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Varicella zoster virus infection increases the risk of developing SLE disease and the modulatory role of IL-10

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ABSTRACT

Herpes zoster (HZ) is a viral infection that occurs following an initial infection with the Varicella-zoster virus (VZV), which causes chickenpox. The virus remains latent in the nerve ganglia and can reactivate due to immune weakness or disorders in infected individuals. Systemic Lupus Erythematosus (SLE) is an autoimmune disease resulting from a specific immune disorder. Simultaneous infections of VZV and SLE have been reported in the literature. Additionally, most research published on scientific platforms has only compared samples from patients with SLE to those from healthy individuals. Through these two reasons above, three groups of patient samples were analyzed in this study: the first group consisted of individuals infected with herpes zoster, the second group included individuals with SLE, and the third group comprised healthy individuals. These groups and two immune markers interleukin-10 (IL-10) and IL-23 were compared with each other. The research aims to explore the potential underlying mechanisms that may link the reactivation of VZV and the presence of SLE, focusing on immunological and inflammatory pathways. The results of this research showed an increase in infections in females compared to males in both diseases. Moreover, there were no statistically significant differences between the two diseases when measuring the concentration levels of VZV IgG in each group of study models. However, there were statistically significant differences in the concentration levels of dsDNA antibodies between the groups, despite the small number of positive samples in the HZ group. As expected, there were statistically significant differences between both disease groups and the healthy group, with a negative correlation observed between the IL10 concentration levels in the HZ group and those in the SLE group.

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Introduction

Varicella-Zoster Virus (VZV), which causes chickenpox, is a mild, highly contagious disease primarily affecting children, characterized clinically by a generalized vesicular eruption of the skin and mucous membranes. The disease may be severe in adults and in immunocompromised individuals. Herpes-zoster (HZ), or shingles, is a sporadic, debilitating disease affecting elderly or immunocompromised individuals, characterized by pain and a vesicular rash limited to the skin innervated by a single sensory ganglion. The lesions are similar to those of varicella. Both diseases are caused by the same virus. While varicella is the acute disease following primary contact with the virus, zoster is the response of the partially immune host to the reactivation of the varicella virus

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present in a latent form in neurons in sensory ganglia (Riedel et al.2019). Both humeral and cell mediated immunity reactivate significantly with age against herpes-zoster virus (Ihsan & Talib, 2023; Hasan et al. 2023).

A higher incidence of herpes-zoster has been observed among bone marrow or stem cell transplant recipients (43.03/1000-person years) compared to solid organ transplant recipients (17.04/1000-person years). HIV, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), cancers, inflammatory bowel disease (IBD), multiple sclerosis, and psoriasis place a patient at higher risk for herpes-zoster (Chen et al. 2014).

Systemic lupus erythematous is a systemic autoimmune disease that can affect any part of the body, causing the immune system to attack the body's cells and tissues, resulting in inflammation and tissue damage. It is characterized by the presence of autoreactive B and T cells and the production of a broad, heterogeneous group of autoantibodies (auto-Ab) (Gordon & David 2016). Chemical substances, hormonal, and environmental factors can also trigger the disease. Abnormal regulation of T cells, impaired immune tolerance, abnormal response to autoantigens, and abnormal signal transmission between T cell receptors contribute to SLE autoimmunity (Hochberg et al. 2011).

Interleukin-10 (IL-10) positively affects B cell differentiation, proliferation, and autoantibody formation, and dysregulation in this cytokine is thought to be associated with many infectious and autoimmune diseases, including SLE (Peng et al. 2013).

Based on questions and gab arising from previous scientific literatures (Wu et al. 2011; Rincón-Delgado et al. 2021; Sundaresan et al. 2023), the potential association between the skin manifestations of herpes-zoster and the presence of SLE was investigated in this study. Additionally, the possible relationship between the inflammatory markers IL-10 and the occurrence of both herpes-zoster and SLE was explored. This study aims to elucidate the potential underlying mechanisms linking the development of Varicella-zoster Virus to the presence of SLE, focusing on immunological and inflammatory pathways.

Materials and Methods

Study design and sampling period

Between November 2023 and February 2024, a case-control study was conducted on three groups: patients with SLE, patients with VZV, and control subjects from AL-Hindia Hospital in Karbalaa city. A total of 120 individuals were included, comprising 40 SLE individuals (all female, aged 16–51 years), 40 VZV patients (17 males and 23 females, aged 15–60 years), and 40 healthy controls (20 males and 20 females, aged 15–66 years). None of the study participants had consumed alcohol or received antiviral treatment.

Blood sample collection

Each patient underwent a vein puncture to obtain a 5 mL sample of fresh blood, collected in anticoagulant-free blood tubes (Gel tubes) for serum preparation. The serum samples were separated by centrifugation for five minutes at 4000 rpm. Subsequently, they were aliquoted into sterile test tubes using a micropipette fitted with disposable, sterile tips. The serum samples were labeled with the patient's name and a serial number, which were then frozen at -70°C until further analysis. The investigations including immunological and diagnostic virological tests.

Kits and assay procedure

The study's kits, along with their manufacturer company and origins, are listed in Table 1. The tests were performed using the ELISA technique (four different procedures) on a manual ELISA device and the work steps were carried out according to the manufacturer's recommendations.

Table 1 The kits used in this study

No.	ELISA Kits	Manufacturer's	Origin
1	VZV-IgM	Vircell	Spain
2	VZV-IgG	Vircell	Spain
3	Anti-dsDNA	Demedetic	Germany
4	IL-10	Solarbio	China

Statistical Analysis

The well-known statistical program Graph Pad Prism version 5 was used. The split groups were compared using one-way analysis of variance (ANOVA) and Tukey's multiple comparisons test. The parameters were measured. The outcomes were reported as (mean ± standard error of mean). Correlation coefficients were calculated to determine relationships between parameters and markers. Correlation and descriptive statistics calculations were carried out using Excel 2010's Mega Stat (Mollysky 2003) (Version v10.12).

Results

Patient demographics

The current study included 120 clinical samples collected and analyzed at Alhindia Teaching Hospital in Holy Karbala, Iraq. These samples were divided into three groups: 40 patients with VZV, 40 patients with SLE, and 40 healthy control individuals, while the HZ samples had

slightly more female than male, and an equal numbers of male and female for the control samples. All SLE samples were from female patients. The herpes-zoster group had slightly more females than males, and the control group had an equal number of males and females.

Sociodemographic characteristics according to age and sex

In the current study, the three groups were divided into three age groups: 15–29 years, 30–44 years, and 45–59 years, with 40 individuals in each group. The results showed similar rates across the groups for shingles, with a slight increase in the 15–29 and 30–44 age groups compared to the 59–45 group. For SLE group, there was a slight increase in the 30–40 age group, followed by the 15–44 and 45–59 age groups, as shown in Figure 1.

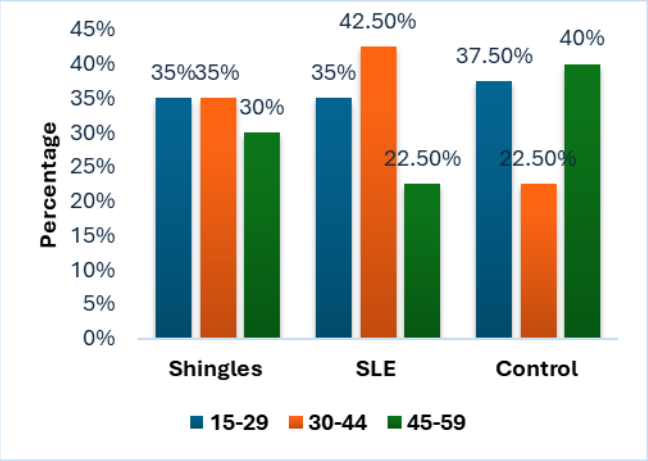

Fig 1. Number of clinical samples and its distribution according to age groups.

An equal distribution of males and females was reported in the control group to minimize sex differences between groups, as shown in Figure 2.

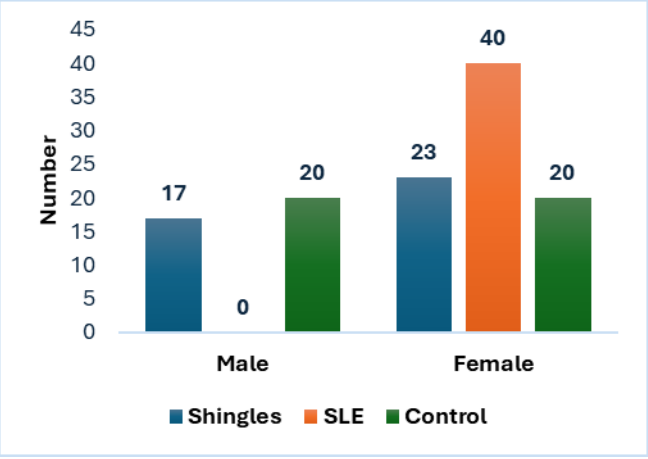

Fig 2. Number and distribution of clinical samples according to sex.

Diagnostic Markers

Varicella-zoster virus IgG concentration in all study groups.

Based on the findings of this investigation, as shown in Figure 3, there was a significant increase (P<0.05) *** in VZV-IgG levels in shingles group (herpes-zoster) were (30.69±5.771) compared with the control group (12.98±0.2314). There was no significant difference (P>0.05) in VZV-IgG levels in shingles group (30.69±5.771) compared with SLE patients (20.57±0.7782). Additionally, there was no significant difference (P>0.05) between SLE and control group.

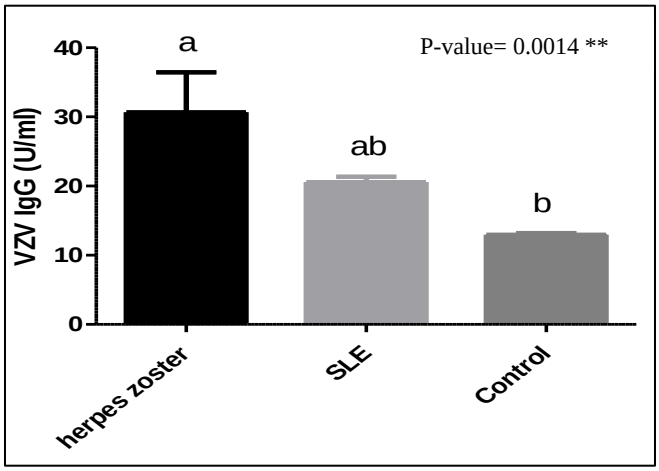

Fig 3. Varicella-zoster virus IgG concentration in all study groups. a, b: Meaning of different letter between groups (similar letters mean non-significant difference, different letters mean significant difference).

IgG concentration of Varicella-zoster virus in herpes-zoster samples by age groups.

Based on the findings of this investigation, as illustrated in Figure 4, no significant differences were found in the VZV-IgG levels between the age groups. Specifically, the VZV-IgG levels in the 15–29 age group (23.23±1.74) were not significantly different (P>0.05) from those in the 30–44 age group (41.43±16.3). Similarly, there was no significant difference (P>0.05) in VZV-IgG levels between the 15–29 age group (23.23±1.74) and the 45–59 age group (26.88±1.847). Furthermore, no discernible change (P>0.05) was observed between the 30–44 age group and the 45–59 age group.

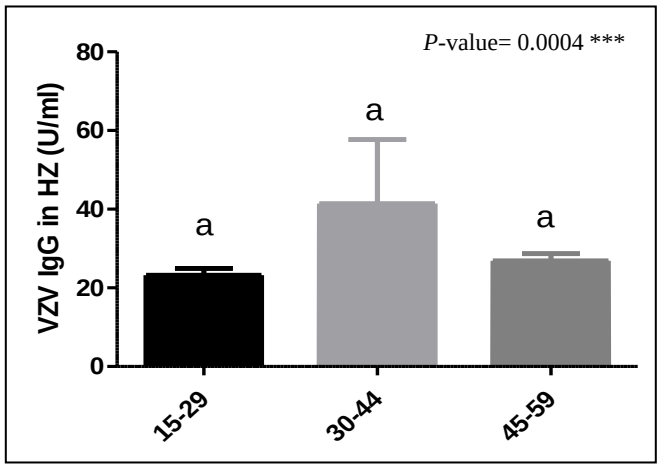

Fig 4. Varicella-zoster virus IgG concentration in herpes-zoster samples according to age groups. a, b, c: different letter means between groups (similar letters mean non-significant difference, different letters mean significant difference).

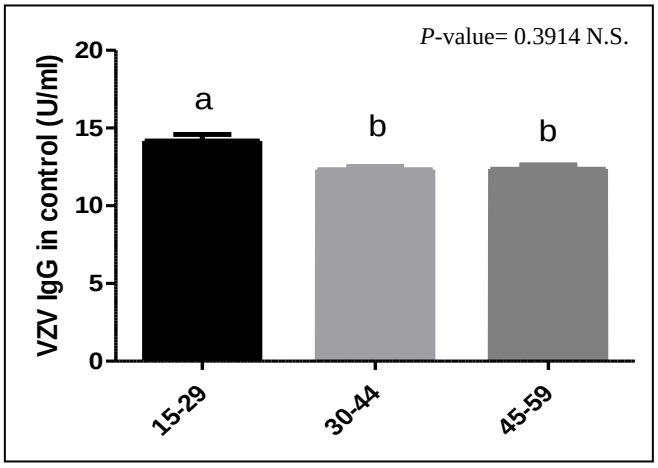

Fig 5. Varicella-zoster virus IgG concentration in control samples according to age groups. a, b: different letter means between groups (similar letters mean non-significant difference, different letters mean significant difference).

Detection of VZV IgG in SLE samples by age groups.

Based on the findings of this investigation as shown in Figures 4 and 5, the results indicated no significant difference (P>0.05) in VZV-IgG levels between the age group 15–29 (19.11±1.155) and the ages group 30–44 (21.52±1.173). Similarly, there was no significant difference (P >0.05) in VZV-IgG levels between the age group 15–29 (19.11±1.155) and the age group 45–59 (21.04±1.974), nor between the age group 30–44 and the age group 45–59, as shown in Table 2.

Table 2 Varicella-zoster virus IgG concentration in Systemic lupus erythematosus (SLE) samples according to age groups

VZV IgG (+)	Mean ±SEM	*P*- value
15–29	19.11±1.155	
30–44	21.52±1.173	0.3855 N.S.
45–59	21.04±1.974	

N.S. no significant difference; SEM: standard error of mean.

Varicella-zoster virus IgG concentration in Control samples according to age groups.

Based on the findings of this investigation as illustrated in Figure 5, the results demonstrated a significant increase in VZV-IgG levels in the age group 15–29 (14.17±0.4126) compared to the age group 30–44 (12.32±0.208). Additionally, there was a significant increase (P<0.05) ** in VZV-IgG levels in the age group 15–29 (14.17±0.4126) compared to the age group 45–59 (12.36±0.2545). There was no significant difference (P> 0.05) between the age group 30–44 and 45–59.

Varicella-zoster virus IgM concentration in all study groups.

Figure 6 and Table 3 showed that there was no significant difference (P>0.05) in VZV-IgM levels in herpes-zoster group (4.683±0.57) compared with the control group (4.173±1.089). Additionally, there was no significant difference (P>0.05) in VZV-IgM levels in herpes-zoster group (30.69±5.771) compared with SLE patients (4.86±0.3439), nor between the SLE and control group.

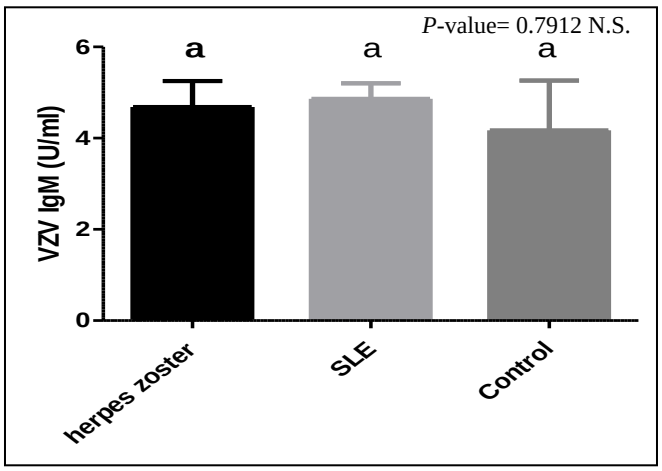

Fig 6. Varicella-zoster virus IgM concentration in all study groups a, b, c: different letter means between groups similar letters mean non-significant difference, different letters mean significant difference).

Table 3: Varicella-zoster virus IgM concentration in all study groups

VZV IgG/Shingles and SLE (+)	Mean ±SEM	*P*- value
Shingles Patients	4.683±0.57	
SLE Patients	4.86±0.3439	0.7912 N.S.
Control	4.173±1.089	

N.S. no significant difference; SEM: standard error of mean.

Varicella-zoster virus IgM concentration in herpes-zoster samples according to age groups.

Based on the findings of this investigation as showed in the Table 4, the results showed no significant difference (P>0.05) in VZV-IgM levels in the age group 15–29 (11.35±0.25) compared to the age group 30–44 (12.03±0.348). Furthermore, there was no significant difference (P>0.05) in VZV-IgM levels in the age group 15–29 (11.35±0.25) compared to the age group 45–59 (11.6±0.3). No significant difference in group 3 (P>0.05) between the age group 30–44 and 45–59.

Table 4 Varicella-zoster virus IgM concentration in herpes-zoster samples according to age groups.

VZV IgM (+)	Mean ±SEM	*P*- value
15–29	11.35±0.25	
30–44	12.03±0.348	0.4013 N.S.
45–59	11.6±0.3	

N.S. no significant difference; SEM: standard error of mean.

Immunological Markers Results

The analysis of immunological markers in serum samples from patients and control individuals showed a significant difference (P< 0.05) in some parameters, while other parameters showed no significant difference (P> 0.05) in others. Multiple serological markers were assessed, some diagnostic to verify the classification of study participants into known groups, and specific inflammatory markers were measured simultaneously in all groups to conduct the study.

Detection of Anti-dsDNA Ab concentration in all study groups

From the screening of anti-dsDNA in all study groups, the results in Figure 7 showed that 27.5% of the herpes-zoster samples were positive, while 72.5% were negative. There were no positive result in the control samples, and all samples (100%) in the SLE group were positive.

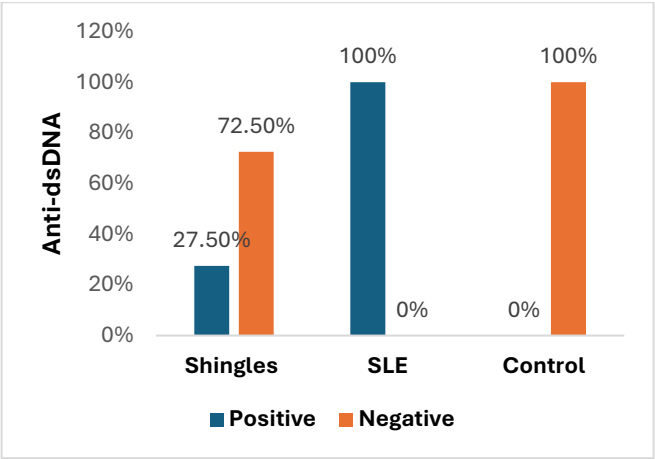

Fig 7. Detection of anti-dsDNA Ab concentration in all study groups.

Anti-dsDNA concentration in all study groups.

The results of the current study, as showed in Figure 8 and Table 5, showed a significant increase (P<0.05) *** in the anti-dsDNA Ab levels in herpes-zoster patients (17.14±1.451) compared to the SLE patients (153.4±16.18). Additionally, significant difference (P<0.05) *** in anti-dsDNA Ab levels in SLE patients (153.4±16.18) compared to control group (6.015±0.9658). There was no significant difference (P> 0.05) between herpes-zoster patients and control group.

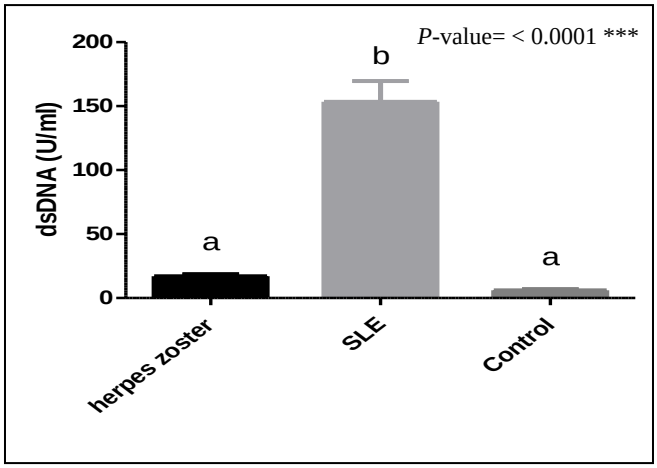

Fig 8. The anti-dsDNA Ab concentration in all study groups. a, b, c: different letter means between groups (similar letters mean non-significant difference, different letters mean significant difference).

Table 5 Anti-dsDNA Ab concentration in all study groups.

ds-DNA/Shingles and SLE (+)	Mean ±SEM	*P*- value
Shingles group	17.14±1.451	
SLE group	153.4±16.18	< 0.0001 ***
Control group	6.015±0.9658	

P<0.05: statistically significant difference; SEM: standard error of mean.

The relation of Interleukin 10 (IL-10) concentration in all study groups

Based on the findings of this investigation as showed in Figure 9 and Table 6, the results showed significant difference (*P*<0.05) *** in IL-10 levels in herpes-zoster patients (91.83±8.939) compared to the control group (41.59±1.504). Additionally, a significant difference (*P*<0.05) *** in IL-10 levels in SLE patients (22.21±0.7389) compared to control group (41.59±1.504). There was a significant difference (*P* <0.05) * between SLE and herpes-zoster patients.

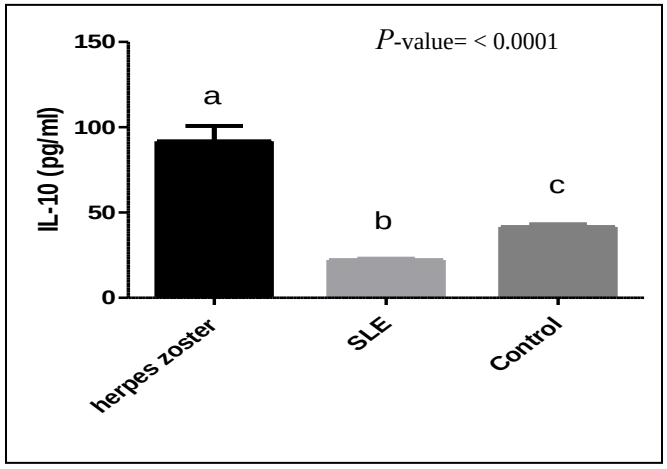

Fig 9. The interleukin 10 (IL-10) concentration in all study groups. a, b, c: different letter means between groups (While distinct letters indicate a significant difference, similar letters indicate a non-significant difference).

Table 6: The interleukin 10 (IL-10) concentration in all study groups.

IL-10/Shingles and SLE (+)	Mean ±SEM	*P*- value
Shingles group	91.83±8.939	
SLE group	22.21±0.7389	< 0.0001 ***
Control group	41.59±1.504	

P<0.05: statistically significant difference; SEM: standard error of mean.

Correlation between biological markers in all study groups

Figure 10 indicates a negative correlation between IL-10 in SLE patients and HZ patients. In contrast, Figure 11 and Figure 12 illustrate a positive correlation between IL-10 and VZV IgM and IgG in patients with SLE, respectively. Additionally, Figure 13 and Figure 14 show a positive correlation between IL-10 and VZV IgM and IgG in patients with HZ, respectively.

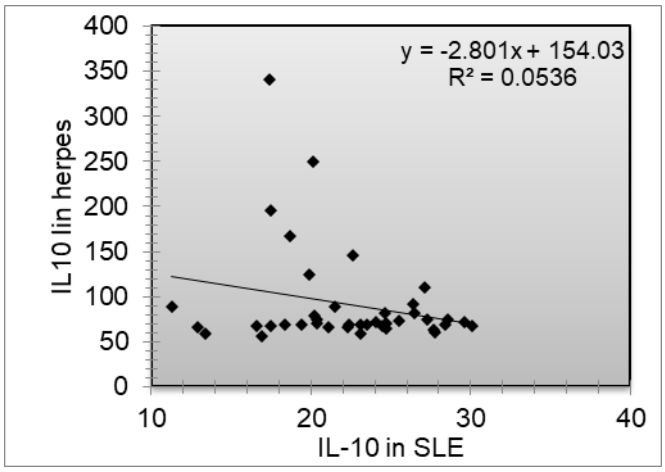

Fig 10. Correlation between increasing the level of IL-10 in patients with SLE and herpes-zoster.

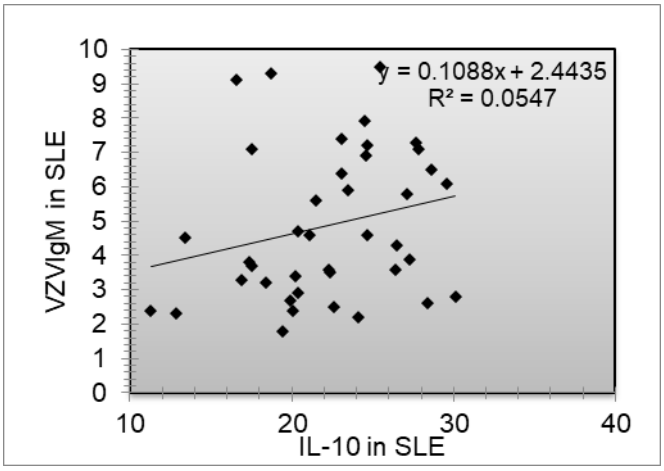

Fig 11. Correlation between increasing the level of IL-10 and VZV IgM in patients with SLE.

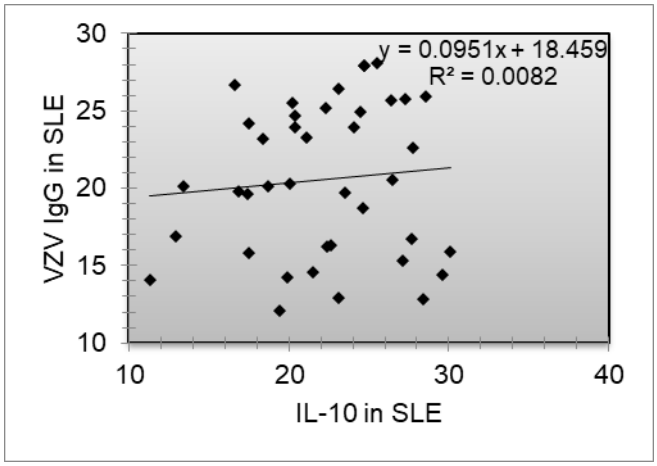

Fig 12. Correlation between increasing the level of IL-10 and VZV IgG in patients with SLE.

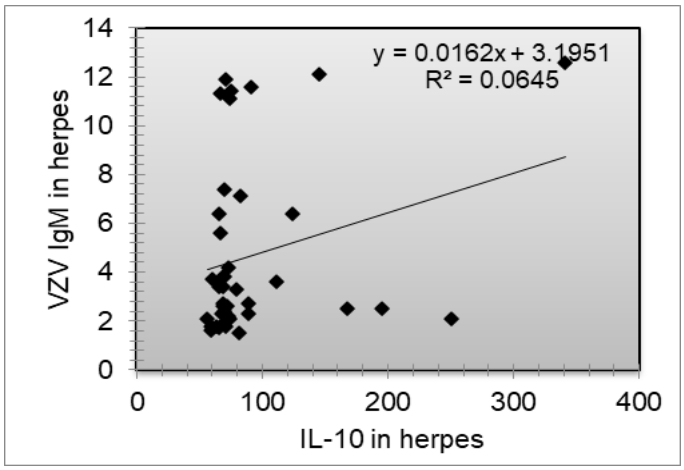

Fig 13. Correlation between increasing the level of IL-10 and VZV IgM in patients with HZ.

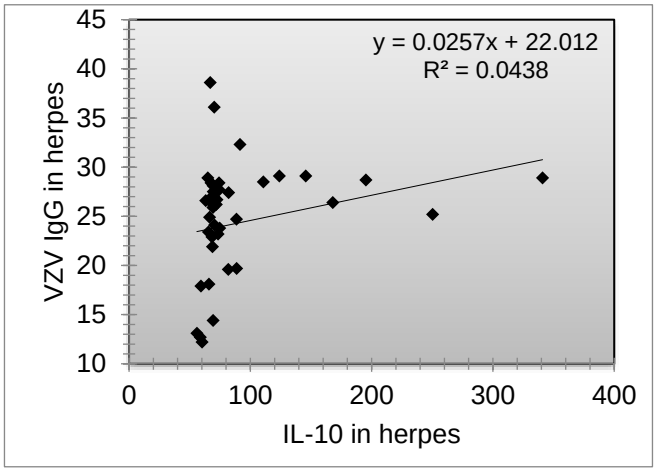

Fig 14. Correlation between increasing the level of IL-10 and VZV IgG in patients with HZ.

Discussion

The age group distribution for shingles was nearly equal, which is an unexpected result since shingles typically tends to affect the elderly who have weakened immune systems and less ability to fight off infections. This observation is supported by a study indicating that individuals over 50 years old are at increased risk of developing shingles due to the decline in VZV-specific cell-mediated immunity with age (Yawn & Gilden 2013). Other studies corroborate that older individual, particularly those with chronic diseases, are more likely to experience shingles. It is well-known that cancer patients and the elderly have decreased cell-mediated immunity, making shingles more common in these populations (Zajkowska et al. 2016). The age differences between the shingles and healthy control groups were not statistically significant (P> 0.05) (Gu et al. 2023). The equal distribution of the shingles sample in this study may be attributed to various factors, including ethnic variation, the microbial environment of each population, immune system status, and stressful conditions, all of which need to be evaluated and studied.

For SLE, the incidence tends to peak during the childbearing years (15–45 years). In women, the incidence increases significantly at the age of 20–25 years, with a second local maximum at menopausal age (Brinks et al. 2016). Thus, the age distribution in this study aligns with most studies. For the control group, the age distribution was different and occurred by chance due to exclusion criteria. As expected, the SLE samples were all females. Approximately 90–95% of SLE patients are female, with a female-to-male ratio ranging from 9:1 (Rider et al. 2018). Another study found the female-to-male ratio in SLE patients to be approximately 9:1 (Izmirly et al. 2017). The shingles samples had slightly more females than males. Supporting evidence for this finding is a meta-analysis that demonstrated a decreased incidence in males relative to females and an increase with age (Curran et al. 2022). The increased risk in females is not clearly understood and may be related to various factors, such as differences in immune function, psychological status, hormonal influences in females, and others.

The Varicella-zoster virus IgG level, as a diagnostic marker for herpes-zoster infection, was significantly increased in the HZ group (shingles) compared to the other two groups, SLE and controls. There was a significant difference (P< 0.05) compared to controls with no significant difference (P > 0.05) compared to SLE patients. This result is supported by studies such as Min et al. (2023), which demonstrated that VZV IgG levels were noticeably higher in the HZ group during both the acute and convalescent phases than in the healthy control group. Another study found that clinical VZV reactivation can

endogenously boost VZV antibody levels, with the degree of boosting depending on the initial level of viral replication (Warren-Gash et al. 2018). Patients with HZ had markedly increased VZV IgG antibody titers, which could be anticipated given the emergence of HZ lesions and VZV reactivation increasing the virus's antibody level (Zajkowska et al. 2016). In the SLE group, the increase in VZV IgG titer may result from previous immunity to VZV and/or frequent VZV reactivation, which affects SLE patients due to impaired immune systems. In addition to hypergammaglobulinemia, as indicated by Rondaan et al. (2018).

This is supported by a study showing HZ incidence to be 5 to 16 times higher in SLE patients than in the general population, related to the use of immunosuppressant medication (Chakravarty et al. 2013).

Elevated VZV-IgG levels in SLE are not linked to lupus disease activity and are not the result of frequent subclinical VZV reactivations. Hypergammaglobulinemia only partially explains the increased VZV-IgG levels (Rondaan et al. 2018). For healthy controls, the increased VZV-IgG levels are clearly due to previous VZV infection during childhood.

The VZV-IgM levels were nearly equal in all study groups with no significant difference between them. This can be easily explained for the first group, as most HZ patients were studied in the early stage of shingles flare-up within 5 days. The previous IgG antibodies were formed many years ago during the first infection with chickenpox, so the adaptive immune response had not yet activated to secrete new IgM antibodies or even class-switch existing IgG antibodies to the IgM type. A 2019 study showed that the VZV-specific IgG test was positive while the IgM VZV test was negative, with real-time polymerase chain reaction (PCR) analysis confirming the presence of VZV (Costa-Silva et al. 2019). Another study suggested that the serological diagnosis of VZV IgM to confirm herpes-zoster is only beneficial within 3.5 weeks after symptom onset (Min et al. 2016).

For the SLE and control groups, the VZV-IgM level is expected to be negative unless SLE patients experience reactivation of dormant Varicella-zoster virus, leading to a more severe infection due to impaired immune response.

As is well-known, patients with SLE have increased levels of anti-dsDNA antibodies according to disease activity, so high levels of this antibody need no interpretation in the SLE group (active disease or no proper treatment). This point is supported by many studies, one of which mentioned that antibodies to dsDNA are useful for diagnosing SLE, monitoring disease activity, and correlating with renal and central nervous system involvements (Cozzani et al. 2014). Another study highlighted the crucial role of dsDNA antibodies in the identification, categorization, and treatment of SLE (Infantino et al. 2021). For the HZ and control groups, they were negative overall, except for a small number in the HZ group (4 out of 40 patients), who were positive for anti-dsDNA antibodies but with a mild increase in titer compared to the SLE group. This increase should be investigated further, as those patients may have undiagnosed or early-stage SLE, or there might be cross-reacting proteins.

The results were evident: IL-10 levels in herpes-zoster patients were significantly higher ($P< 0.05$) compared to the control group, and this difference was also statistically significant ($P< 0.05$). There was a significant difference ($P< 0.05$) between SLE and herpes-zoster patients, with increased IL-10 levels in SLE patients compared to the control group. Immune cells such as macrophages, T lymphocytes, and natural killer cells produce IL-10, a multifunctional immune-regulatory cytokine with both immunosuppressive and anti-angiogenic properties (Sheikhpour et al. 2018). IL-10 is a cytokine that reduces inflammation and controls the immune system (Acuner-Ozbabacan et al. 2014), preventing antigen-presenting cells (APCs) from acting pro-inflammatory by expressing antagonistic costimulatory molecules (Li et al. 2014). Additionally, Fortis et al. (1996) highlighted IL-10's crucial role in regulating inflammatory reactions, infection progression, autoimmunity, transplantation tolerance, and carcinogenesis. It is also referred to as cytokine synthesis inhibitory factor (Hamidullah & Konwar, 2012).

Regarding this study, specifically the HZ group, a meta-analysis provided evidence that IL-10 is associated with the genesis and development of HZ. This marker can be used to improve the diagnosis and treatment of the disease (Yue & Yao 2024). Another study found that patients with severe HZ had significantly higher serum IL-10 levels than patients with mild-to-moderate HZ, suggesting that serum IL-10 levels serve as an objective biomarker for HZ severity (Fukuyasu et al. 2021). According to another study, IL-10 levels in HZ patients were noticeably higher than those in controls (Yue & Yao 2024). For the SLE group, the results show low levels of serum IL-10. SLE is an autoimmune disease with multiple pathologies, and IL-10 is known to suppress inflammatory cytokines (Trifunović et al. 2015). Thus, low IL-10 levels might be expected due to the exhaustion of this cytokine in suppressing the inflammatory process or due to anti-IL-10 antibody formation. Studies supporting these findings include:

Reports that IL-10 inhibits neurological, arthritic, and nephritic symptoms in an SLE mouse model, suggesting low IL-10 levels may be linked to active SLE (Matsushita 2010; Yin et al. 2002). Indications that low IL-10 levels are due to the presence of anti-IL-10 antibodies and reduced

IL-10 production, with numerous autoimmune symptoms linked to antibodies against cytokines (Bonfield et al. 2002). Conversely, Godsell et al. (2016) found high IL-10 levels in SLE patients, potentially related to increased IL-10 production or the effect of anti-IL-10 receptor antibodies or the positive feedback of anti-IL-10 antibodies. The interpretation of increased IL-10 in both SLE and shingles cases could vary. In SLE, IL-10 may reflect an active suppression of inflammation, while in shingles, it might indicate a response to viral infection. Further studies are necessary to understand the precise role and regulation of IL-10 in these conditions.

Conclusion

In recent years, there has been a significant outbreak of shingles, representing the reactivation of the dormant VZV due to various factors, such as a weakened immune system and ongoing life stresses. Shingles has spread widely among both males and females. The expected age for shingles reactivation is not notable in our population. A high percentage of individuals with shingles develop the autoimmune disease SLE, confirmed by anti-dsDNA antibody testing. SLE, an autoimmune disease, is associated with various conditions that weaken the immune response and may lead to the reactivation of latent viruses such as VZV. IL-10 plays dual roles as both a pro-inflammatory and an anti-inflammatory cytokine, and its levels were significantly increased in patients with both shingles and SLE.

Ethical approval

All the participants provided informed consent for inclusion in the study and were assured that all the information provided would be used solely for the purposes of this study and treated confidentially

Conflict of interest

The authors declare that they have no conflict of interest.

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