

ASSOCIATION BETWEEN SERUM 25(OH)D CONCENTRATION AND OBJECTIVE AND SUBJECTIVE MEASURES OF CHRONIC RHINOSINUSITIS SEVERITY

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Introduction: The role of vitamin D in the pathogenesis of chronic rhinosinusitis remains unclear. This study sought to assess the relationship of serum total vitamin D (25(OH)D) concentration with objective and subjective measures of disease severity and to compare these relationships across chronic rhinosinusitis phenotypes.

Methods: This prospective study included 39 adult patients: 17 with chronic rhinosinusitis with nasal polyps, 10 with chronic rhinosinusitis without nasal polyps, and 12 patients scheduled for septoplasty, who served as the control group. Serum 25(OH)D concentration was measured with the use of a competitive binding assay with electrochemiluminescence detection. Disease severity was assessed using the Lund-Mackay and Lund-Kennedy scores, the SNOT-22 questionnaire, and a visual analog scale (VAS). Statistical methods comprised the Kruskal-Wallis test followed by Dunn's post hoc tests, FDR-adjusted Spearman correlations, and linear regression with robust standard errors.

Results: Serum 25(OH)D concentrations did not differ significantly between groups ($p = 0.103$). Significant between-group differences were found for the Lund-Mackay ($p < 0.001$), Lund-Kennedy ($p < 0.001$), SNOT-22 ($p = 0.030$), and VAS ($p = 0.005$) scores. None of the measures assessed showed a significant correlation with 25(OH)D concentration after FDR correction. Regression models showed no significant associations between 25(OH)D and clinical outcomes as well as no moderating effect of group.

Discussion and Conclusions: In the study population, there was no statistically significant association between 25(OH)D concentration and radiologic, endoscopic, or subjective disease severity. The results do not support the use of 25(OH)D concentration as a stand-alone biomarker of chronic rhinosinusitis severity. Larger studies are needed to confirm these findings because the sample was small.

Keywords: chronic rhinosinusitis, SNOT-22, Lund-Mackay score, Lund-Kennedy score, vitamin D

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ABBREVIATIONS

INCS – intranasal corticosteroids
 EPOS 2020 – European Position Paper on Rhinosinusitis and Nasal Polyps 2020
 FDR – false discovery rate
 CRS – chronic rhinosinusitis
 CRSsNP – chronic rhinosinusitis without nasal polyps
 CRSwNP – chronic rhinosinusitis with nasal polyps
 SNOT-22 – Sino-Nasal Outcome Test-22
 CT – computed tomography
 VAS – *visual analog scale*
 25(OH)D – total 25-hydroxyvitamin D concentration

INTRODUCTION

According to a systematic review and meta-analysis published in 2024, covering 28 studies and more than 237 million participants from 20 countries, the prevalence of chronic rhinosinusitis (CRS) is 8.71% [17]. However, reported prevalence varies considerably depending on the diagnostic methodology used. A prevalence above 10% is reported by studies relying solely on patient-reported symptoms, compared with a true prevalence of approximately 5% in analyses requiring both clinical symptoms and objective confirmation by endoscopy or imaging [23]. The proportion of affected individuals also varies considerably by geographic region and diagnostic criteria. In North America and Europe, the prevalence of CRS is estimated at 4.5–12% [6], while the European population-based GA²LEN survey reported a prevalence of 10.9% [12]. Chronic rhinosinusitis with nasal polyps (CRSwNP) accounts for about one-third of all CRS cases, with a global prevalence of 0.65% [17].

In sinonasal mucosal tissue models, vitamin D (25(OH)D) modulates dendritic cell activity, inhibits cytokine production, and reduces fibroblast proliferation and local signaling involving IL-6 and IL-8; through these effects, it plays an important biological role in CRS pathogenesis [2]. More recent studies of the mucosal epithelium also point to impaired local vitamin D3 signaling in patients with CRSwNP. Reduced expression of the vitamin D receptor and of CYP27B1, the enzyme that converts 25(OH)D into its biologically active form, 1,25(OH)₂D₃, has been demonstrated. Increased IL-36 γ expression and more pronounced neutrophilic inflammation accompanied these changes [30].

The Lund-Mackay score (LMS) is a widely used staging system based on computed tomography (CT) for grading the radiologic severity of CRS. Each sinus is scored as fully aerated (0 points), partially opacified (1 point), or completely opacified (2 points),

and each ostiomeatal complex as patent (0 points) or obstructed (2 points), which yields a simple numerical score without the need for specialized training in imaging interpretation [10]. The maximum score is 24, and a score of at least 4 has been proposed as the threshold for surgical treatment [26]. Pathologic changes in the nasal cavity and paranasal sinuses are graded endoscopically using the Lund-Kennedy score (LKS). It takes into account the presence of nasal polyps, mucosal edema, discharge, scarring, and crusting [16]. A modified version of the score, which excludes scarring and crusting, shows higher interrater agreement and a stronger correlation with patient-reported outcomes than the original Lund-Kennedy score [20]. The severity of mucosal inflammation can be assessed reliably and objectively with the LKS, which also allows the response to medical and surgical treatment to be monitored. It should be emphasized, however, that the LMS and LKS assess aspects of the disease different from those assessed by subjective symptom severity scales. They were developed as tools for the objective assessment of radiologic and endoscopic findings, so a close correlation with patient-reported symptom severity should not be expected [10].

The Sino-Nasal Outcome Test-22 (SNOT-22) is a questionnaire that assesses the impact of CRS on health-related quality of life. Physical symptoms, functional limitations, and the emotional consequences of the disease are assessed by the questionnaire [21]. The SNOT-22 is recommended by the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) as the primary tool for the subjective assessment of symptom severity in both research and clinical practice [7]. Each of the 22 items is rated on a six-point scale from 0 (no problem) to 5 (problem as bad as it can be), giving a total score of 0 to 110, with higher scores indicating a greater impact of the disease on the patient's quality of life [13]. Visual analog scale (VAS) scores are significantly associated with CRS-specific quality-of-life questionnaire scores, overall health-related quality of life, and patient-reported disease control [19]. For each symptom, patients rated severity on a scale of 1 to 10 points, with 1 representing minimal severity and 10 the maximum. Patients rated the severity of five symptoms separately: nasal obstruction, facial pain or pressure, loss of smell, rhinorrhea (anterior or posterior), and cough.

Previous studies have focused mainly on comparing 25(OH)D concentrations between patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and controls, or on individual clinical parameters such as radiologic findings or the

presence of nasal polyps (CRSwNP) [2]. Although numerous studies suggest that vitamin D is involved in the pathogenesis of CRS, its relationship with disease severity remains unclear [24].

This study sought to examine how serum 25(OH)D concentration relates to objective (Lund-Mackay, Lund-Kennedy) and subjective (SNOT-22, VAS) measures of chronic rhinosinusitis severity and to compare these relationships across the CRSwNP, CRSsNP, and control groups.

METHODS

Participants

This prospective study included adult patients (aged ≥ 18 years) hospitalized at the Department of Otolaryngology who gave informed consent. In all patients with CRS, the diagnosis was made according to the EPOS 2020 criteria. Eligibility required inflammatory changes on sinus CT and failure of medical treatment, defined as symptoms persisting for more than 12 weeks despite optimal pharmacotherapy.

The control group consisted of patients scheduled for septoplasty to correct a deviated nasal septum. All controls had normal sinus CT findings and did not meet the EPOS 2020 diagnostic criteria for CRS.

Symptom severity was assessed using the SNOT-22 and VAS. The Lund-Mackay and Lund-Kennedy scores were used to assess objective disease severity.

The exclusion criteria were lack of informed consent, disease limited to a single sinus, ciliary dysfunction (e.g., cystic fibrosis), suspected fungal infection, inadequate patient adherence to medical treatment, suspected malignancy or autoimmune disease (particularly granulomatosis with polyangiitis), confirmed or suspected immunodeficiency, coagulation disorders, and preoperative use of systemic corticosteroids.

To eliminate any potential effect of oral vitamin D supplementation on the results, patients taking medications or dietary supplements containing vitamin D were also excluded.

Procedure

A competitive binding assay with electrochemiluminescence detection (Elecys Vitamin D total III), performed on a cobas e402 analyzer (Roche Diagnostics GmbH, Mannheim, Germany), was used to measure serum 25(OH)D concentration on the day of surgery. The measuring range of the assay was 3.0–120 ng/mL, with a limit of detection of 3.0 ng/mL and a limit of quantitation of 6.0 ng/mL.

Based on the results obtained, 25(OH)D concentration was classified as follows:

- deficiency: ≤ 20 ng/mL,
- insufficiency: 21–29 ng/mL,
- sufficiency: ≥ 30 ng/mL.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Bioethics Committee of the Military Medical Chamber (approval No. 13/2023, May 26, 2023).

Statistical analysis

Histograms, box plots, score ranges, and the characteristics of the distributions within each group formed the basis for assessing variable distributions. In the SPSS analyses, Levene's test indicated heterogeneity of variance for the LMS ($p < 0.001$) and LKS ($p = 0.028$). In addition, the LMS and LKS showed a marked floor effect in the control group. The primary method chosen for between-group comparisons was the Kruskal-Wallis test, given the small and unequal group sizes, the restricted range of some scales, and the numerous tied values.

Quantitative variables are presented as the median and the first and third quartiles (Q1–Q3). Bootstrap 95% confidence intervals were calculated for effect sizes. The p values of the Kruskal-Wallis tests were also verified using a Monte Carlo permutation test (20,000 permutations). The Kruskal-Wallis test was used to compare age and BMI. Categorical variables, including sex and intranasal corticosteroid use, were compared using the Fisher-Freeman-Halton exact test; Cramér's V was also reported for contingency tables. In the five main between-group comparisons (LMS, LKS, SNOT-22, VAS, and 25(OH)D), p values were adjusted using the Benjamini-Hochberg method to control the false discovery rate (FDR); adjusted q values are reported in the tables. Nominal asymptotic p values underwent FDR correction, while the Monte Carlo results served as a sensitivity analysis.

Significant Kruskal-Wallis tests were followed by pairwise comparisons using Dunn's test. Bonferroni-adjusted p values, as reported by SPSS, were used as the primary correction for multiple testing in post hoc analyses. Holm-adjusted p values were also calculated as a supplementary analysis. Epsilon-squared (ε^2) quantified the overall effect, whereas Cliff's delta (δ), with a bootstrap 95% confidence interval, quantified differences between pairs of groups. The following thresholds were used to interpret absolute δ values: <0.147 , negligible; 0.147–0.329, small; 0.330–0.473, medium; ≥ 0.474 , large. Because there are no widely accepted

interpretive thresholds for ε^2 , its values are reported without verbal labels.

Associations between prespecified pairs of variables were assessed separately in each group using two-tailed Spearman rank correlations. The 95% confidence intervals for the ρ coefficients were obtained by bootstrapping. Because 21 correlations were computed, the Benjamini-Hochberg correction was applied to control the FDR, both within each group and across the full family of 21 tests. Inferences about correlations were based on q values for the full family of 21 tests; q values calculated separately within groups were treated as supplementary.

The association of 25(OH)D concentration with LMS, LKS, SNOT-22, and VAS scores was explored using ordinary least squares (OLS) linear regression with HC3 robust standard errors. Clinical group was included in the basic models; age, BMI, and sex were added in the adjusted models. The 25(OH)D concentration was centered on the mean of the whole sample (35.92 ng/mL). The 25(OH)D $\times$ group interaction was assessed in separate models, with the CRSwNP group as the reference category. Models of LMS and LKS scores were interpreted cautiously in view of the restricted score range, numerous tied values, and floor effect. All tests were two-tailed, and the significance level was set at $\alpha = 0.05$. Given the unequal sex distribution and the small sample size, adjustment for sex was exploratory; no sex-stratified analyses or tests for sex $\times$ group interaction were performed. Intranasal corticosteroids were not included in the models because their use was

strongly associated with clinical group and absent in the control group; including this variable could have led to unstable estimates and overparameterization. As all analyses were observational and exploratory, they provide no basis for inferring causality.

RESULTS

Characteristics of the study groups

The analysis included patients with CRSwNP (n = 17), patients with CRSsNP (n = 10), and patients scheduled for septoplasty, who served as controls (n = 12). The total sample size was N = 39.

Neither age nor BMI differed significantly between the groups. The median age was 45.0 years in the group with polyps, 42.0 years in the group without polyps, and 41.0 years in the control group. Median BMI ranged from 24.7 to 26.8 kg/m².

However, there were significant differences in sex distribution (exact p = 0.003) and in the frequency of intranasal corticosteroid use (exact p = 0.003). The proportion of women was 47.1% in the CRSwNP group, 90.0% in the CRSsNP group, and 16.7% in the control group. Intranasal corticosteroids were used by 47.1%, 60.0%, and 0% of patients, respectively. None of the comorbidities analyzed differed significantly between groups at the 0.05 level (Tab. 1); given the small group sizes, these results are descriptive only. Cramér's V indicated an association strength of 0.55 between group and sex and 0.51 between group and intranasal corticosteroid use.

Tab. 1. Characteristics of the groups.

Variable	CRSwNP	CRSsNP	Control	H	p
Age	45.00 [37.00–61.00]	42.00 [32.00–59.25]	41.00 [35.00–45.75]	0.989	0.610
BMI	25.30 [22.09–29.05]	24.70 [24.06–27.00]	26.75 [24.64–28.06]	1.085	0.581
Female sex	8 (47.1%)	9 (90.0%)	2 (16.7%)	—	0.003
Asthma	4 (23.5%)	1 (10.0%)	0 (0.0%)	—	0.147
Atopic dermatitis	0 (0.0%)	1 (10.0%)	1 (8.3%)	—	0.312
Allergic rhinitis	7 (41.2%)	4 (40.0%)	3 (25.0%)	—	0.692
Hypertension	6 (35.3%)	5 (50.0%)	3 (25.0%)	—	0.535
History of myocardial infarction	1 (5.9%)	0 (0.0%)	0 (0.0%)	—	1.000
History of stroke	1 (5.9%)	0 (0.0%)	0 (0.0%)	—	1.000
Type 2 diabetes	0 (0.0%)	1 (10.0%)	2 (16.7%)	—	0.169
Osteoporosis	1 (5.9%)	0 (0.0%)	0 (0.0%)	—	1.000
Intranasal corticosteroids	8 (47.1%)	6 (60.0%)	0 (0.0%)	—	0.003

*Quantitative data are presented as Me [Q1–Q3], and categorical data as n (%). Results of the Kruskal-Wallis test are reported for age and BMI, and those of the Fisher-Freeman-Halton exact test for categorical variables. The p values in Tab. 1 are descriptive and were not adjusted for multiple comparisons.

Tab. 2. Monthly distribution of patient recruitment.

Calendar month	CRSwNP	CRSsNP	Control
January	4	2	1
February	0	1	3
March	1	0	3
April	0	1	2
May	4	2	1
June	0	0	0
July	0	0	0
August	0	0	0
September	3	1	2
October	1	3	0
November	4	0	0
December	0	0	0

Descriptive statistics of clinical outcomes

On the objective LMS and LKS scales, the CRSwNP group had the highest scores, followed by the CRSsNP group, while the control group had by far the lowest scores. The median LMS was 14.0, 8.5, and 0.0 points, respectively, and the median LKS was 8.0, 4.0, and 1.0 points. In the control group, the LMS showed a strong floor effect: the median was 0.0, and Q3 was only 0.25 points.

The two clinical groups had more similar

subjective scores. The median SNOT-22 score was 44.0 points in the CRSwNP group and 48.5 points in the CRSsNP group, compared with 28.5 points in the control group. The median VAS score was 25.0, 23.0, and 13.5 points, respectively. The median 25(OH)D concentrations were 28.0, 40.5, and 31.5 ng/mL, respectively.

Figures 1 and 2 and Table 3 present the distributions of individual scores. The plots were reconstructed from the source data and correspond to the box plots in the SPSS output.

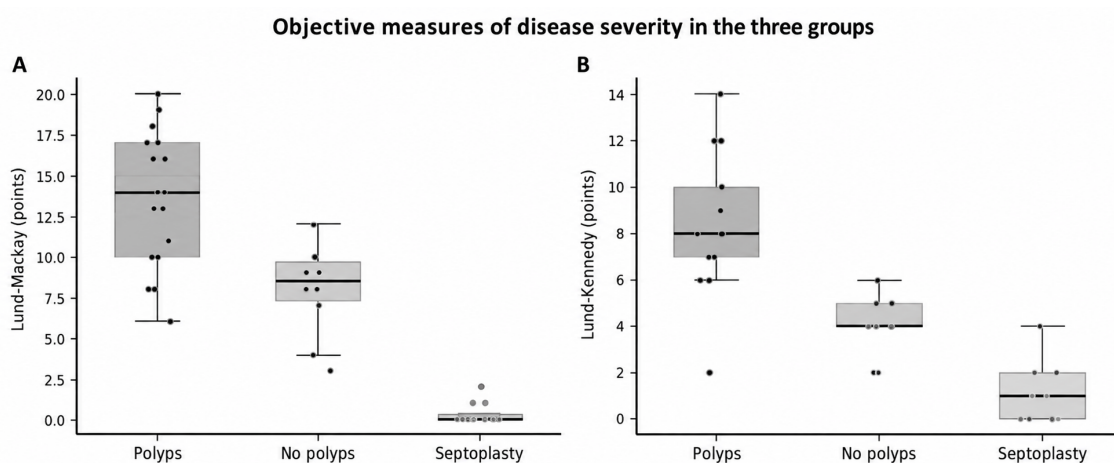


Fig. 1. Distribution of Lund-Mackay (A) and Lund-Kennedy (B) scores in the three groups. Q1–Q3 is represented by each box, the median by the line within it, and individual observations by the dots.

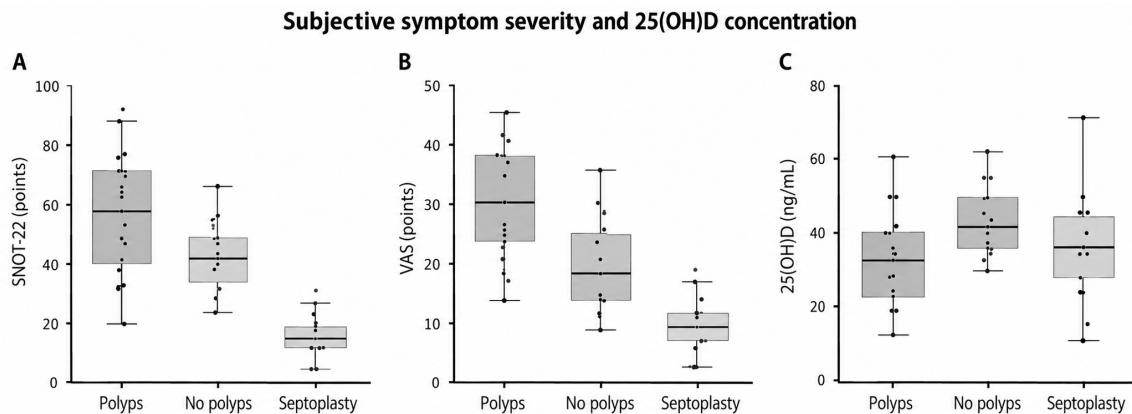


Fig. 2. Distribution of SNOT-22 (A) and VAS (B) scores and 25(OH)D concentrations (C) in the three groups. Q1–Q3 is represented by each box, the median by the line within it, and individual observations by the dots.

Tab. 3. Comparison of clinical outcomes and 25(OH)D concentrations between groups.

Variable	Polyps Me [Q1–Q3]	No polyps Me [Q1–Q3]	Septoplasty Me [Q1–Q3]	H	p	p MC	q FDR	ε^2 [95% CI]
LMS	14 [10–17]	8.50 [7.25–9.75]	0 [0–0.25]	29.129	<0.001	<0.001	<0.001	0.754 [0.671–0.853]
LKS	8 [7–10]	4 [4–5]	1 [0–2]	28.717	<0.001	<0.001	<0.001	0.742 [0.577–0.859]
SNOT-22	44 [33–71]	48.50 [41.75–64]	28.50 [24–40]	7.025	0.030	0.024	0.037	0.140 [0.000–0.417]
VAS	25 [17–30]	23 [15.25–28.25]	13.50 [8–17.50]	10.528	0.005	0.003	0.009	0.237 [0.051–0.507]
25(OH)D	28 [24–34]	40.50 [30.75–46.25]	31.50 [29.75–39.75]	4.539	0.103	0.104	0.103	0.071 [0.000–0.382]

Between-group comparisons

The Kruskal-Wallis test showed significant between-group differences for the LMS, $H(2) = 29.129$, $p < 0.001$; LKS, $H(2) = 28.717$, $p < 0.001$; SNOT-22, $H(2) = 7.025$, $p = 0.030$; and VAS, $H(2) = 10.528$, $p = 0.005$. These results remained significant after FDR correction for the five omnibus tests and in the Monte Carlo analysis. The q values were calculated from the asymptotic p values. There were no significant between-group differences in 25(OH)D, $H(2) = 4.539$, $p = 0.103$.

The epsilon-squared values were $\varepsilon^2 = 0.754$ (95% CI: 0.671 to 0.853) for the LMS, $\varepsilon^2 = 0.742$ (95% CI: 0.577 to 0.859) for the LKS, $\varepsilon^2 = 0.237$ (95% CI: 0.051 to 0.507) for the VAS, $\varepsilon^2 = 0.140$ (95% CI: 0.000 to 0.417) for the SNOT-22, and $\varepsilon^2 = 0.071$ (95% CI: 0.000 to 0.382) for 25(OH)D.

The control group had lower LMS scores than either the CRSwNP or CRSsNP group. The difference between CRSwNP and CRSsNP did not reach significance after Bonferroni correction, despite a large effect size.

For the LKS, the CRSwNP group scored higher than both the CRSsNP and the control groups. After Bonferroni correction, the difference between the CRSsNP and control groups was not significant.

For the SNOT-22, the only significant difference was between the CRSsNP and control groups. No differences were found between the CRSwNP and CRSsNP groups or between the CRSwNP and control groups.

For the VAS, the control group scored lower than both the CRSwNP and the CRSsNP groups. There was no significant difference between the CRSwNP and CRSsNP groups. The data are presented in Tab. 4.

Tab. 4. Post hoc comparisons using Dunn's test.

Variable	Comparison	Z	Bonferroni p	Holm p	Cliff's δ [95% CI]
LMS	CRSwNP vs. CRSsNP	2.113	0.104	0.035	0.706 [0.388–0.930]
LMS	CRSwNP vs. control	5.397	<0.001	<0.001	1.000 [1.000–1.000]
LMS	CRSsNP vs. control	2.786	0.016	0.011	1.000 [1.000–1.000]
LKS	CRSwNP vs. CRSsNP	2.707	0.020	0.014	0.859 [0.623–1.000]
LKS	CRSwNP vs. control	5.315	<0.001	<0.001	0.971 [0.897–1.000]
LKS	CRSsNP vs. control	2.162	0.092	0.031	0.867 [0.642–1.000]
SNOT-22	CRSwNP vs. CRSsNP	−1.045	0.888	0.296	−0.224 [−0.618–0.235]
SNOT-22	CRSwNP vs. control	1.832	0.201	0.134	0.387 [−0.025–0.745]
SNOT-22	CRSsNP vs. control	2.586	0.029	0.029	0.675 [0.300–0.958]
VAS	CRSwNP vs. CRSsNP	0.324	1.000	0.746	0.088 [−0.388–0.547]
VAS	CRSwNP vs. control	3.098	0.006	0.006	0.672 [0.343–0.922]
VAS	CRSsNP vs. control	2.426	0.046	0.031	0.625 [0.200–0.933]

*The main conclusions are based on the Bonferroni correction. With the Holm correction used as a sensitivity analysis, additional significant comparisons emerge for LMS: CRSwNP vs. CRSsNP; LKS: CRSsNP vs. control.

Correlations within groups

In the CRSwNP group, a strong positive correlation was found between LMS and LKS scores; this was the only one of the 21 correlations analyzed that remained significant after FDR correction, both within the seven correlations in this group ($q = 0.009$) and across the full family of 21 tests ($q = 0.027$).

None of the correlations between 25(OH)D concentration and LMS, LKS, SNOT-22, or VAS scores remained significant after FDR correction

in any group. The coefficients for the associations between 25(OH)D and clinical outcomes were characterized by small to moderate absolute values, with wide confidence intervals that included zero. Likewise, FDR correction left the LMS–LKS correlation nonsignificant in both the CRSsNP and control groups. These results should be interpreted in light of the small group sizes and the limited variability of the LMS and LKS within the septoplasty group.

The relationship between LMS and LKS scores in each group is illustrated in Fig. 3 and Tab. 5.

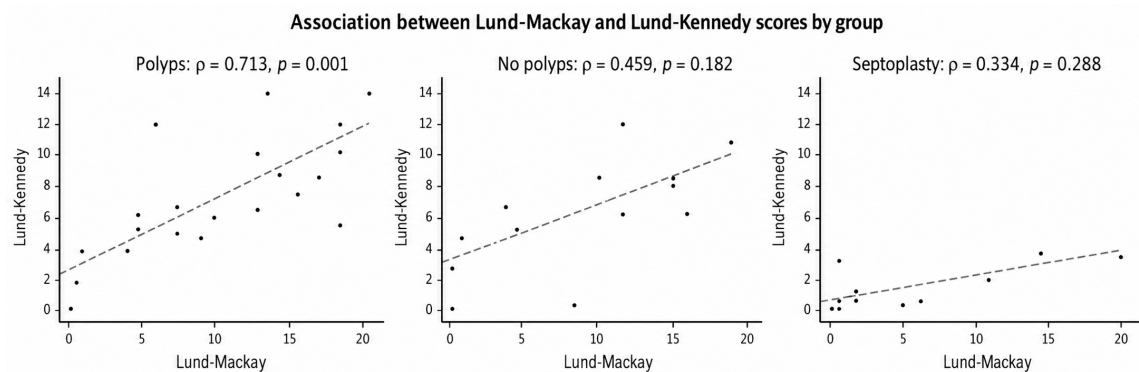


Fig. 3. Association between Lund-Mackay and Lund-Kennedy scores in the CRSwNP (A), CRSsNP (B), and control (C) groups. Spearman rank correlation provided the basis for inference; regression lines serve solely as a visual aid.

Tab. 5. Spearman correlations within groups.

Group	Pair	N	ρ	95% CI	p	q (within group)	q (21 tests)
CRSwNP	LMS–LKS	17	0.713	0.348–0.911	0.001	0.009	0.027
CRSwNP	LMS–SNOT-22	17	0.252	–0.305–0.637	0.329	0.466	0.702
CRSwNP	LMS–VAS	17	0.253	–0.281–0.655	0.328	0.466	0.702
CRSwNP	LMS–25(OH)D	17	–0.321	–0.713–0.247	0.210	0.466	0.702
CRSwNP	LKS–25(OH)D	17	–0.116	–0.637–0.456	0.658	0.768	0.810
CRSwNP	SNOT-22–25(OH)D	17	0.065	–0.539–0.565	0.804	0.804	0.844
CRSwNP	VAS–25(OH)D	17	0.250	–0.300–0.683	0.333	0.466	0.702
CRSsNP	LMS–LKS	10	0.459	–0.129–0.841	0.182	0.742	0.702
CRSsNP	LMS–SNOT-22	10	0.171	–0.648–0.697	0.636	0.742	0.810
CRSsNP	LMS–VAS	10	0.361	–0.374–0.817	0.306	0.742	0.702
CRSsNP	LMS–25(OH)D	10	–0.239	–0.729–0.571	0.507	0.742	0.767
CRSsNP	LKS–25(OH)D	10	0.290	–0.476–0.832	0.416	0.742	0.727
CRSsNP	SNOT-22–25(OH)D	10	0.200	–0.615–0.810	0.580	0.742	0.810
CRSsNP	VAS–25(OH)D	10	–0.042	–0.792–0.597	0.907	0.907	0.907
Septoplasty	LMS–LKS	12	0.334	–0.138–0.785	0.288	0.643	0.702
Septoplasty	LMS–SNOT-22	12	0.286	–0.180–0.762	0.368	0.643	0.702
Septoplasty	LMS–VAS	12	0.301	–0.187–0.687	0.341	0.643	0.702
Septoplasty	LMS–25(OH)D	12	–0.099	–0.659–0.593	0.759	0.759	0.839
Septoplasty	LKS–25(OH)D	12	–0.337	–0.860–0.326	0.285	0.643	0.702
Septoplasty	SNOT-22–25(OH)D	12	0.211	–0.510–0.791	0.511	0.716	0.767
Septoplasty	VAS–25(OH)D	12	–0.127	–0.665–0.497	0.694	0.759	0.810

Regression models for 25(OH)D concentration

In the models including group membership, 25(OH)D concentration was not significantly associated with any of the outcomes analyzed. For the LMS, the coefficient was $B = -0.042$ (95% CI: -0.111 to 0.027 ; $p = 0.229$); for the LKS, $B = -0.018$ (95% CI: -0.059 to 0.023 ; $p = 0.386$); for the SNOT-22, $B = 0.367$ (95% CI: -0.287 to 1.020 ; $p = 0.271$); and for the VAS, $B = 0.070$ (95% CI: -0.102 to 0.242 ; $p = 0.424$).

Further adjustment for age, BMI, and sex did not change the said conclusions. The coefficients for 25(OH)D were as follows: LMS, $B = -0.043$, $p = 0.258$; LKS, $B = -0.022$, $p = 0.421$; SNOT-22, $B = 0.432$, $p = 0.163$; VAS, $B = 0.089$, $p = 0.297$. Marked differences between groups, rather than the contribution of 25(OH)D concentration, were the main reason for the high R^2 values in the LMS and LKS models (Tab. 6).

Figure 4 shows the raw observations and the values predicted by the basic models including clinical group.

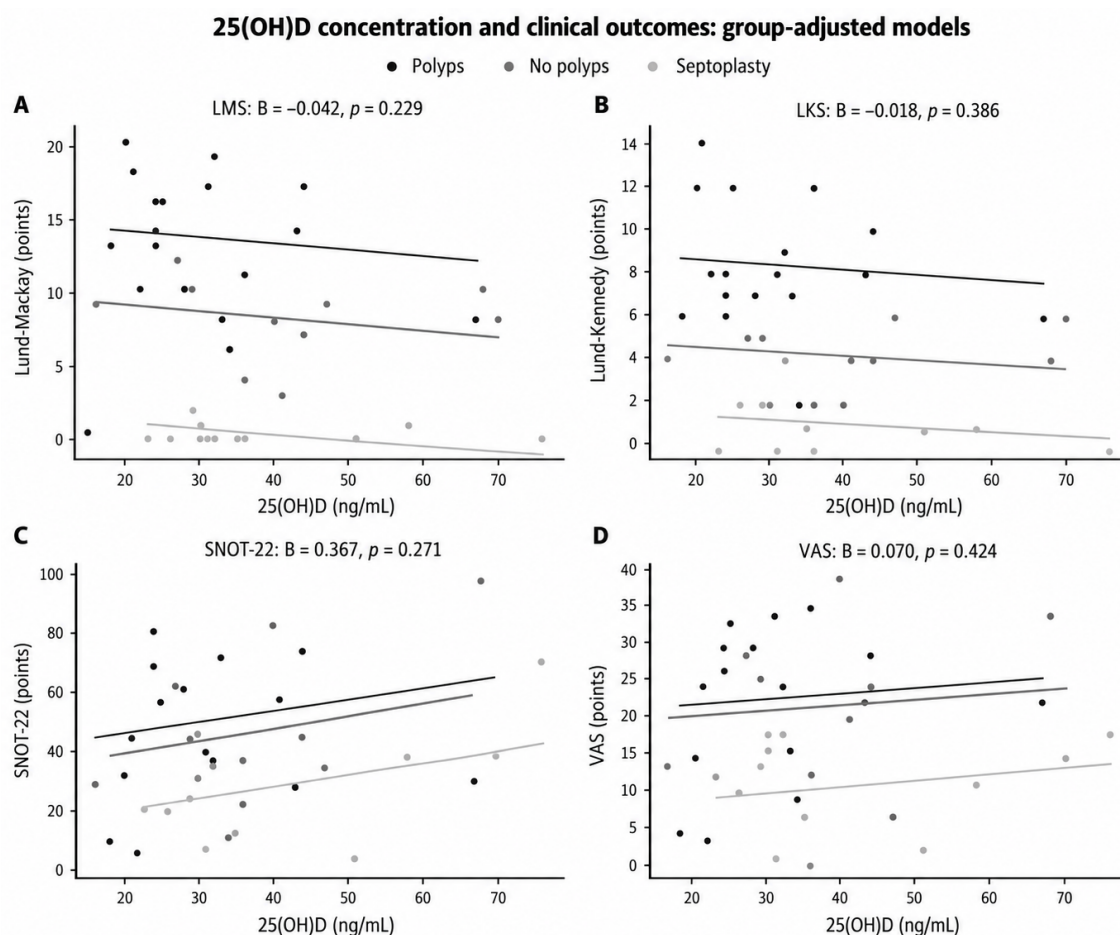


Fig. 4. Association of 25(OH)D concentration with LMS (A), LKS (B), SNOT-22 (C), and VAS (D) scores. Dots represent observations, whereas lines represent values predicted by the 25(OH)D + group model, which in turn assumes a common slope and separate intercepts for each group. No significant coefficient was found for 25(OH)D.

Tab. 6. Association of 25(OH)D concentration with clinical outcomes in regression models.

Model	Outcome	B 25(OH)D	95% CI	p	R ²	Adj. R ²
25(OH)D + group	LMS	-0.042	-0.111–0.027	0.229	0.786	0.768
25(OH)D + group	LKS	-0.018	-0.059–0.023	0.386	0.685	0.658
25(OH)D + group	SNOT-22	0.367	-0.287–1.020	0.271	0.221	0.154
25(OH)D + group	VAS	0.070	-0.102–0.242	0.424	0.288	0.227
25(OH)D + group + age + BMI + sex	LMS	-0.043	-0.117–0.031	0.258	0.799	0.761
25(OH)D + group + age + BMI + sex	LKS	-0.022	-0.075–0.031	0.421	0.706	0.651
25(OH)D + group + age + BMI + sex	SNOT-22	0.432	-0.174–1.038	0.163	0.343	0.219
25(OH)D + group + age + BMI + sex	VAS	0.089	-0.079–0.258	0.297	0.332	0.207

*The B coefficient represents the predicted change in the outcome per 1 ng/mL increase in 25(OH)D, with all other variables at constant levels. HC3 standard errors were used.

Test of group as a moderator

There was no evidence that the association between 25(OH)D concentration and clinical outcomes differed by group membership. No joint

test of the 25(OH)D $\times$ group interaction reached significance for LMS, LKS, SNOT-22, or VAS. Given the limited power of the interaction analysis, the data do not support the conclusion that clinical group modifies the relationships analyzed (Tab. 7).

Tab. 7. Models with the 25(OH)D $\times$ group interaction.

Outcome	B 25(OH)D in the CRSwNP group	95% CI	p 25(OH)D	p interaction	R ²	Adj. R ²
LMS	−0.124	−0.262–0.013	0.076	0.246	0.800	0.770
LKS	−0.053	−0.145–0.039	0.257	0.281	0.698	0.652
SNOT-22	−0.073	−1.115–0.968	0.890	0.686	0.255	0.142
VAS	0.140	−0.376–0.657	0.594	0.945	0.293	0.186

DISCUSSION

Studies in various populations indicate a recurring association between lower 25(OH)D concentrations and more severe inflammatory changes in patients with CRS [2], particularly in those with CRSwNP [15,22,28]. The present study found no significant between-group differences in 25(OH)D concentration. Moreover, neither the within-group correlations nor the regression models adjusted for group, age, BMI, and sex indicated a significant association of 25(OH)D concentration with LMS, LKS, SNOT-22, or VAS scores. Nor did clinical group have a moderating effect. Possible explanations for the lack of significant between-group differences include the small size of the study population and the fact that recruitment spanned an entire calendar year (Tab. 2). Seasonal changes in UVB exposure could have increased variability in 25(OH)D concentrations in the study population through their effect on cutaneous vitamin D synthesis. In addition, some patients in the CRSwNP and CRSsNP groups had been using intranasal corticosteroids (INCS) before surgery. Data on the effect of INCS on serum 25(OH)D concentration are limited. Such an association is suggested by observational studies and post hoc subgroup analyses, although whether it is causal and what its direction is remain unclear. The most direct evidence comes from a retrospective study of 94 children with allergic diseases receiving vitamin D3 supplementation. Patients using INCS ($n = 37$) showed a greater absolute increase in 25(OH)D concentration than those not using these drugs (17.4 ± 14.7 vs. 14.5 ± 11.5 ng/mL) [25]. The authors hypothesized that, despite lower systemic absorption than that of oral formulations, INCS may reach the systemic circulation in substantial amounts and affect vitamin D metabolism by increasing bone turnover and enhancing the conversion of vitamin D3 to 25(OH)D [25]. It should be stressed, however, that the study involved a small sample and was retrospective; the authors themselves regarded the results as preliminary, requiring confirmation in larger studies [25]. Moreover, INCS use was not assessed as an independent factor. It was analyzed together with inhaled corticosteroid therapy, which makes it impossible to determine whether the observed

effect was specific to intranasal treatment [25]. Baseline 25(OH)D concentrations of approximately 15 ng/mL were similar across treatment groups in studies of allergic rhinitis that used INCS sprays. However, none of these studies showed changes in 25(OH)D concentration that could be directly attributed to INCS use [3,11]. Interpretation of total 25(OH)D measurements is further complicated by the effect of corticosteroids on vitamin D-binding protein levels, which may alter the relationship between total and free 25(OH)D [4]. Furthermore, associations observed in observational studies do not establish the direction of causality. INCS use may therefore affect 25(OH)D concentration; equally, lower vitamin D concentrations may be linked to more severe disease and thus to a greater need for INCS treatment [8,18].

The relationship between serum vitamin D concentration and LMS scores, which reflect the extent of changes on sinus CT, is less clear than its relationship with the presence and extent of nasal polyps. Several studies have shown a significant negative correlation between 25(OH)D concentration and LMS scores [2,18,15,31,18]. The findings across studies have not, however, been consistent. Wang's study showed an inverse association between 25(OH)D concentration and LMS scores, but the association did not reach statistical significance [29]. Another study found no significant association between 25(OH)D concentration and LMS scores, despite a significant association with SNOT-22 scores [27].

Previous studies suggest that lower serum 25(OH)D concentrations may be associated with more severe endoscopic findings, as assessed by the Lund-Kennedy score, in patients with CRS, but the results are inconsistent [2]. A significant inverse relationship between 25(OH)D concentration and LKS scores was demonstrated in the studies by He and Bavi [2,9]. In addition, the study by He showed that the Lund-Kennedy score was an independent risk factor for vitamin D3 deficiency and that a score of ≥ 14 points predicted 25(OH)D deficiency with a sensitivity of 92.5% [9]. However, not all studies have confirmed this relationship. In a Polish observational study involving 25 patients with CRSwNP, vitamin D concentration showed no significant correlation with

subjective or objective measures of disease severity, including the Lund-Kennedy score [5]. Contrasting results were also obtained in KNHANES, a nationwide population-based survey in South Korea, in which 25(OH)D concentrations were higher in patients with CRS than in controls, contrary to the hypothesis of an inverse relationship between vitamin D3 concentration and disease severity [14].

Our analysis showed marked between-group differences in the objective LMS and LKS scores. The highest values were observed in the CRSwNP group and the lowest in the control group of patients undergoing septoplasty. After adjustment for multiple testing, only the strong positive correlation between LMS and LKS scores in the CRSwNP group remained significant out of the 21 correlations examined. This finding indicates that more extensive CT changes and more severe endoscopic findings tend to co-occur in this group. Discrepancies between the results of previous studies may stem from differences in population characteristics, CRS phenotypes, group sizes, vitamin D assay methods, and methods of assessing disease severity.

Only limited data are available on how vitamin D concentration relates to VAS scores in patients with CRS. Published studies have produced conflicting results: one showed an improvement in VAS scores after vitamin D supplementation, whereas an observational study found no significant relationship between baseline 25(OH)D concentration and symptom severity measured with this scale [1,5]. By contrast, the vast majority of studies have used the SNOT-22 questionnaire, and its scores have consistently shown an inverse relationship with 25(OH)D concentration.

With regard to subjective symptom severity, most previous studies point to an inverse relationship between serum 25(OH)D concentration and SNOT-22 scores [2,18,27,31].

VAS and SNOT-22 scores were similar between patients with CRSwNP and CRSsNP in this study. For the VAS, the control group scored significantly lower than both clinical groups, whereas for the SNOT-22, the only significant difference was between the CRSsNP and control groups.

Unlike some earlier studies, we found no significant relationship between 25(OH)D concentration and SNOT-22 or VAS scores. Small group sizes, low statistical power, and wide confidence intervals are the main constraints on interpreting this finding. Moreover, both the SNOT-22 and VAS reflect a subjective assessment of symptoms and quality of life, which are influenced by many factors not directly related to the severity of inflammation. The Benjamini-Hochberg correction

reduced the risk of false-positive results but was not responsible for the lack of significance: the unadjusted p values for the correlations of 25(OH)D with SNOT-22 and VAS scores also exceeded 0.05 in all groups.

CONCLUSIONS

In this small sample, no statistically significant association was found between 25(OH)D concentration and LMS, LKS, SNOT-22, or VAS scores. Considering 25(OH)D concentration as a stand-alone biomarker of disease severity or subjective symptom perception is not supported by these data. Given the limited statistical power, wide confidence intervals, and exploratory nature of the regression models, the results need to be confirmed in larger samples.

LIMITATIONS OF THE STUDY

This study has several limitations that should be considered when interpreting the results. The main limitation was the relatively small sample ($N = 39$), comprising groups of 10 to 17 patients. This limited the statistical power of the correlation and regression analyses and reduced the likelihood of detecting weak or moderate associations. This is reflected in the wide confidence intervals, especially for the correlation coefficients and interaction effects, which indicate limited precision of the estimates. Consequently, the lack of statistical significance should not be interpreted as conclusive evidence that no association exists. A marked floor effect in Lund-Mackay and Lund-Kennedy scores among patients scheduled for septoplasty posed another limitation. The low variability of scores in this group limited the ability to detect correlations with other variables and reduced the informative value of analyses involving these scales. It should also be emphasized that the linear regression models used to analyze the relationship between 25(OH)D concentration and LMS and LKS scores were exploratory. The use of HC3 robust standard errors improves the robustness of estimation when the homoscedasticity assumption is violated; however, the restricted score range of these scales and the floor effect still impose limitations. A further limitation was that the groups differed in sex distribution and in the frequency of intranasal corticosteroid use. Age, sex, and body mass index were included in the multivariable analyses, but given the small sample size, we deliberately refrained from building more complex models with more covariates to avoid overparameterization. The sex distribution in the study groups reflects the characteristics of

the participants who met the inclusion criteria and agreed to take part in the study during the recruitment period. Sex was not a criterion for selecting participants, nor was a matching procedure applied. The predominance of one sex in some groups may be a limitation of the study. As for the difference in group sizes, the CRSsNP group was smaller because fewer participants met the predefined inclusion criteria for this subgroup during the study period. Despite successive recruitment, this produced unequal numbers of patients in the CRSwNP and CRSsNP groups.

Despite the listed limitations, the study also has important strengths. These include the prospective design, uniform eligibility criteria consistent with the EPOS 2020 guidelines, a comprehensive assessment of disease severity covering radiologic, endoscopic, and subjective parameters, and rigorous statistical methods, including correction for multiple comparisons and regression models with robust standard errors. The results therefore provide a valuable basis for planning further studies in larger, multicenter cohorts. In addition, clinically relevant differences in 25(OH)D concentration could not be ruled out by the absence of significant between-group differences; wide confidence intervals and small group sizes restricted the precision of the estimates and the ability to detect potential associations with the clinical measures analyzed.

AUTHORS' DECLARATION

Study design: Agnieszka Witkowska-Janik, Andrzej Wojdas. **Conducting the research:** Agnieszka Witkowska-Janik, Andrzej Wojdas. **Statistical analysis:** Marcin Biernacki. **Interpretation of results:** Agnieszka Witkowska-Janik, Marcin Biernacki, Łukasz Dziuda, Andrzej Wojdas. **Manuscript preparation:** Agnieszka Witkowska-Janik, Marcin Biernacki, Łukasz Dziuda, Andrzej Wojdas. The authors declare that they have no conflicts of interest.

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