The Emerging Role and Clinical Impact of Vitamin D Supplementation in Breast Cancer Patients Undergoing Chemotherapy: A Systematic Review

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ABSTRACT

Introduction: Breast cancer is the most common cancer in women and is often diagnosed at an advanced stage. Chemotherapy plays a crucial role in disease control but is limited by toxicity and response variability. Vitamin D, with its biological functions and the high prevalence of deficiency in patients, has potential as an adjuvant therapy to improve treatment response and clinical outcomes.
Objective: To integrate existing evidence on the role of vitamin D supplementation in breast cancer patients undergoing chemotherapy, focusing on its impact on treatment response and clinical outcomes.
Methods: This systematic review followed PRISMA guidelines and included RCTs, cohort, and case-control studies evaluating vitamin D supplementation in adult women with breast cancer undergoing chemotherapy. A comprehensive search across five databases up to June 2025 was conducted, applying the pre-established PICOS criteria, with filtering, data extraction, and quality assessment performed. This systematic review has been prospectively registered in the PROSPERO database (CRD420251142938).
Results: This systematic review identified six eligible studies involving breast cancer patients undergoing chemotherapy, with interventions ranging from low- to high-dose vitamin D, either alone or in combination with synbiotics. Vitamin D supplementation in breast cancer patients undergoing chemotherapy has been associated with improved clinical outcomes, including enhanced nutritional status, reduced inflammatory and cardiotoxic biomarkers, and increased pathological complete response (pCR) and disease-free survival (DFS).
Conclusion: Vitamin D supplementation during chemotherapy shows potential benefits in breast cancer patients, but large-scale standardized trials with long-term follow-up are needed to confirm its impact on survival outcomes.

KEYWORDS

breast cancer; chemotherapy; clinical outcomes; vitamin D supplementation

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INTRODUCTION

Breast cancer is a global health problem with the highest incidence among women in various countries. According to WHO data from 2022, there were approximately 2.3 million new cases and 670,000 deaths from breast cancer worldwide. The prognosis of this disease is strongly influenced by the Human Development Index (HDI), where five-year survival rates can reach over 90% in countries with a high HDI, while in countries with a low HDI, the rate is much lower. Mortality trends show a decline in 29 countries with a very high HDI, and seven of these, including Belgium and Denmark, have achieved the Global Breast Cancer Initiative target of an annual decline of at least 2.5%. Conversely, in about half of the countries monitored, mortality rates are increasing by 1–5% per year. Projections for 2050 predict a significant increase in the burden of this disease, with new cases increasing by 38% and deaths by 68%, which will disproportionately impact countries with a low HDI (1, 2). In Indonesia and Southeast Asia, although data vary, there is a tendency for breast cancer to be diagnosed at an advanced stage due to differences in access to screening and treatment services, which impacts clinical outcomes, with approximately 64.5% of breast cancer cases being diagnosed at stage III or IV (3). Barriers, such as limited early detection facilities, such as mammography, low public awareness, socioeconomic factors, and inadequate health infrastructure, also exacerbate delays in diagnosis and case management (3–5).

Breast cancer management is generally multimodal, including surgery, radiotherapy, hormone therapy, targeted therapy, and chemotherapy, depending on the stage and characteristics of the tumor. Chemotherapy plays a crucial role in breast cancer treatment because it can control micrometastases and improve survival rates, especially in aggressive subtypes, through primary neoadjuvant, adjuvant, and palliative strategies. Neoadjuvant chemotherapy is administered before surgery to shrink the tumor, permitting conservative management and assessing response to therapy. In locally advanced or inoperable cases, this strategy can result in a pathological complete response (pCR), which is associated with improved overall survival (OS) and disease-free survival (DFS) (6, 7). Postoperative adjuvant chemotherapy aims to eliminate residual microscopic cancer cells, reduce the risk of recurrence, and improve prognosis (8, 9). In metastatic cancer, palliative chemotherapy is used to reduce symptoms, slow progression, and improve quality of life, with a median OS of approximately two years. Monotherapy is often chosen to suppress toxicity, while continued administration until progression remains effective without compromising quality of life (10). However, excessive use in low-risk patients raises concerns about overtreatment, requiring an individualized approach based on tumor characteristics (7).

Chemotherapy remains a key component of breast cancer management, but its use faces significant challenges due to toxicity and interpatient response variability. Side effects such as nausea, alopecia, peripheral neuropathy, and organ dysfunction have been reported to seriously impact quality of life, with severe hematologic toxicity occurring in 38.6% of patients and gastrointestinal toxicity in 12.9%, in addition to psychological burdens that reduce well-being (11, 12). Response variability is influenced by tumor characteristics, such as triple-negative subtypes that are more susceptible to toxicity, and genetic factors such as polymorphisms in drug metabolism and DNA repair genes that can exacerbate side effects. In addition to patient factors such as age, nutritional status, and comorbidities, patient factors such as age, nutritional status, and comorbidities (11, 13). This situation results in treatment outcomes that are not always optimal for all patients, so a personalized therapy approach and patient-based outcome reporting are considered essential to increase effectiveness while minimizing side effects (13).

Vitamin D, particularly its active form 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], has biological functions beyond calcium-phosphate regulation by inhibiting proliferation, promoting differentiation, inducing apoptosis, and modulating inflammation and immune responses through the vitamin D receptor (VDR). These activities are associated with anticancer properties, including increased cytotoxicity against tumor cells, enhanced immunity, and suppression of inflammatory processes that contribute to cancer progression (14–16). The VDR receptor expressed on immune cells also contributes to a more effective antitumor response. In a clinical context, over 70% of breast cancer patients are reported to have vitamin D deficiency, which is associated with a poor prognosis and a higher risk of recurrence (17). While higher vitamin D levels are associated with improved survival outcomes, evidence regarding the association between VDR expression and mortality remains inconsistent (18).

Previous studies have shown that breast cancer patients often have very low vitamin D levels. An observational study in Yogyakarta reported an average vitamin D level of around 8.80 ng/mL before chemotherapy, with more than 80% of patients categorized as severely deficient, and this level tended to decrease after therapy (19). A recent randomized clinical trial showed that vitamin D supplementation can improve pathological complete response (pCR) in breast cancer patients undergoing neoadjuvant chemotherapy, with both cholecalciferol 2,000 IU/day for six months and vitamin D3 50,000 IU/week increasing the chance of achieving pCR compared to the control group (20, 21). This evidence supports the potential of vitamin D as an adjuvant therapy to improve treatment response while maintaining nutritional status and reducing inflammation.

However, research results remain variable due to variations in dosage, duration of supplementation, patient characteristics, and outcome parameters studied. A knowledge gap remains regarding the effect of vitamin D supplementation on patient clinical outcomes. Given that chemotherapy, while effective in improving survival, is often limited by toxicity, immunosuppression, and response variability that reduce therapeutic efficacy, adjuvant strategies such as vitamin D supplementation are becoming increasingly important. Therefore, a systematic review is needed to integrate the available evidence regarding the role of vitamin D supplementation in breast cancer patients undergoing chemotherapy.

METHODS

STUDY DESIGN AND SETTING

This study was designed as a systematic review and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to summarize and evaluate the available evidence on the role of vitamin D supplementation in breast cancer patients undergoing chemotherapy, with particular emphasis on its impact on clinical outcomes.

SEARCH STRATEGY

A systematic literature search was carried out across five major databases: PubMed, ScienceDirect, Google Scholar, Cochrane Library, and ProQuest, covering publications from inception until June 2025. The search strategy combined both Medical Subject Headings (MeSH) and free-text keywords such as "vitamin D," "cholecalciferol," "ergocalciferol," "vitamin D supplementation," "breast cancer," "chemotherapy," "pathological complete response," "tumor response," "pathologic response," "treatment response," and "clinical outcomes." The strategy was developed in consultation with a health sciences librarian to ensure comprehensiveness, and manual screening of reference lists from relevant articles and systematic reviews was undertaken to identify additional eligible studies.

ELIGIBILITY CRITERIA

The eligibility criteria of this review were structured according to the PICOS framework. The target population consisted of adult women aged 18 years or older who had a confirmed diagnosis of breast cancer at any stage and were undergoing chemotherapy, including neoadjuvant, adjuvant, or palliative settings. Studies involving male breast cancer patients, individuals not receiving chemotherapy, or pediatric populations were excluded. The intervention of interest was vitamin D supplementation of any dose, frequency, or duration, administered concurrently with chemotherapy, either alone or in combination with other agents. Studies in which vitamin D was evaluated solely as prophylaxis for bone loss or in non-chemotherapy contexts, such as supplementation in postmenopausal women, were excluded. Acceptable comparators included placebo, no vitamin D supplementation, or chemotherapy alone, whereas studies without a comparator group or those comparing only different formulations or doses of vitamin D were excluded. Eligible outcomes encompassed a broad range of clinical endpoints, including tumor response (pCR, ORR), overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), treatment toxicity, safety, quality of life, serum vitamin D levels, nutrition status, inflammatory markers, and other relevant clinical outcomes. Studies reporting only molecular mechanisms without patient-level outcomes were excluded. Regarding study design, randomized controlled trials (RCTs), prospective or retrospective cohort studies, and case-control studies with extractable outcome data were considered eligible. Conversely, case reports, narrative reviews, letters, conference abstracts, in vitro or animal studies, and non-comparative observational studies were excluded.

Tab. 1 Eligibility Criteria Based on the PICOS Framework.

PICOS	Inclusion criteria	Exclusion criteria
Population (P)	Adult women (≥18 years) diagnosed with any stage of breast cancer undergoing chemotherapy (neoadjuvant, adjuvant, or palliative)	Studies involving male breast cancer patients, or those not undergoing chemotherapy, and pediatric populations
Intervention (I)	Vitamin D supplementation of any dose, frequency, and duration, administered concurrently with chemotherapy (alone or in combination with other agents)	Studies assessing vitamin D used only as a prophylactic against bone loss or for non-chemotherapy contexts (e.g., postmenopausal only)
Comparator (C)	Placebo, no vitamin D supplementation, or standard chemotherapy alone	Studies without a control group or comparison group; studies comparing different forms of vitamin D only
Outcomes (O)	Tumor response (pCR, ORR), overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), toxicity, safety, QoL, vitamin D level, nutrition status, inflammatory or treatment response markers, and other clinical outcomes	Studies not reporting clinical outcomes (e.g., reporting only molecular mechanisms without patient outcomes)
Study Design (S)	Randomized controlled trials (RCTs), prospective or retrospective cohort studies, or case-control studies with extractable data on outcomes	Case reports, review articles, letters, conference abstracts, in vitro or animal studies, and non-comparative observational studies.

SCREENING AND DATA EXTRACTION

Study eligibility was determined according to the predefined PICOS framework (Table 1). Initially, three reviewers independently screened titles and abstracts, followed by full-text evaluation. Any disagreements were resolved through consultation with a third reviewer. Data were then extracted into a standardized template, which included study characteristics (author, publication year, country, design, sample size), patient demographics (age), chemotherapy regimen, vitamin D dosage, comparator group, duration of follow-up, and reported outcomes. The outcomes of interest comprised tumor response (pCR or ORR), survival

endpoints (OS, DFS, PFS), toxicity, safety, quality of life, serum vitamin D levels, and inflammatory or treatment response markers. To ensure consistency, outcome definitions were harmonized across studies according to clinical and biochemical criteria.

QUALITY ASSESSMENT

To evaluate methodological quality, RCTs were assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, covering domains such as randomization, allocation concealment, blinding, and outcome measurement. Observational studies were appraised with the Newcastle–Ottawa Scale (NOS). Three reviewers conducted the assessments independently, and any discrepancies were resolved by consensus.

RESULTS

LITERATURE SEARCH

The study selection process is summarized in the PRISMA flow diagram. A total of 770 records were identified through database searches (ScienceDirect, Cochrane, PubMed, ProQuest, and Google Scholar), of which 21 duplicates were removed. After screening 749 titles and abstracts, 691 records were excluded, leaving 58 articles for full-text assessment. Thirty reports could not be retrieved, and 28 were reviewed for eligibility. Of these, 22 were excluded for specific reasons, i.e., two due to an ineligible study design, as they were single-arm trials without a comparator group, and fourteen for lacking a relevant intervention, either because vitamin D supplementation was not provided or the focus was limited to baseline vitamin D status. Six for involving an ineligible population, as participants were not receiving chemotherapy. Ultimately, six studies fulfilled all inclusion criteria and were incorporated into the systematic review (Fig. 1).

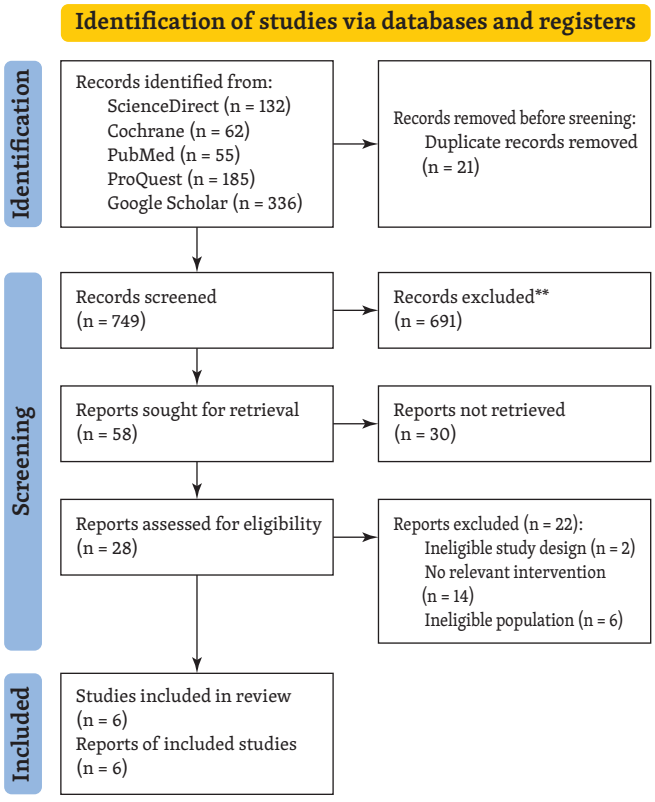

Fig. 1 PRISMA Flowchart.

STUDY CHARACTERISTICS

This systematic review included six studies that investigated the role of vitamin D supplementation in breast cancer patients undergoing chemotherapy, with a primary focus on clinical outcomes. The included studies were conducted across diverse regions, including Palestine, Egypt, Brazil, Turkey, Iran, and the United States. They comprised different methodological approaches, such as randomized controlled trials, prospective randomized designs, double-blind clinical trials, and one retrospective cohort study.

The interventions assessed varied considerably, ranging from vitamin D monotherapy to a combination of vitamin D with synbiotics. Dosages of vitamin D also differed between trials, included 0.5 µg per day, 1000 IU daily, 2000 IU daily, and 50,000 IU once weekly, while one study primarily administered low doses of less than 10,000 IU per week. The control groups typically received standard care or a placebo.

Sample sizes extended from smaller trials with approximately 40 patients to larger cohorts with more than 200 participants. The age of participants spanned from the mid-40s to mid-50s, reflecting a population of middle-aged adults commonly diagnosed with breast cancer. Chemotherapy regimens across studies included adjuvant and neoadjuvant protocols, with some specifically using anthracycline-based therapies, cyclophosphamide, taxane regimens, or trastuzumab-containing combinations. Follow-up periods were heterogeneous, lasting from 9 weeks in the shortest trial to more than 40 months in the longest. Table 2 provides a detailed overview of the characteristics of the included studies.

STUDY OUTCOMES

The included studies evaluated the clinical outcomes of vitamin D supplementation in breast cancer patients undergoing chemotherapy. Primary outcomes mainly included nutritional status, tumor response (pCR, Ki-67, apoptosis), cardiotoxicity biomarkers (LDH, cTnT, IL-6), and disease-free survival. Secondary outcomes comprised adverse events, biochemical markers, overall survival, local recurrence, and inflammatory parameters (Table 3).

Almassri et al. investigated vitamin D supplementation (50,000 IU once weekly for 9 weeks) in patients with node-positive, hormone receptor-negative, and HER2-negative breast cancer, stage II-III, who received first-line Adriamycin-Cyclophosphamide (AC) chemotherapy over four cycles. Weekly vitamin D supplementation can improve the nutritional status of breast cancer patients undergoing therapy, as demonstrated by improvements in Patient-Generated Subjective Global Assessment (PG-SGA) scores, anthropometric parameters, blood albumin levels, and adequate energy and protein intake (22).

Tab. 2 Characteristics of the Included Studies

Authors, Year	Country	Study Design	Population	Total Sample	Age (years)	Chemotherapy	Intervention	Dosage of Vitamin D	Comparator	Follow-up Duration
Almassri et al., 2024[22]	Palestine	RCT (NCT05331807)	Patients with node-positive, hormone receptor-negative, and HER2-negative breast cancer, stage II–III, who received first-line Adriamycin-Cyclophosphamide (AC) chemotherapy over four cycles	44	47.3 (10.0) in intervention group, 47.3 (8.8) in control group	First-line Adriamycin-Cyclophosphamide (AC) chemotherapy	Vitamin D	50,000 IU once weekly	Standard care	9 weeks
El-Bassiouny et al., 2022[23]	Egypt	RCT	Patients with breast cancer who received four cycles of an adjuvant chemotherapy regimen (Doxorubicin and cyclophosphamide)	150	49 (6)	Adjuvant chemotherapy regimen (Doxorubicin and cyclophosphamide)	Vitamin D	0.5 µg once daily	Standard care	After four cycles of chemotherapy
Omodei et al., 2025[20]	Brazil	RCT	Patients with breast cancer who are undergoing neoadjuvant chemotherapy (NCT)	80	≥45	Neoadjuvant chemotherapy (NCT)	Vitamin D	2000 IU daily	Standard care	6 months
Ozkurt et al., 2025[21]	Turkey	Prospective RCT (NCT03986268)	Patients with primary breast cancer stage 1–3 who received neoadjuvant systemic therapy	227	46 (24–74)	Chemotherapy (Standard regimens of anthracyclines and/or taxanes with or without trastuzumab and/or pertuzumab)	Vitamin D	50,000 IU once a week	Standard care	41.4±18.9 weeks
Tirgar et al., 2024[24]	Iran	Double-blind, randomized clinical trial (IRCT20200313046756N1)	Patients with non-metastatic invasive breast cancer stage T1-3, N0-2 who received neoadjuvant chemotherapy	40	46.7 in the intervention group, 50 in the control group	Neoadjuvant chemotherapy	Vitamin D and synbiotics	1000 IU per day	Placebo	18 weeks
Zeichner et al., 2015[25]	United States	Retrospective cohort	Patients with HER2-positive non-metastatic breast cancer treated with trastuzumab-based chemotherapy	246	54 in the intervention group, 49 in the control group	Trastuzumab-based regimens (taxane ± anthracycline + trastuzumab)	Vitamin D	Mostly low dose (<10,000 IU/week)	Standard care	Median DFS follow-up 29.5 months, OS follow-up 40.2 months.

International unit (IU).

El-Bassioumy et al. investigated vitamin D supplementation (0.5 μg once until after four cycles of chemotherapy) in patients with breast cancer who received four cycles of an adjuvant chemotherapy regimen (doxorubicin and cyclophosphamide). Vitamin D supplementation in breast cancer patients undergoing adjuvant chemotherapy has been shown to reduce levels of inflammatory biomarkers (IL-6), LDH, and cTnT, while significantly increasing serum vitamin D levels compared to the control group (23).

Omodei et al. evaluated daily vitamin D supplementation (2000 IU daily for six months) in patients with breast cancer who were undergoing neoadjuvant chemotherapy (NCT). The intervention group demonstrated significantly higher pathological complete response (pCR) rates, increased serum 25(OH)D levels, and reduced adverse events compared to placebo (20).

Ozkurt et al. evaluated supplementation of 50,000 IU vitamin D once a week during neoadjuvant for around 41 weeks in patients with primary breast cancer stage 1–3 who received neoadjuvant systemic therapy. Vitamin D supplementation during neoadjuvant systemic treatment in breast cancer patients is associated with a significant increase in pCR, especially in patients with negative hormone receptor status and high Ki-67 expression (21).

Tirgar et al. investigated supplementation of 1000 IU per day of vitamin D in combination with synbiotics for 18 weeks in patients with non-metastatic invasive breast cancer who received neoadjuvant chemotherapy. Vitamin D supplementation, especially when combined with synbiotics, has shown potential anti-inflammatory effects in breast cancer patients undergoing neoadjuvant therapy, characterized by an increase in the anti-inflammatory index and prevention of IL-10 decline (24).

Zeichner et al. investigated vitamin D supplementation of mostly low doses (<10,000 IU/week) for 29.5–40.2 months in patients with HER2-positive non-metastatic breast cancer treated with trastuzumab-based chemotherapy. Vitamin D supplementation during neoadjuvant chemotherapy in breast cancer patients was associated with improved disease-free survival (DFS), although it did not show a significant difference in overall survival (OS) (25).

Tab. 3 Outcomes of the Included Studies.

Authors, Year	Primary Outcomes	Secondary Outcomes	Main Findings	Quality of the Study/ Risk of Bias
Almassri et al., 2024[22]	Nutritional status, blood albumin	Adverse events, urea, creatinine	Weekly vitamin D supplementation enhanced the nutritional status of the participants. Blood albumin levels significantly increased ($p<0.05$) in the vitamin D group as compared to the baseline.	Low risk of bias
El-Bassiouny et al., 2022[23]	Cardiotoxicity biomarkers (Lactate dehydrogenase (LDH), cardiac troponin T (cTnT), and anti-inflammatory Interleukin 6 (IL-6))	N.R.	Serum levels of LDH, cTnT, and IL-6 were significantly lower ($p<0.001$) in patients in the vitamin D group who took vitamin D supplements than in the control group.	Low risk of bias
Omodei et al., 2025[20]	Pathologic complete response (pCR)	N.R.	Compared to the placebo group, breast cancer patients undergoing NCT who took 2,000 IU of vitamin D supplements had a higher chance of experiencing a pathological complete response.	Low risk of bias
Ozkurt et al., 2025[21]	Pathologic complete response (pCR)	5-Year overall survival, disease-free survival, and Local-regional recurrence-free survival,	In patients with breast cancer, vitamin D supplementation during neoadjuvant systemic therapy significantly affects pCR.	Low risk of bias
Tirgar et al., 2024[24]	Pathologic complete response (pCR)	Inflammatory biomarkers, hormonal biomarkers, tumor proliferation marker (Ki-67)	Vitamin D and synbiotic supplementation showed potential anti-inflammatory effects but no apparent improvement in treatment response.	Low risk of bias
Zeichner et al., 2015[25]	Disease-free survival (DFS)	Overall survival (OS), tumor size, and lymphovascular invasion	Better DFS is linked to vitamin D supplementation in patients with non-metastatic HER2+ breast cancer.	High Quality

Not reported (N.R.); International unit (IU).

RISK OF BIAS

The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias tool, with the results displayed in a bar chart (Fig. 2). Overall, the studies demonstrated a relatively strong methodological profile, as most domains were assessed as having a low risk of bias. Selection bias, including random sequence generation and allocation concealment, was generally well addressed, indicating that randomization procedures and allocation concealment methods were adequately implemented to reduce systematic differences between groups. Blinding of outcome assessments was also categorized mainly as low risk, supporting the reliability and objectivity of the outcomes measured. Conversely, performance bias related to blinding of participants and personnel was assessed as unclear in a small proportion of studies, likely reflecting limitations in reporting or practical difficulties in concealing intervention status to participants. A similar trend was observed in the other bias category, which showed the highest proportion of unclear risk, which could be due to factors such as small sample size, funding source, or other methodological limitations not covered by the standard domains. Both attrition bias and reporting bias were mainly categorized as low risk, although a small number of studies had insufficient information for a complete assessment. It is important to note that no domains were

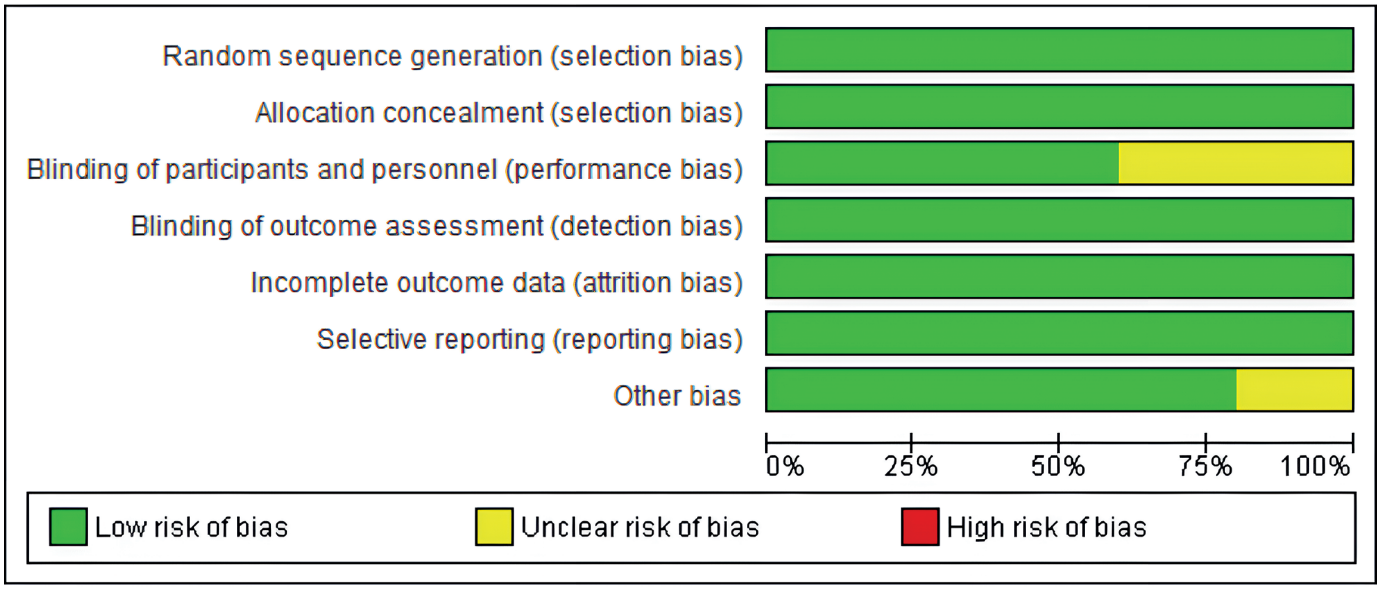

Fig. 2 Risk of bias graph.

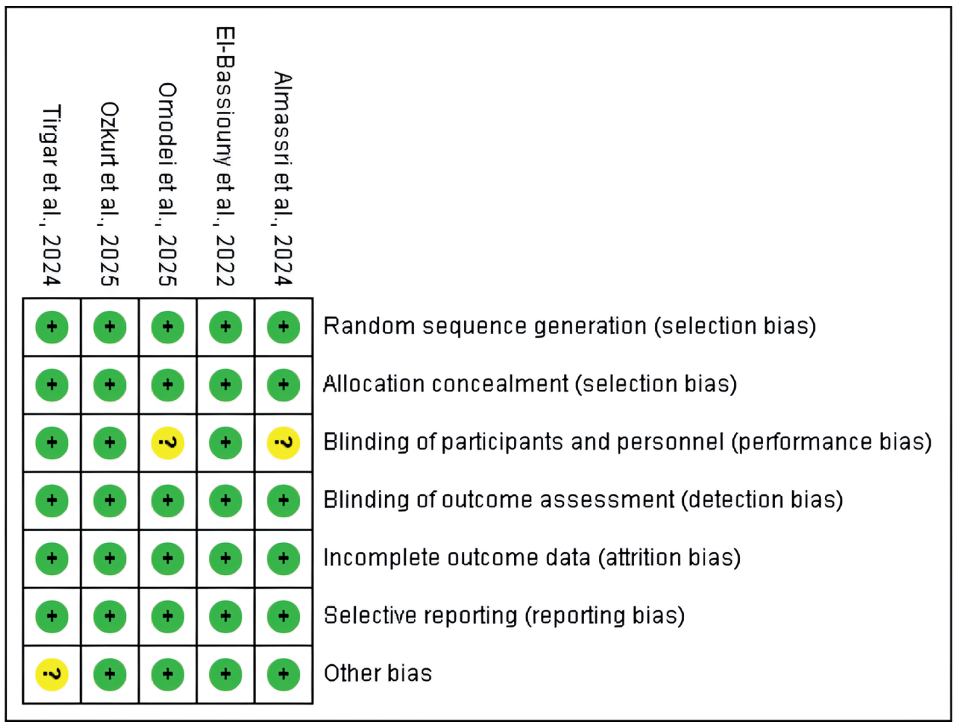

Fig. 3 Risk of bias summary.

assessed as high risk, so although there are some areas of uncertainty, the internal validity of the overall evidence can still be considered strong.

The risk of bias in the randomized controlled trials included in this review was evaluated using the Cochrane Risk of Bias Tool, with the results shown in the figure above. Overall, the methodological quality of the studies was quite good, as most domains were assessed as having a low risk of bias. Nearly all studies demonstrated low risk in the aspects of random sequence generation, blinding of outcome assessment, completeness of outcome data, and selective reporting, reflecting adherence to the basic principles of randomization and blinding to maintain internal validity. However, there were several domains with unclear risk assessments, such as allocation concealment in the studies of Almassri et al. (2024) and Omodei et al. (2025) due to a lack of information regarding methods for preventing allocation bias, and other bias in the study of Tirgar et al. (2024), which is likely related to design limitations such as small sample size or unreported external factors. Nevertheless, no studies were assessed as having a high risk in any domain. Hence, the overall risk of bias profile supports the reliability and robustness of the conclusions drawn from these studies (Figure 3).

DISCUSSION

The results of this systematic review indicate that vitamin D supplementation in breast cancer patients undergoing chemotherapy provides potential benefits in various clinical aspects. In terms of nutritional status, vitamin D supplementation has been shown to be associated with increased serum albumin levels, reflecting improvements in nutritional status and the body's anabolic response to disease stress and cytotoxic therapy (22). Vitamin D plays a role in regulating gene expression that controls cancer cell proliferation, differentiation, and apoptosis, and modulates the immune system, thereby reducing inflammation that contributes to cachexia and malnutrition (26–28). Furthermore, vitamin D deficiency is often associated with fatigue, pain, gastrointestinal disturbances, and decreased appetite. Vitamin D supplementation has been shown to improve these symptoms, increase energy and protein intake, and improve PG-SGA scores and anthropometric parameters (29–31). These effects are also associated with increased serum albumin levels, as improved nutrient intake and suppressed inflammation promote hepatic protein synthesis and decrease albumin degradation (32).

In addition, vitamin D supplementation can also reduce inflammatory biomarkers such as interleukin-6 (IL-6), lactate dehydrogenase (LDH), and cardiac damage biomarkers such as cardiac troponin T (cTnT), which often increase due to chemotherapy toxicity (23). Vitamin D supplementation can suppress the increase in inflammatory biomarkers and tissue damage that arise due to chemotherapy toxicity through several integrated mechanisms, molecularly, the active ligand of vitamin D [1,25-$(OH)_2D_3$] binds to the vitamin D receptor (VDR) which then inhibits pro-inflammatory transcription pathways such as by interfering with the activation of NF-κB and the JAK/STAT pathway, thereby reducing the production of pro-inflammatory cytokines such as IL-6 (33). Reducing IL-6 and other inflammatory mediators will minimize cytokine stress in various tissues and decrease the release of tissue markers released during cell damage, thereby directly reducing measurable IL-6 concentrations (34). Observational studies report an inverse relationship between vitamin D status and LDH levels such that improved vitamin D status is associated with lower LDH, possibly through reduced inflammation and metabolic stabilization of cells (35). For cardiac markers such as cTnT, there is plausible biological evidence that reduction of systemic inflammation and direct protective effects on endothelial cells may reduce chemotherapy-induced troponin release (23, 36).

From the tumor response perspective, vitamin D supplementation is associated with increased pathological complete response (pCR) rates in patients receiving neoadjuvant chemotherapy, as well as increasing the apoptotic index and suppressing cancer cell proliferation (20, 21, 24). Moreover, one of the included studies also reported a positive association between higher vitamin D levels and disease-free survival (DFS) (25). These findings support the growing recognition of vitamin D as a potential chemosensitizer in cancer therapy. Vitamin D supplementation may improve pCR in patients receiving neoadjuvant chemotherapy through several interrelated molecular and tumor microenvironmental mechanisms. Intracellularly, the active form of vitamin D binds to the vitamin D receptor and alters the transcription of target genes that regulate the cell cycle, decreasing proliferation markers and shifting the balance of apoptotic proteins toward pro-apoptotic ones (e.g., ↑BAX, ↓BCL-2), thereby enhancing the cytotoxic effects of chemotherapy (37). In addition, activation of the VDR pathway increases the response to DNA damage so that tumors become less efficient at repairing damage induced by chemotherapeutic agents, resulting in increased chemotherapeutic apoptosis (38). At another cellular level, vitamin D also modulates autophagy and suppresses pro-survival signals and pro-angiogenesis pathways that support tumor growth, so that the combination with chemotherapy is synergistic and reduces the ability of tumors to survive (39). In colorectal cancer, vitamin D enhances the sensitivity of cancer cells to chemotherapy when combined with secreted protein acidic and rich in cysteine. This protein up-regulates the vitamin D receptor. This combination significantly reduces cell viability and enhances chemotherapy-induced apoptosis in therapy-resistant colorectal cancer cells (40). These combined mechanisms may also ultimately reduce the risk of disease recurrence and progression, which is reflected in increased DFS.

Previous study in other cancer populations, such as colorectal cancer, have shown that higher 25(OH)D levels are significantly associated with improved overall survival and CRC-specific survival (41). Other study involving various cancer populations have shown similar results, namely that vitamin D plays an important role in preventing the side effects of neoadjuvant radiotherapy and chemotherapy, including helping to reduce symptoms such as nausea, vomiting, and fatigue due to aggressive therapy (42).

These findings carry important clinical implications. Screening for vitamin D status in breast cancer patients should be considered at baseline, given the high prevalence of vitamin D deficiency in this population. Vitamin D supplementation has the potential to serve as an adjunctive therapy to improve clinical outcomes, both in terms of tumor response and patient quality of life. However, current international guidelines do not yet recommend its routine use in oncology practice. The strength of the available evidence primarily derives from randomized clinical trials assessing relevant outcomes, including pathological complete response (pCR), inflammatory biomarkers, and nutritional parameters, which collectively demonstrate the significant role of vitamin D in cancer therapy. This study is the first to specifically focus on the effects of vitamin D supplementation in breast cancer patients undergoing chemotherapy, thereby contributing novel insights to the field. Nevertheless, limitations such as variation in dosage and duration, heterogeneity of study designs, small sample sizes, and follow-up generally limited to the end of chemotherapy, warrant cautious interpretation of the results.

CONCLUSION

Current evidence suggests that vitamin D supplementation in breast cancer patients undergoing chemotherapy may provide various benefits on clinical outcomes, including improved nutritional status, decreased biomarkers of inflammation and cardiotoxicity, and increased pathological complete response (pCR) and disease-free survival (DFS). These findings support the potential of vitamin D as a beneficial adjuvant therapy. Therefore, large-scale randomized controlled trials with standardized designs, evaluation of optimal dosing, and stratification based on stage, molecular subtype, and baseline vitamin D levels are needed. Furthermore, long-term studies are essential to determine the impact of supplementation on OS and DFS in a comprehensive manner, thereby strengthening the scientific evidence base supporting its integration into breast cancer management.

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