a variety of symptoms. Compound organ impairment in SLE is due to the creation of auto-antibodies, which include auto-antibodies to antigens in the vascular tissues, brain tissues, renal tissues and, ribosomes, nuclear antigens, and phospholipids. Inflammation and intracranial vascular lesions which include vasculitis and thrombosis have been associated with local secretion of cytokines[12,13]. Additionally, recent data indicated that both renal and neuropsychological intervention negatively affect the five-year survival rate. However, the neuropsychological involvement did not alter for the ten-year survival rate, regardless of the fact that the association of the nervous system in SLE persists poorly understood[14]. However, it is not surprising that autoimmune diseases have an effect on the central nervous system or the peripheral nervous system, in which case it could be due to high levels of IgG around the blood vessels. Fatigue in SLE is likely to be multifactorial and is not only associated with disease activity, but also with complications such as hypothyroidism or anemia[12].

In recent years, viral infection and autoimmune diseases have been well studied in Yemen, where many studies have been conducted in this aspect[13-31], but only one previous study discussed SLE in Yemen[12], and another study discussed the association of EBV with diseases Autoimmune (rheumatoid arthritis)[13]. However, there is no study associated with EBV infection with clinical features and SLE in Yemen and this study is the first to discuss this topic. Therefore, the aims of this study was to determine the patient characteristics and clinical manifestations of systemic lupus erythematosus and to know the association of positive IgG with high titer of EBV-VCA with systemic lupus erythematosus - in addition to knowing the association of positive IgG with high titer of EBV-VC with the occurrence of different clinical features of SLE patients.

MATERIALS AND METHODS

The current research was conducted over a interval of one year from October 2020 to November 2021(time capsule for master's thesis fieldwork). A total of 142 Yemeni patients were enrolled, who were admitted to the medical wards and/or to the medical clinics of Al-Thawra Hospital in Sana'a City. All patients met four or more of the American College of Rheumatology (ACR) criteria for a diagnosis of SLE[32]. Specially designed questionnaires were analyzed with retrospective of relevant data for instance patients' gender, age, clinical manifestations at presentation and during follow-up, and their exposure to possible risk factors for lupus erythematosus. Treatments, both at the start and during follow-up appointments, were also recorded, in addition to any complications.

Laboratory data include anemia (hemoglobin <11 g/dL), leukopenia (white blood cells <4000/mm^9), and thrombocytopenia (platelets <100000/mm^9). In vitro data also comprised elevated erythrocyte sedimentation rate, positive ANA, positive rheumatoid factor, and high anti-DNA and anti-SM antibody. ANA was considered by two diverse methods: enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence (IIF), anti-ds deoxyribonucleic acid (anti-dsDNA) and anti-Smith antibodies (anti-Sm) were measured by ELISA (INOVA Diagnostic Toolkit, San Diego, California, USA).

Lupus nephritis was established by kidney biopsy, which was classified consistent with WHO classification II, III, IV or V[33]. Photosensitivity has been identified by certain skin lesions caused by sunlight. The various drugs used in treating patients ranged from non-steroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine and steroids, to intermittent cyclophosphamide with intravenous methylprednisolone in lupus nephritis. Warfarin was an anticoagulant used in cases of venous thrombosis.

EBV detection: Whole blood samples were taken and serum separated for determination of EBV IgG antibodies using the ELISA method. Epstein-Barr virus IgG ELISA (VCA) was used for the qualitative determination of IgG-class antibodies against Epstein-Barr virus antigen (VCA) in human serum or plasma. The test was performed according to the manufacturer's instructions (Demeditec Diagnostics GmbH, Germany).

Data analysis: The *odds ratio* (*OR*) for the association of high positive IgG titer of EBV-VC with clinical presentations of SLE, and their Cornfield 95% confidence limits, were calculated by the analysis of a single table. Furthermore, the Chi-square (X^2) value for statistical significance was calculated using Yates' continuity correction. However Fisher's exact test was employed for small cell sizes with a two-tailed probability value (*p*), using the Epi-Info Version 6 software (Centers for Disease Control and Prevention, Atlanta, Georgia, USA).

Ethical consideration: Ethical approval was acquired from the ethics committee of the Faculty of Medicine and Health Sciences, Sana'a University prior to data collection with No: 754 dated September 27, 2020. An authorized letter was acquired from the Faculty of Medicine and Health Sciences, Sana'a University, to be submitted to the administration of Al-Thawra Hospital to facilitate the conduct of this research work. A consent form was completed by each participant.

RESULTS

Female represent 81% of the total patients, while male represent only 19%, with ratio male: female equal to 1: 4.3. Considering age, most of the patients were adults over 20 years old, with mean age ± SD was 35.8 ± 13.7 years (Table 1).

Table 1: Age and gender distribution of systemic lupus erythematosus patients tested for Epstein-Barr Virus.

Characters	N (%)
Gender (Ratio male:female::1:4.3)	
Female	115 (81)
Male	27 (19)
Age groups	
≥ 19 years	14 (9.9)
20 – 29 years	35 (24.6)
30-39 years	42 (29.6)
40 – 49 years	25 (17.6)
≥ 50 years	26 (18.3)
Total	142 (100)
Mean age	35.8 years
SD	13.7 years
Median	35 years
Mode	30 years
Min	12 years
Max	80 years

The most common signs were joint pain (95.1%), fever (92.3%), persistent fatigue (83.8%), followed by joint swelling (69.7%), Photosensitivity (54.4%), renal involvement (52.8%), weigh loss (49.3%), and alopecia (49.3%) less frequent such as ankle swelling (33.8%), and chest pain during deep breathing (28.9%), and cutaneous lupus (discoid lupus) (26.8%), while butterfly rash (malaria rash), oral ulcers and serositis were very rare (15.5%, 10.6% and 9.2% respectively) (Table 2). In the current study, the positive rate of Epstein-Barr virus IgG among our SLE patients was 97.2%, and 56.3% of them had high level of the antibody ≥ 51 IU (Table 3). There was a significant negative association between the higher positive rate of Epstein-Barr virus IgG and male patients with the rate being only 33.3% compared to 61.7% for females (Table 4). There was an association between a higher positive rate of Epstein-Barr virus IgG and an age group of 20-29 years where 77.1% of this group had a high level of EBV antibody, with an *OR* of 3.7, 95% *CI*.=1.4-8.3, *p*=0.004 (Table 4).

Table 2: The clinical signs of the Systemic Lupus Erythematosus patients tested for Epstein-Barr Virus, (n=142).

Signs	N (%)
Joints pain	135 (95.1)
Fever	131 (92.3)
Constant fatigue	119 (83.8)
Joint swelling	99 (69.7)
Photosensitivity	77 (54.4)
Renal involvement	75 (52.8)
Weigh loss	70 (49.3)
Alopecia	70 (49.3)
Hypertension	52 (36.6)
Swollen ankle	48 (33.8)
Pain in chest during deep breath	41 (28.9)
Cutaneous lupus (discoid lupus)	38 (26.8
Butterfly rash (malar rash)	22 (15.5)
Oral ulcers	15 (10.6)
Serositis	13 (9.3)

Consideration of clinical signs of systemic lupus erythematosus associated with high titer of Epstein-Barr virus IgG antibody. There was a significant association between elevated Epstein-Barr virus IgG antibody titers with fever (*OR*=15.2, *CI*=1.8-122, X^2=10.8, *p*=0.001), and joint pain (*OR*=8.4, *CI*=1.0-72, X^2=5.2, *p*=0.02), weight loss (*OR*=3.9, *CI*=1.96-8, X^2=15.3, *p*<0.0001), and joint swelling (*OR*=3.6, *CI*=1.7 - 7.5, X^2=11.5, *p*< 0.0001), while there was no statistically significant correlation between the high titer of IgG antibody to Epstein-Barr virus with other sing markers (Table 5).

Table 3: The Epstein - Barr virus IgG antibody titration among systemic Lupus Erythematosus patients.

IgG antibody titration	N (%)
≥ 10 IU	4 (2.8)
11-40 IU	21 (14.8)
41 – 50 IU	37 (26.1)
≥ 51 IU	80 (56.3)
Total positive	**138 (97.2)**
Mean	47.1 U
SD	9.6 IU
Median	51 IU
Mode	53 IU
Min	3.2 IU
Max	57 IU

Table 4: Age and gender of systemic Lupus Erythematosus patients associated with high titer of IgG antibody of Epstein-Barr virus (n=80).

Characters	N (%), N=80	*OR*	*95% CI*	X^2	*p* value
Gender					
Female n=115	71 (61.7)	1.2	0.4-3.2	0.09	0.76
Male n=27	9 (33.3)	0.3	0.12-0.71	7.1	0.007
Age groups					
≥ 19 years n=14	9 (64.3)	1.4	0.45-4.5	0.39	0.52
20 – 29 years n=35	27 (77.1)	3.7	1.4-8.3	8.2	0.004
30-39 years n=42	23 (54.8)	0.59	0.28-1.2	1.9	0.16
40 – 49 years n=25	10 (40)	0.44	0.18-1.08	3.3	0.06
≥ 50 years n=26	11 (42.3)	0.49	0.2-1.2	2.5	0.11
Total n=142	80(56.3)				

DISCUSSION

SLE is an autoimmune illness characterized by the production of auto-antibodies and the contribution of multiple organ systems, and is more common in females than males[35,36]. This is one of the first studies in Yemen that aimed to determine the prevalence of diagnostic antibodies, clinical signs, and association with EB virus infection in SLE patients. In the current study, the ratio of male to female patients was 1: 4.3. This result is in agreement with the result of the previous study in Yemen by Al-Shamahi *et al.*, where the ratio of males to females was 1:3[12]. Also, the predominant prevalence of SLE among females compared to males in the current study is similar to other studies in different geographical regions where they reported a more dominant prevalence of SLE among females than males with a ratio higher than 1:4.3 (1:7.2; 1:9.8 and 1: 9.9)[37-39]. This difference can likely be attributed to the undiagnosed SLE status in many parts of Yemen where facilities to perform the baseline ELISA assay are often not available. Moreover, the lower incidence of SLE among Yemeni females compared to females of other countries could be explained by the under-diagnosis among females in Yemen due to socio-economic factors that prevent many females from accessing health care centers or hospitals.

Table 5: Clinical signs of systemic Lupus Erythematosus associated with high titer of IgG antibody of Epstein-Barr virus.

Signs	N (%)	*OR*	*95% CI*	X^2	*p* value
Fever, n=131	79 (60.3)	15.2	1.8-122	10.8	0.001
Joints pain, n=135	79 (58.5)	8.4	1 -72	5.2	0.02
Weight loss, n=70	51 (72.9)	3.9	1.96-8	15.3	<0.0001
Joint swelling, n=99	65 (65.7)	3.6	1.7-7.5	11.5	<0.0001
Cutaneous lupus (discoid lupus) n=38	26 (68.4)	2	0.9-4.3	3.1	0.07
Butterfly rash (malar rash), n=22	15 (68.2)	1.8	0.7-4.7	1.4	0.22
Oral ulcers, n=15	10 (66.7)	1.6	0.5-5.3	0.72	0.39
Skin rash, n=38	23 (60.5)	1.3	0.6-2.7	0.37	0.54
Serositis, n=13	8 (61.5)	1.3	0.3-4	0.15	0.69
Alopecia, n=70	39 (55.7)	0.95	0.49-1.8	0.02	0.88
Swollen ankle, n=48	25 (52)	0.77	0.38-1.6	0.53	0.46
Hypertension, n=52	21(40.4)	0.35	0.17-0.71	8.4	0.003
Pain in chest during deep breath, n=41	25 (61)	0.3	0.1-0.6	9.1	0.002
Photosensitivity, n=77	33 (42.6)	0.28	0.14-0.58	12.4	<0.0001
Constant fatigue, n=119	68 (57.1)	0.2	0.07-1.07	3.8	0.05
Renal involvement, n=75	23 (30.7)	0.07	0.03-0.17	42	<0.0001

Another explanation is that males and females in Yemen are relatively at risk or predisposing factors for the development of SLE with approximately the same frequency but at different points. These factors may include genetic, hormonal, and environmental factors[40,41]. In conclusion, SLE, similar to numerous autoimmune diseases, have an effect on females more than males, with a richness ratio of about 9 to 1[42,43]. The X chromosome holds genes of immune-related, which can mutate and play a part to the onset of SLE. The Y chromosome does not contain specific mutations connected with autoimmune diseases[44]. Also, hormonal mechanisms could explain the increased incidence of SLE in females. The onset of SLE can be attributed to elevated hydroxylation of estrogen and abnormally low levels of androgens in females. In addition, differences in GnRH signaling have also been shown to contribute to the onset of SLE. While females are more likely to relapse than males, the severity of these relapses is the same for both sexes. Additionally to the mechanisms of hormones, precise genetic influences positioned on the X chromosome may also contribute to the occurrence of SLE. Studies show that the X chromosome can reveal levels of sex hormones. An investigation showed a relationship between Klinefelter syndrome and SLE. XXY males with SLE have an atypical X-Y translocation resultant in partial triplication of the PAR1 gene region[45-47].

In the current study, the mean age of SLE patients was 35.8±13.7 years which is slightly older than the age previously reported in Yemen by Al-Shamahy *et al.*,[12] where the mean age of SLE patients was 28.8 years.

Moreover, this study had a mean age (35.8 years) of our patients slightly older than that reported from Spain by Font *et al.*,[48] in which the mean age of the SLE patients is 29 years. In the current study in Yemen, the majority of patients (90.1%) were adults over 19 years of age and (9.9%) were under 19 years of age. This is similar to the previous study in Yemen where the majority of patients (88.6%) were adults and (11.4%) children under 15 years of age[12]. This is also similar to what was reported in Saudi Arabia by Albullah[46]; mostly patients over 15 years old. The higher rate among adults may be related to the sex hormones, which play an important role in triggering the disease[47]. Systemic lupus erythematosus is one of a number of diseases recognized as a "great imitator" because it is frequently imitated or mistaken for other diseases. SLE is a classic component of the differential diagnosis[40] because SLE symptoms vary widely and come and go unexpectedly. Thus the diagnosis can be elusive, with some people having unexplained symptoms of SLE for years. In the current study, the frequencies of the major clinical and serological features of our patients, compared to the other populations, are represented in Table 4. The results of this study showed that the most common clinical symptom in Yemeni patients with SLE was joint pain, which was present in (95.1%). In contrast to other studies in western Saudi Arabia, it occurred in (9.2%) only[49], and in Iran (30.2%)[50]. This can be explained in our patients that joint pain is an important symptom due to the health education background. Also, this increases the concern of clinicians who cannot epitomize the treatment of such a multi-polar disease only by prescribing an analgesic without a persuasive cause. Moreover, this symptom has been associated not only with disease activity or complications such as anemia but also with pain, depression, poor sleep quality, poor fitness and marked lack of social support[12]. Fever also was common in our patients (92.3%), and the temperature usually showed diurnal variation being high in afternoon and evening. It is slightly higher than that reported in Yemen previously in which fever also was common with 81.9%[12], also it was more higher than that reported in Spain (42.0%) and Saudi Arabia (30.0%)[38,48]. The results of this study showed one of the most frequent clinical symptom in Yemeni patients with SLE was fatigue which was present in (83.8%), this is similar to that reported in Yemen by Al-Shamahy *et al.*,[12] in which the rate of fatigue among SLE was 84.6%. In contrast to other studies in western Saudi Arabia, it occurred in (9.5%) only[49], and in Iran (32.2%) only[50]. In the current study, cutaneous lupus (discoid lupus) is present in 26.8% and butterfly rash (malar lupus) in 15.5% of our patients. These results are lower than those reported in literature where up to 70% of people with lupus experience some skin symptoms. The three main categories of lesions are chronic (discoid) lupus, subacute cutaneous lupus, and acute cutaneous lupus. People with discoid lupus may develop thick, red, scaly patches on the skin. Similarly, subacute cutaneous lupus appears as red, scaly patches of skin but with distinct edges. Acute cutaneous lupus appears as a rash. Some have the classic rash (known as butterfly rash) associated with the disease[51] as this rash occurs in 30 to 60% of people with SLE[52]. Also, the butterfly rash (malar rash) that occurred in 15.5% of our patients is lower than what was previously reported in Yemen where malar rash was present in 52.3% of SLE patients[12] and lower than the results in Lebanon (52.0%) and Spain (54.0%)[53,54].

In the current study, the positive rate of Epstein - Barr virus IgG among our SLE patients was 97.2%, and 56.3% of them had high level of the antibody ≥ 51 IU which indicate active infections[2]. To clear this result, there is need to understand that, SLE is an autoimmune illness with no clear pathogenesis. This illness is characterized by polyclonal B cell activation and changed T cell function with the occurrence of impaired cell-mediated immunity and multiple auto-antibodies. It is understood that both environmental and genetic factors contribute to illness development[2]. Virus and bacterial infections are most important environmental factors that may be initiated and engaged in the pathogenesis of SLE. The EBV is of specific interest. It has been reported that Epstein–Barr nuclear antigen-1 (EBNA-1) has a elevated degree of homology with a number of proteins that produce an autoimmune humoral response[3,4]. This molecular mimicry may play an vital role in the introduction of antibodies by EBV infection in SLE patients. Newly, Harley *et al.*, accounted that almost half of SLE risk loci are occupied by the EBNA-2 protein and many co-cluster with transcription factors, provided that an vital new perspective on the mechanism of SLE pathogenesis[5].

The association in the current study between, the positive rate of Epstein-Barr virus IgG and SLE is similar to that reported by Evans *et al.*, in which the first positive connection between EBV infection and SLE was established in 1971[6]. Ever since, a lot of investigators have used a variety of angles to investigate the possibility of this connection. Nevertheless, preceding studies have been unsuccessful to find out a consistent association. The first and only systematic review that reorganized on the connection between SLE and sero-positivity for diverse EBV antibodies was that of Hanlon *et al.*,[7]. These authors discovered a statistically significant higher sero-prevalence of viral capsid antigen (VCA) IgG but not EBNA1 in cases compared with controls. Meta-analyses for early antigen (EA)/D IgG and VCA IgA also considerably confirmed higher ORs in cases compared with controls[7]. In addition, the association in the current study between, the positive rate of Epstein-Barr virus IgG and SLE can be explained by the some authors postulated that the increase in antibodies in SLE was brought about by generalized immune hyper-reactivity in lupus rather than by any specific property of the EBV[8,54]. So the best way to clarify this question would be at the DNA level estimation of EBV genome load.

Considering the gender in the current study, there was a significant negative association between the higher positive rate of Epstein-Barr virus IgG and male patients with the rate being only 33.3% compared to 61.7% for females (Table 4). The present results are

similar to those reported by Ulff-Møller *et al.*,[55] Shoenfeld *et al.*,[56] Chen *et al.*,[57] as the high level rate EBV among females with lupus erythematosus comparing to lower rate in SLE male patients. Considering the age in the current study, there was an association between a higher positive rate of Epstein-Barr virus IgG and an age group of 20-29 years where 77.1% of this group had a high level of EBV antibody, with an *OR* of 3.7, 95% *CI.*=1.4-8.3, *p*=0.004 (Table 4). While there was a low rate of high-level EBV antibodies in children and young adults (age less than 20 years). This result is similar to James *et al.*,[3] and Tsai *et al.*,[11] as slightly higher OR values were observed in the second decade SLE patients comparing with younger adults and pediatric patients. This may be due to the fact that in this age SLE patients tend to be more infected with EBV, which is consistent with James *et al.*,[3]. A high level of Epstein-Barr virus IgG antibodies was significantly associated with the incidence of clinical signs such as joint pain as the associated *odds ratio* was 8.4 with 95% *CI*=1-72, *p*=0.02; also with fever where the associated *odds ratio* was 15.2 with 95% *CI*=1.8 -122, *p*=0.001; in addition to joint swelling where the associated *odds ratio* was 3.6 with 95% *CI*=1.7 - 7.5, *p*=0.00006 (Table 5). These symptoms are usually associated with active EBV infection, so obtained results may indicate that most of our patients have active EBV infection and these findings were confirmed by Cohen[58] and Cohen *et al.*,[59] as these symptoms only accompany active cases among patients with SLE.

CONCLUSIONS

EBV may have an important role in SLE pathogenesis and activity, SLE male: female ratio equals 1:4.3, most patients were adults over 20 years of age, and the most common signs of SLE were joint pain, fever and persistent fatigue. Follow-up of patients with EBV infection is very important to assess the status of patients at risk of developing SLE. Further studies are needed to achieve a more comprehensive understanding of EBV as a trigger for SLE and other autoimmune diseases, severity of signs, risk factors, and characteristics of SLE patients. Finally, the study brings more clarity to the diagnosis of lupus erythematosus among the population of Yemen.

ACKNOWLEDGEMENT

The authors also would like to acknowledge the Ministry of Health and population, Sana'a, Yemen for support.

AUTHOR'S CONTRIBUTION

Al-Mansor MI: writing original draft, designed the study, literature searches. **Al-Moyed KAA:** statistical analysis, formal analysis. **Al-Shehari MM:** conceptualization, methodology. **Al-Shamahy HA:** methodology, supervision. **Al-gunaid EA:** editing, methodology. **Al-Haddad AM:** research design, data collection. All the authors reviewed the results and approved the final version of the manuscript.

DATA AVAILABILITY

The data supporting the findings of this study are not currently available in a public repository but can be made available upon request to the corresponding author.

CONFLICT OF INTEREST

There is no conflict of interest associated with this study.

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