


# The Association of Vitamin D3 With Early Anastomotic Leakage in Patients Undergoing Hemicolectomy Surgery

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## Abstract

**Background:** Anastomotic leak (AL) is one of the most important postoperative complications after hemicolectomy with stapled anastomosis. This study aimed to evaluate the association of preoperative vitamin D3 with early anastomotic leakage after right colon cancer surgery with stapled anastomosis.

**Method:** In this prospective cohort study, 535 patients who underwent right colon cancer surgery (right hemicolectomy) with stapled anastomosis were enrolled. A subset of 315 patients was included in the study after meeting the inclusion criteria. Preoperative vitamin D level was measured and analyzed for association with early AL using univariable and multivariable logistic regression analyses.

**Result:** This study included 315 cases; among them, 18 (5.71%) patients developed early AL. Vitamin D3 was significantly higher among patients without early AL ( $P < .001$ ). Low vitamin D3 status was reported among 111 patients (35.2%) and 204 (64.8%) of patients did not have low vitamin D3 status (sufficient level = 30–100 ng/mL). Sufficient vitamin D3 levels before right colon cancer surgery with stapled anastomosis was associated inversely with early AL (crude OR = .89, 95% CI = .85–.94,  $P < .001$  and adjusted OR = .89, 95% CI = .82–.98,  $P = .02$ ).

**Conclusion:** The vitamin D3 level has a protective association with early AL. As a result, low vitamin D3 status may be a risk factor for early AL development, suggesting that it can be one of the predictors of early AL occurrence.

## Keywords

anastomotic leakage, colon stapled anastomosis, vitamin D3

## Introduction

Colorectal cancer is the third most deadly cancer globally. Almost 1 million people are diagnosed with this cancer, and half a million people die from this type of cancer annually.<sup>1</sup> Anastomotic leakage (AL) is a major surgical postoperative complication after anterior resection,<sup>2</sup> which remained an unsolved problem in patients with colorectal cancer. AL was defined as a communication between the intra- and extraluminal compartments owing to a defect of the integrity of the intestinal wall at the anastomosis.<sup>3</sup> The incidence of intestinal AL rates varies, depending on the anatomic location of the anastomosis, between 2 to 24%.<sup>3</sup> Intestinal anastomotic leakage leads to short-term complications, mortality, and poor functional outcomes.<sup>3</sup> Prevention of anastomotic leakage requires an improved understanding of the actual mechanisms by which it occurs and identifying the causes of this disease.<sup>3</sup>

There are several risk factors associated with AL complications which are divided into 2 main categories of patient-related and operative factors. Patient-related factors include male sex, BMI, preoperative nutritional

status, neoadjuvant therapy, tumor size and stage, postoperative hypoalbuminemia, and postoperative diarrhea. Operative factors include the level of anastomosis, number of linear stapler firings, diverting stoma, trans-anal TME, circular stapler, intraoperative endoscopy, indocyanine green fluorescence angiography, fibrin glue, operative time, conversion, left colic artery ligation, pelvic drainage, trans-anal drainage, gut microbiota, surgeon's experience, hospital size, and perioperative events.<sup>4</sup> Among the mentioned factors, after colorectal surgeries,

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nutrition plays a crucial role in recovering the injured tissue and promotes the wound-healing process.<sup>5</sup>

Proper perioperative nutritional deficiency might diminish immune function and therefore increase postoperative complications.<sup>6</sup> Vitamin D deficiency has been suggested in some studies as a malnutrition factor for colorectal cancer.<sup>7</sup> A review study has shown that genetically low plasma 25 (OH) D concentrations cannot increase the risk of cancer and death, and this lack of association has been reported in colorectal cancer.<sup>8</sup>

Hydroxy (OH) vitamin D levels have been found to be adversely related to colorectal cancer risk by causing adenoma formation in the colon epithelium.<sup>7</sup> The deleterious effects of vitamin D deficiency on medical and surgical critical care outcomes have recently been reviewed, and striking improvements in intensive care mortality after vitamin D replacement therapy have been reported.<sup>9,10</sup> Cohort studies in patients who underwent colorectal surgeries showed that low plasma vitamin D is associated with adverse colorectal cancer survival after surgical resection, independent of systemic inflammatory response.<sup>8</sup>

According to the literature review, the effect of vitamin D on the incidence of AL in patients undergoing right hemicolectomy surgery with stapled anastomosis has not been studied. However, there was a gap among observational studies investigating the association between vitamin D levels and AL incidence of right colon cancer surgery. Therefore, this study aimed to evaluate the association of preoperative serum vitamin D3 levels with early AL in patients undergoing right colon cancer surgery with stapled anastomosis.

## Materials and Method

The study was performed under the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of Urmia University of Medical sciences with code IR.-UMSU.REC.1398.297. All patients provided written informed consent before being included in the study.

This prospective cohort study was conducted among 535 patients who underwent right hemicolectomy with stapled anastomosis between February 2019 and September 2020 at the surgical ward of Urmia Imam Khomeini hospital, Urmia University of Medical Sciences, Iran. A subset of 315 patients was included in the study after meeting the inclusion criteria. The inclusion criteria were age over 18 years, BMI between 20-30 kg/m<sup>2</sup>, the patient undergoing right colon end-to-side linear surgery with stapled anastomosis, and having a normal albumin level. Exclusion criteria were having a history of chemotherapy or radiotherapy, anemia, diverting stoma, history of smoking, history of drug or alcohol consumption, history of corticosteroid or NSAIDs (non-

steroidal anti-inflammatory drugs) use, long time of surgery, preoperative blood transfusion, urgent surgery, high ASA grade, different anastomosis technique, and infection. Before each surgery, after receiving informed written consent, blood samples were taken from the participants to measure 25 (OH) vitamin D concentrations using the ELISA method in a single clinical laboratory.

Vitamin D values below 30 ng/mL indicated less-than-ideal vitamin D status.<sup>11</sup> There is increasing agreement that levels below approximately 30 ng/mL be identified as "low vitamin D status."<sup>12,13</sup> Vitamin D supply of an individual is reflected by measuring 25(OH)D. A serum 25-hydroxyvitamin D level of 30-100 ng/mL was considered sufficient, with values between 20-30 as insufficiency, levels between 7-20 ng/mL as deficiency, and levels below 7 ng/ml as severe deficiency.<sup>9,14</sup> Values below 30 ng/mL are considered low vitamin D status in this study. Preoperative low vitamin D3 status was assessed on early AL (usually occurring during the first 10 days after surgery).

Of 315 patients who underwent colon anastomosis, 31 with symptoms, such as fever, tachycardia, tachypnea, leukocytosis, and acidosis, were suspected of having AL. After performing CT with IV and oral contrast to quantify the risk of anastomotic leak on the suspected patients, 18 had this complication. Furthermore, with surgery, the leak of these 18 patients was confirmed with certainty.

## Statistical Analysis

Mean  $\pm$  SD (standard deviation) was calculated for continuous variables, and frequencies were measured for categorical variables. The logistic regression test was used to assess the association between vitamin D3 level and early AL. We fitted multiple logistic regression models for adjusting age and gender effect. Predictors with P-values less than the cut-off value of .2 were considered to be included in the multiple logistic regression analyses to assess the association of vitamin D levels with early AL. P-value < .05 was considered significant. SPSS statistical software version 17 was used for data analysis.

## Results

This study encompasses 315 patients who underwent right colon cancer surgery. The mean  $\pm$  SD age of patients was 63.4  $\pm$  12.88 years, 74.3% of patients were female. The mean of 25-OH vitamin D levels was 35.66  $\pm$  13.26 mg/dl. Low vitamin D3 status was reported among 111 patients (35.2%). Early AL occurred in 18 patients (5.71%). The age of patients without early AL was significantly higher than patients with early AL (64.9  $\pm$  11.63, 38.34  $\pm$  2.76;  $P < .001$ ). The number of male patients was more among patients without early AL than patients with early AL (24.2 vs 50%,  $P$ -value = .02). The mean 25-OH vitamin D levels were significantly higher among patients without

early AL than patients with early AL ( $36.54 \pm 12.7$  vs  $21 \pm 14.55$ ,  $P < .001$ ).

Of 315 patients, 96 cases (32.3%) had low vitamin D status ( $\leq 30$  ng/mL) among patients without AL. Among patients with AL, 15 (83.3) had low vitamin D status ( $< 30$  ng/mL), and this difference was significant between patients with and without AL ( $P < .001$ ) (Table 1).

Table 2 shows crude and adjusted odds ratios for the association of vitamin D3 level, age, and gender in early AL in patients who underwent right hemicolectomy with stapled anastomosis. In univariable logistic regression analyses, variables associated with early AL occurrence were age, male gender, and preoperative vitamin D3 level ( $P < .001$ ,  $P = .02$ ,  $P < .001$ , respectively). Sufficient vitamin D3 level before right colon cancer surgery with stapled anastomosis decreased the risk of early AL (crude OR = .89, 95% CI = .85-.94,  $P < .001$ ). In multiple logistic regression analyses, after the adjusted effect of age and gender of patients, sufficient vitamin D3 level before right hemicolectomy with stapled anastomosis decreased the risk of early AL (adjusted OR = .89, 95% CI = .82-.98,  $P = .02$ ).

## Discussion

Early anastomotic leakage as a severe complication leads to death after colon cancer surgery and usually occurs during the first 10 days after surgery.<sup>15</sup>

Although many studies have been conducted to demonstrate vitamin D deficiency as a risk factor for cancer, postoperative survival, and other complications,<sup>8,16</sup> the effect of preoperative vitamin D3 level on the occurrence of AL has not been assessed. To our

knowledge, this study is the first of its kind that prospectively investigated the association of low vitamin D status with the occurrence of early AL and the predictive value of AL occurrence due to serum vitamin D levels in patients who underwent right hemicolectomy with stapled anastomosis. This study demonstrated that patients with low vitamin D status had a higher risk of early AL occurrence after right colon cancer surgery with stapled anastomosis.

As reported by previous studies, postoperative complications are increased in hospitalized patients with low vitamin D status<sup>17</sup> due to decreased immunomodulatory effects of low vitamin D status.<sup>18</sup> Also, Ghorbani Abdehghah, in a study, showed that preoperative vitamin D3 levels have a strong effect on postoperative surgical site infection.<sup>17</sup>

The favorable effects of vitamin D supplements on wound healing may be mediated by stimulating the phagocytosis and killing the bacteria by macrophages suppressing interferon-g-mediated macrophage activation.<sup>19</sup> Vitamin D advances the formation of cathelicidin, an antimicrobial peptide the immune system uses to fight off wound infections.<sup>20</sup>

By considering AL as a leak of gastrointestinal tract mucosal and lack of evidence for the effect of low vitamin D status on the occurrence of AL, this article discussed the role of nutrients in the wound-healing mechanism. Vitamin deficiencies affect the functions of immune cells. Low vitamin D status, for example, increases the risk of infectious and inflammatory diseases.<sup>21</sup>

Nutrition has a vital role in wound healing.<sup>22,23</sup> Vitamin D expands the phagocytic activity of macrophages and NK cells through its own receptor in the immune

**Table 1.** Vitamin D3 Status in Patients Who Underwent Right Colon Cancer Surgery With Stapled Anastomosis.

	AL <sup>-</sup> n = 297	AL <sup>+</sup> n = 18	P-value <sup>a</sup>	
Vitamin D3 (ng/ml)	30-100	201 (67.7)	3 (16.7)	< .001
	$\leq 30$	96 (32.3)	15 (83.3)	

AL<sup>+</sup>: with early AL, AL<sup>-</sup>: without early AL.

<sup>a</sup>chi-square test.

**Table 2.** The Association of Vitamin D3 Level and Other Risk Factors on Patients in Logistic Regression Analyses.

				Univariate logistic regression		Multiple logistic regression	
		AL <sup>-</sup>	AL <sup>+</sup>	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Sex	Female	225 (75.8)	9 (50)	1	.02	.02 (.001-.4)	.01
	Male	72 (24.2)	9 (50)	3.12 (1.2-8.2)			
Age (year)		64.9 $\pm$ 11.63	38.34 $\pm$ 2.76	.82 (.75-.9)	< .001	.73 (.6-.92)	.007
Vitamin D3 (mg/dl) <sup>a</sup>		36.54 $\pm$ 12.7	21 $\pm$ 14.55	.89 (.85-.94)	< .001	.89 (.82-.98)	.02

<sup>a</sup>Vitamin D3 level was considered as a continuous variable.

cells. Additionally, by restricting the regulatory sequences of antimicrobial peptides genes, vitamin D enhances the microbicidal activity of phagocytes. Hindrance of differentiation and development of antigen-presenting dendritic cells, as well as the direct influence on their contact with T lymphocytes, significantly affect the type of immune response.<sup>19</sup> Therefore, a decrease in collagen synthesis at the anastomosis site was associated with complications in malnourished patients.<sup>24</sup>

Furthermore, vitamin C has a vital role as an enzymatic cofactor in collagen biosynthesis and reduces the inflammatory process by intense antioxidant action and elimination of reactive sepsis.<sup>23</sup> In a study by Danielski LG on malnourished rats, vitamin C supplementation was associated with intestinal anastomosis healing. They indicated the importance of vitamin C in increasing influential factors in wound healing and reducing postoperative complications in patients undergoing right colon cancer stapled anastomosis surgery.<sup>23</sup> The role of malnutrition-related factors in increasing AL has also been highlighted.<sup>24</sup> Xu and Kong<sup>24</sup> conducted a study that showed the occurrence of postoperative AL in rectal cancer patients with poor nutritional status has a high risk. In a review study, Smith K found that slow healing of hard-to-heal wounds in patients was associated with serum vitamin D deficiency.<sup>25</sup>

Moreover, Iglar PG, by conducting a review study, demonstrated that low perioperative vitamin D status is associated with a diversity of adverse outcomes.<sup>16</sup> However, none of the outcomes of the study was about AL occurrence. These findings are somehow consistent with the result of this study.

In contrast with the present study, some observational studies conducted on the association of vitamin D and surgical outcomes showed no significant difference was noted in the occurrence of opposite results among groups with lower and higher vitamin D status.<sup>16</sup> Another randomized, double-blind, placebo-controlled trial, by Dai et al, indicated that vitamin D, contrasted with placebo, involved a more critical improvement in wound parameters.<sup>5</sup>

C-reactive protein (CRP), a measure of the systemic inflammatory response, could confound the effect of low vitamin D status on poor outcome incidence. However, according to the result of Vaughan-Shaw PH's study, low vitamin D status is associated with adverse survival outcomes in 2 large cohorts, which is independent of time of sample and CRP.<sup>8</sup> Therefore, these results confirm the results of our study.

The effect of low vitamin D status on cancer, mortality, and surgical site infection in colorectal cancers was confirmed in observational studies.<sup>7,26</sup> Also, sufficient evidence in this area demonstrates that interventional studies to settle vitamin D supplementation therapy as

a standard approach to reduce postoperative reported complications are necessary.

Based on the presented findings, low vitamin D status could be a risk factor in postoperative consequences. Furthermore, by considering it as a mediator factor that is a marker of deficiency of other vitamins,<sup>16</sup> we can prevent AL accompanied by high mortality and morbidity by reducing the prevalence of low vitamin D status. Accordingly, conducting further studies is suggested to predict AL occurrence as a complication of colon surgeries.

## Conclusion

To our knowledge, this is the first study investigating the association of 25-OH vitamin D levels on postoperative early AL in patients undergoing right hemicolectomy surgery. Preoperative vitamin D3 levels have a protective association with early AL. As a result, low vitamin D status may be a risk factor for the development of early AL, and it could be one of the predictors of early AL occurrence. We suggest that it is better serum 25-OH vitamin D levels to be measured preoperatively for all patients undergoing elective surgery. Furthermore, vitamin D supplementation should be given in a preoperative setting to improve short-term outcomes.

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## Author Contributions

HL and MYK conceived and designed the experiments. VM and AM collected the data. MA and MYK developed the theory and performed the computations. MA and MYK contributed to the analysis and interpretation of the results. MA wrote the article. All authors discussed the results and contributed to the final manuscript.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical approval

This study conformed with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Urmia University of Medical Sciences.

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