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Vitamin D Supplementation and Colorectal Cancer Patients Outcomes

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Abstract

Colorectal cancer is the third most encountered malignancy worldwide in 2018. Some earlier studies indicate a significant influence of vitamin D supplementation on the 5-year survival rate and the rate of metastasis progression in colorectal cancer patients. Studies investigating the effects of vitamin D supplementation on the outcomes of colorectal cancer patients are limited in Indonesia. Therefore, a double-blinded Randomized Controlled Trial (RCT) of the effect of vitamin D supplementation on the outcome of colorectal cancer patients was conducted from April 2022 to March 2023 at the digestive surgery outpatient clinic of Dr. Hasan Sadikin General Hospital Bandung, Indonesia. In this study, 36 patients received vitamin D and 34 patients received a placebo. Data analysis performed using the multivariate analysis with multiple regression revealed no significant relationship between vitamin D supplementation and colorectal cancer patient outcomes. Furthermore, ANOVA analysis indicated no relationship between the analyzed independent and dependent variables in this study. No relationship was found between vitamin D supplementation and the outcomes of metastasis, mortality, and Karnofsky scores in colorectal cancer patients. Further research with a larger population is still needed to determine the benefits of vitamin D supplementation on the outcomes of colorectal cancer patients.

Keywords: Colorectal neoplasms, neoplasm metastasis, mortality, vitamin D , supplementation

Introduction

According to data from the Global Cancer Observatory (GLOBOCAN) in 2018, colorectal cancer is the third most commonly diagnosed malignancy worldwide.[1,2] In Indonesia, it ranks fourth among the most frequently occurring cancers, with approximately 35,000 new cases reported each year. At Dr. Hasan Sadikin General Hospital in Bandung, there were 163 colorectal cancer patients treated at the Digestive Surgery Polyclinic between January 2005 and December 2008. Among these patients, 11.7% were under 40 years of age, while 37.4% were over 55 years old.

Vitamin D plays a role in regulating bone metabolism through the absorption of calcium from the digestive tract and bone cell remodeling. Intrinsic exposure to UVB radiation is the primary source of most vitamin D. UVB transforms 7-dehydrocholesterol into vitamin D in the skin, which is then hydroxylated into 25-hydroxyvitamin D, known as 25(OH)D, a secosteroid chemical. Subsequently, 25(OH) D is converted into 1,25-dihydroxyvitamin D, the most active vitamin D metabolite, by 1α-hydroxylase.[3]

Vitamin D deficiency (defined as a serum concentration of 25-hydroxyvitamin D ≤20 ng/mL) is common in the United States, especially among individuals of Hispanic and Black ethnicities.[3] Vitamin D deficiency is more prevalent in older patients, those who are obese, or hypertensive. These factors have been associated with poorer outcomes in patients with severe diseases.[3,4]

Several previous studies have indicated an inverse relationship between serum vitamin D levels and the frequency of colorectal cancer growth in humans.[3,5,6] Some studies have shown

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higher dietary vitamin D3 levels in patients associated with lower rates of intestinal disease, polyp recurrence, and higher resistance in colorectal patients.[3,6] Recent research by the Women's Health Initiative suggests that a decrease in vitamin D levels, 25(OH)D <12 ng/mL (30 nmol/L), significantly increases the risk of colorectal cancer incidence by 253% after 8 years.[7]

Earlier studies have suggested that vitamin D supplementation may significantly influence the 5-year survival rate and the progression of metastasis in colorectal cancer patients.[8–10] However, no established protocol exists for the use of vitamin D supplements in the management of colorectal cancer. Research on the effects of vitamin D supplementation in colorectal cancer patients is limited in Indonesia, particularly at Dr. Hasan Sadikin General Hospital in Bandung. This study aims to evaluate the impact of vitamin D supplementation on the outcomes of colorectal cancer patients at Dr. Hasan Sadikin General Hospital in Bandung.

Methods

This study is a prospective analytical experimental study with a randomized controlled trial design using a cohort method. The research data consists of primary data from colorectal cancer patients who visited the Digestive Surgery Polyclinic at Dr. Hasan Sadikin General Hospital in Bandung between April 1, 2022, and March 30, 2023. The study was reviewed and approved by the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung (Ethical approval number: LB.02.01/X.6.5/127/2023).

he target population for this study was all patients with colorectal cancer at Dr. Hasan Sadikin General Hospital. The accessible population included all colorectal cancer patients at the hospital during the period from April 2022 to March 2023. The inclusion criteria for this study were as follows: (1) Patients at Dr. Hasan Sadikin General Hospital diagnosed with colorectal cancer, confirmed through radiological examinations, colonoscopy results, or histopathological findings; (2) Patients aged ≥ 18 years; (3) Patients who have not consumed vitamin D in the 3 months prior to the start of the study; (4) Patients willing to participate by signing informed consent; and (5) Colorectal cancer patients with normal, insufficient, or deficient levels of vitamin D.

The exclusion criteria of this study are: (1) Allergic to vitamin D, with a history of experiencing symptoms such as nausea, vomiting, pruritus, and redness on the face and body following vitamin D consumption; (2) Patients with short bowel syndrome or those who have undergone gastric bypass surgery; (3) Patients regularly taking medications such as phenobarbital, carbamazepine, dexamethasone, nifedipine, spironolactone, clotrimazole, and rifampicin; (4) Patients with comorbidities of liver failure and kidney failure; (5) Patients experiencing symptoms of genitourinary stones in the last year; (6) Patients taking thiazide diuretics; (7) Patients with a history of stroke or malignancy other than colorectal cancer; (8) Patients with chronic infections; and (9) Pregnant, breastfeeding, or using oral contraceptives. Information regarding the exclusion criteria is found through medical records and direct interviews with study participants. The dropout criteria of this study include: (1) the patient does not take vitamin D supplements regularly every day and (2) loss-to-follow-up.

The study sample consists of primary data from colorectal cancer patients at the Digestive Surgery Outpatient Department of Dr. Hasan Sadikin General Hospital Bandung who meet the inclusion and exclusion criteria. The sample size was calculated using the formula for experimental research with a cohort design.

$$n = \frac{2\sigma^2 \left(z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2}{(\mu_1 - \mu_2)^2}$$

Information:
n = Sample size for each group
$Z_{1-\alpha/2}$ = The value on the standard normal distribution corresponding to the significance level α (for α = 0.05, is 1.96)
Z_{1-b} = The value on the standard normal distribution corresponding to the desired power (for β = 0.1, is 1.28).
σ = Standard deviation of the outcome
μ_1 = Mean outcome of the unexposed group
μ_2 = Mean outcome of the exposed group

From the calculation, the result obtained was 25, so the required sample size for each group (placebo and vitamin D supplementation [Hi-D]) is a minimum of 25 samples, with a total of 50 samples. The sampling method used in this study was consecutive sampling, where subjects who meet the research criteria are selected until the minimum required sample size is reached.

Patient medical record data and anamnesis

were used to obtain personal information such as age, occupation, education, sex, diabetes, hypertension, alcohol consumption, depression, smoking, diet/supplement use, and sensitivity to vitamins or dietary supplements. At the beginning and end of the study, participants' height (cm) and weight (kg) were measured using a Seca scale.

Data collection was obtained from all colorectal cancer patients who visited the Digestive Surgery Polyclinic at Dr. Hasan Sadikin General Hospital Bandung. Patient data, including identity, anthropometry, alcohol consumption history, smoking history, comorbidities, vitamin D level examination results, and diagnosis, were recorded. Patients who met the inclusion and exclusion criteria were divided into the vitamin D and placebo groups. The placebo group was given placebo capsules (edible paraffin), while the intervention group received 10,000 IU/day of vitamin D for six months. After six months, patient data were recorded again, and outcomes related to metastasis, mortality, and the Karnofsky score were assessed. The research flow diagram is shown in Figure 1.

The data in this experimental research was taken quantitatively, especially in data analysis related to the hypothesis test that will be carried out. This research is randomized clinical trial, which divided the sample into two groups randomly: the group that received treatment (vitamin D) and the group that did not receive treatment (placebo).

In the initial stage, each group and the sample will undergo univariate analysis related to general sociodemographic features and basic clinical conditions. Numeric data such as the age of patients are presented with the mean, standard deviation, median, and range. Categorical data such as gender is coded and presented as a frequency distribution and percentage.

Statistical analysis was performed using the SPSS 26 program. The Chi-square test was used to compare categorical variables. The independent samples t-test was employed to compare the means of quantitative data between the two groups. In cases where the intervention variable was related to demographic variables, ANOVA was used. A paired t-test was applied to compare pre- and post-intervention values within a group. For variables with non-normal distribution, non-parametric tests (Wilcoxon or Mann-Whitney U test) were used. Results were considered statistically significant if the p-value was <0.05, with a 95% confidence level.

Bivariate analysis utilizes simple logistic regression, aiming to analyse the relationship between one or more independent variables and a categorical dependent variable. A p-value <0.05 was considered significant, and odds ratios (OR) greater than or equal to 1.00 were regarded as risk factors or predictors.

Analysis between numeric and categorical variables used independent samples t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data. The normality of data was assessed using the one-sample Kolmogorov-Smirnov test. Variables with p<0.25 were considered candidates for multivariate analysis. Multivariate analysis employed a multiple logistic regression model. A p-value <0.05 was considered meaningful.

he ethical aspect of this research pertains to the confidentiality of patients' medical and laboratory records within the academic community at the Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin Hospital Bandung. All participants were provided with an explanation of the purpose, benefits, and procedures of the research, including any potential discomfort related to the study. Those willing to participate were asked to sign an informed consent form. All data and information regarding the participants are kept confidential. Participants have the right to withdraw from the study at any time without having to provide any reasons.

Results

This study included 70 respondents with the following characteristics. In terms of age, the average age of colorectal cancer patients was 57.23 years (SD=9.621), with a p-value of 0.613. The oldest patient was 77 years old, while the youngest was 28 years old. Regarding the Karnofsky score, the average score of colorectal cancer patients was 80.71 (SD=7.484), with a p-value of 0.540.

Based on the occurrence of metastasis, this study found that most respondents did not experience metastasis. The incidence of metastasis did not differ significantly between the group given vitamin D and the group not given vitamin D. Based on mortality, this study found that most respondents did not experience mortality during the monitoring period. Mortality occurred only in the placebo group, with 1 person.

Table 2 shows that the highest percentage of age is in the 60–79 years age group in the

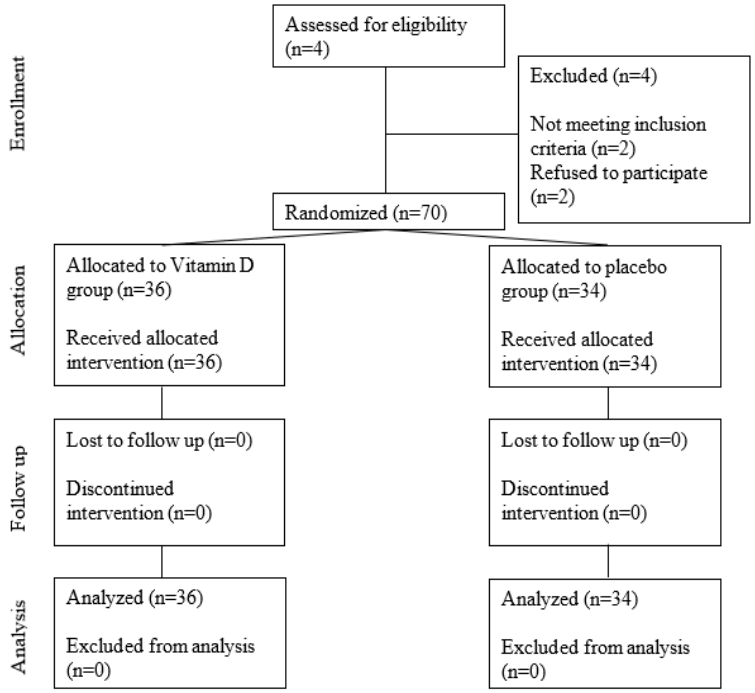

Figure 1 CONSORT Flow Diagram of The Study

placebo group (50%), and 50–59 years in the vitamin D group (36.11%). In addition, the functional capacity, Karnofsky score, is mostly 80 in both groups (61.11% in the vitamin D group and 44.12% in the placebo group). Among all participants, patients with normal pre-supplementation vitamin D levels were 9 people in the vitamin D group (25%) and 11 in the placebo group (32.4%). After supplementation, the number of participants with normal vitamin D levels increased to 16 people in the vitamin D group (44.4%) and 12 in the placebo group (35.3%). However, most participants still had vitamin D levels below normal even after supplementation. Chi-square analysis did not show any significant differences in all variables between the groups receiving vitamin D supplementation and placebo.

The chi-square analysis indicates no statistically significant relationship between the variables: age (p=0.261), vitamin D supplementation (p=0.522, OR=2.188 95% CI 0.189-25.295), gender (p=0.095), alcohol consumption (p=0.831), BMI (p=0.956),

Table 1 Cross-tabulation of Vitamin D Supplementation (Hi-D) Against the Incidence of Metastasis and Mortality in Colorectal Cancer Patient

Outcome	Vitamin D Supplementation (Hi-D)	+ (n)	- (n)	Total (n)
Metastasis	Vitamin D	1	35	36
	Placebo	2	32	34
	Total	3	67	70
Mortality				
	Vitamin D	0	36	36
	Placebo	1	33	34
	Total	0	70	70

Table 2 Simple Regression Analysis of Vitamin D Supplementation (Hi-D) on the Outcomes of Colorectal Cancer

Variable	Vit D (Hi D)	Placebo	OR	CI 95%	p-value*
	n	n	min.	max.	
Age					
< 50 years old	11	3			0.613
50–59 years old	13	14			
60–79 years old	12	17			
Karnofsky score					
60	1	1			0.540
70	5	6			
80	22	15			
90	8	12			
Metastasis					
(+)	1	2	0.189	25.295	0.522
(-)	35	32			
Mortality					
(+)	0	1	0.374	0.612	0.300
(-)	36	33			
Sex					
Male	18	15	0.494	3.245	0.622
Female	18	19			
Family history					
(+)	3	5	0.417	8.635	0.402
(-)	33	29			
Smoking history					
(+)	9	11	0.506	4.067	0.496
(-)	27	23			
(+)	1	0	0.00	0.00	0.328
(-)	35	34			
Normal	9	11			
Insufficiency	15	17			
Deficiency	12	6			
Normal	16	12			
Insufficiency	15	15			
Deficiency	5	7			
BMI					
Underweight	23	19			
Normal	12	15			
Overweight	1	0			
Obese	0	0			
(+)	0	3	0.00	0.00	0.068

Table 2 Continued

Variable	Vit D (Hi D)	Placebo	OR	CI 95%	p-value*
	n	n	min.	max.	
(-)	36	31			
Diabetes comorbid					
(+)	0	1	0.00	0.00	0.300
(-)	36	33			
Cancer duration					
< 6 months	29	24	0.571	5.222	0.945
> 6 months	7	10			
De Gramont	27	27	3.951	1.286	0.193
Folfox	9	7			
Cancer location					
Colon	20	17	3.201	1.250	0.217
Rectum	16	17			

Note: *) based on Chi-square test

family history (p=0.223, OR=4.286 95% CI 0.343-53.526), smoking (p=0.263), comorbid hypertension (p= 0.708), comorbid diabetes (p= 0.831), pre-supplementation vitamin D levels (p=0.568), post-supplementation vitamin D levels with metastasis occurrence (p=0.748), and cancer duration (p=0.08 OR 6.933 95% CI 0.578-81.824) with metastasis occurrence.

The chi-square analysis indicates no statistically significant relationship between the variables: age (p=0.222), vitamin D supplementation (p=0.300), gender (p= 0.341), alcohol consumption (p=0.903), BMI (p=0.713), family history (p= 0.05), smoking (p=0.524), comorbid hypertension (p= 0.831), comorbid diabetes (p=0.903), pre-supplementation vitamin D levels (p=0.548), post-supplementation vitamin D levels (p= 0.086), and cancer duration (p= 0.075) with mortality occurrence.

From the Kolmogorov-Smirnov normality test results on the distribution of Karnofsky scores in subjects, a significance value of 0.000 was found, indicating that the data is not normally distributed. Therefore, data analysis was performed using Mann-Whitney for variables with 2 groups and Kruskal-Wallis for variables with >2 groups. Based on the Mann-Whitney analysis results, variables such as vitamin D supplementation, sex, alcohol consumption, smoking history, family history, hypertension, diabetes, and cancer duration do not have a significant effect on the Karnofsky scores. According to the Kruskal-Wallis analysis results, variables such as age, pre-supplementation vitamin D levels, post-supplementation vitamin D levels, and BMI do not have a significant effect on the Karnofsky scores.

Table 5 presents the results of the multivariate analysis on metastasis outcomes. It was found that no variable had a p-value <0.05, indicating that vitamin D supplementation, age, gender, alcohol consumption, post-supplementation vitamin D levels, BMI, family history, smoking, cancer duration, pre-supplementation vitamin D levels, hypertension, and diabetes do not significantly influence metastasis outcomes.

Table 6 presents the results of the multivariate analysis on the mortality outcome. It was found that no variable had a p-value <0.05, indicating that vitamin D supplementation, age, gender, alcohol consumption, post-supplementation vitamin D levels, BMI, family history, smoking, cancer duration, pre-supplementation vitamin D levels, hypertension, and diabetes do not significantly influence mortality outcomes

Table 6 also shows the results of the multivariate analysis on Karnofsky scores. The variable of age was found to have a significance value of p=0.025, indicating a significant relationship between age and Karnofsky scores. Additionally, the calculated t-value of 2.296, which exceeds the tabulated t-value of 2.00247, further supports the significant relationship between age and Karnofsky scores. The t-value of -2.296 indicates a negative relationship,

Table 3 Bivariate Analysis of Independent Variables on Metastasis and Mortality

Variable	Metastasis p-value	Mortality p-value
Age	0.261	0.222
Sex	0.095	0.341
Vitamin D Supplementation	0.522	0.300
Alcohol consumption	0.831	0.903
Vitamin D levels (post-supplementation)	0.748	0.086
BMI	0.956	0.713
Family history	0.223	0.05
Smoking history	0.263	0.524
Cancer duration	0.08	0.075
Vitamin D levels (pre-supplementation)	0.568	0.458
Hypertension comorbid	0.708	0.831
Diabetes comorbid	0.831	0.903

Note: *) based on Chi-square test

suggesting that as age increases, Karnofsky scores decrease. Other variables did not show a significant relationship in the multivariate analysis. The ANOVA analysis indicates a tabulated F-value of 1.92 with a calculated F-value of 1.323. This means that the calculated F-value is less than the tabulated F-value, indicating no simultaneous relationship between independent and dependent variables.

Table 4 Bivariate Analysis of Independent Variables on Karnofsky Score

Variable	p-value
Age	0.334**
Sex	0.556*
Vitamin D Supplementation	0.53*
Alcohol consumption	0.849*
Vitamin D levels (post-supplementation)	0.186**
BMI	0.435**
Family history	0.919*
Smoking history	0.678*
Cancer duration	0.497*
Vitamin D levels (pre-supplementation)	0.120**
Hypertension	0.566*
Diabetes	0.268*

Note: *) Mann-Whitney test, **) Kruskal Wallis

Discussion

The results of this study indicate no significant relationship between vitamin D supplementation and the Karnofsky score outcome in colorectal cancer patients. The analysis of vitamin D administration on the functional capacity outcome assessed through the Karnofsky score has been previously conducted in patients with chronic kidney disease (CKD). CKD patients with higher Karnofsky scores had significantly higher serum 25(OH)D levels compared to those with lower Karnofsky scores, and only 5% of patients with adequate vitamin D levels had low scores. This can be explained by the fact that patients with better functional capacity have more sun exposure.[11] Previous research on the effect of vitamin D supplementation on colorectal cancer patients' outcomes, specifically the Karnofsky score, is limited. Vitamin D deficiency is a poor prognostic factor in metastatic colorectal cancer, but targeted supplementation trials have yielded limited results. A recent study comparing oral vitamin D3 therapy at two different doses (4000 vs. 400 IU/day) in combination with standard first-line chemotherapy for metastatic colorectal cancer found that high-dose vitamin D was associated with a significant increase in survival.[12,13] Higher concentrations of 25(OH)D were associated with better cancer outcomes. The Vit D–VDR complex has the potential to provide downstream biological effects, regulating the expression of several target genes, including some with anti-tumor properties. The complex

Table 5 Multiple Regression Analysis of High-Dose Vitamin D Supplementation (Hi-D) on Metastasis and Mortality Outcome

Metastasis Outcome

Variable	B	S.E	Wald	df	P value	Exp(B)
Age	-12.522	370.337	.001	1	.973	0.000
Vit D supplementation	-202.875	40176.482	.000	1	.996	.000
Sex	349.570	24109.368	.000	1	.988	6.550E+151
Alcohol consumption	583.711	49175.775	.000	1	.991	3.180E+253
Vitamin D levels (post-supplementation)	141.649	40025.501	.000	1	.997	3.290E+61
BMI	-56.677	16674,988	.000	1	.997	0.000
Family history	-30.955	30089.065	.000	1	.999	0.000
Smoking history	-550.784	27395.661	.000	1	.984	0.000
Cancer duration	127.242	33352.836	.000	1	.997	1.821E+55
Vitamin D levels (pre-supplementation)	-59.214	22018.941	.000	1	.998	0.000
Hypertension	297.071	21471.148	.000	1	.989	1.038E+129
Diabetes	205.101	42062.932	.000	1	.996	1.187E+89

Mortality Outcome

Variable	B	S.E.	Wald	df	P value	Exp(B)
Vitamin D levels (post-supplementation)	38.526	9286.841	0.000	1	.997	5389849771179 7200.000
Vitamin D levels (pre-supplementation)	-38.116	10409.298	0.000	1	.997	0.000
Alcohol consumption	37.884	41843.502	0.000	1	.999	28369560523183 464.000
Family history	1.364	8322.615	0.000	1	1.000	3.913
Cancer duration	0.928	7939.657	0.000	1	1.000	2.529
Sex	1.052	10065.119	0.000	1	1.000	2.863
BMI	0.317	4513.969	0.000	1	1.000	1.373
Age	-0.034	458.994	0.000	1	1.000	0.967
Vit D Supplementation	-0.475	8990.752	0.000	1	1.000	0.622
Hypertension	-0.755	22624.048	0.000	1	1.000	0.470
Vit D Supplementation	-0.397	8972.671	0.000	1	1.000	0.673
Diabetes	-0.281	41753.498	0.000	1	1.000	0.755

B = Regression coefficient: This represents the change in the outcome variable (metastasis or mortality) for a one-unit change in the predictor variable; S.E. = Standard error: Measures the accuracy of the regression coefficient; df = Degrees of freedom: Number of parameters being tested; Exp(B) = Exponent of the regression coefficient: It gives the odds ratio, indicating the change in odds for a one-unit increase in the predictor variable.

interplay of VitD–VDR may influence cancer risk and survival. The three aspects strengthening the understanding of the relationship between vitamin D and cancer impact are: increasing cancer incidence and mortality, widespread vitamin D deficiency worldwide, especially in healthy individuals and cancer patients, and modifiable vitamin D deficiency as a risk factor based on research reporting a connection between vitamin D deficiency and worse cancer outcomes. It is proposed that vitamin D may have potential value as an additional chemotherapy

Table 6 Multiple Regression Analysis of High-Dose Vitamin D Supplementation (Hi-D) on Karnofsky Score Outcome

Variable	Unstandardized B	Std. Error	Standardized Coefficient B	t	Sig
Age	-0.246	0.107	-.0317	-2.296	0.025
Vit D supplementation	2.646	2.149	0.178	1.232	0.223
Sex	-2.748	2.034	-0.185	-1.351	0.182
Alcohol consumption	-2.470	7.787	-0.039	-0.317	0.752
Vitamin D levels (post-supplementation)	-3.410	2.475	-0.331	-1.378	0.174
BMI	-0.721	0.957	-0.094	-0.753	0.455
Family history	2.916	2.900	0.125	1.006	0.319
Smoking history	0.187	2.160	0.011	0.086	0.931
Hypertension	1.194	4.674	0.033	0.255	0.799
Diabetes	6.618	7.726	0.106	0.857	0.395
Cancer duration	-4.191	2.294	-0.242	-1.827	0.073
Vitamin D levels (pre-supplementation)	1.055	2.452	0.105	0.430	0.669

agent, especially since vitamin D supplements are inexpensive, safe, and easily accessible.[14]

his study indicates that vitamin D supplementation does not have a significant effect on the Karnofsky score outcome. This finding is consistent with previous research. The VITamin D and OmegA-3 Trial (VITAL) did not show a significant relationship between vitamin D supplementation and a reduced risk of colorectal adenomas or polyps. Several studies have previously suggested that vitamin D supplementation, on its own, does not yield statistically significant clinical effects.

Some observational studies have linked higher vitamin D intake and circulating 25(OH) D levels to a decreased risk of conventional adenoma, although there are confounding factors that can be dismissed. Conversely, the only RCT specifically examining colorectal neoplasia as a primary endpoint did not find any benefits of vitamin D supplementation at a dose of 1000 IU per day against conventional adenoma recurrence. However, as this study was conducted on participants with a history of conventional adenoma, it remains unclear whether vitamin D can protect against polyp occurrence in individuals with average risk. The zero findings in the VITAL study indicate that daily vitamin D supplementation at a dose of 2000 IU does not affect the overall risk of conventional adenoma among individuals not selected for vitamin D deficiency.[15]

Another review study mentions that, despite many studies showing a significant association between higher 25(OH)D levels and a reduced risk of colorectal cancer, these effects appear to vary. While 25(OH)D concentrations significantly reduce the risk of colorectal cancer in women, this association is not observed in the male population. The optimal concentration of 25(OH) D for reducing the risk of colorectal cancer is reported to be between 75 and 100 nmol/L, which exceeds the current recommendations.[16] This study did not consider sex when evaluating the relationship between vitamin D supplementation and outcomes, which may be an important confounding variable. Additionally, the study focused on the presence or absence of vitamin D supplementation for colorectal cancer outcomes, rather than the 25(OH)D levels, which previous studies have emphasized as having a greater impact on outcomes and reducing the risk of colorectal cancer. The study results show no relationship between vitamin D supplementation and the incidence of metastasis and mortality in colorectal cancer patients. This differs from studies by Milczarek et al.[17] and Ng et al.[18] Milczarek et al.[17] stated that vitamin D analog administration enhances the anticancer activity of 5-fluorouracil in an induced colorectal cancer mouse model. With vitamin D analogs, the activity of 5-fluorouracil significantly increases along

with a decrease in tumor growth, metastasis, and improved survival in mice. This in vivo study was later confirmed by a randomized controlled trial by Ng et al.[18] According to them, treatment with chemotherapy plus high-dose vitamin D3 supplementation compared to chemotherapy plus standard-dose vitamin D3 results in a median progression-free survival of 13 months vs. 11 months, which is not statistically significant but has a significant multivariable hazard ratio of 0.64 for progression-free survival or statistically significant death-free.[18] This may be explained by Klamfer, who mentioned that calcitriol, through its interaction with the vitamin D receptor, inhibits the Wnt signaling pathway, thus inhibiting cancer growth and metastasis.[19] A review study by Vaughan-Shaw et al. indicated that vitamin D supplementation at doses of 2000–4000 IU/day may provide clinically significant benefits, such as improved survival in colorectal cancer patients. This differs from the generally recommended daily dosage of 400 IU.[13] Previous studies have indicated that the administration of vitamin D supplementation enhances the tumoricidal activity of 5-FU in in vivo models.[20] However, in this study, chemotherapy agents were divided into two regimens: De Gramont, which uses 5-FU, and Folfox, which combines 5-FU with oxaliplatin. The differences in the regimens used in this study compared to previous research may serve as a confounding factor influencing the study's outcomes. A study by Milczarek et al. found that vitamin D analogs improve survival in in vivo models treated with oxaliplatin; however, at high doses, these analogs may interact antagonistically with oxaliplatin.

The limitations of this study include the observed variances, which suggest the need for randomized controlled trials with a larger sample size, particularly within the Indonesian population. While a larger number of participants could enhance the study, the sample size in this research is still adequate to draw meaningful conclusions. Additionally, it is important to investigate the effects of vitamin D supplementation in colorectal cancer patients receiving 5-FU chemotherapy compared to those receiving a combination of 5-FU and oxaliplatin. Future studies should focus on refining the inclusion and exclusion criteria.

In conclusion, no significant relationship was found between vitamin D supplementation and the outcomes of metastasis, mortality, or Karnofsky scores in colorectal cancer patients. However, further research with a larger population is necessary to better understand the potential benefits of vitamin D supplementation on the outcomes of colorectal cancer patients.

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