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ORIGINAL ARTICLE

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Vitamin D as a predictor of clinical response among patients with cardiac resynchronization therapy (CRT)

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Abstract

Introduction: Cardiovascular and noncardiovascular comorbidities have been recognized as predictors of clinical response in patients receiving cardiac resynchronization therapy (CRT). However, data on vitamin D as a predictor of CRT response are conflicting.

Method: We identified studies from MEDLINE and Embase databases, searching from inception to May 2024, to investigate the association between 25-OH vitamin D levels before CRT implantation and outcomes. Studies had to report 25-OH vitamin D levels or the proportion of patients with vitamin D insufficiency and categorize outcomes as CRT responders or nonresponders. We extracted mean 25-OH vitamin D and standard deviations for both groups from each study and calculated the pooled mean difference (MD). We also retrieved risk ratios, and 95% confidence intervals (CIs) for the association between vitamin D insufficiency and lack of CRT response, combining them using the generic inverse variance method.

Results: Our meta-analysis included four studies. CRT responders had higher levels of 25-OH vitamin D than nonresponders, with a pooled MD of 8.04 ng/mL (95% CI: 3.16–12.93; $I^2 = 48\%$, $p < .001$). Patients with vitamin D insufficiency before implantation had higher odds of lacking response to CRT, with a pooled RR of 3.28 (95% CI: 1.43–7.50; $I^2 = 0\%$, $p = .005$) compared to those with normal vitamin D.

Conclusions: CRT responders had higher 25-OH vitamin D levels compared to nonresponders. Vitamin D insufficiency was associated with a higher risk of nonresponse to CRT. These findings highlight the importance of monitoring and managing vitamin D levels in these patients.

KEYWORDS
25-hydroxy vitamin D, cardiac resynchronization therapy, meta-analysis, systematic review

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) has been shown to improve cardiovascular outcomes in patients with left ventricular systolic dysfunction and ventricular desynchrony.[1] It is indicated for patients with heart failure with reduced ejection fraction who have left ventricular ejection fraction (LVEF) below 35% along with significant left bundle branch block despite guideline-directed medical therapy and other device-based treatments.[2] CRT achieves near-simultaneous pacing of the left and right ventricles, restoring synchrony and enhancing LVEF, cardiac output, heart failure (HF) symptoms, and quality of life.[3]

Despite its efficacy in treatment of HF, some patients undergoing CRT do not benefit from the implantation, defined as CRT nonresponders.[4] These patients show no improvement in left ventricular end-systolic volume (LVESV) or functional capacity in the 6-min walk test after 6 months.[5] Several studies have identified pre-implantation QRS morphology and duration, the etiology of HF, and various comorbid factors as predictors of nonresponse.[6] Therefore, exploring and identifying reversible factors is essential to improve outcomes in these patients.

Vitamin D insufficiency is found to affect nearly 30%–50% of the global population regardless of age group and racial distribution and is identified as a significant public health concern.[7] Emerging evidence suggests that vitamin D influences cardiac structure and contractile function, linking its deficiency to cardiovascular diseases such as acute coronary syndrome, hypertension, and HF.[8] Recent data indicate that vitamin D insufficiency is common in patients with advanced HF and is associated with increased mortality risk and various adverse outcomes.[9] Interestingly, current literature found that lower pre-CRT implantation vitamin D levels are observed in patients identified as CRT nonresponders compared to those with responders.[10–13] Moreover, vitamin D insufficiency was linked to higher odds of a lack of clinical response to CRT device.[11,12] However, data remain limited due to small sample sizes. Therefore, we conducted a systematic review and meta-analysis of observational studies to examine the impact of vitamin D levels on the clinical response in patients undergoing CRT implantation.

2 | METHOD

2.1 | Search strategy

Three investigators (PW, TS, and VP) independently searched MEDLINE and Embase from inception to May 2024 using search terms related to "25-hydroxy vitamin D," "25-hydroxycholecalciferol," "vitamin D," and combining with the term "cardiac resynchronization therapy." No language restrictions were applied. The same investigators independently assessed the eligibility of the retrieved records, with further discussions involving a senior investigator (AA) to resolve conflicts. Abstracts and unpublished studies were also included in this current study.

2.2 | Eligibility criteria

Eligible studies had to be observational (case–control, cross-sectional, or cohort) and published as original research, assessing the association between pre-CRT implantation 25-OH vitamin D levels and clinical outcomes with CRT. Included studies needed to report the levels of 25-OH vitamin D prior to CRT implantation or the proportions of individuals with 25-OH vitamin D insufficiency or deficiency who underwent CRT, categorizing outcomes as either CRT responders or nonresponders. For effect size measures, means and standard deviations were extracted from each patient group (CRT responders and nonresponders) and reported as pooled mean differences. Additionally, studies that reported the association between vitamin D insufficiency or deficiency and the lack of response to CRT were included, with extracted data such as odds ratios (OR), risk ratio (RR), and their 95% confidence intervals (CIs) for the pooled risk ratio to consolidate the association.

2.3 | Data extraction

We employed a standardized data collection protocol to extract the following information: the first author's last name, country of origin, study design type, total number of participants, detailed participant information, measurement of 25-OH vitamin D levels, type of CRT included, follow-up duration, definition of CRT responder, baseline population characteristics (age and gender), and variables adjusted for in multivariable analysis. Furthermore, two investigators (PW and TS) applied the Newcastle–Ottawa Scale for cohort studies to evaluate research quality, focusing on the quality of participant recruitment, comparability between groups, and accuracy of outcome ascertainment.

2.4 | Statistical analysis

Data analysis was conducted using Review Manager 5.4 software from the Cochrane Collaboration. Mean 25-OH vitamin D levels and standard deviations (SD) of participants in both groups were extracted from each study, and the mean difference (MD) was calculated. The pooled MD was computed by combining the MDs of each study using a random effects model. For the analysis of the association between vitamin D insufficiency and the risk of nonresponse to CRT, point estimates with standard errors from each study were combined using DerSimonian and Laird's generic inverse variance method.[14] Due to heterogeneous background populations

and protocols among the studies, a random-effects model was employed. Statistical heterogeneity was assessed using Cochran's Q test, supplemented by I^2 statistics to quantify the proportion of total variation across studies attributable to heterogeneity rather than chance. I^2 values categorize heterogeneity as insignificant (0%–25%), low (26%–50%), moderate (51%–75%), or high (>75%).[15] A funnel plot will be utilized to examine potential publication bias if sufficient studies are available.

3 | RESULTS

Our search strategy identified 88 studies, with 85 from Embase and 3 from MEDLINE. After removing 2 duplicates, we reviewed 86 studies by title and abstract, excluding 50 that did not meet the eligibility criteria related to study design, participants, or article type. Subsequently, we thoroughly reviewed 36 articles and excluded 32 for not reporting the relevant outcome. Ultimately, four studies met the eligibility criteria for our meta-analysis. Figure 1 illustrates our search methodology and selection process, and Table 1 details the characteristics and quality assessment of the included studies.

A total of four cohort studies with 262 participants investigated the association between 25-OH vitamin D levels and the outcomes of cardiac resynchronization therapy. The average participant age was 66.2 years, 75.6% were male, and 33.9% had no response to cardiac resynchronization therapy as shown in Table 1. The pooled analysis revealed that individuals with responses to cardiac resynchronization therapy had a higher level of 25-OH vitamin D, with a pooled MD of 8.04 ng/mL (95% CI: 3.16 to 12.93; $p < .001$, Figure 2), when compared to individuals lacking response to CRT. Low statistical heterogeneity was observed ($I^2 = 48\%$). In addition, a pooled analysis from two studies indicated that patients with 25-OH vitamin D insufficiency were at a higher risk of lacking response to CRT, with a pooled RR of 3.28 (95% CI: 1.43 to 7.50, $p = .005$, Figure 3) compared to those with normal vitamin D status. No statistical heterogeneity was observed ($I^2 = 0\%$). Since only four studies were included in this meta-analysis, the evaluation for publication bias was not performed.

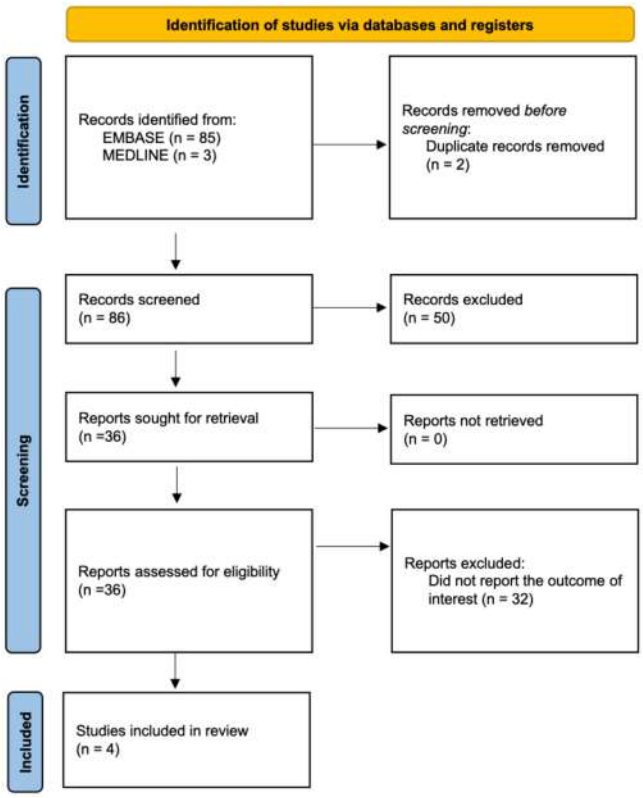

FIGURE 1 Study identification and literature review process.

4 | DISCUSSION

This current study is the first systematic review and meta-analysis to summarize data on the association between 25-OH vitamin D levels and CRT outcomes. We found that CRT responders had higher serum 25-OH vitamin D levels than nonresponders, with an average difference of 8.04 ng/mL. Additionally, patients with vitamin D insufficiency before CRT implantation had a 3.28-fold higher risk of not achieving a clinical response to CRT. These findings indicated that 25-OH vitamin D levels are one of the predictors of response to CRT, highlighting the potential benefit of recognizing and managing vitamin D status to improve clinical outcomes.

While the relationship between 25-OH vitamin D levels and outcomes among CRT patients is not fully understood, several explanations exist. It is likely attributed to the pleiotropic effects of vitamin D, which involves complex interactions in cellular differentiation, hormone secretion, and neurohormonal regulation in the cardiovascular system.[16,17] Numerous animal studies have shown that vitamin D exerts antihypertrophic effects on cardiac myocytes through vitamin D-dependent signaling pathways, enhancing myocyte contraction and relaxation by modulating calcium influx.[18,19] Insufficient vitamin D diminishes these effects, potentially leading to hypertrophy, extracellular matrix deposition, and myocardial fibrosis.[20] In addition, data have shown that in HF patients, vitamin D insufficiency is linked to increased activation of the renin–angiotensin system, contributing to cardiac hypertrophy, hypertension, saltwater retention, and adverse cardiovascular outcomes.[21,22] Moreover, vitamin D has anti-inflammatory effects and is inversely correlated with C-reactive protein and various pro-inflammatory markers.[23] The deficiency in vitamin D could lead to poor regulation of extracellular matrix turnover, exacerbating the condition in HF patients.[23–25] Altogether, inadequate vitamin D levels may lead to a suboptimal response to CRT.

TABLE 1 Main characteristics of the cohort studies included in the meta-analysis.

	Sunman et al.	Separham et al.	Perge et al.	Mills et al.
Year of publication	2016	2017	2019	2021
Country of origin	Turkey	Iran	Hungary	United Kingdom
Study design	Prospective cohort study	Prospective cohort study	Prospective cohort study	Prospective cohort study
Total number of participants	57 participants	50 participants	136 participants	19 participants
Study participants	Patients undergoing CRT-D implantation were recruited at Hacettepe University from December 2010 to February 2011.	Patients undergoing CRT implantation were recruited from the Heart Center at Tabriz University of Medical Sciences between January 2015 and January 2016.	Patients undergoing CRT implantation were recruited from the Heart and Vascular Center at Semmelweis University, Budapest, between September 2009 and December 2010.	Patients undergoing CRT implantation were recruited from a single center in the United Kingdom.
Measurement of 25-OH vitamin D	25-OH vitamin D levels were measured before CRT implantation using enzyme-linked immunosorbent assay kits	25-OH vitamin D levels were measured before CRT implantation and categorized as insufficient if below 30 ng/mL.	25-OH vitamin D levels were measured before CRT implantation and categorized as insufficient if below 24.13 ng/mL.	25-OH vitamin D levels were measured before CRT implantation.
Reported data on Vitamin D levels	Vitamin D levels were reported as the mean ± standard deviation.	Vitamin D levels were reported as the mean ± standard deviation.	Vitamin D levels were reported as the median ± interquartile range	Vitamin D levels were reported as the mean ± standard deviation.
Type of CRT	CRT-D	N/A	CRT-P and CRT-D	N/A
Follow-up duration	6 months	6 months	5 years	6 months
Definition of CRT responders	CRT responders were defined as patients who were alive and had a reduction in LVESV of more than 15% after 6 months of CRT implantation.	CRT responders were defined as patients who were alive with more than 15% reduction in LVESV and more than 10% (or 50-meter) improvement in the 6-min walk test after 6 months of CRT implantation.	CRT responders were defined as patients who showed more than 15% increase in LVEF after 6 months of CRT implantation.	CRT responders were defined as patients who showed improvement in all four domains after 6 months of CRT implantation as followed: an increase in peak VO2 by more than 1 mL/kg/min, a reduction in LVESV by at least 10%, a decrease in symptoms by at least 10% as measured by the MLWHFQ, and an increase in 6-min walk distance by over 10%.
CRT response rate	Overall: 59.6%	Overall: 78%	Overall: 67%	Overall: 47%
Age of participants (years)	All subjects: 62 CRT responders: 64 CRT nonresponders: 58	All subjects: 66 CRT responders: 64.7 CRT nonresponders: 69.6	All subjects (Median): 67	All subjects: 70
Percentage of male	All subjects: 66.7% CRT responders: 67.6% CRT nonresponders: 65.2%	All subjects: 60% CRT responders: 56.4% CRT nonresponders: 72.8%	All subjects: 81%	All subjects: 95%

TABLE 1 (Continued)

	Sunman et al.	Separham et al.	Perge et al.	Mills et al.
Variables adjusted in multivariate analysis	Age, hypertension, diabetes mellitus, ischemic cardiomyopathy, QRS morphology, preimplantation QRS duration, vitamin D levels, and BNP	History of ischemic cardiomyopathy, serum creatinine level, vitamin D	History of hypertension, hyperlipidemia, mineralocorticoid receptor inhibitory therapy, NT-proBNP, and vitamin D levels	N/A
Newcastle–Ottawa score	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 2	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 1 Outcome: 3

Abbreviations: CRT-D, Cardiac resynchronization therapy with implantable cardioverter defibrillator; CRT-P, Cardiac resynchronization therapy pacemaker; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; LVESV, Left ventricular end-systolic volume; LVEF, Left ventricular ejection fraction; MLWHFQ, Minnesota living with heart failure questionnaire; N/A, Not available; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; NYHA, New York Heart Association; Peak VO2, Peak oxygen consumption; 25-OH vitamin D, 25-hydroxy vitamin D.

Considering previous data among patient with HF, Szabo et al. studied 70 HF patients and found that 25-OH vitamin D levels were independently associated with LVEF in both univariate and multiple regression analyses, even after adjusting for age, gender, and comorbidities.[26] Additionally, Zhao et al.'s meta-analysis of RCTs on vitamin D supplementation in HF patients showed improvements in ventricular remodeling, with a pooled mean difference of −2.31 mm in left ventricular end-diastolic diameter (95% CI −4.15 to −0.47, $p = .01$) and a pooled mean difference of 4.18% in LVEF (95% CI 0.36 to 7.99, $p = .03$).[27] This suggests that monitoring and managing vitamin D levels could be a valuable adjunct component of HF treatment strategies to improve cardiac function and patient outcomes.

Given the variation in responder rates across the four studies, it is important to note that pivotal studies have demonstrated the benefits of CRT, yet the nonresponder rate at 6 months still varies by approximately 25%–33%, depending on the definition of a CRT responder.[28,29] In the included articles, the definitions of CRT responders are specified in Table 1. Sunman et al. defined a CRT responder as an improvement in LVESV after 6 months. Separham et al. used both LVESV improvement and a 6-min walk test improvement. Perge et al. defined it as a 15% improvement in LVEF. Mills et al. employed a multimodal approach, including echocardiographic parameters, cardiopulmonary exercise testing, and the 6-min walk test.[10–13] Therefore, it is crucial to interpret these results with caution.

This study has limitations that should be considered when analyzing the results. First, although our data reflect all available studies on vitamin D among patients with CRT, the patient population is relatively small, so generalizability to a larger population should be cautiously approached. Secondly, the current meta-analysis only shows the impact of vitamin D levels and insufficiency in vitamin D on outcomes among patients who underwent CRT. However, data on vitamin D supplementation in those with insufficiency among patients with CRT are still needed to further explore the therapeutic effect on outcomes. In addition, a single measurement of vitamin D levels as a baseline prior to CRT implantation may not accurately reflect long-term status due to fluctuations from seasonal changes, diet, and lifestyle.[30] Therefore, longitudinal and serial measurements, along with data on vitamin D supplementation, are needed to determine whether these factors can improve the rate of CRT responders. Moreover, our meta-analysis primarily includes studies from Turkey, Iran, Hungary, and the United Kingdom. As a result, there were no participants of African descent, limiting the generalizability of our findings to Black individuals. The influence of racial disparities on the relationship between vitamin D status and CRT response remains unclear and warrants further research. Future studies should explore the potential effects of racial differences as an effect modifier on the outcomes between vitamin D status and CRT response. Lastly, vitamin D insufficiency may indicate poor general health and more severe cardiovascular disease.[10,12] Further research is required in order to determine whether this finding reflects a true biological phenomenon or is confounded by unmeasured variables.

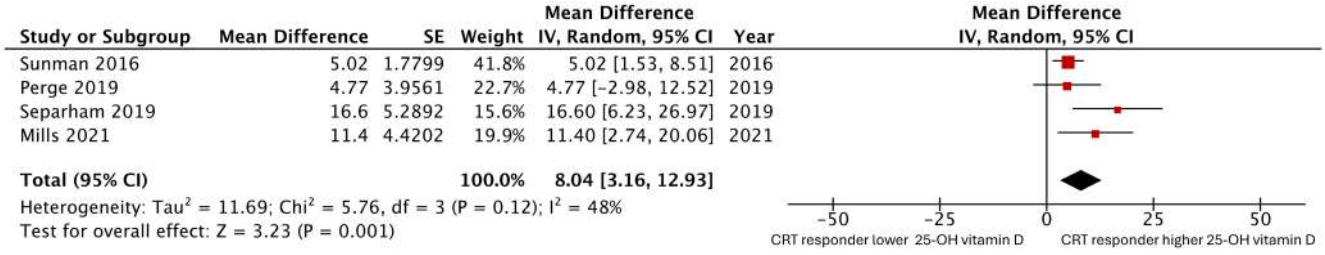

FIGURE 2 Forest plot of mean difference of 25-OH vitamin D between CRT responders and nonresponders.

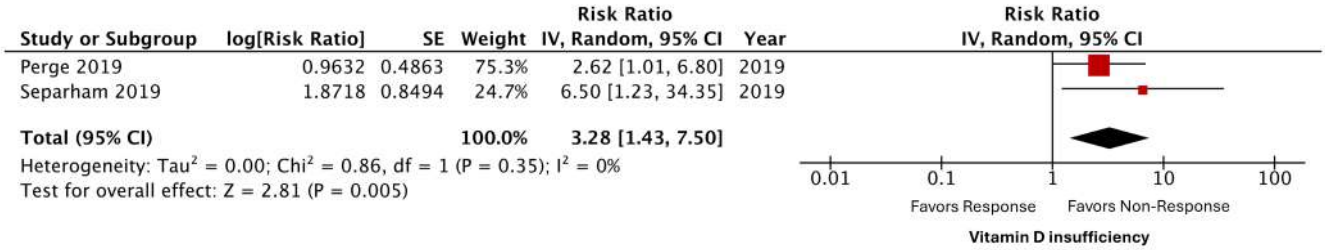

FIGURE 3 Forest plot of association between vitamin D insufficiency and lack of CRT response.

5 | CONCLUSION

Our meta-analysis found that CRT nonresponders had lower serum 25-OH vitamin D levels compared to responders. Additionally, vitamin D insufficiency was associated with a higher risk of not responding to CRT. Further research on vitamin D supplementation and the biological mechanisms linking vitamin D to poor CRT response is needed to improve patient outcomes.

AUTHOR CONTRIBUTIONS

All authors had access to the data and a role in writing the manuscript.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

All the authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data from the findings of this study were inferred and can be obtained from the author upon reasonable request.

ETHICS STATEMENT

For this type of study, ethics approval is not required.

PATIENT CONSENT STATEMENT

For this type of study, formal consent is not required.

CLINICAL TRIAL REGISTRATION

Not applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

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