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# Vitamin D deficiency in restless legs syndrome and chronic venous insufficiency: A comparative study

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## *Abstract*

*Background & Objectives*: Restless legs syndrome (RLS) and chronic venous insufficiency (CVI) are prevalent disorders with overlapping symptoms, complicating diagnosis. Vitamin D deficiency has been linked to neurological and vascular diseases, yet direct comparisons between RLS and CVI are scarce. This multicenter study evaluated serum vitamin D levels in patients with RLS, patients with CVI without RLS, and healthy controls to clarify disorder-specific associations. *Methods:* We retrospectively analyzed 381 participants aged 18–65 years (127 RLS, 127 CVI, 127 controls) between October 2022 and March 2025. Demographic and biochemical parameters, including 25(OH)D, calcium, phosphorus, creatinine, and parathyroid hormone (PTH), were compared. Correlation analyses assessed relationships with disease duration and severity. *Results:* Mean serum vitamin D was significantly lower in RLS (18.0 ± 9.4 ng/mL) and CVI (20.1 ± 6.6 ng/mL) compared with controls (24.8 ± 10.0 ng/mL, p<.001). Deficiency (<20 ng/mL) was found in 64.6% of RLS and 56.7% of CVI patients versus 27.6% of controls. In RLS, vitamin D levels negatively correlated with disease duration (r= –0.25, p=.032) and severity (r= –0.48, p<.001). In CVI, lower vitamin D correlated with longer disease duration (r= –0.28, p=.018) and higher clinical stage (r= –0.26, p<.001). PTH was significantly elevated in both patient groups. *Conclusions:* Vitamin D deficiency is highly prevalent in RLS and CVI and correlates with disease burden, particularly in severe RLS. These findings indicate an association between reduced vitamin D levels and disease burden in both RLS and CVI, without implying a causal relationship. Routine screening of vitamin D status may be considered as part of clinical evaluation, although interventional implications require confirmation in prospective studies

*Keywords:* Restless legs syndrome, venous insufficiency, vitamin D, vitamin D deficiency, vitamin D insufficiency

## INTRODUCTION

Restless legs syndrome (RLS) is a sensorimotor neurological disorder characterized by an uncontrollable urge to move the legs, usually in response to uncomfortable or unpleasant sensations. Symptoms are typically exacerbated during periods of rest or inactivity and tend to worsen in the evening or at night, while temporary relief is often achieved through movement, such as walking.[1] The estimated prevalence of RLS in the adult population ranges from 5% to 8.8%, with higher prevalence reported among females, older individuals, pregnant women, and certain racial groups 2.[2] RLS has been associated with significant health, economic, and social burdens.[3] Although its pathophysiology remains incompletely understood, central iron deficiency and dopaminergic dysfunction are widely accepted as the two main proposed mechanisms underlying the disorder.[4]

Chronic venous insufficiency (CVI), commonly observed in clinical practice, is a condition that impairs quality of life and is associated with the development of severe complications, including varicose veins and venous ulcers. CVI is estimated to affect between 20% and 40% of the population.[5] The primary pathophysiological mechanisms include venous valve incompetence and obstruction, both of which increase venous pressure in the

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lower extremities and contribute to venous hypertension. Clinical symptoms such as pain, cramps, heaviness, burning, and paresthesia, and signs like telangiectasias, varicose veins, edema, skin changes, or ulcers are commonly reported in CVI patients.[6] Importantly, these symptoms may mimic RLS manifestations.[7] CVI has a multifactorial etiology, with recognized risk factors including age, female sex, obesity, genetic predisposition, pregnancy, intra-abdominal malignancies, thrombophlebitis, prior leg injury, and prolonged standing.[8]

Vitamin D is crucial for skeletal health and neuromuscular activity. Its hormonally active metabolite, calcitriol [$1,25(OH)_2D_3$], contributes to calcium–phosphate regulation and bone mineralization. Nevertheless, inadequate vitamin D status remains a common global health concern.[9] Risk factors include advanced age, high body mass index, sunscreen use, limited sun exposure, darker skin pigmentation, and geographic location.[10] Recent years have witnessed a surge in interest surrounding the extra-skeletal functions of vitamin D. Deficiency of this vitamin has been implicated in various conditions, including diabetes, obesity, cardiovascular diseases, infections, asthma, inflammatory bowel disease, neurological disorders, and cancer.[11, 12]

Emerging studies have suggested an association between vitamin D status and RLS. Several studies have indicated that patients with RLS often present with reduced serum vitamin D concentrations, and some reports have described symptomatic improvement following supplementation; however, these findings do not establish causality.[13, 14] Moreover, vitamin D has been linked to biological pathways implicated in RLS, such as dopaminergic signaling and iron metabolism.[15, 16]

However, the association between vitamin D status and chronic disorders that exhibit clinical similarities to RLS, including CVI, has not been sufficiently investigated. Recent studies have expanded this understanding by revealing associations between low vitamin D levels and increased RLS severity, poor sleep quality, and mood disturbances.[17-19] Interventional studies have shown that vitamin D supplementation, especially when used adjunctively, may alleviate RLS symptoms and improve sleep-related parameters.[20-22] Additional observational research has identified vitamin D deficiency as potential associated factor for RLS in various populations, including those with migraine, post-stroke status, or hormonal changes.[19,23] Several systematic reviews further corroborate these observations, concluding that vitamin D deficiency is common among RLS patients and that supplementation has been associated with symptom improvement in selected cases.[13,24-26] Nonetheless, some inconsistencies exist across studies, and the exact nature of this relationship remains to be clarified. In this study, CVI was included as a disease control group to serve as a clinical comparator with overlapping symptoms, rather than as a confounder or a mechanistic or causal factor in RLS pathophysiology. Our study aims to fill this gap by providing a direct comparison of serum vitamin D levels across patients with RLS, those with CVI without RLS, and healthy individuals, offering new insights into the disorder-specific relevance of vitamin D status.

These findings point toward a possible link between vitamin D status and both vascular and neuromuscular disorders. A 2022 study reported similar findings in patients with both CVI and RLS.[27] In 2023, an Indian study examining vitamin D status in 197 patients with CVI also reported high prevalence of deficiency.[28] Additionally, studies conducted in 2021 and 2022, including retrospective analyses and case-control investigations, have repeatedly reported that patients with venous thrombotic events, such as deep or superficial vein thromboses, frequently exhibit vitamin D deficiency, indicating its possible association as a biomarker for venous thrombosis.[29,30] A prospective study in 2023 indicated a high prevalence of vitamin D deficiency in patients with CVI, linking long-standing CVI with joint degeneration[28], while a meta-analysis confirmed an increased VTE risk associated with vitamin D deficiency.[31] Additionally, a recent pilot study found that vitamin D administration reduced oxidative stress in varicose veins, suggesting a possible association with vascular protective mechanisms in the context of chronic venous disease.[32] These data are consistent with an association between vitamin D status and both musculoskeletal and vascular health.

While vitamin D deficiency has been associated with the severity and course of RLS symptoms, its possible relevance in CVI has also gained increasing attention in recent years. Vitamin D's putative associations with inflammatory regulation and its contribution to endothelial function have been proposed as relevant factors in the context of venous

pathology. Hypovitaminosis D has been associated with markers of venous disease severity, potentially through inflammatory and endothelial pathways.[33,34]

Despite this emerging evidence, studies examining serum vitamin D levels in patients with CVI without RLS are lacking. Moreover, the comparative evaluation of vitamin D levels between patients with RLS and those with CVI but without RLS has not been adequately addressed in the literature. Therefore, this study aims to assess and compare serum vitamin D concentrations in patients with RLS, patients with CVI without RLS, and healthy controls. By identifying differences in vitamin D levels across these groups, this study may provide insights into the association between vitamin D status and both disorders and inform future therapeutic research. To the best of our knowledge, this is the first study to compare serum vitamin D levels across these three distinct groups in a single design, offering novel insights into the differential diagnostic and therapeutic implications of vitamin D deficiency. To date, no study has provided a three-arm comparison including RLS, CVI without RLS, and healthy individuals, which makes this study uniquely positioned to address this gap

## METHODS

This multicenter retrospective cross-sectional study was conducted in the Physical Medicine and Rehabilitation outpatient clinics of City Hospital, and University Faculty of Medicine between October 2022 and March 2025. The study protocol was approved by the Non-Invasive Clinical Research Ethics Committee of University (2025-GOKAEK-2511_2025.06.04_485). All procedures involving human participants were conducted in accordance with the ethical guidelines of the relevant institutional or national committees, as well as in line with the principles outlined in the 1964 Helsinki Declaration and its subsequent revisions or equivalent ethical frameworks.

### *Participants*

The study included individuals aged 18 to 65 years with documented serum vitamin D levels. Participants were divided into three groups. The patient group consisted of individuals diagnosed with RLS; the disease control group included age- and sex-matched individuals diagnosed with CVI who did not meet the diagnostic criteria for RLS; and the healthy control group consisted of age- and sex-matched healthy individuals without chronic disease or a diagnosis of RLS. The diagnosis of RLS was made based on the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria as documented in patient records All groups included only participants for whom serum vitamin D (25-hydroxyvitamin D) levels had been measured during the study period. As this was a retrospective study, inclusion was limited to individuals with documented vitamin D measurements and recorded disease severity scales, which may have introduced selection bias. To minimize bias, participants with conditions affecting vitamin D metabolism such as chronic kidney disease, liver disease, or malabsorption syndromes were excluded.

RLS severity was assessed retrospectively using the International Restless Legs Syndrome Study Group Severity Rating Scale (IRLSSG-SRS). Total IRLSSG-SRS scores (range 0–40) were categorized as follows: mild (1–10), moderate (11–20), severe (21–30), and very severe (31–40). Since the study is retrospective, only those RLS patients with documented IRLSSG-SRS scores in their electronic medical records were included; patients without such recorded severity scores were excluded. Similarly, CVI severity was determined based on the Clinical–Etiological–Anatomical–Pathophysiological (CEAP) clinical classification system (C0–C6). Only those CVI patients with recorded CEAP clinical class in their electronic medical records were included; patients without documented CEAP staging were excluded.

### *Data collection*

Data were obtained retrospectively from the Hospital Information Management System (HBYS) statistics module. Key demographic variables (age and sex), laboratory parameters including serum 25(OH)D (vitamin D), calcium, phosphorus, and creatinine levels, and when available, parathyroid hormone (PTH) levels were recorded for all participants. These laboratory results were retrieved from any hospital unit where the tests had been ordered as part of routine clinical care; no additional laboratory investigations were specifically requested for the purposes of this study.

To ensure the exclusion of secondary causes of vitamin D deficiency, patients with missing creatinine or PTH values were excluded when

necessary. The data for patients diagnosed with RLS, those diagnosed with CVI but without RLS, and healthy controls were identified using diagnostic and laboratory records available in the HBYS system. All laboratory measurements used in the study were originally obtained for clinical reasons unrelated to this research. To control for seasonal variation in serum vitamin D levels, the study initially encompassed patients evaluated during the October–March period.

*Statistical analysis*

Categorical variables were analyzed using Pearson chi-square and Fischer's exact test according to the expected frequency for between-group differences. The analysis of the difference between groups for continuous variables was compared using Mann-Whitney U test and Kruskal Wallis Test. Post-hoc Dunn tests were used to compare numerical variables of more than two groups. Spearman correlation analysis was used for correlation analysis of factors associated with Vitamin D level in RLS, and CVI group.

## RESULTS

A total of 381 individuals were included in the study. The study enrolled three cohorts: a case cohort comprising 127 patients diagnosed with RLS; a disease control cohort of 127 patients diagnosed with CVI, without RLS, and a reference control cohort of 127 age- and sex-matched healthy participants. Demographic and clinical characteristics of the participants in the RLS, CVI, and control groups are presented in Table 1. Mean age was similar in all three groups. Age and sex distributions were comparable across RLS, CVI, and control participants, with no significant differences ($p>.05$). The prevalence of comorbidities such as hypertension and hypothyroidism also showed no significant variation between groups. In the CVI group, venous insufficiency was most frequently classified as CEAP C3, followed by C2. Among RLS patients, the mean disease duration was 4.31±4.26 years, and severity scores indicated that the majority had moderate to severe disease. Notably, vitamin D deficiency (<20 ng/mL) was markedly more prevalent in both patient groups, particularly in RLS, compared with controls ($p<.001$) (Table 1).

Serum vitamin D levels were significantly lower in both RLS and CVI groups compared with controls ($p<.001$), while no difference was observed between RLS and CVI. Post-hoc Dunn analysis confirmed that the significant difference was confined to patient–control comparisons. Calcium was higher in RLS compared with CVI, and phosphorus was reduced in CVI relative to both RLS and controls ($p<.05$). Creatinine was significantly lower in controls than in both patient groups ($p<.05$). PTH levels were elevated in RLS and CVI compared with controls ($p<.001$). Taken together, these results indicate that alterations in vitamin D and associated biochemical markers predominantly distinguish patient groups from healthy individuals, highlighting an association between these biochemical changes and disease status in RLS and CVI (Table 2).

In the RLS cohort, correlation analysis revealed no significant associations between serum vitamin D levels and age (rho = –0.041, p = .649), sex (rho = 0.142, p = .111), or comorbid conditions (rho = –0.111, p = .212). Conversely, a negative correlation was observed between disease duration and vitamin D concentrations (rho = –0.252, p = .032). Moreover, disease severity showed a strong inverse relationship with vitamin D levels (rho = –0.478, p < .001), indicating an association between lower vitamin D concentrations and higher RLS severity scores (Table 3).

In the CVI group, serum vitamin D levels did not correlate significantly with age (rho = –0.061, p = .749), sex (rho = 0.172, p = .221), or comorbidity status (rho = –0.151, p = .252). However, both longer disease duration (rho = –0.276, p = .018) and higher CVI stage (rho = –0.258, p < .001) were significantly associated with lower vitamin D concentrations. These findings indicate that hypovitaminosis D is statistically associated with disease duration and severity in CVI; however, no causal relationship can be inferred due to the retrospective cross-sectional study design (Table 4).

## DISCUSSION

The present study provides a comparative perspective on vitamin D status across patients with RLS, those with CVI without RLS, and healthy individuals. By including both a neurological and a vascular patient group alongside controls, this design allows for a more nuanced evaluation of whether vitamin D deficiency is disorder-specific or represents a shared risk factor across conditions with overlapping clinical features. Such an approach

**Table 1: Demographic and clinical features of the patients in each group**

| | RLS group (n=127) | CVI group (n=127) | Control group (n=127) | p |
|---|---|---|---|---|
| Age (Mean± SD) | 48.89 ± 5.23 | 50.20 ± 5.26 | 49.57 ± 5.30 | 0.073 [a] |
| Gender - Female (n/%) | 92 (72.4) | 103 (81.1) | 95 (74.8) | 0.246[b] |
| Male(n/%) | 35 (27.6) | 24 (18.9) | 32 (25.2) | |
| Comorbid diseases (n/%) | | | | 0.136[b] |
| None | 80 (63) | 90 (70.9) | - | |
| HT | 20 (15.7) | 15 (11.8) | - | |
| Hypothyroidism | 14 (11) | 9 (7.1) | - | |
| CAD | 8 (6.3) | 9 (7.1) | - | |
| Other | 5 (3.9) | 4 (3.1) | - | |
| Diagnosis period (years) (Mean± SD) | 4.31±4.26 | 5.12±4.3 | - | 0.331[c] |
| Stage of venous insufficiency to CEAP Classification (n/%) | | | | |
| CEAP- C1 | - | 28 (22) | - | |
| CEAP- C2 | - | 64 (50) | - | |
| CEAP- C3 | - | 19 (15) | - | |
| CEAP- C4 | - | 10 (8) | - | |
| CEAP- C5 | - | 6 (5) | - | |
| Mild RLS (n/%) | 20 (15.7) | - | - | |
| Moderate RLS (n/%) | 50 (39.4) | - | - | |
| Severe RLS (n/%) | 48 (37.8) | - | - | |
| Very severe RLS(n/%) | 9 (7.1) | - | - | |
| Vitamin D status (n/%) | | | | |
| Deficiency (<20 ng/mL) | 82 64.6) | 72 (56.7) | 35 (27.6) | **<0.001** [b] |
| Insufficiency (20-30 ng/mL) | 22 (17.3) | 42 (33.1) | 45 (35.4) | **<0.001** [b] |
| Normal (>30 ng/mL) | 23 (18.1) | 13 (10.2) | 47 (37) | **<0.001** [b] |

*RLS: Restless Legs Syndrome, CVI: Chronic Venous Insufficiency, SD: standard deviation, n: Number, [a] Kruskal Wallis Test, [b] Chi-square test, [c] Mann-Whitney U test, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary arterial disease, CEAP Classification: Clinical-Etiological-Anatomical-Pathophysiological Classification*

helps to clarify the possible associations between vitamin D status and the interplay between neuromuscular and vascular pathologies, an area that remains insufficiently addressed in the existing literature. By incorporating a vascular disease control group, our design allows differentiation of whether vitamin D deficiency is merely a systemic background phenomenon or

**Table 2: Comparison of laboratory parameters between groups**

| | RLS group (n=127) | CVI group (n=127) | Control group (n=127) | p |
|---|---|---|---|---|
| Vitamin D level (ng/mL) (Mean± SD) | 18.01 ± 9.43 | 20.07 ± 6.55 | 24.78 ± 9.99 | **<0.001**[a*] |
| Calcium level (mg/dL) (Mean± SD) | 9.34 ± 0.40 | 9.17 ± 0.28 | 9.28 ± 0.35 | **<0.001**[a*] |
| Phosphorus level (mg/dL) (Mean± SD) | 3.85 ± 0.33 | 3.65 ± 0.43 | 3.92 ± 0.18 | **<0.001**[a*] |
| Creatinine level (mg/dL) (Mean± SD) | 0.67 ± 0.11 | 0.69 ± 0.12 | 0.63 ± 0.09 | **<0.001**[a*] |
| Parathyroid hormone pg/mL) (Mean± SD) | 51.99±15.29 | 49.22±14.25 | 37.05±15.81 | **<0.001**[a*] |

*RLS: Restless Legs Syndrome, CVI: Chronic Venous Insufficiency, SD: standard deviation, n: Number, [a] Kruskal Wallis Test and [*]post-hoc Dunn Test*

**Table 3: Correlation analysis of factors associated with Vitamin D level in RLS group**

| | | Vitamin D level |
|---|---|---|
| Age | rho | -0.041 |
| | p | 0.649 [a] |
| Gender | rho | 0.142 |
| | p | 0.111 [a] |
| Comorbid diseases | rho | -0.111 |
| | p | 0.212 [a] |
| Diagnosis period (years) | rho | **-0.252**[*] |
| | p | **0.032** [a] |
| Stage of RLS | rho | **-0.478**[**] |
| | p | **<0.001**[a] |

*RLS: Restless Legs Syndrome [a] Spearmon correlation analysis, [*]The correlation is significant at the 0.05 level (2-tailed), [**]The correlation is significant at the 0.01 level (2-tailed)*

**Table 4: Correlation analysis of factors associated with Vitamin D level in CVI group**

| | | Vitamin D level |
|---|---|---|
| Age | rho | -0.061 |
| | p | 0.749 [a] |
| Gender | rho | 0.172 |
| | p | .0221 [a] |
| Comorbid diseases | rho | -0.151 |
| | p | 0.252 [a] |
| Diagnosis period (years) | rho | **-0.276**[*] |
| | p | **0.018** [a] |
| Stage of CVI | rho | **-0.258**[**] |
| | p | **<0.001**[a] |

*CVI: Chronic Venous Insufficiency, [a] Spearmon correlation analysis, [*]The correlation is significant at the 0.05 level (2-tailed), [**]The correlation is significant at the 0.01 level (2-tailed)*

a disorder-specific marker.

Our results revealed that serum vitamin D concentrations were markedly reduced in RLS patients when compared with both CVI patients and healthy controls. The mean ages of the three groups were comparable (RLS: 48.89 ± 5.23 years; CVI: 50.20 ± 5.26 years; controls: 49.57 ± 5.30 years), and the distribution of female participants was in accordance with previously reported data.[2,35] Importantly, we identified a significant negative correlation between vitamin D levels and RLS stage (rho = –0.478, p < .001), indicating an association between lower vitamin D concentrations and higher RLS severity score, although the causal direction of this association remains uncertain. This association may reflect shared biological pathways rather than a direct mechanistic effect. At present, available evidence, including our findings, supports an association between vitamin D deficiency and RLS severity, rather than a definitive causal role in RLS pathophysiology. Given the retrospective cross-sectional design, it is not possible to determine whether vitamin D deficiency precedes disease progression or occurs as a consequence of more severe disease. The predominance of women in our cohort is consistent with epidemiological evidence indicating that both RLS and CVI occur more frequently among females.[2,5,35] Potential explanations include hormonal influences, pregnancy-related changes, and sex-specific differences in venous and neuromuscular physiology.[2,8] Taken together, these findings reinforce the view that female sex represents an important risk factor for both disorders and underline the necessity for increased clinical vigilance and preventive strategies in this population.

Previous population-based studies have reported variable prevalence rates of vitamin D deficiency depending on geography, lifestyle, and study population, with estimates ranging between 30% and 50% in adults.[9,10] In our cohort, the prevalence was substantially higher, reaching 64.6% in RLS and 56.7% in CVI patients, compared with 27.6% in healthy controls. These findings underscore a particularly high burden of hypovitaminosis D among neurological and vascular patient groups, exceeding that observed in the general population. This suggests that vitamin D deficiency may not only reflect background prevalence but also represent a condition-associated clinical feature, highlighting the clinical relevance of routine screening in such patients. CVI should therefore be interpreted as a comparator condition with symptomatic overlap, not as a confounder or causal mediator in RLS.

Previous research has indicated a potential link between low serum vitamin D levels and increased severity of RLS symptoms, sleep disturbances, and mood changes.[18,20,21] Interventional studies have also reported that vitamin D supplementation may alleviate RLS

symptoms, particularly when used alongside standard treatment.[20-22] Observational studies in special populations such as post-stroke patients or individuals with hormonal comorbidities have further highlighted vitamin D deficiency as an independent risk factor for RLS.[19,23] However, not all findings have been consistent; some case-control studies failed to find significant differences in vitamin D levels between RLS patients and controls[24], and genetic studies have even reported higher levels in certain subgroups.[25] Systematic reviews and meta-analyses suggest that while vitamin D deficiency is common in RLS, its role in pathogenesis and treatment remains partially understood, requiring further clarification.[13,25,26]

In line with these reports, our study also demonstrated significantly lower vitamin D levels in patients with RLS compared to healthy controls, and importantly, revealed a strong inverse correlation between vitamin D concentrations and disease severity. This finding is in line with the notion that vitamin D status may be closely associated with both the presence and severity of RLS symptoms, consistent with prior studies linking deficiency to greater symptom burden.[18,20,21] At the same time, our results diverge from case-control and genetic studies that failed to confirm this association[24,25], suggesting that population differences or methodological variability may underlie these discrepancies. By incorporating a disease control group with CVI an aspect largely overlooked in earlier research our work extends the current evidence base and demonstrates that while vitamin D deficiency is prevalent in both vascular and neurological conditions, its relationship with symptom severity appears more pronounced in RLS. This highlights the disorder-specific relevance of vitamin D deficiency and underscores the potential importance of screening and supplementation strategies in this population. Nevertheless, the threshold levels of vitamin D required to achieve neurological versus vascular benefits may differ. Future interventional studies should stratify patients by baseline severity and aim to determine optimal supplementation regimens tailored to RLS or CVI.

Recent studies have examined the association between vitamin D status and venous pathologies. Retrospective and case-control studies from 2021 and 2022 consistently demonstrated that vitamin D deficiency is prevalent among patients with VTE, DVT, and SVT, suggesting its potential association as a biomarker for venous thrombosis.[29,30] A prospective study in 2023 indicated a high prevalence of vitamin D deficiency in patients with CVI, linking long-standing CVI with joint degeneration, while a meta-analysis confirmed an increased VTE risk associated with vitamin D deficiency.[28,31] Additionally, a 2025 pilot study found that vitamin D administration reduced oxidative stress in varicose veins, indicating a possible association with vascular protective mechanisms in chronic venous disease.[32] Collectively, these findings highlight the relevance of evaluating vitamin D status in patients with venous disorders, including CVI, as part of risk assessment and management strategies. Potential mechanisms may involve endothelial dysfunction, pro-inflammatory cytokine activation, and increased oxidative stress in venous walls, all of which could be mitigated by adequate vitamin D levels.

Consistent with these previous reports, our study also confirmed a high prevalence of vitamin D deficiency among patients with CVI compared to healthy controls, suggesting an association with venous pathophysiology rather than a causal role. Similar to earlier findings that linked deficiency with thrombotic disorders[29,30] and disease chronicity[28,31], we observed that lower vitamin D levels were significantly correlated with longer disease duration and higher CVI stage, indicating an association with more advanced clinical stages of CVI. Unlike interventional studies that have reported associations with vascular protective outcomes following supplementation.[32] Our cross-sectional design does not address causality but emphasizes the clinical association between hypovitaminosis D and CVI severity. By directly comparing CVI patients with both RLS patients and healthy individuals, our study expands on existing evidence and demonstrates that vitamin D deficiency is not only common in vascular disorders but may represent a shared metabolic disturbance across conditions with overlapping clinical manifestations. This provides novel insight into the broader clinical relevance of vitamin D in chronic disease and highlights the importance of considering vitamin D status in the management of CVI.

While previous research has primarily focused on serum vitamin D concentrations, alterations in related biochemical parameters such as calcium, phosphorus, and PTH have rarely been addressed in the context of RLS or CVI. Our findings demonstrated significantly higher PTH levels

in both patient groups compared with controls, alongside lower phosphorus in CVI and slightly elevated calcium in RLS. These results suggest a possible secondary hyperparathyroidism associated with chronic vitamin D deficiency, which may exacerbate neuromuscular and vascular dysfunction.[9,33,34] To our knowledge, few studies have simultaneously examined these biochemical markers in RLS and CVI, making this an important novel contribution of our work and pointing to potential metabolic pathways that warrant further investigation.

This study has several limitations. Its retrospective design may introduce selection bias, and seasonal variations in sun exposure could not be entirely controlled. Additionally, data on RLS severity and sleep quality, which could have strengthened the analysis, were not available. The exclusively female sample limits generalizability to male populations. Despite these limitations, the multicenter design and large sample size enhance the study's reliability. Additionally, lifestyle data such as dietary vitamin D intake, sunlight exposure, and physical activity were unavailable, which could have influenced serum vitamin D levels. Additional unmeasured confounding factors such as menopausal status, body mass index, dietary vitamin D intake, and physical activity levels may also have influenced serum vitamin D concentrations and should be accounted for in future studies.

This study demonstrates that vitamin D deficiency is significantly more common in patients with RLS and CVI compared with healthy controls, with deficiency correlating strongly with disease severity in RLS and with disease stage in CVI. By including both neurological and vascular disease groups, our work provides the first direct comparative evidence that vitamin D status is not only a general risk factor but may be differentially associated with disease-specific clinical features. The clinical implications are twofold: (1) for RLS, vitamin D deficiency was strongly associated with greater symptom severity, highlighting its potential relevance as a modifiable clinical parameter; and (2) for CVI, low vitamin D was associated with more advanced disease stages, underscoring its possible clinical significance in venous pathology. Importantly, our results highlight the potential utility of vitamin D screening as part of the diagnostic and therapeutic algorithm in both conditions. Our findings call for prospective, multicenter randomized trials to test whether correction of vitamin D deficiency can slow disease progression, reduce symptom burden, or improve quality of life in RLS and CVI patients. From a scientific perspective, this is the first study to simultaneously analyze RLS, CVI, and healthy controls, thereby filling a critical gap in the literature. It suggests that vitamin D deficiency should not be considered an incidental finding but rather a clinically relevant comorbidity. Future longitudinal and interventional trials are warranted to test whether vitamin D supplementation could improve outcomes in these patient populations.

This study has several important limitations. First, its retrospective design and the inclusion of only patients with documented serum vitamin D measurements and recorded disease severity scales may have introduced selection bias. This requirement may have preferentially selected individuals with more severe symptoms or greater healthcare utilization, thereby limiting the representativeness of the study population. Second, data on iron status, including serum ferritin and other iron parameters, were not available. Iron deficiency is a well-established contributor to RLS pathophysiology and has been associated with alterations in vitamin D metabolism. The absence of iron-related measures limits our ability to determine whether the observed associations between vitamin D deficiency and RLS severity are independent or partially mediated by iron deficiency, which therefore remains an important unmeasured confounder. Finally, the predominance of female participants may have influenced the observed associations, as sex-specific hormonal, behavioral, and metabolic factors can affect both vitamin D status and disease expression. Consequently, the generalizability of the findings to male populations is limited. Future prospective studies incorporating comprehensive iron profiling and more balanced sex representation are warranted to further clarify these relationships.

## DISCLOSURE

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of interest: None

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