Prevalence of Vitamin D deficiency among individuals with Fontan palliation: A systematic review and meta-analysis

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ABSTRACT

Background : **Children with one functional ventricle might receive the Fontan procedure as palliative management to prolong their lives. However, the heart remains functionally univentricular, which may result in disrupted absorption of nutrients, including Vitamin D. Individuals with Fontan circulation have limited physical activity and sun exposure, which might further contribute to Vitamin D deficiency.**

Objective : **This study aimed to estimate the prevalence of Vitamin D deficiency among individuals with Fontan circulation and analyze probable contributing factors to it through meta-regression analysis.**

Methods : **A predetermined search strategy was applied on PubMed, Scopus, Scilit, Web of Science, Europe PMC, and Google Scholar to identify relevant literature as of July 2024. In general, studies reporting the prevalence or incidence of Vitamin D deficiency (<20 ng/mL) among Fontan patients were eligible for inclusion. Only cohort and cross-sectional studies were included. The pooled estimates were carried out using a restricted maximum-likelihood model and Freeman–Tukey double-arcsine transformation (FTT).**

Results : **Six studies were included, comprising 255 individuals with the Fontan circulation. The prevalence of Vitamin D deficiency was 51% (95% confidence interval: 35%– 67%) with noticeable heterogeneity (I^2 = 84.38%; *p*-Het <0.001). Extracardiac conduit/lateral tunnel (*P* = 0.003) was the main contributor to the heterogeneity.**

Conclusion : **Vitamin D deficiency is highly prevalent among individuals with Fontan palliation, highlighting the need for active monitoring and investigation into the benefits of Vitamin D supplementation.**
PROSPERO registration: CRD42024574724.

Keywords : 25-hydroxyvitamin D, congenital heart disease, single ventricle palliation, surgery, Vitamin D

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INTRODUCTION

The Fontan procedure is a palliative surgical option for children with complex congenital heart disease (CHD), characterized by single ventricle physiology and low pulmonary vascular resistance.[1] Fontan procedure reduces the mixing of deoxygenated and oxygenated blood and mitigates single ventricle volume overload. However, the resulting circulation, with systemic and pulmonary circuits in series, remains hemodynamically abnormal.[2,3] While most patients survive into adulthood, they experience reduced quality of life, exercise capacity, and life expectancy.[4] The prevalence of Fontan patients is projected to rise by nearly 20%, from 66 people per million in 2020 to 79 people per million by 2030.[5] The survival rate 25 years after surgery was reported to be over 75%, but long-term morbidity remains high.[6] The Fontan physiology is associated with chronic venous hypertension, which results in reduced vascular perfusion and subsequent organ fibrosis.[3] Chronic venous hypertension also impairs gastrointestinal perfusion, contributing to chronic intestinal inflammation, protein-losing enteropathy, and malabsorption of nutrients such as Vitamin D and calcium.[7]

Although the underlying pathological mechanism remains unclear, multiple studies have reported a high prevalence of Vitamin D deficiency in Fontan patients.[8-10] To the best of our knowledge, no meta-analysis has been conducted to estimate the prevalence of Vitamin D deficiency in a larger Fontan population. The aim of this study was to estimate the prevalence of Vitamin D deficiency among Fontan patients based on published individual studies across countries.

METHODS

Study design and setting

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered on PROSPERO (CRD42024574724). The research questions were: (a) What was the prevalence of Vitamin D deficiency among those who have undergone the Fontan procedure? and (b) What were the key factors influencing this prevalence?

Search strategy

A literature review was conducted across six databases: PubMed, Scopus, Scilit, Web of Science (WoS), Europe PMC, and Google Scholar. The search covered records from each database's inception through July 2024. Boolean operators and MeSH terms were applied, focusing on keywords related to Vitamin D and the Fontan procedure [Table 1].

Table 1: Keyword combinations employed across databases

Database	Fields	Keywords combination
PubMed	All	((Fontan OR "Fontan Operation" OR "Norwood Procedure" OR "Fontan Palliation" OR "Hemi Fontan" OR "Norwood" OR "Bidirectional Glenn" OR "Bidirectional Cavopulmonary Shunt" OR "Bidirectional Glenn Shunt" OR "Fontan Circulation" OR "Fontan Circuit") AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxy vitamin D" OR nutrient OR nutrition))
Scopus	All	((Fontan OR "Fontan Operation" OR "Norwood Procedure" OR "Fontan Palliation" OR "Hemi Fontan" OR Norwood OR "Bidirectional Glenn" OR "Bidirectional Cavopulmonary Shunt" OR "Bidirectional Glenn Shunt" OR "Fontan Circulation" OR "Fontan Circuit") AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxy vitamin D" OR nutri*))
Scilit	All	Fontan AND Vitamin D
WoS	All	(Fontan OR "Fontan Operation" OR "Stage 3 Norwood Procedure" OR "Fontan Palliation" OR "Hemi Fontan" OR "Norwood" OR "Stage 2 Norwood Procedure" OR "Bidirectional Glenn" OR "Bidirectional Cavopulmonary Shunt" OR "Bidirectional Glenn Shunt" OR "Fontan Circulation" OR "Fontan Circuit") AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxy vitamin D" OR nutrient OR nutrition)
Europe PMC	Title	(Fontan OR "Fontan Operation" OR "Stage 3 Norwood Procedure" OR "Fontan Palliation" OR "Hemi Fontan" OR "Norwood" OR "Stage 2 Norwood Procedure" OR "Bidirectional Glenn" OR "Bidirectional Cavopulmonary Shunt" OR "Bidirectional Glenn Shunt" OR "Fontan Circulation" OR "Fontan Circuit") AND ("vitamin D" OR "25-hydroxyvitamin D" OR "25-OH vitamin" OR Calciferol OR Cholecalciferol OR Ergocalciferol OR "1,25-dihydroxy vitamin D" OR nutrient OR nutrition)
Google Scholar	Title	Fontan AND Vitamin D

WoS: Web of Science

Eligibility criteria

Inclusion criteria were categorized according to the Population, Exposure, Comparison, Outcome, and Study Design (PECOS) framework. The population included Fontan patients, with exposure focusing on Vitamin D deficiency. The comparison group consisted of Fontan patients with normal Vitamin D levels, serving as controls. The primary outcome measured was the proportion of Fontan patients with Vitamin D deficiency, defined as serum 25-hydroxyvitamin D levels below 20 ng/mL. Finally, the study design included cross-sectional and cohort studies assessing the prevalence or incidence of Vitamin D deficiency in Fontan patients. The exclusion criteria were non-English articles and review articles. The

eligibility criteria were established in accordance with the protocols outlined in previously published pooled prevalence studies.[11]

Screening and selection

Duplicate records identified across databases were automatically removed using Zotero Desktop (version 6.0.36). Screening was first based on titles and abstracts, followed by a full-text review according to predetermined eligibility criteria. Two reviewers (F. K. and M. B. D.) independently conducted the screening and selection process. Discrepancies were resolved through reevaluation and discussion, with consultation from a third reviewer (M. H. G.) when necessary.

Data extraction and quality assessment

Data extracted from the research included patient details, specifics of the Fontan procedure, and associated outcomes. Patient characteristics included age, gender, body mass index (BMI), as well as the prevalence of Vitamin D deficiency within the sample size. The quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS), which evaluates three main parameters: selection, comparability, and outcome.[12]

Statistical analysis

Meta-analysis was performed using Rstudio version 2024.04.2 (Posit PBC, Boston, Massachusetts, the United States). Data heterogeneity were determined using I^2 >50% or P < 0.1 as the criteria. The restricted maximum-likelihood model and Freeman–Tukey double-arcsine transformation (FTT) were employed to calculate the total proportion, which was subsequently converted to prevalence by multiplying it by 100%.

RESULTS

Searching results

The present study encompassed six articles, including a total of 255 participants, among which 126 cases of Vitamin D deficiency were reported in Fontan patients. The initial search identified 825 published articles, with 29 duplicates removed. Screening of titles and abstracts resulted in excluding 782 articles deemed irrelevant to the research question. Following this, 12 articles were subjected to full-text screening, leading to the exclusion of six articles that did not meet the eligibility criteria. Consequently, six articles were included in the systematic review and meta-analysis.[8-10,13-15] The screening and selection process of the articles is illustrated in the PRISMA flow chart [Figure 1].

Characteristics of the included studies

Characteristics of the included studies (n = 6) encompassing a sample size of 255 participants are presented in Table 2. The included studies were cross-sectional (n = 3)[9,13,15] or cohorts (n = 3).[8,10,14] A higher number of the recruited patients received extracardiac conduit (ECC) as compared to the lateral tunnel (LT) Fontan procedure.[8,9,13,15] The mean age of the patients was below 15 years old in four studies,[8,13-15] and above 30 years old in one study.[10] Serum Vitamin D was measured through laboratory testing, particularly using tandem mass spectrometry,[13,15] liquid chromatography-tandem mass spectrometry,[9] and electrochemiluminescence immunoassay.[8]

Quality of included studies

Since the Fontan procedure is rare, we considered the minimum sample size of 30 as sufficient. Four studies recruited more than 30 Fontan patients,[9,13-15] with only one study that did not successfully recruit sufficient samples.[8] None of the included cross-sectional studies specifically reported a sample size calculation.[9,13,15] Most of the cohort studies reported nonbiased Vitamin D status,[8,14] except for one study that recruited individuals under Vitamin D supplementation.[10] All cross-sectional studies used medical records of the recruited patients to assure the Fontan palliation status.[9,13,15] Two studies adjusted their findings to sex and race,[13,15] while the adjustment variable in one study was not clearly reported.[9] Two studies did not control the confounding factors such as sex and age, either through eligibility criteria or statistical adjustment.[8,10] A study exclusively included a control group with similar age and sex, but no further adjustments were made to address bias from other factors.[14] All studies used standard laboratory tests to determine the level of circulating Vitamin D. Moreover, the studies reported complete statistical analysis protocols and presented all necessary statistical parameters.[8-10,13-15] In summary, four of the included studies were of good quality, and the two others were of poor quality [Table 3].

Prevalence of Vitamin D deficiency in Fontan patients

A pooled estimate of Vitamin D deficiency among Fontan patients was determined based on six included studies, with the results presented in Figure 2. The prevalence of Vitamin D deficiency was found to be 51% (95% confidence interval [CI]: 35%– 67%). This pooled analysis had high heterogeneity with I^2 of 84.38% and p-Het<0.001.

Meta-regression

Meta-regression with total sample size as a covariate revealed that sample size did not have a significant effect on the proportion, with a P = 0.441 [Figure 3]. Similarly, age (P = 0.382) and BMI (P = 0.382) did not significantly influence the proportion. ECC/LT (P = 0.003) was a statistically significant contributor to the heterogeneity of the proportion of Vitamin D deficiency [Figure 3]. Covariate sex was not analyzed in the meta-regression

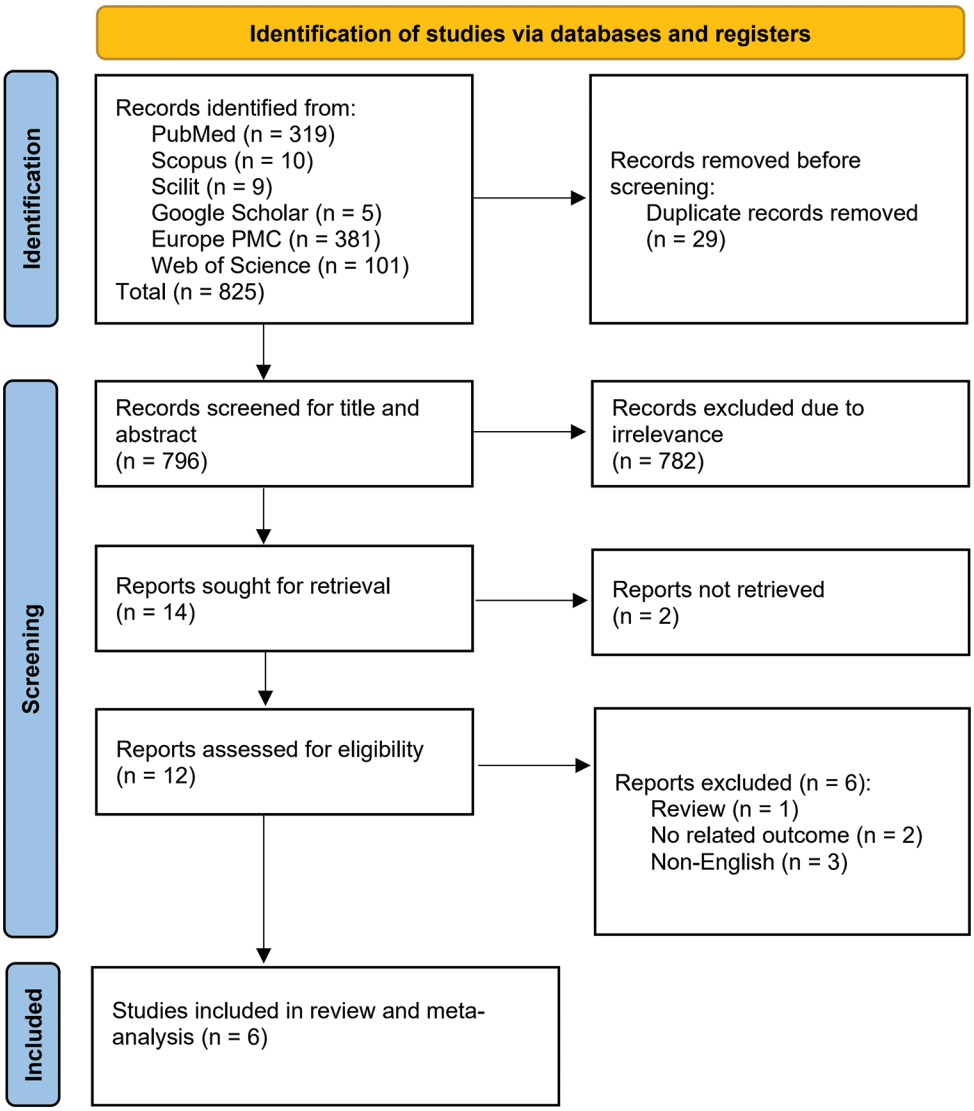

Figure 1: PRISMA flowchart of the included studies

Table 2: Characteristics and outcome of the included studies

Author, year[16]	Country	Design	Characteristics					Vitamin D measurement	VDD, *n* (%)	NOS quality
			Total, *n*	Fontan (ECC/LT)	Age (years)	BMI (kg/m^2)	Sex (male/female)			
Avitabile *et al.*, 2014[13]	United States	Cross-sectional	50	29/21	12.87±6.33	0.15±0.98[a]	26/24	MS/MS	20 (40.00)	Good
Hansson *et al.*, 2022[14]	Sweden	Prospective cohort	36	Not specified	12.3±3.9	0.23±1.1[a]	NR	NR	15 (41.67)	Good
Holler *et al.*, 2016[8]	Germany	Retrospective cohort	27	25/2	8.1±5.3	−0.6±1.6[a]	15/12	ECLI[A]	19 (70.37)	Poor
Avitabile *et al.*, 2015[15]	United States	Cross-sectional	43	25/18	14.05±6.5	0.16±0.88[a]	21/22	MS/MS	11 (25.58)	Good
Diab *et al.*, 2019[9]	Norway	Cross-sectional	64	49/10	Not specified	19.1±5.51	38/26	LC/MS	34 (53.12)	Good
Löffler *et al.*, 2024[10]	Germany	Retrospective cohort	35	Not specified	33±7.5	24.9±4.42	24/11	NR	27 (77.14)	Poor

[a]Reported as *Z*-score. ECC: Extracardiac conduit, ECLIA: Electrochemiluminescence immunoassay, LC: Liquid chromatography, LT: Lateral tunnel, MS: Mass spectroscopy, NYHA: New York Heart Association, NR: Not reported, VDD: Vitamin D deficiency, BMI: Body mass index, NOS: Newcastle–Ottawa Scale

because the ratio of male-to-female participants was similar across studies. Meta-regression on such data could be misleading and should, therefore be avoided in the meta-analysis report.[17]

Table 3: Quality of the included studies based on Newcastle–Ottawa Scale criteria

Study	Study design	Selection quality	Comparability	Outcome measures and analysis	Score	Quality
Avitabile *et al.*, 2014[13]	Cross-sectional	★★★★	★	★★★	8/10	Good
Hansson *et al.*, 2022[14]	Prospective cohort	★★★★	★	★★	7/9	Good
Holler *et al.*, 2016[8]	Retrospective cohort	★★★	-	★★	5/9	Poor
Avitabile *et al.*, 2015[15]	Cross-sectional	★★★★	★	★★★	8/10	Good
Diab *et al.*, 2019[9]	Cross-sectional	★★★★	★	★★★	8/10	Good
Löffler *et al.*, 2024[10]	Retrospective cohort	★★★	-	★★	7/9	Poor

-: No score, ★: Each represents one score

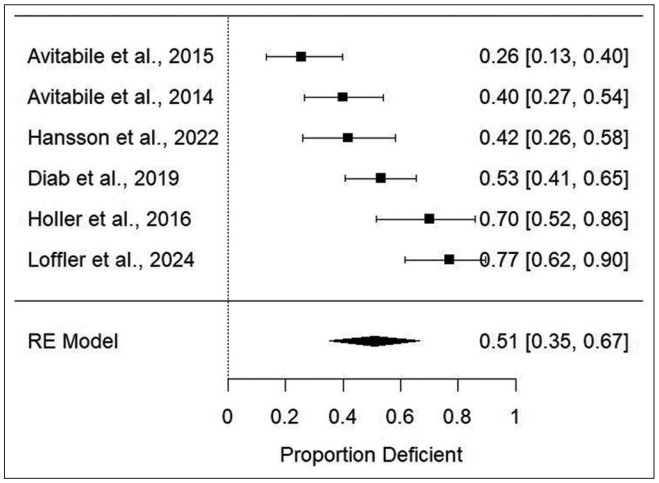

Figure 2: Forest plot for the pooled estimate of Vitamin D deficiency proportion among Fontan patients. Pooled proportion: 0.51 (95%: 0.35–0.67), I^2 = 84.38%, *P*-Het < 0.001

Vitamin D deficiency-related outcome

Avitabile *et al.* reported a significant association between serum Vitamin D level and leg lean mass.[13] In addition, a positive correlation between serum Vitamin D and serum Ca^{2+} levels was witnessed.[8] In Fontan patients, the New York Heart Association (NYHA) class was inversely correlated with both Vitamin D levels and ventricular ejection fraction.[10] Although Vitamin D levels were noted to decrease with age,[9] Holler *et al.* indicated no association between age and serum Vitamin D levels.[8] Furthermore, the interval between Vitamin D measurement and Fontan surgery did not significantly impact serum Vitamin D levels.[8] Several studies reported no associations between Vitamin D and body composition, liver biomarkers, or bone mineral density.[8,14,15] While there is no association between serum Vitamin D and PTH levels, Vitamin D supplementation significantly reduced parathyroid hormone levels.[8]

DISCUSSION

The prevalence of Vitamin D deficiency among Fontan patients in the present study was 51.0% (95% CI: 35.0%–67.0%), based on pooled data from 255 patients. Significant heterogeneity was observed (I^2 =84.4%). As a comparison, the global prevalence of Vitamin D deficiency (<30 nmol/L) among apparently healthy individuals was 15.7%.[18] A previous study reported that postoperative CHD patients exhibited a Vitamin D deficiency rate of 73%.[19] In addition, a study reported a 40% prevalence of Vitamin D deficiency among pediatric postoperative cardiac surgery patients.[20] Intraoperative fluid shifts, blood loss, and ultrafiltration contribute to the dilution of circulating 25(OH) D concentrations.[21] In addition, postoperative inflammation increases vascular permeability, leading to the leakage of Vitamin D-binding proteins, further reducing bioavailable Vitamin D.[22,23]

The present study found that ECC/LT status was a statistically significant factor in determining the prevalence of Vitamin D deficiency. The impacts of different approaches in Fontan completion on the metabolic process, particularly the Vitamin D metabolism, remain unclear. In a previous study, patients who received ECC were found to have poorer hemodynamic parameters compared to those who received LT.[24] The ECC approach uses a noncontractile prosthetic conduit to channel blood from the superior vena cava and inferior vena cava to the pulmonary arteries. Unlike the LT approach, which utilizes the patient's native tissue to form a contractile pathway, the rigid nature of the prosthetic conduit in ECC can lead to less efficient passive venous return.[1,9] This reduced flow dynamics may compromise pulmonary perfusion, potentially affecting metabolic processes such as Vitamin D metabolism and increasing the likelihood of deficiency. However, further evidence is needed to substantiate this connection between conduit type and metabolic impact fully. Moreover, while the ECC procedure aims to minimize myocardial ischemia and involves fewer suture lines, it may also lead to longer recovery times and increased postoperative complications.[10] These factors can contribute to a less stable clinical condition, affecting Vitamin D levels through decreased mobility and lifestyle factors such as reduced sun exposure and dietary intake.

Considering the high prevalence of Vitamin D deficiency among individuals receiving Fontan palliation, it is imperative to monitor the serum Vitamin D level among this population. Despite unclear effects of Vitamin D in this specific population, the serum levels have been positively associated with

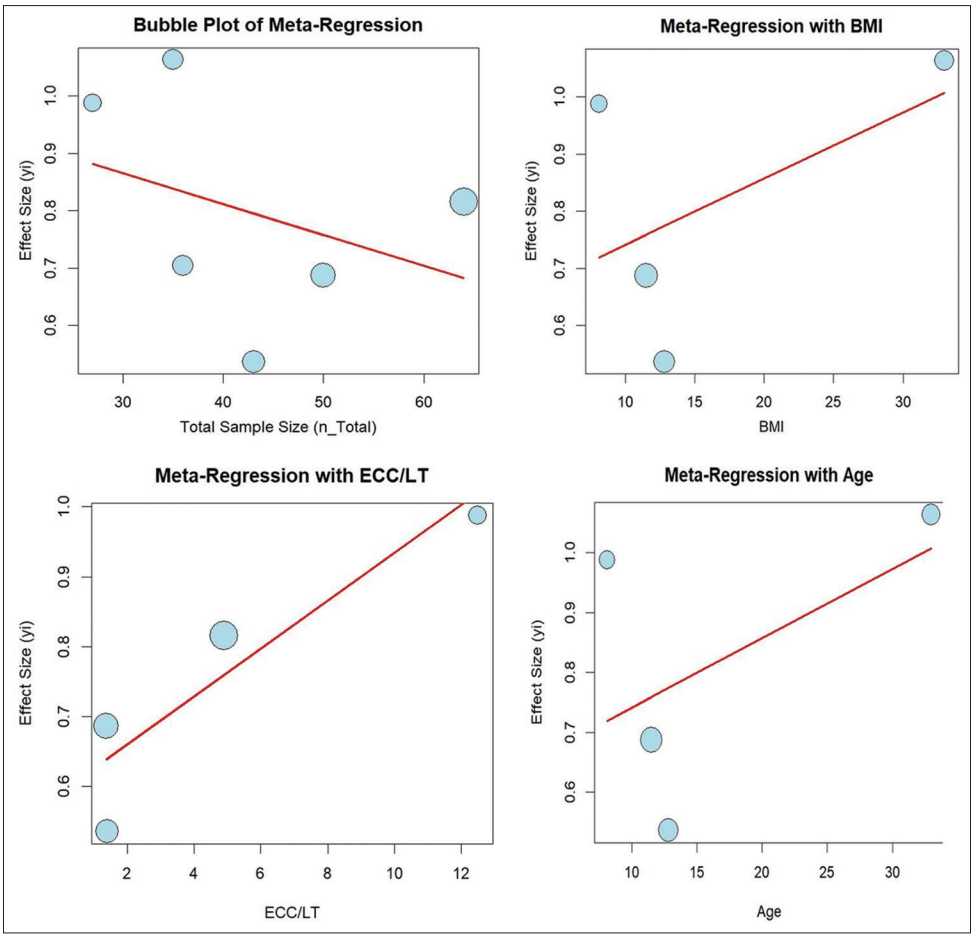

Figure 3: Buble plots for the meta-regression of Vitamin D deficiency proportion with sample size, body mass index (BMI), extracardiac conduit/lateral tunnel (ECC/LT) ratio, and age as covariates

leg lean mass,[13] serum Ca^{2+} levels,[8] and ventricular ejection fraction.[10] Interestingly, a study reported that Vitamin D supplementation could reduce PTH levels, a marker of poor cardiovascular health, regardless of baseline serum Vitamin D levels.[8] This reduction occurred even in the absence of a detectable association between serum Vitamin D and PTH, suggesting that the benefits of supplementation might be present even when serum levels do not reflect it directly.[8] This raises the possibility that the effectiveness of Vitamin D supplementation may be underestimated when solely relying on serum level estimation. Furthermore, Vitamin D supplementation has been suggested to induce higher anti-inflammatory cytokines (interleukin-10) during cardiac surgery, thus could mitigate the surgery-related inflammatory reaction.[21] The benefits of Vitamin D supplementation in improving cardiovascular health have been reported.[25] Therefore, it is critical to investigate the benefits of Vitamin D supplementation among patients with Fontan circulation.

The present study has several limitations, including the inclusion of both cross-sectional and cohort studies in the meta-analysis, which may contribute to the observed methodological heterogeneity. Moreover, the individual studies included in the meta-analysis had relatively small sample sizes. While the implications of Vitamin D deficiency are not fully understood, Vitamin D supplementation is essential for reducing parathyroid hormone levels. Therefore, randomized clinical trials are needed to assess the impact of Vitamin D supplementation on cardiac health and its benefits for Fontan patients.

CONCLUSIONS

Vitamin D deficiency was prevalent among individuals with Fontan circulation, with a pooled estimate of 51%. While the effects of this deficiency in this population are not fully understood, Vitamin D supplementation is essential for improving patient outcomes. Randomized clinical trials are needed to clarify the impact of Vitamin D supplementation on cardiac health and other benefits for Fontan patients.

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Conflicts of interest

There are no conflicts of interest.

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