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Vitamin D Status and SLE Disease Activity among Dubai Hospital Lupus Patients

Naureen Ali and Fakhriya Alalawi

ABSTRACT

***Background*: Vitamin D deficiency is common worldwide, but is particularly prevalent in the Middle Eastern region, where cultural and religious factors influence its incidence further. As patients with Systemic Lupus Erythematosus (SLE) avoid sun exposure and use medications that could potentially result in vitamin D deficiency, this problem becomes more apparent. Unfortunately, there are no data available on the prevalence of vitamin D deficiency among patients with SLE in our local area.**

***Objective*: To assess the prevalence of vitamin D deficiency among patients with a new onset of systemic lupus erythematosus in Dubai, and to determine whether low vitamin D levels are correlated with disease activity.**

***Methodology and Data Collection:* a retrospective cohort study of patients with new onset of Systemic Lupus Erythematosus, being diagnosed in less than 1 year and were followed up at Dubai Hospital (UAE) from January 2009 till December 2012. Demographic and clinical data were collected as well as 25(OH) D3 levels. The incidence of vitamin D insufficiency was calculated as a ratio between the numbers of patients with 25(OH) D levels below the specified cut-off values (30ng/ml and 10ng/ml, respectively). SLE was diagnosed according to the American college of rheumatology (ACR SLE) classification criteria of 1997. Patients with drug-induced SLE and vitamin D deficiency were excluded.**

***Results:* a total number of 150 patients were included. 87% (n=131) were females and 13% (n=19) were males. The mean vitamin D level at the baseline was 21.6+/- 47 (mean +/- SD), increased to 27.8+/- 16 at 1 year, while the SLEDAI has improved from 8.3+/-5 (mean +/- SD) to 2.4 +/- 2.9 at 1 year respectively. The changes in vitamin D level as well as the SLEDAI were statistically significant with a P value <0.001. Spearman correlation test showed a statistically significant inverse correlation between vitamin D level versus SLEDAI % from baseline to 1-year later.**

***Conclusion:* This study showed a direct inverse relationship between lupus activity and a low level of vitamin D. Furthermore, the SLE disease activity score got better with the improvement in vitamin D level, measured at baseline, and after 12 months period.**

Keywords: SLE, SLEDAI, vitamin D deficiency.

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I. Introduction

Systemic lupus erythematosus (SLE) is a worldwide disease; however, the prevalence and severity of the disease depend on different clinical manifestations among each ethnic group [1]. Lupus prevalence has nearly tripled over the past 40 years, as a result of an increasingly confident approach in diagnosing the disease.

The Center for Disease Control and Prevention (CDC) estimates a prevalence of 72.8 per 100,000 person-years in the United States, while the estimated annual incidence of SLE in North America, South America, and Europe ranges from 2 to 8 cases per 100,000 population per year [2], [3]. Women are affected almost nine times more than men [3]. The disease has been found to be more common in urban than rural areas. About 65 percent of patients with SLE are diagnosed between the ages of 16 and 55, 20% before 16 years of age, and 15% after the age of 55 [4].

SLE is a chronic disease with unpredicted morbidity and mortality. Ethnicity is associated with disease progression and severity. Afro-American lupus patients were found to have higher mortality than their Caucasian counterparts. The difference in outcome was attributed to genetics and other factors such as education, culture, socioeconomic status, etc [4]-[11]. Clinical and immunological features of lupus have been described also in Arabs. A number of studies have compared Arab patients with Caucasian counterparts; except for the high prevalence of anti-Ro antibodies among Arabs, there were no other significant differences [12].

A. Vitamin D

Vitamin D belongs to a group of fat-soluble steroids which are responsible for the intestinal absorption of calcium, iron, magnesium, phosphate, and zinc. The most important compounds are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Ergocalciferol (vitamin D2) is converted from ergosterol found in fungi or yeast on exposure to UVB light [13]. The human body can also synthesize vitamin D (specifically cholecalciferol; vitamin D3) in the skin, from cholesterol, when expose to adequate sunlight [14]-[16]. Upon exposure to ultraviolet B radiation, the human skin acts on 7-dehydrocholesterol to convert it to pre-vitamin D3 which in turn isomerize into vitamin D3 [14]. Similarly, following dietary ingestion of vitamin D as a fat-soluble vitamin, it will be converted into chylomicrons and transported from lymphatics to the venous system. Most of the endogenously synthesized vitamin D is transported to the liver and the remaining is extracted by adipose tissue and muscle. The hepatocytes metabolize vitamin D 25-hydroxylases (microsomal CYP2R1 and mitochondrial CYP27A1) by the cytochrome P450 enzymes to 25-hydroxy vitamin D (25(OH)D) [17]. Another cytochrome P450 enzyme, 1α-hydroxylase (CYP27B1), acts on 25(OH)D and converts it to active metabolite form of vitamin D, 1,25-hydroxy vitamin D (1,25(OH)2D) in the proximal tubules of the kidneys [18], [19]. A large concentration of 25(OH)D in the human body is found in the adipose tissue and muscles, while the maximum level noted in the plasma and measured in the serum is 20-150 nmol/L or 8-60 ng/ml [20]. The circulating half-life of 25(OH)D is about 10-15 days [17]-[21], however, it has a half-life of 2-3 months when released effectively from tissue stores [22]. The kidney produces 1,25(OH)2D that circulates in the blood at levels in a picomolar range, which is equivalent to about one-thousandth of 25(OH) D. The hormone (PTH) and fibroblast growth factor 23 (FGF23) responds to serum calcium and phosphate, and thus controls the rate-limiting step in the synthetic pathway via 1α-hydroxylation [23]. 85-90% of the vitamin D metabolites produced in these pathways are bound to vitamin D-binding protein (DBP, also known as group-specific component globulin, Gc-globulin) and about 10-15% is bound to albumin, while less than 1% is transported in the circulation in the free form [24], [25]. Nearly all DBP is produced in the liver, where its regulation is influenced by estrogen, glucocorticoids and inflammatory cytokines but not by vitamin D itself [24].

B. Epidemiology and Etiology of Vitamin D Deficiency

Vitamin D deficiency has become a worldwide pandemic. Lack of exposure to the sun is the major cause of vitamin D deficiency [26]. Vitamin D can be found naturally in a limited number of foods, while the amount of vitamin-D in fortified foods is often insufficient to meet the vitamin-D necessities [27].

Vitamin D deficiency contributes to diseases like rickets in children and osteopenia, osteoporosis, and fractures in adults. Certain studies showed that Vitamin D deficiency has been associated with an increased risk of common cancers, autoimmune diseases, hypertension, and infectious diseases [28]. Vitamin D's health benefits are maximized when its circulating levels are >75 nmol/L or 30 ng/mL [28]. Supplementation of vitamin D3 with 800-1000 IU/day is required in the absence of adequate sun exposure [28].

Vitamin D production is known to decline with ageing, making older populations more dependent on dietary vitamin D [29]. Additionally, it has been noted in several analyses that vitamin D status can fluctuate throughout the year based on climate, with levels of 25(OH)D peaking after the summer and falling after winter, with nearly two-thirds of healthy, young adults were vitamin D insufficient by the end of winter [30], [31]. Blacks have a higher prevalence of vitamin D insufficiency compared to non-Hispanic white individuals. This was explained by Holick and co-authors as darker skin might interfere with the cutaneous synthesis of vitamin D leading to less vitamin D production since melanin requires more ultraviolet radiation to increase vitamin D levels. Thus, non-Hispanic blacks may require six times the amount of UV radiation to produce serum vitamin D concentrations comparable to those of non-Hispanic whites [32]. On different analysis in Boston, 73% of the black elderly population were vitamin D insufficient, compared to 35% of elderly non-Hispanic whites, while another study found 40% of black women to be vitamin D deficient (25(OH)D < 16 ng/mL), compared to 4% of white women [33], [34]. In a study from the Middle East involving 316 young adults aged 30-50 years, 72.8% had 25(OH)D levels less than 15 ng/dL (severely deficient). Women were significantly more affected than men (83.9% vs 48.5%, respectively), likely due to religious and cultural practices resulting in reduced skin exposure in women. This difference in prevalence highlights the impact of gender-based cultural norms on skin health [35], [36].

In developing countries, hypovitaminosis-D is a highly alarming issue across all age groups. In undeveloped countries, randomized controlled trials are needed to determine the optimal dosage, timing, and impact of vitamin D supplementation on various health conditions. Based on local studies, these policies would need to be tailored to local contexts and preferences [37].

C. Vitamin D and Protective Immunity

Vitamin D classically acts on promoting calcium homeostasis and bone formation. It enhances the absorption of calcium from the small intestine and promotes osteoclast differentiation. The reabsorption of calcium thus helps to promote the mineralization of the collagen matrix in bone [18]. Vitamin D receptors are also expressed in other body tissues such as cells in the bone marrow, brain, colon, breast, malignant cells and immune cells (B cells, T cells and antigen-presenting cells), suggesting the role of vitamin D goes beyond its effects on calcium and bone homeostasis [38]. Vitamin D can act in a local immunological milieu in an autocrine manner [39]. The expression of vitamin D receptors by cells of the immune system has challenged the research on the immunomodulatory properties of vitamin D. The immune system which consists of innate and adaptive immune systems are composed of cells such as macrophages, dendritic cells, T cells, and B cells which express vitamin D receptors that may respond to the biologically active form of vitamin D (1,25-dihydroxy vitamin D) [40], [41]. By activating the innate immune system, vitamin D contributes to protective immunity, where macrophages can recognize

lipopolysaccharide (LPS) through toll-like receptors (TLR), triggering a cascade of actions to generate peptides with powerful bactericidal activities, such as cathelicidin and beta-defensin. In the phagosomes of ingested bacteria, these peptides possess potent anti-microbacterial properties by interacting with the cell wall membrane [42]. Thus, Vitamin D deficiency has been associated with an increased infection rate in multiple cross-sectional studies. A report from 1988 and 1994 studied almost 19,000 subjects found that people with low vitamin D levels (<30 ng/ml) have higher rates of upper respiratory tract infections compared to people with sufficient levels, even when other variables like race, season, gender, weight, and age are adjusted [43]. Similarly, 800 military workers in Finland were stratified based on their vit. D levels in a cross-sectional study. Workers with lower vitamin D levels had a greater number of days of absence from active duty as a result of upper respiratory infections than workers with elevated vitamin D levels (above 40 nmol) [44]. Several other studies that looked at vitamin D levels and rates of influenza, bacterial vaginosis, and HIV have all reported an association between low vitamin D levels and increased infection rates [45]-[48]. The benefits of vitamin D administration to decrease infection, however, have been inconsistent across studies, probably as a result of different methodologies. In a recent prospective double-blind placebo study, vitamin D administration was associated with a statistically significant (42% reduction) in influenza infection rates [49], [50].

Similarly, vitamin D has been linked to lupus cases in numerous studies. Compared to the general population, patients with lupus had a high prevalence of vitamin D deficiency. Furthermore, vitamin D deficiency was inversely related to Lupus disease activity [51]. Interestingly, similar findings of this inverse correlation were described in patients with other autoimmune diseases such as Rheumatoid arthritis (RA) and Multiple sclerosis [52]-[56].

The effect of vitamin D is linked with cells within the immune system, and it has the ability to inhibit B cell proliferation and blocks B cell differentiation and immunoglobulin synthesis [40], [41]. Probably through the direct effect of 1,25(OH)2D on B-cell homoeostasis, inhibition of plasma cells and switched memory cells differentiation. These effects are believed to be relevant to B-cell-related autoimmune disorders such as systemic lupus erythematosus (SLE) and IL-10 and CCR10, suggesting vitamin D has a repertoire of B-cell responses that extend beyond its effects on B-cell proliferation and Ig production [41], [57], [58].

Furthermore, vitamin D suppresses T cells proliferation which results in a shift from a Th1 to a Th2 phenotype and influences T cell maturation by changing away from the inflammatory Th17 phenotype and facilitates the induction of T regulatory cells. This process results in reduced inflammatory cytokines (IL-17, IL-21) production, inhibits monocyte production (IL-1, IL-6, IL-8, IL-12 and TNF) and increases the formation of anti-inflammatory cytokines such as IL-10. These additionally inhibit DC differentiation and maturation and preserve the immature phenotype as demonstrated by decreased expression of the MHC class [59]-[68]. Inhibition of DC differentiation and maturation is critical in the context of autoimmunity and the abolition of self-tolerance. Antigen presentation to a T cell by a mature DC accelerates an immune reaction against that antigen, while antigen presentation by an immature DC facilitates tolerance [39].

In different autoimmune diseases, the vitamin D responsiveness by immunologic components follows B cells. Vitamin D may partially reverse B cell abnormalities in lupus patients. The B cells produced from both spontaneous and stimulated immunoglobulin from active lupus patients; are significantly decreased by pre-incubating cells with 1,25 vitamin D. Furthermore, pre-incubation with vitamin D drastically reduces spontaneous anti-DNA antibodies production by almost 60% [69].

II. Methodology

A. *Objective*

To assess the incidence of vitamin D deficiency in individuals with new-onset systemic lupus erythematosus in Dubai, and to verify if low vitamin D levels are associated with disease activity among those lupus patients.

B. Study Design and Study Population

A retrospective cohort study was conducted at Dubai Hospital (DUBAI, UAE) between January 2009 and December 2012 on patients newly diagnosed with Systemic Lupus Erythematosus (diagnosed in less than 1 year). All cases that fulfilled the inclusion criteria in the determined period were allocated and enrolled in the study.

The inclusion criteria included:

1. All UAE nationals male and females,
2. Patients fulfilling ACR1997 diagnostic criteria for diagnosis of systemic lupus erythematosus,
3. Patients with vitamin D3 checked at Dubai hospital labs were included to avoid laboratory variations

Patients less than 18 years of age were excluded. Also, patients with drug induced SLE and vitamin D deficiency were excluded.

A total of 150 SLE patients had fulfilled the criteria were included, all were United Arab Emirates nationals.

C. Methodology and Biochemical Analysis

All cases of Systemic lupus erythematosus were identified by a rheumatologist, based on 1997-revised American College of Rheumatology classification criteria. SLE disease activity was calculated by SLE Disease Activity Index (SLEDAI). It is a weight-pointed questionnaire that describes active lupus within 10 days of assessment, ranging from 0-105 points, and it includes both clinical and laboratory parameters. Active lupus disease was considered if the SLEDAI score was above 10 and inactive if the score was below 4. The SLEDAI measurement was performed for all patients, along with the measurement of the 25OH level at the same time.

Vitamin D3 (25(OH) D) levels for deficiency were determined as <20ng/ml, and insufficiency at levels between 20-30ng/ml, based on the definitions of the American Association of Clinical Endocrinologists, while sufficiency is diagnosed with 25(OH) D levels >30 ng/dl [70]. The frequency of vitamin D deficiency is assessed as a ratio of patients with 25(OH)D levels below 30 ng/dl compared to the

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total number of patients included. The vitamin D levels are calculated for the lupus patient at baseline (i.e., at the time of first presentation, prior to vit D supplementation) and at 1 year with lupus disease activity. During the entire study period, all vitamin D measurements were performed locally at Dubai Hospital's biochemistry lab, using a radioimmunoassay technique (Diasource, Louvain-la-Neuve, Belgium). Demographic, clinical and laboratory data were collected. Data were cross-checked with the electronic data system (SAM) to confirm accuracy.

D. Statistical Methodology

Analysis of data was done using SPSS (statistical program for social science version 12). Quantitative variables were described as mean, SD and range, and the qualitative variables as numbers and percentages. The chi-square test was used to compare qualitative variables between groups. Wilcoxon test was applied to compare quantitative non-parametric data in the same group and the Spearman Correlation coefficient test was applied to rank variables versus each other positively or inversely. *P* value >0.05 was considered as insignificant, *P*<0.05 as significant and *P*<0.01 as highly significant.

III. Results

The vitamin D levels are calculated for the lupus patient at the baseline (at the time of first presentation and prior to vitamin D supplementation) and at 1 year following lupus disease activity. Table I shows vitamin D level at the baseline which was 12.6 ng/ml (SD 18+16 ng/ml) and a year later, which has an average improvement to 18.2 ng/ml (SD 29+17 ng/ml). The improvement was seen in 94.8% (p <0.001) of lupus patients. Table II describes SLEDAI at baseline and at 1 year which has a statistically significant improvement from a mean of 4 (2-6 SD 6+5) at a baseline to 2 (0-4 SD 2+3) at 1 year, p=<0.001. The percentage of patients who had a vitamin D level of less than 8 ng/dl at baseline was 21% (n=31) and this has dropped to only 3% at one year, reflecting an improvement in vitamin D level.

TABLE I: Changes in Vit D at Baseline and after A Year of Follow-up (using Wilcoxon Test)

Variables	Mean ± SD	% of change	z	P
Vitamin D at baseline	12.6 (7-20) 18±16			
Vitamin D after 1 year	18.2 (11.4-30) 29±17	94.8%	6.2	<0.001

TABLE II: Changes in SLEDI at Baseline and after 1-Year Follow-up

Variables	Mean ± SD	% of change	z	P
SLEADI baseline	4 (2-6) 6±5			
SLEDAI after 1 year	2 (0-4) 2±3	7.8%	7.8	<0.001HS

Similarly, those with vitamin D levels between 8-20 ng/dl had dropped from 49% to 20% at one year, while the number of patients with vitamin D levels >20 ng/dl at one year rose from 22% to 41%, expectedly; Fig. 1. Using spearman correlation, we were able to find a statistically significant inverse correlation between vitamin D and SLEDAI at different intervals following the correction of vitamin D, as seen in Fig. 2, Tables III and IV.

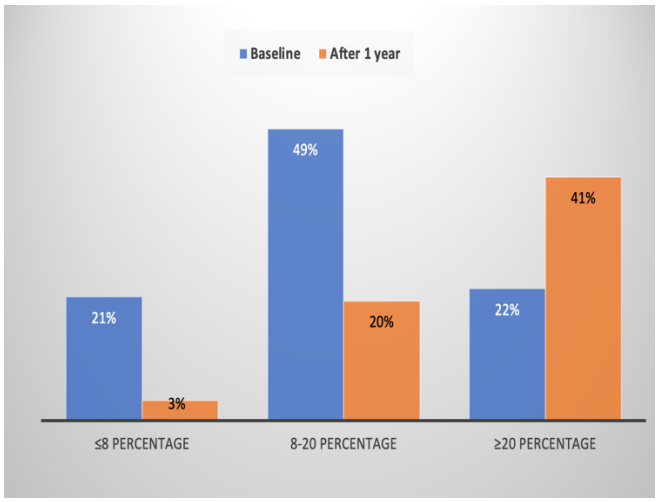

Fig. 1. Improvement in vitamin D levels following correction.

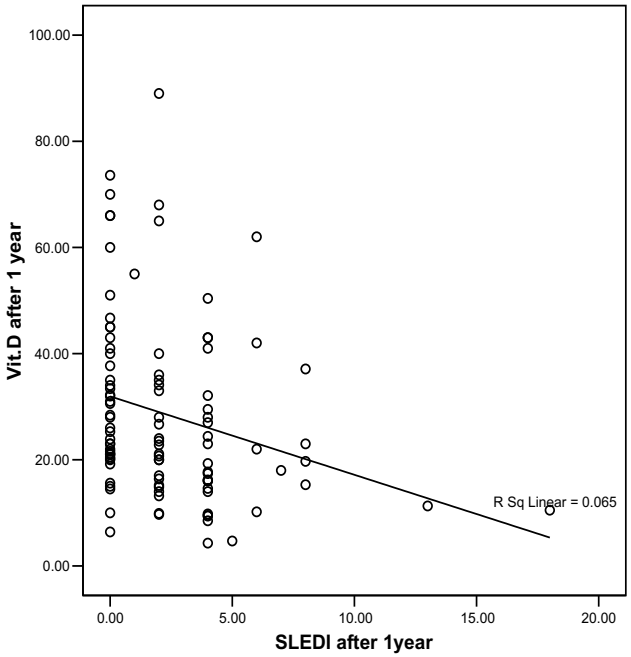

Fig. 2. An inverse correlation between vitamin D and SLE disease activity (SLEDAI) from the baseline and at 1 year, following the correction of vitamin D.

TABLE III: Distribution of the Studied Group, based on Lab Data and SLEDAI at Baseline and A Year of Follow-up

Variables	Mean ± SD	Range	median (IQR)
Vitamin D baseline	21.6 ± 47	3-70	12.6 (7-20)
Vitamin D after 1 year	27.8 ± 16	4.3-89	18.2 (11.4-30)
SLEDAI baseline	8.3 ± 5	0-25	4 (2-6)
SLEDAI after 1 year	2.4 ± 2.9	0-18	2 (0-4)

TABLE IV: Correlation between SLEDAI versus Vitamin D among the Studied Cases

Correlation	SLEDAI baseline	SLEDAI after 1 year
	-0.20*	-0.30*

IV. Discussion

This is a retrospective cohort study to explore the prevalence of vitamin D deficiency among newly diagnosed Lupus patients and to investigate the relationship between vitamin D levels and SLE disease activity in patients following up at Dubai Hospital (Dubai population) of the United Arab Emirates. This study was conducted in a hot-climate country where the sun is excessively exposed throughout the year, which is conducive to vitamin D synthesis. Nevertheless, it showed that low vitamin D levels were common in SLE patients residing in Dubai. Moreover, those with low vitamin D had a higher level of disease activity in inverse correlation and vice versa. The same finding of vitamin D deficiency was reported by Damanhouri in 165 Saudi patients with SLE [71].

Reference [72] reported significantly lower levels of 25(OH)D in patients with active SLE compared to those with inactive disease (p=0.04). Additionally, they reported a significant negative correlation between 25(OH) D and anti-ds-DNA (p<0.001); and a positive correlation between 25(OH)D levels and C4 level (p=0.25). In other words, lupus patients had a higher risk of developing 25(OH)D deficiency in the presence of low serum C3, C4, and high anti-dsDNA levels [72]. Similarly, [73] described a high prevalence of vitamin D deficiency among lupus patients in Indonesia, compared to healthy controls and the low vitamin D level was positively correlated with the disease activity, similar to our findings. The association between SLE and hypovitaminosis D had been confirmed in different analyses [74]-[78]. A recent analysis in China conducted on 290 lupus patients, also demonstrated a reciprocal relationship between vitamin D level and SLEDAI score, independent of age, sex, disease duration, vitamin D supplements and immunosuppressive agents [79]. A multi-centered study conducted in Europe and the Middle East involving 378 SLE patients [80] and a study in Brazil involving 36 SLE patients [81] also found a similar correlation. Similar observations were reported as well in different places and among different ethnicity, which concluded that vitamin D is important for disease severity in SLE patients. The findings also supported the hypothesis that vitamin D deficiency might be a risk factor for severe disease activity in autoimmune diseases [82], [83]. In contrast, other studies did not demonstrate a such an association. Reference [84] reported no significant correlations between vitamin D and immune markers or disease activity score before and after vitamin D and calcium supplementation, though patients who received supplementation showed significant (P= 0.002) improvements in bone mineral density. Similarly, [75] in Korea reported that vitamin D was not correlated with the disease activity; this study involved a relatively well-controlled group.

Various factors can contribute to hypovitaminosis D in SLE patients, such as using long-term sunscreens, avoidance of the sun lights due to photosensitive rashes and the possibility of disease flare, lack of dietary intake, and full-coverage clothing as a cultural norm [37], [46], [51], [85]. Additionally, Anti-vitamin D antibodies were observed in a subgroup of patients with SLE, contributing further to low vitamin D levels [86].

In our study, we could demonstrate that supplementation with vitamin D had improved the disease activity measured by SLEDAI. Many experts have supported adding vitamin D to overcome vitamin D deficiency in lupus patients [73]. However, the therapeutic advantages of vitamin D supplementation have not yet been confirmed [73], [87], and additional interventional studies are necessary to establish its efficacy.

Although UAE is considered to be a sun-blessed country, evidence suggests that vitamin D deficiency could be a major health concern among young Emirati adults [88].

SLE and hypovitaminosis D are not well studied in UAE, and the available literature in UAE has been performed on Vitamin D deficiency among various adult populations [89]-[92]. To our knowledge, this is the first study to assess vitamin D deficiency among lupus patients in Dubai, UAE and studied the relationship between low vitamin D levels and lupus disease activity.

V. Conclusion

Based on the results of this small-scale retrospective cohort study, vitamin D deficiency seems to influence SLE disease activity. Therefore, all patients with SLE should have their vitamin D levels checked and supplemented accordingly. To validate the conclusions of this study, prospective analyses on a larger scale are needed. This will provide a clearer understanding of the results and ensure that any conclusions drawn can be reliably supported.

Study Limitations

This is a retrospective study and has all the limitations of a single-centre registry and is therefore subjective to possible bias and confounding.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

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