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## Normalization of Plasma 25-hydroxy Vitamin D is Associated with Reduced Risk of Surgery in Crohn's Disease

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### Abstract

**Introduction**—Vitamin D may have an immunological role in Crohn's disease (CD) and ulcerative colitis (UC). Retrospective studies suggested a weak association between vitamin D status and disease activity but have significant limitations.

**Methods**—Using a multi-institution inflammatory bowel disease (IBD) cohort, we identified all CD and UC patients who had at least one measured plasma 25-hydroxy vitamin D [25(OH)D]. Plasma 25(OH)D was considered sufficient at levels  $\geq 30$ ng/mL. Logistic regression models adjusting for potential confounders were used to identify impact of measured plasma 25(OH)D on subsequent risk of IBD-related surgery or hospitalization. In a subset of patients where multiple

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measures of 25(OH)D were available, we examined impact of normalization of vitamin D status on study outcomes.

**Results**—Our study included 3,217 patients (55% CD, mean age 49 yrs). The median lowest plasma 25(OH)D was 26ng/ml (IQR 17–35ng/ml). In CD, on multivariable analysis, plasma 25(OH)D < 20ng/ml was associated with an increased risk of surgery (OR 1.76 (1.24 – 2.51) and IBD-related hospitalization (OR 2.07, 95% CI 1.59 – 2.68) compared to those with 25(OH)D 30ng/ml. Similar estimates were also seen for UC. Furthermore, CD patients who had initial levels < 30ng/ml but subsequently normalized their 25(OH)D had a reduced likelihood of surgery (OR 0.56, 95% CI 0.32 – 0.98) compared to those who remained deficient.

**Conclusion**—Low plasma 25(OH)D is associated with increased risk of surgery and hospitalizations in both CD and UC and normalization of 25(OH)D status is associated with a reduction in the risk of CD-related surgery.

### Keywords

Crohn's disease; ulcerative colitis; vitamin D; surgery; hospitalization

## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic immunologically mediated diseases that often have their onset at a young age and are associated with recurrent episodes of relapsing disease activity<sup>1</sup>. Nearly two-thirds of patients with CD and one-fifth of those with UC will eventually require surgery for management of their refractory disease or disease-related complication<sup>2–6</sup>. A larger proportion of patients will require at least one IBD-related hospitalization<sup>2</sup>. Thus, both surgery and hospitalization represent major events in the natural history of inflammatory bowel diseases (IBD; CD and UC) and are responsible for a substantial portion of the estimated \$6 billion in annual healthcare costs associated with these diseases<sup>7</sup>. Identification of risk factors for such adverse outcomes and interventions that may reduce the risk of such adverse outcomes are an important need.

Vitamin D has been classically described in association with its effect on bone mineralization. However, there is considerable interest in the immunological effects of vitamin D<sup>8–14</sup>. Indeed, a recent body of literature has substantiated a significant role of vitamin D in IBD. Residence in areas with reduced ultraviolet light exposure<sup>15</sup> or a lower predicted plasma vitamin D level<sup>16</sup> is associated with an increased risk for CD. Furthermore, retrospective or cross-sectional studies have suggested an association between lower vitamin D and disease activity in CD<sup>17–19</sup>. However, they have been limited by the inability to temporally separate the effect of plasma 25(OH)D, the best measure of an individual's vitamin D status, and subsequent adverse outcomes. Consequently, there is a need for prospective studies examining the association between vitamin D status and risk for subsequent surgery or hospitalization. In addition, it is also of interest to examine if a change in vitamin D status, in particular, normalization of plasma 25(OH)D levels, can attenuate the risk associated with deficient vitamin D. This hypothesis is supported by laboratory data from animal models where vitamin D supplementation ameliorated colitis<sup>20</sup>, and from a randomized controlled trial where CD patients in remission randomized to vitamin D had a lower rate of relapse over 12 months compared to placebo<sup>21</sup>.

We performed the present study with the aims of (1) examining the association between plasma 25(OH)D and risk of subsequent IBD-related surgery or hospitalization in a large cohort of CD and UC patients; and (2) analyzing whether normalization of vitamin D status in those with insufficient or deficient levels is associated with a reduction in risk for surgery or hospital stays.

## METHODS

### Study Population

The data source for our study was an electronic medical record (EMR) based cohort of CD and UC patients from two tertiary medical centers in Boston serving a population of over 4 million patients in the Greater Boston area as well as neighboring states. The development and validation of our cohort has been described in detail in previous publications<sup>22</sup>. From among patients with at least one International Classification of Diseases, 9<sup>th</sup> edition (ICD-9-CM) clinical modification code for CD (555.x) or UC (556.x) (n = 24,182), we refined our cohort by developing an algorithm incorporating codified data as well as narrative free text concepts from the EMR identified using natural language processing tools. The positive predictive value of our final algorithms were 97% for both CD and UC, confirmed in an independent validation cohort, and yielded a final CD cohort of 5,506 patients and 5,522 UC patients.

### Development of the study cohort

This study was restricted to a subset of 3,217 CD or UC patients with at least one measured plasma 25(OH)D level. Patients who had 1 plasma 25(OH)D measure were similar in age to those without a vitamin D level, but were more likely to be female (61% vs. 50%), use immunomodulator or anti-TNF therapy, and undergo an IBD-related surgery (16% vs. 10%) or hospitalization (40% vs. 27%). The plasma 25(OH)D was measured as part of routine clinical care at the two hospitals using high performance liquid chromatography with mass spectrometry since 2008 and radioimmunoassay prior to that with similar normal values across both assays. The dates of plasma 25(OH)D measurements, the lowest, and highest values were retrieved and modeled as normal (> 30ng/ml), insufficient (20 – 29.9ng/ml) or deficient (< 20ng/ml) according to current recommendations<sup>23–25</sup>.

### Variables and Outcomes

Information on current age, age at first ICD-9-CM code for CD or UC, gender, race (white or non-white) and non-IBD co-morbidity modeled using the Deyo modification of the Charlson co-morbidity index<sup>26</sup> were obtained as was duration of follow-up within our healthcare system. Using the electronic prescription function of our EMR, we ascertained use of IBD-related medications including aminosalicylates, systemic corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and anti-tumor necrosis factor  $\alpha$  monoclonal antibodies (anti-TNF). We also additionally assessed for use of prescription vitamin D supplementation as well as use of high dose ergocalciferol (50,000 international units (IU) weekly).

Our primary outcomes were undergoing an IBD-related surgery or hospitalization identified using the appropriate procedure ICD-9 codes for surgical procedures (Supplemental Table 1) or the presence of CD or UC as the primary diagnosis for hospitalizations. Patients were censored at the first such event and plasma 25(OH)D measures beyond this time point were excluded from the analysis.

### Statistical Analysis

Data was analyzed using Stata 11.1 (StataCorp, College Station, TX). Continuous variables were summarized using means and standard deviations while categorical variables were expressed as percentages. The t-test was used to compare continuous variables with the chi-square test being used for comparison of categorical variables. Univariate logistic regression was used to identify predictors of IBD-related surgery, constructing separate models for CD and UC and modeling plasma 25(OH)D status using the lowest measured level (prior to surgery or end of follow-up) and the three strata described above. Multivariable logistic

regression was then used to examine the independent effect of vitamin D status on risk of IBD-related surgery or hospitalization. A two-sided p-value < 0.05 indicated statistical significance.

For the analysis of the effect of normalization of vitamin D status, we restricted the cohort to patients with at least 2 measures of plasma 25(OH)D examining whether they had ever achieved a normal level of plasma 25(OH)D prior to the event of interest (surgery or hospitalization). Similar multivariable regression models were constructed to examine both predictors of normalization of plasma 25(OH)D as well as to examine the effect of such normalization on risk of surgery and hospitalization. Ethical approval for our study was obtained from the Institutional Review Board of Partners Healthcare.

## RESULTS

### Study Population

Our study included a total of 3,217 patients (55% CD, 45% UC) with at least one measured plasma 25(OH) D. The mean age of the cohort was 49 years with a mean age of 41 years at the first ICD-9 code for CD or UC (Table 1). Most of the patients were Caucasian (81%) and a majority were female (61%). At least half the patients had a history of systemic corticosteroid use (54%) while just under a quarter had a history of anti-TNF use (21%). The median lowest plasma 25(OH)D was 26 ng/ml (interquartile range (IQR) 17 – 35ng/ml) with median highest plasma 25(OH)D of 35ng/ml (IQR 26 – 44 ng/ml). Just under a third of patients each had insufficient (28%) or deficient (32%) 25(OH)D levels. The median number of 25(OH)D measurements prior to surgery or end of follow up was 1 (IQR 1–3); half the cohort (49%) had 2 or more measurements.

### Plasma 25(OH)D and risk of IBD-related surgery and hospitalization

Table 2 describes the association between the lowest measured plasma 25(OH)D and subsequent risk of surgery. Only 10% of CD patients who were never deficient in vitamin D subsequently underwent an IBD-related surgery compared to 13% of those with insufficient levels (Odds ratio (OR) 1.70, 95% confidence interval (CI) 1.24 – 2.34) and 17% of those with deficient levels below 20ng/ml (OR 2.05, 95% CI 1.53 – 2.75). The association between plasma 25(OH)D and surgery remained significant on multivariable analysis adjusting for age, gender, Charlson co-morbidity, season of measurement, duration of follow up and use of immunomodulator or anti-TNF therapies. A similar association was seen for CD-related hospitalizations with a dose-response effect observed for progressively lower levels of 25(OH)D (Table 2).

For patients with UC, an association between plasma 25(OH)D below 20ng/ml and elevated risk of surgery and hospitalization was observed with an effect size similar to that observed for CD. However, the stratum with insufficient vitamin D (levels between 20–29.9ng/ml) did not demonstrate a statistically significant elevation in risk of surgery or hospitalization (Table 2).

### Predictors of Normalization of Vitamin D status

We examined predictors of normalization of vitamin D status in patients with at least 2 measurements of plasma 25(OH)D (median interval between the two measures was 294 days). Just over three-quarters of patients with CD (404/538, 75%) and UC (80%) had a normal plasma 25(OH)D > 30ng/ml following an initial measure below this threshold (“normalized” patients). Table 3 describes the variables associated with normalization. Older age increased likelihood of normalization (OR 1.16 for every 10 year increase in age, 95% CI 1.06 – 1.28) as did a higher baseline vitamin D level (OR 1.12, 95% CI 1.09 – 1.15

for every 1ng/ml). Supplemental vitamin D use was seen in 52% of those with low vitamin D levels and was associated with a higher likelihood of normalization (OR 1.87, 95% CI 1.31 – 2.66). Non-white race was associated with a significant lower likelihood of normalization (OR 0.53, 95% CI 0.30 – 0.92).

### Effect of normalization of vitamin D status on risk of surgery and hospitalization

We then examined if normalization of vitamin D status influenced risk of surgery and hospitalization in CD and UC. In patients with CD, those who had an initial low level of 25(OH)D but subsequently normalized their values had a significantly lower likelihood of requiring surgery on multivariable analysis (OR 0.56, 95% CI 0.32 – 0.98) compared to those who remained low (Table 4, Figure 1). While this difference was also seen for hospitalizations on univariate analysis, the effect did not achieve independent statistical significance on multivariable analysis. In contrast, we did not observe a reduction in the likelihood of surgery or hospitalization associated with normalization of vitamin D status in UC patients. CD patients who normalized their vitamin D status also had a significantly lower median C-reactive protein (10.7mg/dl vs. 16.2 mg/dl, adjusted regression co-efficient ( $\beta$ ): -5.2, 95% CI -9.5 to -1.02) that those who remained low; this effect was not seen in UC ( $\beta$ : -8.5mg/dl, 95% CI -35.2 to 18.2 mg/dl).

We repeated the analysis including all patients with at least one measure of vitamin D status, carrying forward the single plasma 25(OH)D measure for those with only one lab value. The association between normalization of plasma 25(OH)D and reduced risk of surgery in CD remained (OR 0.48, 95% CI 0.32 – 0.70) with a significant effect also observed for reduced risk of hospitalization (OR 0.52, 95% CI 0.38 – 0.69). No effect was observed for ulcerative colitis.

## DISCUSSION

Vitamin D plays an important immunologic role in inflammatory bowel diseases<sup>9-13</sup>. In a large IBD cohort, we demonstrate that (1) low plasma 25(OH)D is an independent risk factor for both UC and CD-related surgery and hospitalization; and (2) CD patients who normalize their vitamin D status have a lower risk of subsequent CD-related surgery that those whose levels remained low.

There has been growing data on vitamin D status in cohorts of IBD patients. However, many of the studies have limitations that preclude drawing conclusions regarding the immunologic effect of vitamin D. First, a majority of studies focused on describing a cross-sectional prevalence of insufficient or deficient vitamin D in their cohorts, or risk factors thereof, with a limited ability to prospectively examine consequences of vitamin D deficiency<sup>17-19, 27</sup>. Second, the studies that did examine the association with disease activity were limited by retrospective ascertainment of cumulative disease burden such that the low vitamin D could have temporally followed the outcome measured<sup>17-19</sup>. In this study, using a large cohort of over 3,200 IBD patients with at least one measured plasma 25(OH)D, we demonstrate that low plasma 25(OH)D is independently associated with an increased risk of subsequent surgery and hospitalization in both CD and UC patients. Furthermore, in CD, we also observed a dose-response effect with a progressively higher frequency of surgery and hospitalizations in those with insufficient (25(OH)D between 20–29.9ng/ml) and deficient (25(OH)D < 20ng/ml) levels.

Though one cannot exclude the possibility that improvement in vitamin D status was consequent to increasing physical activity and outdoor sun exposure as better control of disease is achieved, considerable evidence both from our study and prior work suggests this is unlikely to be the explanation for our findings. First, in our study, the effect of

normalization of plasma 25(OH)D on reduction in risk of CD-related surgery remained significant after adjusting for inflammatory burden quantified using median C-reactive protein levels, as well as use of medical therapies (immunomodulator or anti-TNF) initiated to achieve disease control, suggesting that vitamin D status is not merely a marker of disease activity or severity but potentially a biologically relevant parameter. Furthermore, there is also supporting biologic evidence on how vitamin D could influence disease activity in CD. In an IL-10 knockout model of colitis, Cantorna *et al.* demonstrated that administration of 1,25-dihydroxy cholecalciferol was associated with amelioration of colitis with a dose-response effect similar to that observed in our study<sup>20</sup>. In a second study, a vitamin D analogue similarly ameliorated TNBS mediated colitis and decreased both clinical and macroscopic activity scores<sup>28</sup>. In addition, Zhu *et al.* demonstrated that administration of vitamin D was associated with a reduction in the colonic expression of TNF-related genes<sup>29</sup>.

A randomized controlled trial examined the effect of vitamin D supplementation on disease activity in CD. Jorgensen *et al.* randomized 94 patients to placebo or vitamin D 1200 IU daily in conjunction with 1200mg/day of calcium in both arms<sup>21</sup>. At the end of one year, there was a trend towards lower frequency of relapse in the vitamin D (13%) compared to the placebo arm (29%,  $p=0.06$ ). The median plasma 25(OH)D increased from 27ng/ml to 38ng/ml at 3 months and was sustained at the higher level through 12 months. Our findings of the effect of normalization similarly support that attainment of a vitamin D level above 30ng/ml is associated with a reduction in risk of CD-related surgery. In our study, though reduction in CD-related hospitalizations was not statistically significant on multivariable analysis, we did find a statistically significant drop in rate of hospitalizations of a similar magnitude when the cohort was expanded to include those with at least one measured plasma 25(OH)D, suggesting consistency in effects. In a smaller study, Miheller *et al.* compared two different vitamin D formulations – cholecalciferol 1000 IU/day and alfacalcidol 0.50mcg/day and found a reduction in the Crohn's disease activity index (CDAI), C-reactive protein and SIBDQ<sup>30</sup>. Our findings support this and expand it to a larger cohort by additionally demonstrating that CD patients who normalized their plasma 25(OH)D measurements had a lower median C-reactive protein than those who remained low.

It was interesting that we observed this effect of normalization among CD but not UC patients. First, this may indicate that a higher plasma 25(OH)D threshold is required to attain immunologic activity in UC compared to CD. The lack of an effect of insufficient (plasma 25(OH)D 20–29.9mg/dl) vitamin D on risk of surgery or hospitalization in UC supports this plausibility. However, there is also biological evidence suggesting a stronger interplay between vitamin D status and CD compared to UC. In a previous study, Ananthakrishnan *et al.* found that lower predicted plasma 25(OH)D was associated with an increased risk for incident CD but not UC<sup>16</sup>. Similarly, Ulitsky *et al.* identified an association between low vitamin D and disease activity in CD but not UC<sup>17</sup>. Using chromatin immunoprecipitation and parallel DNA sequencing (ChIP-Seq), Ramagopalan *et al.* found that calcitriol administration led to enrichment of vitamin D receptor (VDR) binding sites in proximity to several autoimmune loci including the nucleotide-binding oligomerization domain containing 2 locus (NOD2) on chromosome 16<sup>31</sup>. NOD2 is a risk allele with a strong effect on CD but not UC, and is associated with ileal disease location, fibrostenosing phenotype, and need for surgery<sup>32</sup>. Also mediated through VDR, administration of calcitriol leads to induction of NF- $\kappa$ B inhibitory proteins, and reduction in NF- $\kappa$ B mediated production of TNF and other inflammatory cytokines<sup>33</sup>. Binding of VDR by 1,25(OH)D regulates NOD2 transcription and induces NF- $\kappa$ B-mediated expression of defensins (*DEFB2/HBD2*)<sup>34</sup>.

Our findings have a few clinical implications. To our knowledge, ours is the largest cohort examining the effect of vitamin D status on natural history and outcomes of CD and UC.

Furthermore, prior studies have been limited by cross-sectional assessment of vitamin D status at a single time point, or cumulative average of vitamin D measures over the entire study period<sup>17-19</sup>. Using our distinct and repeated measures of plasma 25(OH)D, we were able to additionally demonstrate that CD patients who normalized their vitamin D had a lower likelihood of surgery. This finding, in conjunction with the supportive laboratory data<sup>10, 20</sup> and the Jorgensen trial<sup>21</sup> suggest a need for prospective studies of vitamin D as an intervention in the management of IBD. Further data is also needed on whether the role of vitamin D is restricted to maintenance of remission as examined in the trial, or if it could also play a role in induction in combination with existing therapy.

There are a few limitations to our study. First, plasma 25(OH)D levels were not available for all patients in our cohort; there likely exists both a provider- and a patient-level bias in obtaining vitamin D levels. However, patients for whom measures of vitamin D status was available were sicker than those without a measured level suggesting that our findings are particularly relevant in a cohort enriched for adverse outcomes. Second, not all patients had multiple measures of plasma vitamin D, and at pre-defined time points. However, our findings remained robust in analyses that included those with single or multiple measures. Third, we did not have information on dietary vitamin D or supplemental vitamin D that was not captured in the electronic medical records. However, since our primary variable, directly measured plasma 25(OH)D, is a comprehensive reflection of dietary intake, vitamin D absorption, and vitamin D from other sources including sun exposure, we believe our findings to have greater biological relevance than studies examining vitamin D intake alone. As in most observational studies, the effect of unmeasured confounders cannot be excluded. We also did not have the ability to adjust in detail for disease location which could predict need for surgery. However, for small bowel disease location to be a confounder, it would have to be associated with both our predictor (vitamin D) and outcome (surgery), and several prior studies have failed to identify an association between small bowel CD with low vitamin D status<sup>17-19</sup>. Furthermore, vitamin D intake contributes to only a small fraction on an individual's overall vitamin D status<sup>35</sup>. Finally, it is also possible that vitamin D repletion is a marker of compliance with treatment, or overall health status. Causality cannot be inferred from an observational study, but the wealth of laboratory data supporting a bioactive role of vitamin D in intestinal inflammation provides significant biologic plausibility to this association.

In conclusion, we demonstrate that low plasma 25(OH)D is associated with increased risk of surgery in CD and UC, with a dose-response relationship observed in CD. Furthermore, CD patients who normalized their vitamin D had a lower risk of subsequent surgery than those who remained deficient suggesting a need to examine the role of vitamin D supplementation as an intervention in the management of CD. However, only a subset of patients had measured 25(OH)D at multiple time points, and detailed dietary vitamin D intake, physical activity, or sunlight exposure was not available. Larger prospective studies in other cohorts as well as randomized intervention trials are required to definitively establish if modulating vitamin D status can help in the therapy of IBD and improve patient outcomes.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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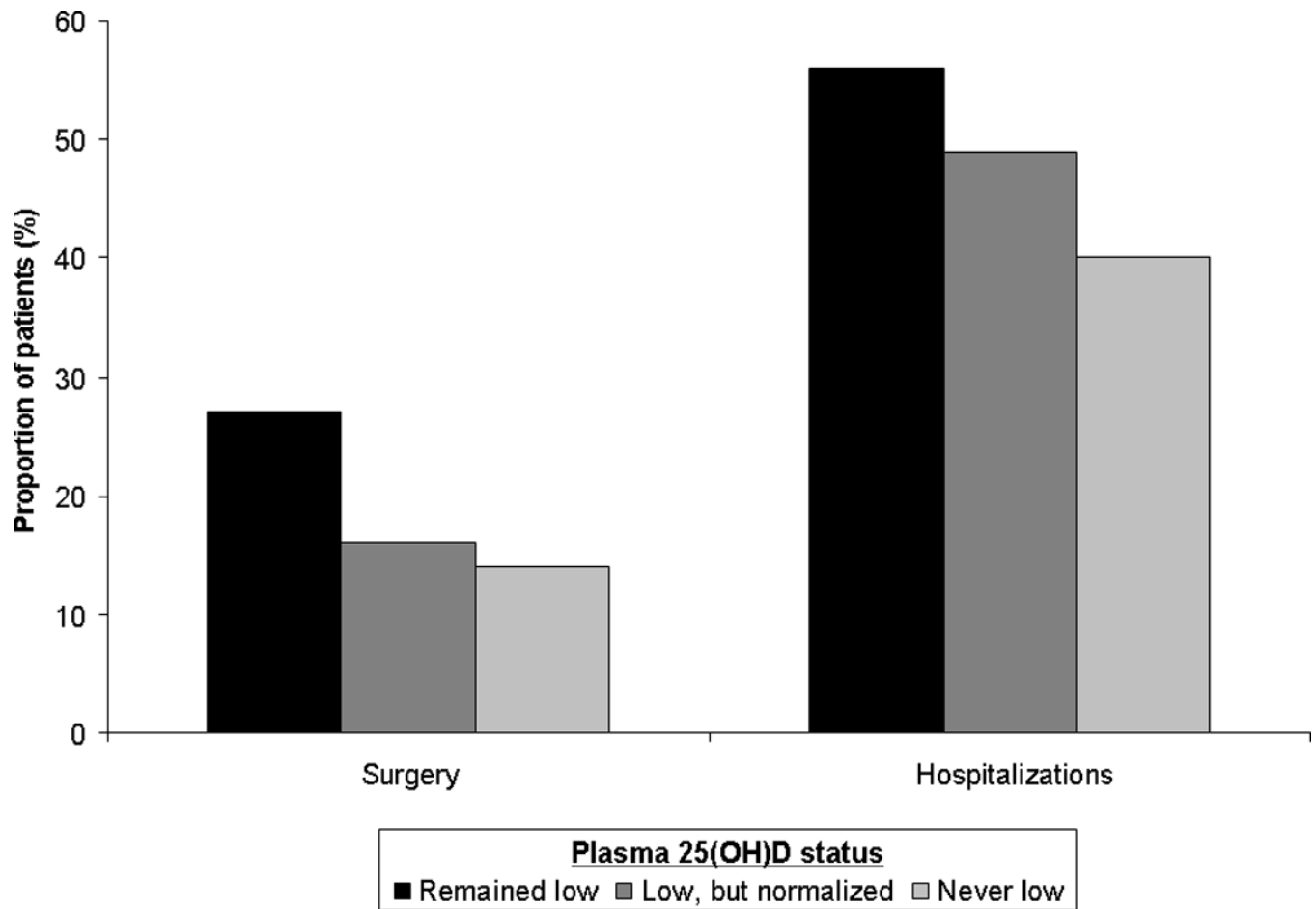
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**Figure 1.** Normalization of plasma 25(OH)D and risk of surgery in Crohn's disease and ulcerative colitis

**Table 1**

## Characteristics of the study cohort

Characteristic	Number (%)
Total	3,217 (100%)
Median age (in years) (IQR)	48 (34 – 63)
Median age at first IBD ICD-9 code (in years) (IQR)	40 (28 – 54)
Female	1,954 (61%)
Race	
White	2,812 (87%)
Non-white	238 (8%)
Other/Unknown	167 (5%)
Mean Charlson score (SD)	3.7 (3.6)
IBD type	
Crohn's disease	1,763 (55%)
Ulcerative colitis	1,454 (45%)
IBD-related medications	
Corticosteroids	1,732 (54%)
5-aminosalicylates	1,942 (60%)
Immunomodulators	1,255 (39%)
Anti-TNF biologics	688 (21%)
IBD-related surgery	525 (16%)
IBD-related hospitalization	1,293 (40%)
Median lowest plasma 25(OH)D measurement (IQR)	26 ng/mL (17 – 35)
Median highest plasma 25(OH)D measurement (IQR)	35 ng/mL (26 – 44)

IBD – inflammatory bowel diseases, IQR – interquartile range, SD – standard deviation, TNF – tumor necrosis factor

**Table 2**

Plasma 25(OH)D and risk of IBD-related surgery and hospitalization

	Surgery			Hospitalizations		
	30ng/ml	20 – 29.9 ng/ml	< 20 ng/mL	30ng/ml	20 – 29.9 ng/ml	< 20 ng/mL
Crohn's disease						
Unadjusted	1.0	1.70 (1.24 – 2.34)	2.05 (1.53 – 2.75)	1.0	1.65 (1.30 – 2.10)	2.49 (1.98 – 3.12)
Adjusted <sup>†</sup>	1.0	1.54 (1.06 – 2.25)	1.76 (1.24 – 2.51)	1.0	1.56 (1.20 – 2.04)	2.07 (1.59 – 2.68)
Ulcerative colitis						
Unadjusted	1.0	1.17 (0.80 – 1.72)	1.75 (1.21 – 2.52)	1.0	1.27 (0.96 – 1.66)	2.22 (1.70 – 2.91)
Adjusted <sup>†</sup>	1.0	1.13 (0.68 – 1.86)	2.10 (1.32 – 3.34)	1.0	1.18 (0.87 – 1.62)	2.26 (1.66 – 3.06)

<sup>†</sup> Adjusted for age, gender, race, Charlson co-morbidity, season of measurement of vitamin D, use of immunomodulators or anti-TNF biologics, and duration of follow-up

**Table 3**

Multivariate Analysis of Predictors of Normalization of plasma 25(OH)D in patients with Crohn's disease and ulcerative colitis

Predictor	Odds Ratio	95% confidence interval
Age (for every 10 years)	1.16	1.06 – 1.28
Non-white race	0.53	0.30 – 0.92
Lowest vitamin D level (for every 1 ng/ml increase)	1.12	1.09 – 1.15
Supplemental Vitamin D use	1.87	1.31 – 2.66
Season of initial measurement		
Spring	Reference	
Summer	1.29	0.78 – 2.15
Fall	1.16	0.75 – 1.82
Winter	1.49	0.99 – 2.26

**Table 4**

Effect of normalization of plasma 25(OH)D and risk of surgery and hospitalizations in Crohn's disease and ulcerative colitis

	Surgery		Hospitalizations	
	Did not normalize	Normalize	Did not normalize	Normalized
Crohn's disease				
Unadjusted	1.0	0.51 (0.32 – 0.82)	1.0	0.64 (0.44 – 0.96)
Adjusted <sup>†</sup>	1.0	0.56 (0.32 – 0.98)	1.0	0.78 (0.51 – 1.25)
Ulcerative colitis				
Unadjusted	1.0	1.02 (0.45 – 2.31)	1.0	0.88 (0.52 – 1.47)
Adjusted <sup>†</sup>	1.0	0.75 (0.29 – 1.93)	1.0	0.78 (0.44 – 1.40)

<sup>†</sup> Adjusted for age, gender, race, Charlson co-morbidity, use of immunomodulators or anti-TNF biologics, and duration of follow-up