

The relation of preoperative 25-OH Vitamin D Levels with Postoperative Complications in Patients undergoing Colorectal Cancer Surgery

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Abstract

Background: To investigate the effect of preoperative 25-OH vitamin D levels on postoperative complications in patients undergoing colorectal cancer surgery.

Methods: Consecutive newly diagnosed colorectal cancer patients who met the inclusion criteria were prospectively included in this single-center observational study. Preoperative 25-OH vitamin D levels were measured and analyzed for association with postoperative complications using univariable and multivariable logistic regression analyses.

Results: A total of 104 colorectal cancer patients were included in this study. Preoperative 25-OH vitamin D levels were found to be <10 ng/ml in 31 (29.8%) patients, 10-20 ng/ml in 42 (40.4%) patients, between 20-30 ng/ml in 25 (24%) patients and >30 ng/ml in 6 (5.8%) patients. In patients with infective complications, the mean value of 25-OH vitamin D levels were 12.33 (± 6.306) ng/ml which was found to be statistically significant ($p:0.026$). In univariable logistic regression analyses, variables found to be associated with postoperative complications were age ≥ 65 , male gender and preoperative 25-OH vitamin D levels, whereas in multivariable analyses, preoperative levels of 25-OH vitamin D were not found to be related with postoperative complications.

Conclusions: We demonstrated that vitamin D deficiency is a significant risk factor for development of infective complications and seems to be independently associated with postoperative complications in patients undergoing colorectal cancer surgery.

Background

Colorectal cancer is the fourth most common cause of cancer-related mortality worldwide and radical resection is still the treatment of choice (1). Despite improvements in postoperative care, the rate of postoperative complication is changed between 19–30% in patients undergoing elective colorectal surgery (2). The most common known factors related with postoperative complications are nutritional status, comorbid diseases and timing of the operation (3–5). Inflammatory markers such as C-reactive protein (CRP), albumin and procalcitonin have been widely used in clinical practice for early detection of complications (6–9). As reported by numerous studies, postoperative complications have a great impact on not only short-term outcomes but also on overall survival in colorectal cancer patients (10–12).

25-hydroxy (OH) vitamin D levels have been found to be adversely related with colorectal cancer risk by causing adenoma formation in colon epithelium (13–16). 25-OH vitamin D levels have also been associated with long term survival and increased response to oncological treatment, however its effect on postoperative complications have not been thoroughly investigated (17, 18).

The aim of the present study was to evaluate the effect of serum 25-OH vitamin D levels on postoperative complications and short-term outcomes in colorectal cancer patients.

Methods

This study was designed as a prospective observational study which was approved by the Ethics Committee of Izmir Tepecik Training and Research Hospital, University of Health Sciences. All patients' informed consents were obtained after oral and written explanations were made.

Patients' selection

We performed this study in patients undergoing colorectal cancer surgery between September 2017 and March 2019 at the department of General Surgery, Izmir Tepecik Training and Research Hospital, University of Health Sciences. Consecutive patients who met the inclusion criteria were included in this study. The inclusion criteria were as follows; 1) histopathological evidence of colorectal cancer, 2) patients older than 18 years, 3) patients underwent curative resection. The exclusion criteria were as follows; 1) unresectable disease, 2) systemic metastases, 3) patients received neoadjuvant chemoradiotherapy, 4) patients underwent emergent operation or operated with palliative intent.

Data Collection

The routine preoperative work-up including complete blood count, liver and kidney function tests were done with an addition of preoperative serum levels of 25-OH vitamin D and carcinoembryogenic antigen (CEA). Patients' nutritional status were evaluated using nutritional risk score-2002 (NRS) and comorbid diseases were classified according to American Society of Anesthesiologists (ASA)(19, 20). Postoperative complications occurring within 30 days of surgery were graded based on Clavien-Dindo scale (21). Pathology results were also recorded including histopathological grading and pathological tumor-node-metastasis (pTNM) staging (22).

Patients were divided into four vitamin D groups based on their preoperative 25-OH vitamin D levels as below 10 ng/ml (level of severe deficiency), between 10–20 ng/ml (level of mild deficiency), between 20–30 ng/ml (level of insufficiency) and above 30 ng/ml (normal level) according to Endocrine Society guidelines (23). Each vitamin D group was analyzed for development of postoperative complications (infective/non-infective) and also for the assessment of relation with Clavien-Dindo scale.

Study Objectives

The primary objective in our study was to demonstrate the effect of 25-OH vitamin D levels on postoperative complications, thus 30-day morbidity. The secondary objective was to evaluate its effect on histopathological grading and pTNM staging.

Statistical Analysis

The data was analyzed with IBM SPSS 21.0. Categorical and continuous variables were analyzed using chi-square test and student t-test. Pearson correlation test was used for analyzing the relation between laboratory parameters (albumin, hemoglobin, CEA) and 25-OH vitamin D levels. The potential risk factors

for postoperative complications (gender, age, 25-OH vitamin D, hemoglobin, albumin, ASA and NRS scores, tumor location, histopathological grading and pTNM staging) were evaluated using univariable and multivariable logistic regression analysis. Variables with a p value < 0.2 in univariable logistic regression analyses were included in the multivariable logistic regression analyses and p value < 0.05 was accepted as significant for all analyses except univariable analysis.

Results

104 patients (40 female, 64 male) who met the inclusion criteria were included in this study and the mean age was found to be 62.71 (\pm 12.41). The mean value of preoperative albumin, CEA and 25-OH vitamin D levels were 3.8 (\pm 0.5) gr/dl, 7.4 (\pm 11.6) μ g/l and 15.95 (\pm 9.08) ng/ml, respectively. Patients' demographic and clinical characteristics are shown in Table 1.

Tumor locations were demonstrated as colon in 74 patients (71.1%) and as rectum in 30 patients (28.8%) (Table 2). Metachronous colon tumor was found in 1 patient and synchronous colon tumors in 2 patients. Laparoscopic approach was chosen in 9 patients. The number of patients with postoperative complications were 25 (24%) and major complications (Clavien-Dindo scale 3–5) were seen in 10 patients (Table 3). Infective complications including wound infection, pneumonia, anastomotic leak and intra-abdominal abscess were observed in 18 patients (17.3%). Anastomotic leak occurred in 7 patients (6.73%), non-operative management was chosen in 2 patients and Hartmann procedure was performed in 5 patients.

Table 1
Patients demographic and clinical characteristics (n = 104)

Variables	N (%) or mean (\pm SD)
Age	62.71 (\pm 12.41)
Female/Male	40 (38.5%)/64 (61.5%)
ASA scores	17 (16.3%)
1	56 (53.8%)
2	31 (29.8%)
3	
NRS scores	58 (55.8%)
0	31 (29.8%)
1	14 (13.5%)
2	1 (1%)
3	
CEA ($\mu\text{g/l}$)	7.4 (\pm 11,6)
Albumin (gr/dl)	3.8 (\pm 0,5)
Hemoglobin (gr/l)	12.6 (\pm 1.99)
WBC ($10^3/\mu\text{l}$)	8080 (\pm 2274)
25-OH Vitamin D	31 (29.8%)
<10 ng/ml	42 (40.4%)
10–20 ng/ml	25 (24%)
20–30 ng/ml	6 (5.8%)
> 30 ng/ml	
Abbreviations: SD, standard deviation; ASA, American Society of Anesthesiologists; NRS, Nutritional Risk Score-2002; CEA, carcinoembryogenic antigen; WBC, White blood cells	

Table 2
Operative and pathological data (n = 104)

Variables	N (%) or mean (\pm SD)
Tumor location	74 (71.1%)
Colon	30 (28.8%)
Rectum	
Operative Procedures	20 (19.2%)
Right Hemicolectomy	5 (4.8%)
Extended Right Hemicolectomy	6 (5.7%)
Left Hemicolectomy	8 (7.6%)
Extended Left Hemicolectomy	14 (13.4%)
Anterior Resection	39 (37.5%)
Low Anterior Resection	6 (5.7%)
Abdominoperineal Resection	6 (5.7%)
Total Colectomy	
pTNM Staging	19 (18.3%)
1	45 (43.3%)
2	38 (36.5%)
3	1(1%)
4	
Histopathological Results	2
Carcinoma in-situ	88
Adenocarcinoma	12
Mucinous Adenocarcinoma	1
Signet Cell Carcinoma	1
Malignant Fibrous Histiocytoma	

Abbreviations: SD, standard deviation; pTNM, pathological tumor-node-metastasis

Variables	N (%) or mean (± SD)
Pathological Grading	22
G1	74
G2	5
G3	
Abbreviations: SD, standard deviation; pTNM, pathological tumor-node-metastasis	

Table 3
Short-term outcomes (n = 104)

Variables	N (%) or median (min-max)
Number of patients with complications	25 (24%)
Infective Complications	9 (8.6%)
Wound Infection	7 (6.73%)
Anastomotic Leak	1 (0.96%)
Intra-abdominal abscess	4 (3.84%)
Pneumonia	3 (2.88%)
Non-infective Complications	3 (2.88%)
Wound Dehiscence	1 (0.96%)
Postoperative Ileus	1 (0.96%)
Pneumothorax	1 (0.96%)
Myocardial Infarction	
Arrhythmia	
Clavien-Dindo Scale	79 (75.9%)
0	15 (14.4%)
1–2	8 (7.69%)
3–4	2 (1.92%)
5	
Length of Hospital Stay	7 (3–29)
30-day mortality	2 (1.92%)

The mean value of preoperative 25-OH vitamin D levels were 13.11 (\pm 6.18) and 16.83 (\pm 9.68) ng/ml in patients with and without complications, respectively (p:0.07). Preoperative 25-OH vitamin D levels were found to be < 10 ng/ml in 31 (29.8%) patients, 10–20 ng/ml in 42 (40.4%) patients, between 20–30 ng/ml in 25 (24%) patients and > 30 ng/ml in 6 (5.8%) patients. In patients with infective complications, the mean value of 25-OH vitamin D levels were 12.33 (\pm 6.306) ng/ml which was found to be statistically significant (p:0.026). Whereas, there was no significant difference observed for development of infective or postoperative complications between vitamin D groups.

Preoperative levels of 25-OH vitamin D were not found to be related with NRS scores, pathological grading and pTNM staging. Also, there was no correlation detected between 25-OH vitamin D levels and hemoglobin, albumin and CEA levels.

Obtained data were changed to categorical variables (age \geq 65, ASA \geq 3, albumin \geq 3.4 gr/ dl, hemoglobin \geq 10 gr/dl, NRS \geq 2) in order to perform logistic regression analyses (Table 4). In univariable logistic regression analyses, variables found to be associated with postoperative complications were age \geq 65, male gender and preoperative 25-OH vitamin D levels (p:0.041, p:0.024, p:0.138). However, in multivariable analyses, preoperative levels of 25-OH vitamin D were not found to be related with postoperative complications. Moreover, there was no association found between Clavien-Dindo scale and preoperative 25-OH vitamin D levels.

Table 4

Logistic regression analyses of potential risk factors related with postoperative complications

Variables	Univariable		Multivariable	
	HR (%95 CI)	p value	HR (%95 CI)	p value
Age \geq 65	3.78(1.05–13.49)	0.041*	3.26(1.21–8.76)	0.019**
Male gender	4.48(1.21–16.49)	0.024*	0.26(0.083–0.81)	0.02**
ASA \geq 3	0.72(0.19–2.70)	0.63	-	-
Albumin \geq 3.4 gr/ dl	1.94(0.45–8.23)	0.36	-	-
Hemoglobin \geq 10 gr/dl	0.28(0.02–2.92)	0.29	-	-
NRS \geq 2	0.81(0.17–3.74)	0.79	-	-
Colon/Rectum	0.71(0.20–2.50)	0.59	-	-
25-OH vitamin D	0.94(0.87–1.01)	0.138*	1.06(0.99–1.14)	0.091
Pathological grading	1.78(0.55–5.78)	0.33	-	-
pTNM staging	1.18(0.55–2.53)	0.66	-	-
Abbreviations: HR, Hazard ratio; CI, confidential interval; ASA, American Society of Anesthesiologists; NRS, Nutritional Risk Score-2002; pTNM, pathological tumor-node-metastasis				
*Level of significance was accepted as $p < 0.2$ in univariable analyses				
**Level of significance was accepted as $p < 0.05$ in multivariable analyses				

Discussion

In present study, we found significantly decreased preoperative 25-OH vitamin D levels in patients with infective complications. Also we observed that preoperative levels of 25-OH vitamin D were one of the potential risk factors for development of postoperative complications in patients undergoing colorectal cancer surgery.

In recent years, there has been an increasing number of studies investigating the effect of 25-OH vitamin D on progression-free survival and overall survival in patients with colorectal cancer (24–26). It has been also revealed that infective complications are increased in hospitalized patients with vitamin D deficiency because of its decreased immunomodulatory effects (27, 28). As reported by previous studies, preoperative 25-OH vitamin D levels were found to be adversely related with surgical site infections in

patients undergoing cardiac surgery and total knee arthroplasty (29, 30). Quraishi et. al have also reported that hospital acquired infections are associated with preoperative 25-OH vitamin D levels in patients following bariatric surgery (31).

In order to assess the effect of 25-OH vitamin D levels on postoperative complications better, we excluded the patients operated in emergency settings and patients received neoadjuvant chemoradiotherapy. As a result, our sample size was reduced to 104 patients with a mean 25-OH vitamin D value of 15.95 (\pm 9.08) ng/ml which corresponds to vitamin D deficiency. Similar to previous studies we observed a significant association between preoperative 25-OH vitamin D levels and infective complications. Laviano et. al revealed that preoperative 25-OH vitamin D levels were not only related with development of hospital acquired infections but also with Clavien-Dindo scale of postoperative complications (32). In contrast to their results, we observed no association between Clavien-Dindo scale and 25-OH vitamin D levels in our study.

In a recent study conducted in patients undergoing varied types of gastrointestinal tract, hepatobiliary, thoracic, and vascular operations, preoperative 25-OH vitamin D levels were found to be independent predictors of surgical site infections in addition to ASA scores, albumin and hemoglobin levels (33). However, we did not find any relation between postoperative complications and ASA scores, albumin and hemoglobin levels.

Our secondary objective was to evaluate the effect of 25-OH vitamin D levels on histopathological grading and pTNM staging based on the fact that decreased 25-OH vitamin D levels are linked with poorer survival in colorectal cancer patients (34). However we found no association of 25-OH vitamin D levels with pathological grading and pTNM staging in our study. Whereas Värynen et. al revealed that 25-OH vitamin D levels were lower in pTNM stage 2–4 colorectal cancer patients compared to pTNM stage 1 colorectal cancer patients (16).

The major limitation of our study was the small sample size with a significantly high prevalence of vitamin D deficiency (94%) which causes heterogeneous vitamin D groups in terms of number of patients. Therefore, we could not draw firm results for associations between vitamin D groups and postoperative complications or Clavien-Dindo scale. Furthermore, dose-response analysis of vitamin D levels for infective complications could not be performed in this study.

Conclusions

To our knowledge, this is the first study investigating the effect of 25-OH vitamin D levels on infective and overall postoperative complications in patients undergoing colorectal cancer surgery. As a result, vitamin D deficiency is a significant risk factor for development of infective complications and seems to be independently associated with postoperative complications. Considering recent studies and our study, we suggest that serum 25-OH vitamin D levels should be measured preoperatively for all patients undergoing elective surgery and vitamin D supplementation should be given in a preoperative setting in order to improve short-term outcomes.

Declarations

Ethics approval and consent to participate: This study was designed as a prospective observational study which was approved by the Ethics Committee of Izmir Tepecik Training and Research Hospital, University of Health Sciences. All patients' informed consents were obtained after oral and written explanations were made. All methods in present study were carried out in accordance with relevant guidelines and regulations.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: BB contributed to investigation, data collection, formal analysis and writing the original draft. OC contributed to methodology, formal analysis, writing-review and editing. GK contributed to investigation and data collection. BC contributed to methodology, review and editing. CA contributed to methodology, review and editing, supervision.

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