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Vitamin D and Diagnostic Colonoscopy for Colorectal Cancer in Indonesian Population: A Cross-sectional Study

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Abstract

BACKGROUND: Colorectal cancer (CRC) is the world's third most common type of cancer. Case studies have shown an inverse correlation between serum Vitamin D levels and the incidence of human colorectal cancer.

AIM: This study aims to assess Vitamin D levels in patients who underwent colonoscopy for diagnostic colorectal cancer.

METHODS: This research is a cross-sectional study. This study's subjects were patients who visited the Digestive Surgery polyclinic and underwent a colonoscopy to diagnose colorectal cancer. Level of Vitamin D was collected before the colonoscopy examination and categorized into three groups: Vitamin D with a value of < 20 ng/mL indicates a deficiency, a level of 20–30 ng/mL as an insufficiency level, and a value > 30 ng/mL as a sufficient value. A colonoscopy examination was performed to obtain a diagnosis of colorectal cancer based on anatomical pathology examination.

RESULTS: Examination of Vitamin D levels from 120 subjects showed that the average vitamin level was 16.36 ng/mL, which indicates Vitamin D deficiency levels. A total of 85 (70.8%) subjects showed Vitamin D deficiency, as many as 24 (20%) showed Vitamin D insufficiency levels, and only 11 (9.2%) study subjects showed sufficient Vitamin D levels. The colonoscopy showed 60 (50%) subjects with colorectal cancer. The relationship between Vitamin D levels and the diagnosis of CRC showed a value of p = 0.60 (p > 0.05).

CONCLUSION: There is no significant difference between low levels of Vitamin D and the diagnosis of colorectal cancer patients.

Introduction

According to GLOBOCAN in 2018, colorectal cancer (CRC) is the world's third most common type of cancer. Based on data from the American Cancer Society, CRC is the third most common cancer and the third leading cause of death in the United States, with about 150,000 new cases per year [1]. In 2018, approximately 1,800,000 new cases and 881,000 deaths were reported due to CRC, which accounts for nearly 10% of new cancer cases and deaths worldwide. It is estimated that there will be nearly 2.5 million new cases of CRC by 2035 [2]. Meanwhile, data in Indonesia, based on GLOBOCAN in 2020, show CRC in the fourth position, with new cases ranging from 35,000 yearly [1], [3]. The etiology of colorectal cancer is still unclear, but it is known that the development of CRC generally is an interaction between various risk factors, both modifiable and not [3]. Non-modifiable risk factors are age and hereditary or genetic history [4]. Modifiable risk factors include diet and nutrition, lack of physical activity and obesity, smoking and alcohol consumption, and low levels of Vitamin D in the blood [5], [6], [7], [8], [9], [10]. Case studies have shown an inverse correlation between serum Vitamin D levels and the incidence of human colorectal cancer, and several studies have proposed lower colon cancer incidence, polyp recurrence, and overall survival for patients with colon cancer with higher Vitamin D3 levels [2], [10]. Vitamin D regulates bone metabolism mainly through calcium absorption from the intestines and bone remodeling. Endogenous exposure to ultraviolet B radiation is the main source of Vitamin D for most people, which then converts 7-dehydrocholesterol in the skin into Vitamin D, which is then hydroxylated to 25-hydroxyvitamin D, namely 25(OH)D, which is a secosteroid hormone. 25(OH)D is converted to 1,25-dihydroxyvitamin D, which is 1,25(OH)2D, the most active Vitamin D metabolite by the enzyme 1-α-hydroxylase [2].

The relationship between Vitamin D status and colorectal cancer risk has been studied since 1980. Researchers have investigated this hypothesis in various ways, including direct measurement of circulating 25(OH)D, surrogates or determinants of 25(OH)D, studying the region of residence, intake, and estimated sun exposure, or a combination of these. Most epidemiological studies have reported that high serum

25(OH)D levels are associated with lower incidence rates of colon, breast, and ovarian cancers [11]. Vitamin D is also involved in various physiological pathways, including cell cycle regulation, cell proliferation, angiogenesis, apoptosis, and molecular cell signaling. 1,25(OH)2D binds to specific Vitamin D receptors (VDRs), members of the nuclear receptor superfamily. Then, the VDR will bind to the retinoid X receptor (RXR), and the VDR-RXR heterodimer binds to the Vitamin D response element (VDRE), which then controls the activation or repression of gene expression [2], [3].

Research has identified several potential pathways for Vitamin D involvement in colorectal cancer, including increased calcium-sensing receptor (CaSR) expression, which then inhibits the catenin/T-cell factor (TCF) transcription complex, promotes E-cadherin activity, and decreases CYP24A1 concentrations [12]. Other studies have also described the WNT signaling pathway that develops in colorectal cancer [13]. The apoptotic process of colorectal cancer is also influenced by Vitamin D through the downregulation of BAG1 and the upregulation of BAK1 that triggers apoptosis. Inflammatory pathways that develop in colorectal cancer have also been shown to be influenced by Vitamin D [14]. In the Women's Health Initiative, women who had Vitamin D levels 25(OH)D < 12 ng/mL (30 nmol/L) had a 253% risk of developing colorectal cancer after 8 years [15]. This study aimed to measure the level of Vitamin D in patients who underwent colonoscopy for diagnosis of colorectal cancer.

Materials and Methods

Study design and setting

This study is cross-sectional and follows the Strengthening The Reporting of Cohort Studies in Surgery (STROCSS) guideline 2019 [16]. The research subjects were patients who came to the Digestive Surgery polyclinic, with suspicious signs and symptoms of colorectal cancer, and received a colonoscopy. The exclusion criteria were patients who had been diagnosed with CRC or had CRC therapy, patients with short bowel syndrome or patients undergoing gastric bypass surgery, patients regularly taking phenobarbital, carbamazepine, dexamethasone, nifedipine, spironolactone, clotrimazole, and rifampin drugs, and patients with comorbid of liver or kidney failure. A total of 134 subjects were screened to enlist 120 subjects into the study, 11 subjects were unsuitable because they meet the exclusion criteria, and three subjects were not willing to participate. The estimate of sample size for the present study was based on the difference in proportions, with the proportion of low-level Vitamin D adapted from a previous study by Savoie et al. in 2019 [17]. To prevent bias, all participants recruited for this study followed a period of time until the sample size was met, to be exact 120 subjects. The Hospital Ethics Committee approved the study with a waiver of informed consent.

Blood sampling and data collection

Blood sampling of research subjects was carried out prior to a colonoscopy examination. A vitamin D examination was carried out using the ELISA test, and vitamin data were classified into normal values if the vitamin D level was >30 ng/mL, insufficiency at a level of 20–29 ng/mL, and deficiency at a level of 20 ng/mL [18], [19]. Clinical data were taken from the patient's medical record. In contrast, colonoscopy data were grouped into two groups, namely the group of subjects with colorectal cancer confirmed by anatomical pathology examination and non-colorectal cancer.

Statistical analysis

The statistical analysis of the variable was performed using the SPSS 26 software. The comparison of the qualitative and quantitative variables was based on the Chi-square test.

Results

Subject characteristics

A total of 120 patients were included in the study (Figure 1). There were 71 female and 49 male patients. The median age was 51.5 years ± 14.4 (range: 19–80 years), and 58.3% of patients were older than 50. Most of the patients showed symptoms of constipation (63.3%), blood in the stool (22.5%), and

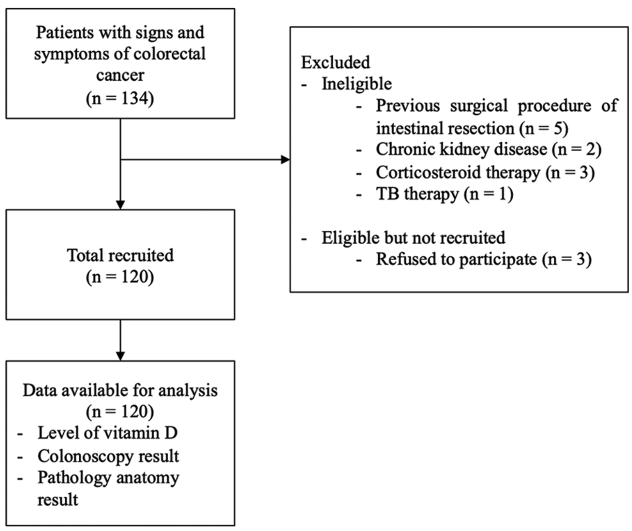

Figure 1: The flowchart of the study selection process

abdominal pain (14.2%). The median level of Vitamin D was 15.05 ng/mL ± 8.74 (range: 2.2–44.9 ng/mL), and 70.8% of patients showed a deficiency of Vitamin D and 20% of patients showed insufficiency of Vitamin D. Only 9.2% of patients showed a normal level of Vitamin D. There were 60 colorectal and 60 non-colorectal colonoscopy results. In the colorectal group, 90% of patients showed pathologic adenocarcinoma, 5% mucinous carcinoma, and 5% neuroendocrine carcinoma. In the non-colorectal group, 58.4% of patients showed normal colonoscopy, 8.3% of patients showed pathologic of another carcinoma (B-cell lymphoma and Langerhans carcinoma), 8.3% of patients showed pathologic of colitis, and 25% of patients showed another benign pathologic result. Most of the patients, or 71.7%, showed normal body mass index (BMI), 20% showed underweight BMI, and 8.3% of the patients showed overweight BMI (Table 1).

Statistical analysis

Univariate analysis of variables and level of Vitamin D

In univariate analysis among five variables related to the level of Vitamin D, one variable, namely clinical symptom, was significantly ($p < 0.05$) associated with the level of Vitamin D. There were 40.8% of patients with symptom of constipation, 15.8% of patient with the symptom of blood in stool, and 14.2% of patients with symptom of abdominal pain who showed a deficient level of Vitamin D (Table 2 and Figure 2).

Table 1: Characteristics of research subjects

Variable	Proportion (%)
Sex	
Female	71 (59.2)
Male	49 (40.8)
Age (years)	
Mean ± SD	50.32 ± 14.4
Median	51.5
Minimum	19
Maximum	80
Clinical symptom	
Constipation	76 (63.3)
Blood in stool	27 (22.5)
Abdominal pain	17 (14.2)
Vitamin D	
Mean ± SD	16.36 ± 8.74 ng/mL
Median	15.05 ng/mL
Deficient (<20 ng/mL)	85 (70.8)
Insufficient (20–30 ng/mL)	24 (20.0)
Normal (>30 ng/mL)	11 (9.2)
Minimum (ng/mL)	2.20
Maximum (ng/mL)	44.9
Colonoscopy	
Colorectal cancer	60 (50.0)
Adenocarcinoma	54 (45.0)
Mucinous carcinoma	3 (2.5)
Neuroendocrine carcinoma	3 (2.5)
Noncolorectal cancer	60 (50.0)
Normal colonoscopy	35 (29.2)
Colitis	5 (4.1)
B-cell lymphoma	4 (3.3)
Hemorrhoid	4 (3.3)
Inflammatory nonspecific	3 (2.5)
Fistula	2 (1.7)
Low-grade dysplasia	2 (1.7)
Tubular adenoma	2 (1.7)
Granulation nonspecific	1 (0.8)
Hirschsprung's disease	1 (0.8)
Langerhans carcinoma	1 (0.8)
BMI	
Underweight (<18.5 kg/m^2)	24 (20.0)
Normal (18.5–24.9 kg/m2)	86 (71.7)
Overweight (25.0–29.9 kg/m^2)	10 (8.3)

BMI: Body mass index, SD: Standard deviation.

Table 2: Univariate analysis between variables with the level of Vitamin D

Variable	Level of Vitamin D			p*
	Deficient (%)	Insufficient (%)	Normal (%)	
Sex				
Female	52 (43.3)	14 (11.7)	5 (4.2)	0.60
Male	33 (27.5	10 (8.3)	6 (5.0)	
Age (years)				
≥50	48 (40.0)	13 (10.8)	9 (7.5)	0.24
<50	37 (30.8)	11 (9.2)	2 (1.7)	
Clinical symptom				
Constipation	49 (40.8)	20 (16.7)	7 (5.8)	0.03
Blood in stool	19 (15.8)	4 (3.3)	4 (3.3)	
Abdominal pain	17 (14.2)	0	0	
Colonoscopy				
Colorectal cancer	43 (35.8)	13 (10.8)	4 (3.3)	0.60
Noncolorectal cancer	42 (35.)	11 (9.2)	7 (5.8)	
BMI				
Underweight	20 (16.7)	3 (2.5)	1 (0.8)	0.41
Normal	57 (47.0)	19 (15.8)	10 (8.3)	
Overweight	8 (6.7)	2 (1.7)	-	

*Chi-square analysis. BMI: Body mass index.

Univariate analysis of variables and diagnosis of colorectal cancer

Three of the five variables were significantly ($p < 0.05$) associated with the diagnosis of colorectal cancer. In the age group analysis, two-thirds (66.7%) of patients with the diagnosis of CRC showed an age above 50. In the symptoms group analysis with colorectal versus non-colorectal group, 43 (35.8%) versus 33 (27.5%) patients showed symptoms of constipation. In contrast, for blood in stool symptoms, it was 13 (10.8%) versus 14 (11.7%) patients; it was 4 (3.3%) versus 13 (10.8%) patients for abdominal pain symptoms. In the BMI group analysis with colorectal versus non-colorectal group, there were 19 (15.8%) versus 5 (4.2%) patients with underweight BMI and 35 (29.2%) versus 51 (42, 5%) patients with normal BMI and 6 (5%) versus 4 (3.3%) patients with overweight BMI (Table 3).

Discussion

This study is a single-center cross-sectional study describing and analyzing the Vitamin D level in the patient who came with suspicious symptoms of colorectal cancer and taking diagnosis colonoscopy. One of the significantly associated variables ($p = 0.03$) with the cause of low levels of Vitamin D in 120 patients is the symptom of constipation. There were 76 (63.3%) patients who came with symptoms of constipation. In the study by Panarese *et al*. in 2019, which assessed the relationship between chronic constipation and Vitamin D levels from 86 subjects with chronic constipation and 86 healthy subjects, the study showed that the average Vitamin D level in the group with constipation was 14.6 ng/mL (deficient). The average level of Vitamin D

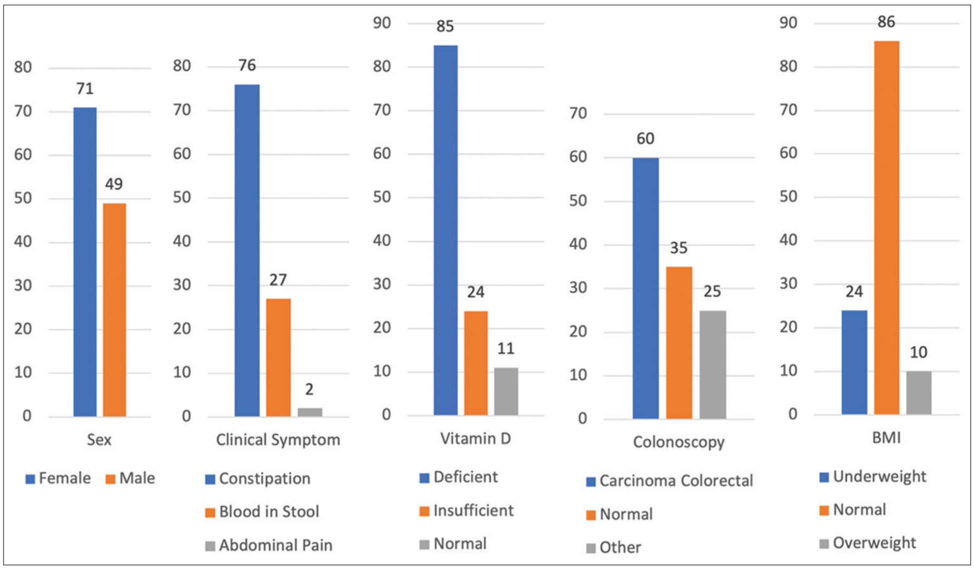

Figure 2: The diagram of the distribution of the variables

Table 3: Univariate analysis between variables with colonoscopy result

Variable	Colonoscopy result (%)		p*
	Colorectal cancer	Noncolorectal cancer	
Sex			
Female	38 (31.7)	33 (27.5)	0.35
Male	22 (18.3)	27 (24.5)	
Age (years)			
>50	40 (33.3)	30 (25.0)	0.04
<50	20 (16.7)	30 (25.0)	
Vitamin D			
Deficient	43 (35.8)	42 (35.0)	0.60
Insufficient	13 (10.8)	11 (9.2)	
Normal	4 (3.3)	7 (5.8)	
Clinical symptom			
Constipation	43 (35.8)	33 (27.5)	0.04
Blood in stool	13 (10.8	14 (11.7)	
Abdominal pain	4 (3.3)	13 (10.8)	
BMI			
Underweight	19 (15.8)	5 (4.2)	0.003
Normal	35 (29.2)	51 (42.5)	
Overweight	6 (5.0)	4 (3.3)	

*Chi-square analysis. BMI: Body mass index.

in the control group was 28.4 ng/mL (insufficient), and there was a significant relationship between constipation and low levels of Vitamin D ($p < 0.001$) [20].

Analysis of the relationship between age categories and the diagnosis of CRC showed a significant association with p = 0.04. This indicated that there was a significant difference between the age above 50 years and the age under 50 years. The results of this study are in line with existing studies. Data that the risk of CRC increases in the fifth decade of life have been widely cited in several studies, with the risk rate increasing by up to 1% for every 10 years of age starting from age 50 [4], [21].

The level of Vitamin D from 120 patients showed that the median is 15.05 ± 8.74 ng/mL. This value indicates the deficiency of Vitamin D. The Vitamin D level showed no significant association with the diagnosis of CRC, with p = 0.60 ($p > 0.05$). One reason that may be related to data on low levels of Vitamin D in research subjects is the prevalence of Vitamin D deficiency which is indeed low in Asian or Indonesian populations in particular, as the study from Sari *et al*. in 2017 showed Vitamin D levels of 292 women in North Sumatra, as many as 122 (41.7%) subjects showed a deficient level of Vitamin D, and 158 (54.1%) subjects showed an insufficient level of Vitamin D [22]. The study from Sudiro *et al*. in 2017 showed that from 76 subjects, which consisted of 46 subjects with allergic rhinitis and 30 healthy subjects at the ear, nose and throat (ENT) Polyclinic, Dr. Hasan Sadikin Hospital, Bandung, West Java, as many as 73 (96%) subjects showed a deficient level of Vitamin D. Two (2.6%) subjects showed an insufficient level of Vitamin D [23]. In the study from Judistiani et al. in 2019, it was shown that of 203 pregnant women at the Gynecology Polyclinic, Dr. Hasan Sadikin Hospital, Bandung, West Java, also suffered from deficient levels of vitamin D at a rate as high as 75% [24]. In the study from Arjana *et al*. in 2021, in the group of adolescents in Yogyakarta, as many as 26 (43.3%) people showed a deficient level of Vitamin D, and 31 (51.7%) people showed an insufficient level of Vitamin D [25].

A number of studies have found a significant relationship between levels of Vitamin D and the risk and incidence of colorectal cancer; however, there are also studies which show that there is no significant relationship between Vitamin D and colorectal carcinogenesis. Randomized controlled trial (RCT) data are still inconclusive. The incidence of cancer was not shown to be influenced by Vitamin D deficiency or supplementation, according to a recent meta-analysis (relative risk, 1.03; 95% confidence interval [CI], 0.91–1.15). These inconsistent results between observational studies and RCTs may not be due to any significant biological association or may be the result of RCT flaws such as poor adherence, insufficient Vitamin D dose and duration, low prevalence of Vitamin D deficiency in the study population, or a combination of these factors [14], [26], [27]. The impact of Vitamin D on colorectal cancer remains a big question. The reason for the insignificant relationship between Vitamin D and the diagnosis of colorectal cancer in this study may be related to the small sample size and high number of people deficient in Vitamin D in the Indonesian population.

Data on Vitamin D levels in the colorectal group alone showed that 43 (71.7%) patients showed a deficient level of Vitamin D, 13 (21.7%) patients showed an insufficient level of Vitamin D, and 4 (6.6%) patients showed normal Vitamin D levels. Low levels of Vitamin D in CRC patients have been discussed in several studies; for example, a study by Kimmie *et al*. in 2011 showed that as many as 50% of CRC patients had a deficient level of Vitamin D, and 32% had an insufficient level of Vitamin D [19]. A study by Chandler *et al*. in 2015, in 274 women with colorectal cancer and 274 women as a control population, showed that the average Vitamin D level in the CRC group was 21.9 ng/mL (insufficient) and in the control group was 23.9 ng/mL (insufficient) [28].

The analysis between clinical symptoms and diagnosis of CRC showed p = 0.04 (p < 0.05), indicating a significant association between clinical symptoms and the diagnosis of CRC. This is in line with the research of Hamilton *et al*. in 2005 and Astin *et al*. in 2011, who showed symptoms of constipation as a possible sign of CRC and could be found in 26% of CRC patients [29], [30]. Likewise, the study by Holtedahl *et al*. in 2021 and Boiles *et al*. in 2021 mentioned blood in stool and abdominal pain as the main symptoms of CRC patients and can be found in 37% and 34%, respectively, of patients with CRC [4], [31].

The analysis of BMI and diagnosis of colorectal cancer showed a significant association with p = 0.003 (p < 0.05), which means that there is a significant difference between the nutritional status of colorectal and non-colorectal patients. The results of this study are in line with other studies, which state that patients with CRC have a higher prevalence of risk for malnutrition than healthy people. The study by Negrichi and Taleb in 2020 mentioned that poor nutritional status reached 14.4% in patients with CRC [32]. The study by Zietarska *et al*. in 2017 reported a weight loss of up to 5% in about 23.5% of patients with CRC [33]. The study by Lewandoska *et al*. in 2022 reported that about 10–20% of CRC patients died due to malnutrition-related conditions [34].

Our study indeed has a limitation; we did not collect information regarding the research participant history of Vitamin D supplementation, sun exposure, usage of sunblock, or sun blockage apparel. Conversely, the relationship between Vitamin D levels and diagnosis of colorectal cancer in this study showed insignificant differences. This may be related to the higher prevalence of low levels of Vitamin D in the Indonesian population. Therefore, we suggest that Vitamin D serum levels should be routinely measured and Vitamin D supplementation should be considered, especially in patients with changes in bowel habits and colorectal patients.

Conclusion

There is no significant difference between low levels of Vitamin D and the diagnosis of colorectal cancer patients, and there is a high prevalence of low levels of Vitamin D in patients showing signs of colorectal cancer.

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