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Case Report

Effect of Vitamin D Supplementation on Overall Survival and Progression-Free Survival of Colorectal Cancer Patients

Ni Wayan Eka Widyartini[1], Diyah Eka Andayani[2]

[1] *Department of Nutrition, Faculty of Medicine, University of Indonesia - Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia*

A B S T R A C T

Abstrak

Pendahuluan: Kanker kolorektal merupakan kanker keempat terbanyak dan penyebab kematian akibat kanker kelima di Indonesia. Meskipun terapi sistemik telah berkembang, prognosis kanker kolorektal tetap buruk, dengan angka kekambuhan tinggi dan kelangsungan hidup jangka panjang yang rendah. Vitamin D belakangan ini menjadi perhatian karena perannya dalam menghambat progresi tumor dan meningkatkan luaran kelangsungan hidup.

Objektif: Mengevaluasi efek suplementasi vitamin D terhadap *overall survival* (OS) dan *progression-free survival* (PFS) pada pasien kanker kolorektal.

Metode: Pencarian literatur dilakukan secara sistematis melalui database PubMed, Cochrane Library, dan Google Scholar, difokuskan pada publikasi tahun 2020–2025. Studi yang memenuhi syarat mencakup uji klinis teracak (RCT), tinjauan sistematis, dan meta-analisis pada pasien dewasa dengan kanker kolorektal yang menerima suplementasi vitamin D. Penilaian kualitas studi dilakukan menggunakan kriteria dari *Oxford Centre for Evidence-Based Medicine* (CEBM).

Hasil:

Dua studi meta-analisis memenuhi kriteria inklusi. Meta- analisis oleh Vaughan-Shaw et al. menunjukkan peningkatan signifikan pada PFS (HR = 0,65) dengan suplementasi vitamin D dosis tinggi (4.000 IU/hari selama 23 bulan) pada pasien kanker kolorektal metastatik. Sebaliknya, studi Xu et al. melaporkan temuan yang tidak konsisten, sebagian besar berdasarkan data observasional tanpa dosis yang jelas. Keterbatasan utama meliputi ukuran sampel kecil, populasi heterogen, dan pelaporan hasil yang tidak konsisten.

Kesimpulan:

Suplementasi vitamin D dosis tinggi berpotensi meningkatkan PFS pada kanker kolorektal. Namun, dibutuhkan bukti yang lebih kuat dari uji klinis berskala besar untuk memastikan efektivitasnya dan mendukung penerapan klinis.

Kata kunci: Kanker kolorektal, suplementasi vitamin D, *progression-free survival, overall survival*

Abstract

Introduction: *Colorectal cancer (CRC) is the fourth most common cancer and the fifth leading cause of cancer death in Indonesia. Despite treatment advances, prognosis remains poor, with high recurrence rates and low long-term survival. Vitamin D has recently emerged as a potential adjunct due to its role in modulating tumor progression and improving survival outcomes.*

Objective: *To evaluate the effect of vitamin D supplementation on overall survival (OS) and progression-free survival (PFS) in patients with colorectal cancer.*

Methods: *A structured literature search was conducted using PubMed, Cochrane Library, and Google Scholar, focusing on studies published between 2020 and 2025. Eligible studies included randomized controlled trials (RCTs), systematic reviews, and meta-analyses involving adult CRC patients receiving vitamin D supplementation. Articles were appraised using the Oxford Centre for Evidence-Based Medicine (CEBM) criteria.*

Results: *Two meta-analyses studies met the inclusion criteria. The meta- analyses by Vaughan-Shaw et al. demonstrated a significant improvement in PFS (HR = 0.65) with vitamin D supplementation, particularly at a dose of 4,000 IU/day for 23 months in metastatic CRC patients. Whereas the meta-analyses by Xu et al. reported inconsistent findings, primarily based on observational data with unclear dosing. Major limitations included small sample sizes, heterogeneous populations, and inconsistent reporting of outcomes and dosages.*

Conclusions*: High-dose vitamin D supplementation may improve progression-free survival in colorectal cancer. However, stronger evidence from large, well-designed trials is needed to confirm its effectiveness and inform clinical practice.*

Keywords: *Colorectal cancer, vitamin D supplementation, progression-free survival, overall survival*

What is already known?

Colorectal cancer (CRC) is a malignancy that affects the colon or rectum with high recurrence rates and low overall survival.

What does this study add?

Effect of vitamin D supplementation on overall survival and progression-free survival of colorectal cancer patients.

CORRESPONDING AUTHOR

Phone: +6281246767533
E-mail: widyartinieka@gmail.com

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Introduction

Colorectal cancer (CRC) is a malignancy that affects the colon or rectum and remains one of the most significant global health challenges. As of 2022, CRC holds the third highest incidence and the second highest mortality rate among all cancers worldwide. In Indonesia, it ranks fourth in cancer incidence with an estimated 35,676 new cases, and fifth in mortality with 19,255 deaths annually.[1,2]

Despite substantial advancements in systemic treatments, the prognosis of CRC, particularly in advanced stages, remains poor, with high recurrence rates and a 5-year overall survival (OS) rate of less than 15%.[3] Vitamin D is increasingly recognized for its potential protective role against colorectal cancer (CRC) through several biological mechanisms. The active form of vitamin D, 1,25-dihydroxyvitamin D (calcitriol), binds to the vitamin D receptor (VDR), which is expressed in intestinal epithelial cells, cancer-associated fibroblasts (CAFs), immune cells, and other components of the tumor microenvironment. This interaction modulates gene expression and interferes with key oncogenic pathways.[3,4]

Multiple studies have examined the prognostic implications of vitamin D in CRC. Peixoto et al.[5] highlighted the potential of vitamin D supplementation to reduce tumor progression and mortality of colorectal cancer through its biological effects on proliferation, inflammation, and metastasis.[5] Ng et al.[6] found that high-dose vitamin D supplementation (4,000 IU/day) combined with chemotherapy improved progression-free survival (PFS) compared to standard-dose (400 IU/day) in metastatic CRC patients.[6] However, a recent meta-analyses of randomized trials by Fu et al. concluded that vitamin D supplementation had no significant effect on colorectal cancer mortality (RR = 0.82, 95% CI: 0.56–1.21; p = 0.32), suggesting limited survival benefit.[7]

Therefore, this Evidence-Based Case Report (EBCR) aims to assess the effect of vitamin D supplementation on overall survival and progression-free survival of colorectal cancer patients.

Case

A 62-year-old male patient was hospitalized in the surgical ward for a recovery from a right hemicolectomy performed for stage III colorectal cancer. His postoperative course has been stable, and he is expected to start adjuvant chemotherapy within the next few weeks.

During routine evaluation, laboratory tests revealed a serum 25-hydroxyvitamin D [25(OH)D] level of 14 ng/mL, indicating vitamin D deficiency. The patient reports limited sun exposure and minimal physical activity prior to surgery. There is no history of chronic liver, kidney, or bone disorders. A correction dose of 5000 IU of vitamin D per day was administered for the next 3 months. Evaluation of patient's vitamin D serum was planned to be carried out afterwards.

Given the increasing evidence suggesting a potential role of vitamin D in cancer prognosis, the attending physician begins to consider whether vitamin D supplementation may have a beneficial effect on the patient's overall survival (OS) and progression-free survival (PFS).

Methods

Clinical question

The clinical question was determined based on this research's population, intervention, comparation and outcome (PICO). The clinical question: Does vitamin D supplementation improve overall survival and progression-free survival in patients with colorectal cancer compared to standard treatment alone?

P : Patients with colorectal cancer
I : Vitamin D supplementation
C : No supplementation / standard care
O : Overall survival and progression-free survival

Search Stategy

Literature search was performed using combination of MeSH terms and Title/Abstract on three large databases: Pubmed, Cochrane Library and Google Scholar (table 1). Search was conducted

on May 23rd, 2025. The keywords used in the search strategy are adjusted to the components in PICO, with following terms: vitamin D and Colorectal Cancer. Critical assessment tools and levels of evidence are based on the Oxford Center for Evidence-Based Medicine.

Table 1. Resources and Search Strategy

Database	Terminology	Hits	Eligible
Pubmed	((vitamin D[MeSH Terms]) AND (colorectal cancer[MeSH Terms])) OR (CRC[MeSH Terms])	25	1
Cochrane	#1 MeSH descriptor: [Vitamin D] explode all trees #2 MeSH descriptor: [Colorectal Neoplasms] explode all trees #3 #1 AND #2	22	1
Google Scholar	allintitle: vitamin D colorectal cancer randomized OR controlled OR trial OR meta-analyses	19	0

Eligibility Criteria

The inclusion criteria encompassed participants aged 18 years or older who had been diagnosed with colorectal cancer, received vitamin D supplementation, and were part of a study designed as a randomized controlled trial (RCT), systematic review or meta-analyses. These studies needed to report outcomes related to overall survival and have been published between 2020 and 2025, with the publication being in English. On the other hand, exclusion criteria consisted of animal studies, received co-supplementation, and articles that were not accessible in full text.

Results

A systematic search of the literature was performed across PubMed, the Cochrane Library, and Google Scholar databases, identifying 169 relevant studies. Following de-duplication and filtering for publications within the last five years using Covidence, 42 unique articles remained. These were then screened by title and abstract according to predefined PICO criteria, narrowing the selection to 6 studies for full-text assessment. After a thorough evaluation, 4 studies was excluded, and 2 articles were retained for critical appraisal: systematic reviews and meta-analyses by Vaughan-shaw et al.[8], and Xu et al.[9] The process of study identification and selection is outlined in Figure 1. Characteristic (Table 2) and appraisal of the included studies was conducted using the Centre for Evidence-Based Medicine (CEBM) criteria for assessing the validity and applicability of therapeutic studies (Tables 3 and 4).

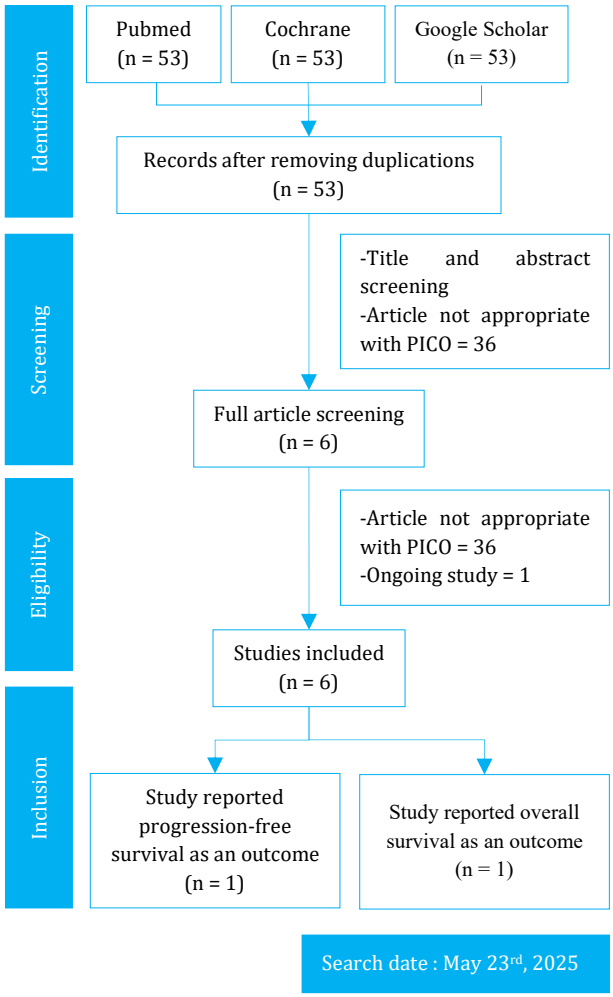

Figure 1. Literature Search Flow

Discussion

Vitamin D improves survival in colorectal cancer (CRC) patients through a combination of effects on tumor cells, stromal components, and the immune microenvironment. The active form, 1α,25-dihydroxyvitamin D_3 (calcitriol), exerts anti-tumor effects by binding to the vitamin D receptor (VDR), which is expressed not only on carcinoma cells but importantly on tumor-associated stromal fibroblasts. High VDR expression in these fibroblasts correlates with better overall and progression-free survival. Calcitriol inhibits fibroblast activation, reducing collagen gel contraction and their ability to promote cancer cell migration. This modulation of the stroma also involves the induction of a protective gene signature, including upregulation of CD82 and downregulation of S100A4, which is linked to improved prognosis.[3]

Table 2. Study Characteristic

Article	Study design	Population	Intervention	Outcome	Key results
Vaughan-Shaw et al. (2020)[10]	Systematic review and meta-analyses of RCTs	2 RCT studies of CRC patients (n = 340)	Vitamin D supplementation (400–4000 IU/day)	Progression-free survival	Vitamin D supplementation significantly improved Progression-free survival (HR = 0.65; 95% CI: 0.36 - 0.94).
Xu et al. (2021)[11]	Systematic review and meta-analyses of cohort and RCT	1 RCT and 2 cohort studies of CRC patients (n = 4646)	1 study 2000 IU vitamin D supplementation 2 study no specific dose	Overall Survival	The use of supplementary Vitamin D improved OS of CRC (HR = 0.88; 95% CI: 0.77-0.99)

CRC = colorectal cancer; RCT = randomized controlled trial; HR = hazard ratio; CI = confidence interval

Tabel 3. Validity Criteria

	Study design	Number of patient	Randomization	Similarity treatment and control	Blinding comparable treatment	Domain	Determinant	Measurement of outcomes	Quality of evidence*	Level of evidence**
Vaughan-Shaw et al., (2020)	+	+	+	+	+	+	+	+	High	1a
Xu et al., (2021)	+	+	-	?	-	+	+	+	Low	2b

* Quality of evidence according to GRADE guidelines, https://www.ncbi.nlm.nih.gov/pubmed/21208779

** Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), http://www.cebm.net.

\+ Clearly mentioned in the article; - not done; ? not stated clearly

Tabel 4. Relevance Criteria

	Similarity population	Similarity determinant/intervention	Similarity outcome
Clark et al., (2019)	+	+	+
Yang SJ., (2019)	+	+	+

Beyond the stromal effects, vitamin D directly influences tumor cell biology by suppressing proliferation via cell cycle arrest mediated by upregulation of p21 and p27, and by restoring TGF-β sensitivity through increased TGF-β receptor expression. Calcitriol antagonizes aberrant Wnt/β-catenin signaling—a key driver in CRC—by promoting VDR/β-catenin binding, increasing E-cadherin to sequester β-catenin at the membrane, and enhancing expression of Wnt inhibitors like DKK-1. Additionally, vitamin D induces apoptosis by modulating BCL-2 family proteins and facilitating mitochondrial cytochrome c release. It also exerts anti-angiogenic effects by downregulating VEGF and HIF-1, and anti-inflammatory effects by interfering with prostaglandin synthesis and cytokine production. Clinically, vitamin D supplementation has been shown to increase $CD8^+$ memory T-cell infiltration and enhance their spatial proximity to tumor cells, suggesting an immunomodulatory role in enhancing anti-tumor immunity in CRC patients. Moreover, vitamin D influences gut microbiota composition, further contributing to intestinal homeostasis and possibly modulating tumor behavior.[10,11]

The clinical efficacy of vitamin D in CRC has been explored in several studies. The systematic review and meta-analyses by Vaughan-Shaw et al.[8] provides the higher level of evidence included in this EBCR. It has two main focus, to identify trials of vitamin D supplementation in CRC patients, and to identify trials of vitamin D supplementation in non cancer cohorts, which included cancer mortality as a trial outcome. Appropriate to this research's PICO, this study pooled data from two

randomized controlled trials, namely the SUNSHINE trial and the AMATERASU trial, encompassing 340 CRC patients, and demonstrated significant improvement on progression-free survival (HR = 0.65; 95% CI: 0.36–0.94). The RCTs in this study showed different results from two different intervention dose of vitamin D. SUNSHINE observed intervention dose of 4000 IU/day vitamin D3 adjunct to standard chemotherapy compared to 400 IU/day vitamin D3 for 23 months on metastatic CRC patients, showed significant improvement on progression-free survival (HR = 0.64; 95% CI: 0-0.90). On the other hand AMATERASU observed intervention dose of 2000 IU/day vitamin D3 adjunct to standard chemotherapy compared to placebo for 3.5 years on epithelial carcinoma of digestive tract (stage 1-3) patients, showed no significant result.[8]

The meta-analyses by Xu et al.[9] focuses primarily on observational studies, incorporating 21 cohort studies for incidence and 4 for prognosis, with a total of 904,152 participants. The authors reported that the use of supplementary vitamin D improved overall survival of CRC (HR = 0.88; 95% CI: 0.77-0.99), but this result is inconsistent because the reported p = 0.909.[9] Researcher underwent further investigation on the 3 studies in this meta-analyses to found out that the results were all not statistically significant. Two studies by Jeffreys et al.[12] and Lewis et al.[13] never mentioned specific dose of the vitamin D supplementation, whereas Golubic et al.[14] compared two groups of newly diagnosed metastatic CRC patients, with and without vitamin D 2000 IU daily supplementation for 2 years.[12,13,14]

A broad range of studies—including reviews, randomized controlled trials, and meta-analyses—highlight the multifaceted and developing role of vitamin D supplementation in colorectal cancer. Its therapeutic effects are thought to involve several pathways, such as molecular signaling, stromal interactions, immune modulation, and alterations in the gut microbiome. Notably, SUNSHINE study supports a daily dose of 4,000 IU over a treatment duration of up to 23 months.[6]

Despite the promising findings, several limitations must be acknowledged from the reviewed studies. The meta-analyses by Vaughan-Shaw et al.[8] included only two randomized controlled trials with a relatively small total sample size limiting the statistical power and generalizability of the findings. Furthermore, the two RCTs used different dosing regimens and heterogeneous populations. The meta-analyses by Xu et al.[9] primarily incorporated observational studies, which are inherently susceptible to confounding factors and biases. Additionally, inconsistencies in the reported outcomes such as the contradictory hazard ratio and p-value further reduce the reliability of the conclusions. None of the included studies in Xu's analysis reported significant effects when examined individually, and some lacked clear information regarding the dose or duration of vitamin D supplementation, making it difficult to draw firm conclusions about causality or optimal therapeutic regimens. Future studies are encouraged to implement randomized controlled trials involving larger populations, consistent vitamin D dosages, and standardized treatment durations to improve the accuracy of therapeutic assessments and ensure broader clinical relevance.

Conclusion

Vitamin D supplementation shows promising biological and clinical potential in improving outcomes for colorectal cancer patients through multiple mechanisms, including modulation of tumor growth, stromal activity, immune responses, and microbiota composition. Among the reviewed studies, a high-dose regimen of 4,000 IU/day for 23 months demonstrated a significant improvement in progression-free survival in metastatic CRC patients. However, the overall evidence remains limited by small sample sizes, heterogeneity in study designs, and inconsistent results. While current findings support the potential benefit of vitamin D as an adjunct to standard therapy, further large-scale randomized controlled trials with standardized regimens are needed to establish its definitive role in colorectal cancer management.

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