



Prevalence of Vitamin D Deficiency and its Association with Disease Activity in Patients with Systemic Lupus Erythematosus: A Cross-Sectional Study from Southeast Iran

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ABSTRACT

Background: vitamin D plays a critical immunomodulatory role, and its deficiency has been consistently associated with the pathogenesis and activity of various autoimmune diseases. Despite high ambient sunlight in Southeast Iran, sociocultural factors and disease-related sun avoidance may increase hypovitaminosis D risk in patients with systemic lupus erythematosus (SLE).

Objective: To determine the prevalence of vitamin D deficiency among patients with SLE in Zahedan, Iran, and to evaluate its association with disease activity.

Methods: We conducted a cross-sectional study of 100 adult SLE patients at a major referral center. We measured disease activity using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). Blood samples were tested for 25-hydroxyvitamin D [25(OH)D] levels using a chemiluminescence immunoassay. We grouped patients into three categories: deficient (below 20 ng/mL), insufficient (20–29.9 ng/mL), or sufficient (30 ng/mL or above). Data were analyzed using Spearman's correlation and one-way ANOVA.

Results: The mean serum 25(OH)D level was 22.9 ± 12.2 ng/mL. Only 23% of patients exhibited sufficient vitamin D levels, whereas the remaining 77% demonstrated suboptimal levels (33% deficient, 44% insufficient). A significant inverse correlation was observed between serum 25(OH)D levels and SLEDAI-2K scores ($r = -0.375$, $p < 0.001$). Furthermore, vitamin D levels demonstrated a graded decline with increasing disease severity; patients with high disease activity had significantly lower mean 25(OH)D concentrations compared to those with mild activity (11.95 ± 7.96 ng/mL vs. 25.18 ± 13.03 ng/mL; $p = 0.048$).

Conclusion: Vitamin D deficiency is highly prevalent in SLE patients in Southeast Iran and is significantly associated with greater disease activity. Routine screening and further research into vitamin D supplementation are warranted.

Keywords: Disease Activity; Lupus Erythematosus, Systemic; Vitamin D Deficiency

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Cite this article as:

Nosratzehl M, Baluchzehl Z,
Nosratzehl S. Prevalence of
Vitamin D Deficiency and its
Association with Disease Activity
in Patients with Systemic Lupus
Erythematosus: A Cross-Sectional
Study from Southeast Iran. *Iran J
Immunol.* 2026; 23(3): ,
doi: 10.22034/iji.2026.110428.3176.

Received: 2025-10-09

Revised: 2026-06-24

Accepted: 2026-07-17

INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic chronic autoimmune disease characterized by loss of immune tolerance, autoantibody production, and immune-mediated inflammation leading to multisystem involvement (1). The disease course is typically characterized by fluctuating activity with unpredictable flares and remissions, and despite substantial therapeutic advances, many patients continue to experience significant morbidity and progressive organ damage (2, 3). Accordingly, the identification of modifiable factors influencing disease activity remains a priority in both clinical management and translational research efforts (3).

Vitamin D, a secosteroid hormone classically involved in calcium and bone metabolism, has garnered considerable attention in recent years for its pleiotropic immunomodulatory properties (4). The biologically active metabolite, 1,25-dihydroxyvitamin D₃, exerts its effects through the vitamin D receptor (VDR) that is widely expressed on immune cells, including dendritic cells, T lymphocytes, and B lymphocytes (5). Activation of the VDR signaling pathway promotes immune tolerance by inhibiting dendritic cell maturation, suppressing pro-inflammatory T helper 1 and T helper 17 responses, enhancing regulatory T-cell function, and reducing B-cell activation and autoantibody production (6, 7). These mechanisms provide a biologically plausible link between vitamin D status and autoimmune disease activity in SLE (8, 9).

Supporting this immunological paradigm, epidemiological studies have consistently reported a high prevalence of vitamin D deficiency and insufficiency among patients with SLE, frequently exceeding that observed in the general population (10). Hypovitaminosis D in SLE appears to be multifactorial, resulting from photosensitivity-related sun avoidance, routine use of

sunscreens, chronic inflammation, and renal involvement with urinary loss of vitamin D-binding protein, and glucocorticoid-induced alterations in vitamin D metabolism (11). Critically, numerous observational studies have demonstrated an inverse association between serum 25-hydroxyvitamin D [25(OH)D] levels and disease activity, as assessed by validated indices such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (12, 13).

Recent investigations have extended these findings by demonstrating that lower serum 25(OH)D levels are associated not only with higher disease activity but also with greater cumulative organ damage in adult SLE populations (14, 15). Additionally, studies examining seasonal fluctuations in vitamin D status have shown that vitamin D sufficiency is associated with an increased likelihood of achieving a lupus low disease activity state, suggesting a potential role for vitamin D in disease stabilization (16). Evidence from pediatric and early-onset SLE cohorts further supports this association, with lower vitamin D levels correlating with higher disease activity and increased renal involvement, indicating that vitamin D deficiency may exert its effects from the earliest stages of disease (14).

Despite these observations, the clinical implications of vitamin D deficiency in SLE remain incompletely elucidated. The majority of available evidence are observational, precluding definitive conclusions regarding causality, and interventional studies evaluating vitamin D supplementation have yielded conflicting and heterogeneous results. Moreover, vitamin D status is strongly influenced by geographical, environmental, and sociocultural factors, including latitude, ultraviolet B exposure, clothing practices, skin pigmentation, and lifestyle behaviors (17). Consequently, the prevalence and clinical impact of vitamin D deficiency in SLE may vary substantially across regions and populations. Addressing this knowledge gap may help inform region-specific clinical

practice and support the integration of vitamin D assessment into routine SLE management. Accordingly, the present study was designed to determine the prevalence of vitamin D deficiency and insufficiency among patients with SLE in Zahedan, Southeast Iran, and to evaluate the association between serum 25-hydroxyvitamin D [25(OH)D] levels and disease activity, as measured by the SLEDAI-2K.

MATERIALS AND METHOD

Study Design and Setting

A cross-sectional study was conducted from March 2023 to March 2024 at the Rheumatology Clinic of Ali Ibn Abi Taleb Hospital, the main tertiary referral center in Zahedan, Sistan and Baluchestan Province, Southeast Iran. This clinic serves a large catchment area, including both urban and rural populations.

Study Population and Eligibility Criteria

Consecutive adult patients (≥ 18 years) with a diagnosis of systemic lupus erythematosus (SLE) who were newly referred to the rheumatology clinic during the study period were assessed for eligibility. All participants fulfilled the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for SLE (18).

Exclusion criteria were carefully defined to minimize potential confounding of serum vitamin D status or its relationship with disease activity. Patients were excluded if they had used vitamin D supplements at doses exceeding 400 IU/day, or calcium–vitamin D combination preparations, within the preceding six months. Individuals with gastrointestinal disorders affecting intestinal absorption or vitamin D metabolism, including inflammatory bowel disease, celiac disease, chronic diarrhea, or a history of bariatric or major gastrointestinal surgery, were not eligible. Pregnant or lactating women were

excluded due to physiological alterations in vitamin D metabolism. Patients with advanced chronic kidney disease (stage 4 or 5, defined as an estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²) or hepatic failure were also excluded, as these conditions independently impair renal 1 α -hydroxylation and hepatic 25-hydroxylation of vitamin D. In addition, individuals who had received a blood transfusion within the previous six months or who were using antiepileptic medications known to induce vitamin D catabolism (including phenobarbital and phenytoin), were excluded from the study.

Study Population and Sample Size

During the study period, 100 consecutive patients with SLE were enrolled. The sample size was considered adequate to estimate the prevalence of vitamin D deficiency and to assess its overall association with disease activity, based on feasibility and prevalence estimates reported in previous cross-sectional studies of comparable SLE populations (19). All data were systematically collected using a structured case report form (CRF) specifically designed for the study objectives.

2.4. Clinical Assessment and Disease Activity

Patient demographic and clinical data, including age, sex, and disease duration from the time of diagnosis, were recorded. Disease activity was evaluated by a rheumatologist using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), based on clinical and laboratory manifestations present within the 10 days preceding enrollment (20). For analytical purposes, disease activity was stratified according to established cutoffs: no activity (SLEDAI-2K = 0), mild activity (SLEDAI-2K = 1–4), moderate activity (SLEDAI-2K = 5–10), and high activity (SLEDAI-2K > 10).

Laboratory Measurements

To determine vitamin D status, a 5 ml fasting venous blood sample was collected from each participant, with the serum separated and stored at -80°C until

analysis. Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured using a standardized chemiluminescence immunoassay (CLIA) on a Liaison XL analyzer (DiaSorin, Italy) within a laboratory participating in an external quality assurance program. Vitamin D status was classified according to the Endocrine Society Clinical Practice Guidelines, where deficiency was defined as 25(OH)D < 20 ng/mL (< 50 nmol/L), insufficiency as 20–29 ng/mL (50–74 nmol/L), and sufficiency as 30 ng/mL (75 nmol/L). Vitamin D deficiency served as the primary exposure variable in this study. Additional laboratory parameters relevant to SLE activity were extracted from medical records, provided they were performed within the 10-day window of the SLEDAI assessment. These included anti-dsDNA antibody titers measured by ELISA, complement C3 and C4 levels, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Exploratory correlation analyses were performed to assess associations between serum 25(OH)D levels and serological markers of disease activity.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of Zahedan University of Medical Sciences (Approval Code: IR.ZAUMS.REC.1403.463). The study was conducted in full accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants after a detailed explanation of the study's objectives, procedures, potential benefits, and risks. Participants were assured of the confidentiality of their data and their right to withdraw from the study at any time without affecting their standard of care.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY: IBM Corp). The normality of continuous data was assessed using the Kolmogorov-Smirnov test. Descriptive statistics are presented as mean $\pm$ standard

deviation (SD) for normally distributed variables and as median with interquartile range (IQR) for non-normally distributed data. Categorical variables are expressed as absolute frequencies and percentages.

The prevalence of vitamin D deficiency and insufficiency was calculated with 95% confidence intervals (CI). For comparisons of quantitative variables between two groups (e.g., sufficient vs. deficient), the independent samples Student's t-test or the Mann-Whitney U test was employed for normal and non-normal distributions, respectively. Comparisons across more than two groups, such as SLEDAI-2K activity categories, were conducted using one-way ANOVA followed by Tukey's post-hoc test, or the Kruskal-Wallis test, as appropriate. Associations between categorical variables were analyzed using the Chi-square test or Fisher's exact test.

The correlation between continuous serum 25-hydroxyvitamin D [25(OH)D] levels and SLEDAI-2K scores was evaluated using Spearman's rank correlation coefficient (ρ), given the non-normal distribution of disease activity scores. Correlation strength was interpreted as weak ($|\rho| < 0.30$), moderate ($|\rho| = 0.30–0.59$), or strong ($|\rho| \geq 0.60$). All statistical tests were two-tailed, and exact p-values are reported. A p-value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of the Study Population

During the study period, 100 eligible patients with SLE were enrolled. The cohort was predominantly females (n=90, 90%), with a mean age of 39.5 ± 12.1 years (range: 18–75 years). The median disease duration was 2.5 years (IQR: 1–5 years). The mean SLEDAI-2K score was 4.1 ± 3.3 , with a median of 5 (IQR: 2–7), indicating low to moderate disease activity in the overall cohort. Stratification by disease activity categories revealed that 65 patients (65%) exhibited mild

activity (SLEDAI-2K 1–4), 31 patients (31%) demonstrated moderate (SLEDAI-2K 5–10), and 4 patients (4%) had high disease activity (SLEDAI-2K > 10).

Prevalence of Vitamin D Deficiency

The mean serum 25-hydroxyvitamin D (25(OH)D) level was 22.9 ± 12.2 ng/mL (range: 2–50 ng/mL). The median level was 22.45 ng/mL (IQR: 12.55–31.40 ng/mL). As presented in Table 1, only 23 patients (23.0%) had sufficient vitamin D levels (≥ 30 ng/mL). The remaining 77 patients (77.0%) exhibited suboptimal levels, comprising 44 patients (44.0%) with insufficiency (20–29.9 ng/mL), and 33 patients (33.0%) with deficiency (<20 ng/mL). Notably, severe deficiency, defined as 25(OH)D < 10 ng/mL, was observed in 19 patients (19.0%).

Between Vitamin D Status and Disease Activity

As illustrated in Figure 1, a clear gradient in serum 25(OH)D concentrations was observed across the strata of disease activity. Patients with inactive disease exhibited the highest mean levels at 28.0 ng/mL, which progressively declined to 22.5 ng/mL in those

with mild-to-moderate activity and further decreased to 15.0 ng/mL in patients with high disease activity. Analysis of the relationship between vitamin D status and disease activity revealed a statistically significant moderate inverse correlation between serum 25(OH)D levels and SLEDAI-2K scores (Spearman's $\rho = -0.375$, $p < 0.001$), indicating that lower vitamin D concentrations were associated with higher global disease activity.

Mean serum 25(OH)D levels decreased progressively across disease activity categories (Table 2). Patients with high disease activity exhibited markedly lower vitamin D levels compared with those with mild activity (11.95 ± 7.96 ng/mL vs. 25.18 ± 13.03 ng/mL; $p = 0.048$, one-way ANOVA with Tukey's post-hoc test). Given the small number of patients with high disease activity ($n = 4$), this finding should be interpreted as preliminary and hypothesis-generating rather than confirmatory.

Association between Vitamin D Status and Demographic Factors

Analysis of demographic variables revealed no significant linear correlation between patient age and serum 25(OH)D levels (Pearson's $r =$

Table 1. Distribution of Serum 25-Hydroxyvitamin D Levels Among Patients with Systemic Lupus Erythematosus (N = 100)

Vitamin D Status	Serum 25(OH)D (ng/mL)	Frequency, n (%)
Sufficient	≥ 30	23 (23.0%)
Insufficient	20 – 29.9	44 (44.0%)
Deficient	< 20	33 (33.0%)
Severe Deficiency	< 10	19 (19.0%)

Table 2. Association between Serum 25(OH)D Levels and SLE Disease Activity Categories (N=100)

Disease Activity (SLEDAI-2K)	n (%)	Mean 25(OH)D $\pm$ SD (ng/mL)	95% CI of Mean
Mild (1-4)	65 (65%)	25.18 ± 13.03	22.0 – 28.4
Moderate (5-10)	31 (31%)	20.04 ± 12.12	15.6 – 24.5
High (>10)	4 (4%)	11.95 ± 7.96	3.8 – 20.1

Data are presented as mean $\pm$ SD. Differences among disease activity categories were evaluated using one-way ANOVA, followed by Tukey's post hoc test. The reported p-value refers to the Tukey-adjusted pairwise comparison between the mild- and high-activity groups ($p = 0.048$)

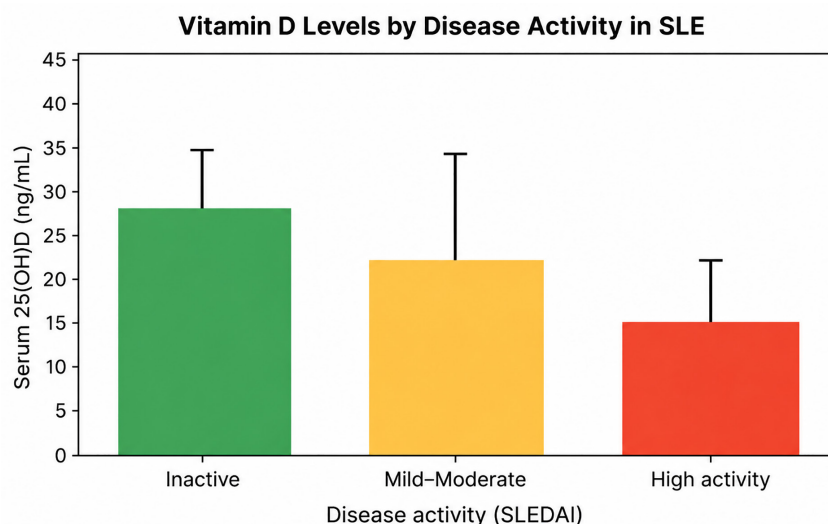


Figure 1. Mean serum 25-hydroxyvitamin D levels across SLE disease activity categories. Bars represent mean serum 25-hydroxyvitamin D (25(OH)D) concentrations, and error bars indicate standard deviations (mean $\pm$ SD). Patients were categorized according to the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) as having inactive disease, mild-to-moderate disease activity, or high disease activity. Mean serum 25(OH)D levels progressively decreased from 28.0 ng/mL in patients with inactive disease to 22.5 ng/mL in those with mild-to-moderate activity and 15.0 ng/mL in those with high disease activity. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

-0.011, $p = 0.914$). Regarding sex, although male patients exhibited a numerically higher mean 25(OH)D concentration compared with female patients (27.97 ± 14.49 ng/mL vs. 22.65 ± 12.68 ng/mL, respectively), this difference did not reach statistical significance ($p = 0.218$, Independent samples t-test).

Exploratory Analysis: Association with Serological Markers

In an exploratory analysis, lower serum 25(OH)D levels demonstrated a non-significant trend toward inverse correlation with anti-dsDNA titers ($\rho = -0.25$, $p = 0.08$) and a positive correlation with C3 complement levels ($\rho = 0.22$, $p = 0.11$). No significant correlations were observed between serum 25(OH)D levels and C4, ESR, or CRP.

DISCUSSION

This cross-sectional study provides the first comprehensive evaluation of vitamin D status and its association with disease

activity among patients with systemic lupus erythematosus (SLE) in Zahedan, Southeast Iran. Two principal findings emerge from this investigation. First, we observed a strikingly high burden of hypovitaminosis D, with more than three-quarters of patients exhibiting suboptimal serum 25-hydroxyvitamin D (25(OH)D) levels and one-third meeting criteria for frank deficiency. Second, lower serum 25(OH)D concentrations were significantly associated with higher disease activity, as assessed by SLEDAI-2K, indicating a clinically relevant inverse relationship between vitamin D status and lupus activity in this population.

The prevalence of vitamin D deficiency observed in our cohort (33%) is consistent with reports from other SLE populations worldwide, where deficiency rates generally range from 20% to 60% (21-23). A large systematic review and meta-analysis encompassing 43 studies and nearly 3,000 patients demonstrated significantly lower vitamin D levels in SLE patients compared with healthy controls, reinforcing the notion that hypovitaminosis D is a pervasive feature

of SLE irrespective of ethnicity or geographic location (8). Our prevalence rate is comparable to those reported in studies from Egypt and the United States, which documented vitamin D deficiency rates of 40% and 67%, respectively, in multi-ethnic cohorts (24, 25). Notably, the proportion of patients with suboptimal vitamin D levels (<30 ng/mL) in our study (77%) exceeds that reported in several Western European cohorts (21, 26, 27). This apparent discrepancy underscores the importance of contextual, non-latitudinal determinants of vitamin D status. Despite high ambient solar radiation in Southeast Iran, cultural practices involving extensive photoprotective clothing, limited outdoor activity, and strict sun avoidance—often recommended to patients with photosensitive autoimmune disease—likely contribute to a paradoxical “high sun–high deficiency” environment (28). These findings highlight that assumptions based solely on latitude or climate may substantially underestimate vitamin D deficiency risk in SLE.

The inverse correlation between serum 25(OH)D levels and SLE disease activity is concordant with a substantial body of observational evidence from Asia, the Middle East, and Europe (27, 29, 30). Importantly, while this association was observed across disease activity categories, the finding in the subgroup with high disease activity should be interpreted cautiously. This group comprised only four patients, and therefore the observed differences must be regarded as preliminary and hypothesis-generating rather than definitive, a limitation inherent to the sample distribution. Nevertheless, the overall trend across activity strata supports a biologically coherent relationship between vitamin D deficiency and heightened disease activity.

From a mechanistic perspective, this association is biologically plausible. Vitamin D exerts pleiotropic immunomodulatory effects through the vitamin D receptor (VDR), which is expressed on key immune cells implicated in SLE pathogenesis. Adequate

vitamin D signaling promotes regulatory T cell (Treg) differentiation, suppresses pro-inflammatory Th1 and Th17 responses, inhibits B cell activation and plasma cell differentiation, and reduces autoantibody production (31-33). In the context of SLE, characterized by loss of immune tolerance, aberrant interferon signaling, and sustained autoantibody production, vitamin D deficiency may exacerbate immune dysregulation and perpetuate inflammatory activity (34). The observed trend toward an inverse association between serum 25(OH)D levels and anti-dsDNA titers in our cohort lends further support to this immunological link, although confirmation in larger, adequately powered studies is required.

Not all studies, however, have demonstrated a clear relationship between vitamin D levels and standardized disease activity indices. Investigations by Irastorza et al. and Toloza et al., for example, reported a high prevalence of deficiency without a significant association with disease activity scores (19, 35). Such heterogeneity likely reflects methodological differences, including variation in disease activity instruments, vitamin D assay techniques, seasonal timing of blood sampling, and adjustment for confounders such as glucocorticoid exposure, renal involvement, and hydroxychloroquine use. These discrepancies emphasize the need for cautious interpretation of observational findings and underscore the importance of standardized methodologies in future research.

The inverse relationship we found between serum 25(OH)D levels and SLEDAI-2K scores is supported by multiple observational studies. For instance, an original cross-sectional study demonstrated that vitamin D deficiency was associated with high SLEDAI scores and increased odds of high disease activity, suggesting a bidirectional relationship where low vitamin D may both influence and reflect active disease (36). Other cohort data have similarly shown that lower vitamin D levels are associated with

higher disease activity, although not always predictive of future flares, underscoring that vitamin D status may be more reflective of current disease state than a predictor of imminent flare (37).

In contrast to patterns observed in the general population, we found no significant association between serum 25(OH)D levels and age or sex. This may reflect the dominant influence of disease-specific factors in SLE, such as chronic inflammation, renal dysfunction, reduced mobility, and long-term corticosteroid therapies, which can substantially alter vitamin D metabolism and may override conventional demographic determinants (38, 39). Although women comprised approximately 90% of our cohort, consistent with the known epidemiology of SLE, the absence of a sex-based difference in vitamin D levels aligns with several lupus-specific observational studies and likely reflects the limited number of male patients rather than true biological equivalence (40, 41). While our cohort showed no significant sex-based difference in vitamin D levels, this contrasts with other reports in SLE and general populations where women often have lower serum 25(OH)D, possibly related to greater sun avoidance, clothing practices, or hormonal factors (21, 42).

From a clinical perspective, our findings have important implications. Vitamin D deficiency is a potentially modifiable factor, and accumulating evidence from interventional studies suggests that supplementation can improve serum 25(OH)D levels and may modestly reduce disease activity in SLE. A recent meta-analysis including more than 3,000 patients reported significant improvements in vitamin D status and reductions in SLEDAI scores among supplemented patients compared with controls (43). However, results across randomized trials remain heterogeneous, with some studies demonstrating improvements in immunologic markers, fatigue, or complement levels, while others show limited or no clinical benefit (44, 45). These

inconsistencies likely reflect differences in baseline vitamin D status, supplementation regimens, disease severity, and outcome measures, highlighting the complexity of SLE and the need for rigorously designed, adequately powered trials.

Several limitations of this study merit explicit consideration. The cross-sectional design precludes causal inference, and it remains unclear whether vitamin D deficiency contributes to increased disease activity or is a consequence of active disease through reduced sun exposure, systemic inflammation, or treatment effects. The sample size of 100 patients, while sufficient for estimating prevalence and detecting overall associations, limited subgroup analyses—particularly among patients with severe disease activity and among men—and findings in these subgroups should therefore be interpreted as exploratory. In addition, we did not adjust for several potential confounding variables, including body mass index, seasonal variation in vitamin D measurement, detailed dietary intake, or cumulative and current doses of medications known to influence vitamin D metabolism, such as glucocorticoids and antimalarials. Although our center serves as the primary referral clinic for SLE in the region, the single-center design may also limit generalizability.

Despite these limitations, this study provides clinically relevant, region-specific evidence highlighting a substantial and often underrecognized burden of vitamin D deficiency among patients with SLE in Southeast Iran. For local clinicians and health policymakers, these findings support the pragmatic incorporation of routine vitamin D assessment into the standard evaluation of SLE patients, particularly in regions with a high prevalence of deficiency and sociocultural barriers to adequate sun exposure. Addressing vitamin D deficiency may represent a low-cost, adjunctive strategy to optimize overall disease management while awaiting definitive evidence from large randomized controlled trials.

CONCLUSION

In conclusion, this study highlights an important public health and clinical concern: vitamin D deficiency is highly prevalent and is significantly associated with increased disease activity among patients with systemic lupus erythematosus in Southeast Iran. Notably, patients with higher disease activity predominantly exhibited serum 25-hydroxyvitamin D levels below 20 ng/mL, a threshold commonly used to define deficiency in clinical practice. These findings support the potential value of routine assessment of vitamin D status in the standard management of SLE, particularly in regions with a high baseline prevalence of deficiency.

While the cross-sectional design precludes causal inference, our results add to the growing body of evidence suggesting that maintaining serum 25(OH)D levels ≥ 30 ng/mL, a range often considered sufficient for musculoskeletal and immunomodulatory health, may be clinically relevant for patients with SLE. Well-designed randomized controlled trials are now needed to determine whether vitamin D supplementation targeted to these thresholds can meaningfully reduce disease activity and improve long-term outcomes in SLE populations.

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