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Investigating the relationship between vitamin D levels and immune-mediated colitis

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Abstract

Background The aim of this study was to evaluate the potential association between serum vitamin D levels and the incidence and severity of immune-mediated colitis (IMC), and to explore the potential role of vitamin D supplementation as a preventative or therapeutic intervention.

Methods This was a single-center study in which we retrospectively reviewed patients who received immune checkpoint inhibitor (ICI) treatment, had serum vitamin D levels measured within 6 months before or after starting treatment, and subsequently developed IMC.

Results A total of 179 patients were included in the study. Patients were stratified by serum vitamin D levels: 121 (67.6%) had levels ≤40 ng/mL, and 58 (32.4%) had levels >40 ng/mL. Individuals with vitamin D levels ≤40 ng/mL had more severe diarrhea (65.0%) and severe colitis (48.0%), both defined as common terminology criteria for adverse events grade ≥2, compared to those with vitamin D levels >40 ng/mL (45.6% and 28.6%, respectively; P=0.022 and P=0.034). Univariate analysis revealed that patients receiving vitamin D during ICI therapy had ~1.9 times higher odds of requiring steroid treatment (odds ratio [OR] 1.899, 95% confidence interval [CI] 1.0338-3.474; P=0.038). Patients with grade ≥2 diarrhea had 11 times higher odds of requiring steroids (OR 11.11, 95%CI 5.35-22.73; P<0.001). Patients with colitis grade ≥2 had 3 times higher odds of steroid use (OR 3.08, 95%CI 1.54-6.13; P=0.001).

Conclusions This study suggests that there is a relationship between serum vitamin D levels and IMC. Vitamin D deficiency in those with IMC was associated with more severe disease, and those with more severe disease were more likely to require steroid therapy.

Keywords Immune checkpoint inhibitor, immune mediated colitis, vitamin D

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Conflict of Interest: None

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Introduction

The use of immune checkpoint inhibitors (ICIs) has rapidly expanded in oncology, given their ability to generate sustained clinical responses in various cancer types [1]. These monoclonal antibodies enhance antitumor immunity by blocking regulatory pathways that restrain T-cell activity, leading to unchecked immune activation [2]. However, this heightened immune response predisposes patients to immune-related adverse events, with immune-mediated colitis (IMC) among the most common and clinically significant [3].

IMC is characterized by inflammation of the colon that shares several phenotypic, histological and serological features with classical inflammatory bowel disease (IBD) such as Crohn's

disease and ulcerative colitis [4]. These similarities suggest overlapping pathogenic mechanisms, including dysregulated mucosal immunity and alterations in the gut microbiome, as well as similar risk factors and disease modifiers such as vitamin D [5]. Vitamin D is a key modulator of gastrointestinal homeostasis. It influences epithelial barrier function, shapes microbial diversity, and modulates both innate and adaptive immune responses [6,7]. Vitamin D deficiency has been widely reported in patients with IBD, and has been associated with greater disease activity and poorer outcomes [5-7]. Although it remains unclear whether this deficiency is a cause or a consequence of disease, vitamin D supplementation has shown promise in reducing disease severity and flares in IBD. Given the mechanistic parallels between IBD and IMC, it is plausible that vitamin D may also play a protective or therapeutic role in the latter context. However, this relationship remains underexplored.

Therefore, the aim of this study was to evaluate the association between serum vitamin D levels and the incidence and severity of IMC, and to explore the potential role of vitamin D supplementation as a preventative or therapeutic intervention.

Patients and methods

Study design and patient selection

This was a single-center, retrospective study conducted at a tertiary care cancer center, including patients who received ICI therapy between January 2019 and December 2022, and subsequently developed IMC. IMC was identified through manual chart review, and was defined by a combination of clinical symptoms, elevated inflammatory markers (fecal lactoferrin and/or calprotectin), and endoscopic findings consistent with colitis.

Patients were excluded if they were younger than 18 years, if alternative etiologies for colitis were identified (e.g., infectious, autoimmune, other medications), or if no serum vitamin D level was documented within 6 months before or after the first ICI dose. Only patients with confirmed IMC and a documented vitamin D level during this window were included in the final analysis.

Clinical data collection

All data were obtained from the institutional electronic medical record, and included demographics (age, sex, race), cancer characteristics (type, stage per American Joint Committee on Cancer 8th edition, treatment), and IMC-related variables: symptom details, peak common terminology criteria for adverse events (CTCAE) grade, duration, stool biomarkers (calprotectin, lactoferrin), vitamin D supplementation (before and during ICI), treatments, colonoscopy/biopsy findings, and information on ICI being held/resumed during and after IMC development.

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Statistical analysis

The distribution of continuous variables was summarized using mean (± standard deviation), or median and interquartile range (IQR). The distribution of categorical variables was summarized using frequencies and percentages. Continuous variables were compared among groups (vitamin D levels) using the Wilcoxon rank-sum test. The Fisher exact test or a chi-square test was used to evaluate associations between categorical variables. Univariate analysis using logistic regression was conducted to evaluate the relationship between various variables and both the need for steroid treatment and the factors contributing to recurrence. All statistical tests were 2-sided, and P-values less than or equal to 0.05 were considered significant. Statistical analyses were performed using SPSS software (version 24.0; IBM).

Ethical considerations

MD Anderson Institutional Review Board approval was obtained, and informed consent was waived due to the study's retrospective nature.

Results

Patient demographic baseline characteristics

A total of 179 patients with IMC were included in the study. The median age was 64 years (IQR 56.5-72.0), and the majority were male (n=111, 62.0%) and White (n=139, 77.7%). Most patients had genitourinary malignancies (n=58, 32.4%) and stage IV disease at the time of ICI initiation (n=126, 70.0%). Pembrolizumab was the most frequently administered immune checkpoint inhibitor (n=78, 43.6%) (Table 1). Patients were also stratified by serum vitamin D levels: 121 (67.6%) had levels ≤40 ng/mL, and 58 (32.4%) had levels >40 ng/mL. No significant differences in demographic or oncologic characteristics were observed between the 2 vitamin D groups (Table 2).

Clinical characteristics of IMC

The median time of IMC onset after ICI initiation was 88 days (IQR 36-195). Diarrhea was the predominant symptom, occurring in 91.1% of patients. Severe diarrhea (CTCAE grade ≥2) was present in 58.4% of the cohort, while severe colitis was observed in 41.7%. The median duration of IMC symptoms was

Table 1 Patient demographic characteristics, n=179

Characteristics	No. (%)
Age at the time of first dose of ICI, median (IQR), *years*	64 (56.6-72.0)
Sex – Male	111 (62)
Race – White	139 (77.7)
Cancer type	
Genitourinary	58 (32.4)
Lung	20 (11.2)
Hematologic	20 (11.2)
Melanoma	17 (9.4)
Head and neck	13 (7.3)
WEndocrine	17 (9.5)
GYN	10 (5.6)
GI/hepatobiliary	12 (6.7)
Others	11 (6.1)
Cancer stage	
I	6 (3.3)
II	11 (6.1)
III	22 (12.2)
IV	126 (70.0)
Unspecified	13 (7.4)
ICI therapy received	
Pembrolizumab	78 (43.6)
Nivolumab	74 (41.3)
Ipilimumab	57 (31.7)
Atezolizumab	15 (8.3)
Tremelimumab	1 (0.6)
Durvalumab	2 (1.1)
Class of ICI therapy received	
PD-1	105 (59.0)
Combination	46 (25.8)
PDL-1	19 (10.7)
CTLA-4	6 (3.4)
ECOG	
0	50 (28.4)
1	97 (55.1)
2-4	29 (16.2)
All-cause mortality	102 (57.0)
Length of follow-up, median (IQR), *years*	1.5 (0.5-2.8)

ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; GYN, gynecologic; ICI, immune checkpoint inhibitor; IQR, interquartile range

Table 2 Association between patient demographic characteristics and vitamin D levels, n=179

Characteristics	No. (%)		
	Vit D level ≤40, n=121	Vit D levels >40, n=58	P-value
Age at the time of first dose of ICI, median (IQR), *years*	63 (55.0-70.7)	68 (60.0-73.0)	0.012
Sex – Male, n=111	75 (62.0)	36 (62.1)	>0.99
Race – White	80 (76.2)	43 (89.6)	0.078
Cancer type			
Genitourinary	35 (28.9)	23 (39.7)	0.174
Lung	14 (11.6)	6 (10.3)	>0.99
Hematologic	15 (12.4)	5 (8.6)	0.614
Melanoma	11 (9.1)	6 (10.3)	0.790
Head and neck	11 (9.1)	2 (5.2)	0.553
Endocrine	11 (9.1)	6 (10.3)	0.790
GYN	5 (4.1)	5 (8.6)	0.297
GI/hepatobiliary	10 (8.3)	2 (3.4)	0.342
Others	9 (7.4)	2 (3.4)	0.507
Cancer stage			
I-II	10 (10.6)	5 (10.4)	>0.99
III-IV	84 (89.4)	43 (89.6)	>0.99
ICI therapy received			
Pembrolizumab	53 (43.8)	25 (43.1)	>0.99
Nivolumab	49 (40.5)	25 (43.1)	0.748
Ipilimumab	36 (29.8)	21 (36.2)	0.396
Atezolizumab	12 (9.9)	3 (5.2)	0.392
Tremelimumab	0	1 (1.7)	0.324
Durvalumab	1 (0.8)	1 (1.7)	0.544
Class of ICI therapy received			
PD-1	71 (58.7)	34 (58.6)	>0.99
Combination	30 (24.8)	16 (27.6)	0.717
CTLA-4	3 (2.5)	3 (5.2)	0.391
PDL-1	15 (12.4)	4 (6.9)	0.311
ECOG			
0	36 (37.1)	14 (28.0)	0.358
1	61 (62.9)	36 (72.0)	0.358
2-4	17 (16.7)	7 (14.6)	0.816
All-cause mortality	69 (57.0)	33 (56.9)	>0.99
Length of follow up, median (IQR), years	1.4 (0.4-2.9)	1.5 (0.6-2.6)	0.855

ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal; GYN, gynecologic; ICI, immune checkpoint inhibitor; IQR, interquartile range

14 days (IQR 7-51). Vitamin D supplementation was reported in 41.0% of patients prior to ICI initiation and in 56.4% after starting therapy. Among the 85 patients who underwent endoscopic evaluation, 21.2% had ulcerative inflammation and 42.4% had non-ulcerative findings. Treatment for IMC included oral corticosteroids in 50.8% of cases and biologic therapy in 31.4%. Hospitalization was required in 42.3% of patients, with a median hospital stay of 7 days (IQR 4-10) (Table 3).

Association between vitamin D and IMC severity

The cohort was divided into 2 groups based on vitamin D levels (≤40 vs. >40 ng/mL), and IMC characteristics were compared. There were no significant associations between specific symptoms and vitamin D levels. However, individuals with vitamin D levels ≤40 ng/mL had significantly more severe diarrhea (65.0%) and severe colitis (48.0%), both defined as CTCAE grade ≥2, compared to those with vitamin D levels >40 ng/mL (45.6% and 28.6%, respectively; P=0.022 and P=0.034). Conversely, patients with vitamin D levels >40 ng/mL were significantly more likely to experience less severe diarrhea (51.9% vs. 33.9%, P=0.030) and less severe colitis (71.4% vs. 52.0%, P=0.034), as defined by CTCAE grade <2.

There was no significant difference in the median duration of IMC symptoms between the 2 cohorts (16 vs. 14 days). While not significant, there was a larger percentage of patients with

Table 3 Characteristics of IMC, n=179

Characteristics	No. (%)
Presenting symptoms	
Diarrhea	164 (91.1)
Nausea	26 (14.4)
Abdominal pain	23 (12.8)
Vomiting	23 (12.8)
Hematochezia/melena	9 (5.0)
CTCAE Grade, diarrhea	
<2	68 (39.5)
≥2	104 (58.4)
CTCAE Grade, colitis	
<2	88 (58.3)
≥2	63 (41.7)
Time from ICI initiation to IMC onset, median (IQR), *days*	88 (36-195)
Duration of GI symptoms, median (IQR), *days*	14 (7-51)
Lactoferrin positive, n=101	83 (82.2)
First calprotectin levels, median (IQR), n=103	243 (81.6-685)
Received vitamin D supplementation (before ICI)	73 (41.0)
Received vitamin D supplementation (during ICI)	101 (56.4)
Endoscopy (within 6 months before or after IMC diagnosis), n=85	
Ulcerative inflammation	18 (21.2)
Non-ulcerative inflammation	36 (42.4)
Normal findings	31 (36.5)
Treatment of IMC	
Steroids	90 (50.8)
Biologics	54 (31.4)
Hospitalization for IMC	74 (42.3)
Length of hospitalization, median (IQR), *days*	7 (4-10)
ICI held	94 (55.3)
ICI resumed	37 (32.7)
IMC clinical remission	153 (85.5)

CTCAE, common terminology criteria for adverse events; GI, gastrointestinal; ICI, immune checkpoint inhibitor; IMC, immune mediated colitis

ulcerative inflammation on endoscopy in the lower vitamin D group (24.6% vs. 12.5%, P=0.256). In addition, hospitalization and remission rates did not differ significantly between the 2 groups. As expected, vitamin D supplementation prior to ICI initiation was associated with a vitamin D level >40 ng/mL (56.9% vs. 33.3%, P=0.011).

Univariate analysis

In our sample of patients with IMC, we identified factors associated with need for steroid therapy. In particular, patients receiving vitamin D during ICI had ~1.9 times significantly higher odds of requiring steroid treatment, suggesting a possible association (odds ratio [OR] 1.899, 95% confidence interval [CI] 1.0338-3.474; P=0.038). Patients with grade ≥2 diarrhea had 11 times higher odds of requiring steroids: a strong positive predictor (OR 11.11, 95%CI 5.35-22.73; P<0.001). Patients with colitis grade ≥2 had 3 times higher odds of steroid use: a moderate positive predictor (OR 3.08, 95%CI 1.54-6.13; P=0.001). Biomarkers, including positive calprotectin (OR 2.025, 95%CI 0.817-5.018; P=0.128), lactoferrin (OR 1.718, 95%CI 0.564-5.238; P=0.341), and colonoscopy findings (OR 3.640, 95%CI 0.438-30.281; P=0.232) did not show significant associations.

Discussion

Vitamin D is a fat-soluble hormone, primarily synthesized in the skin upon exposure to ultraviolet B radiation, with additional contributions from dietary intake and supplementation [8]. Given the importance of sun exposure in vitamin D synthesis, skin pigmentation is a vital factor in this process, as higher melanin content in certain patient populations limits the cutaneous ultraviolet B-mediated production of vitamin D. Vitamin D has a well-established role in calcium and phosphate metabolism, but emerging research has expanded our understanding of its broader immunological and anti-inflammatory functions. Beyond its classical endocrine functions, vitamin D is now recognized as a key modulator of gut homeostasis in conditions of bowel inflammation [5]. Additionally, in both animal models and human studies, vitamin D deficiency has been implicated in the pathogenesis and exacerbation of IBD [5,6]. The role of vitamin D in IBD has been well studied, with some studies finding that reduced vitamin D receptor (VDR) expression is a common finding in IBD [9]. In fact, while the exact mechanism of action is unclear, various studies have indicated a relationship between gut inflammation and reduced VDR expression [10,11].

Given the overlapping immunopathology between IBD and IMC—both characterized by dysregulated T-cell activity and mucosal inflammation—it is possible that a similar relation exists between vitamin D and IMC. Furthermore, vitamin D may be a modifiable factor that contributes to maintaining the balance of minimizing toxicity without compromising anti-tumor effects in patients receiving ICIs. Ultimately, our study did support the potential for a relationship between IMC and vitamin D primarily in regard to disease severity.

The results of our study showed that the 2 comparison groups were not dissimilar in regard to cancer demographics. Furthermore, the results from the comparative and univariate analyses indicate that those with low levels of vitamin D had more severe IMC (i.e., diarrhea/colitis CTCAE≥2) and those with sufficient levels of vitamin D had less severe colitis (i.e., diarrhea/colitis CTCAE<2). Additionally, those receiving vitamin D supplementation during ICI therapy, which probably indicates a vitamin D deficiency, had higher odds of requiring treatment of IMC with steroids. While this result does not establish a causal relationship, it does suggest that a need for supplementation during ICI therapy is an indication of more severe disease. Overall, the findings suggest that vitamin D may have a significant role in the development of IMC and IMC severity. Given that vitamin D-sufficient patients had less

Table 4 Association between severity of IMC and vitamin D levels, n=179

Characteristics	No. (%)		
	Vit D level ≤40, n=121	Vit D levels >40, n=58	P-value
Presenting symptoms			
Nausea	17 (14.0)	9 (15.5)	0.823
Vomiting	15 (12.4)	8 (13.8)	0.814
Diarrhea	111 (91.7)	53 (91.4)	>0.99
Abdominal pain	15 (12.4)	8 (13.8)	0.814
Hematochezia/melena	8 (6.6)	1 (1.7)	0.275
CTCAE grade, diarrhea			
<2	40 (33.9)	28 (51.9)	0.030
≥2	78 (65.0)	26 (45.6)	0.022
CTCAE grade, colitis			
<2	53 (52.0)	35 (71.4)	0.034
≥2	49 (48.0)	14 (28.6)	0.034
Duration of GI symptoms, median (IQR), *days*	16 (7-49)	14 (8-50)	0.907
Lactoferrin positive, n=101	11 (14.7)	7 (26.9)	0.232
Calprotectin levels, median (IQR) in mcg/g, n=103	223 (82.3-660.0)	262 (63.3-755)	0.726
Vitamin D supplementation (before ICI)	40 (33.3)	33 (56.9)	0.011
Vitamin D supplementation (during ICI)	68 (56.2)	33 (56.9)	>0.99
Endoscopy characteristics (within 6 months before or after IMC diagnosis), n=85			
Ulcerative inflammation	15 (24.6)	3 (12.5)	0.256
Non-ulcerative inflammation	22 (36.1)	14 (58.3)	0.088
Normal findings	24 (39.3)	7 (29.2)	0.458
Treatment of IMC			
Steroids	64 (52.9)	26 (47.3)	0.519
Biologics	37 (31.1)	17 (32.1)	>0.99
Hospitalization for IMC	53 (44.5)	21 (37.5)	0.488
Length of hospitalization, median (IQR), *days*	7 (4-9)	8 (4-12)	0.444
IMC clinical remission	105 (92.9)	48 (92.3)	>0.99
All-cause mortality	69 (57.0)	33 (56.9)	>0.99

CTCAE, common terminology criteria for adverse events; GI, gastrointestinal; ICI, immune checkpoint inhibitor; IMC, immune mediated colitis; IQR, interquartile range

severe colitis, vitamin D may also be a protective factor in IMC. However, the retrospective nature of our study means that causality cannot be inferred. This conclusion is consistent with our hypothesis, based on the various studies of the relationship and protective role of vitamin D in IBD and in other conditions of gastrointestinal inflammation.

Vitamin D is a vital micronutrient, and is especially important in patients with cancer, given that the prevalence of vitamin D deficiency has been observed to be greater than 75% in some cancer populations [12]. Furthermore, the presence

Table 5 Univariate analysis for factors associated with steroid treatment

Factors	Odds ratio (95% confidence interval)	P-value
Vit D supplementation before ICI	0.935 (0.511-1.71)	0.827
Vit D supplementation during ICI	1.899 (1.0338-3.474)	0.038
First vitamin D level (≤40 or >40)	0.798 (0.422-1.512)	0.490
CTCAE grades of diarrhea ≥2	0.090 (0.44-0.187)	<0.001
CTCAE grade of colitis ≥2	0.325 (0.163-0.649)	0.001
Calprotectin positive	2.025 (0.817-5.018)	0.128
Lactoferrin positive	1.718 (0.564-5.238)	0.341
Endoscopy positive	3.640 (0.438-30.281)	0.232

CTCAE, common terminology criteria for adverse events; ICI, immune checkpoint inhibitor

of adequate vitamin D levels in cancer populations has been linked to a better treatment response, longer progression-free survival, and a better overall prognosis [13]. It is likely that vitamin D has an even greater benefit for those with cancer and concurrent conditions of bowel inflammation, given its reported relationship to disease activity in IBD. Several studies have found that vitamin D deficiency is commonly found in IBD and is strongly associated with greater disease activity and high relapse rates. This population has also been found to have elevated inflammatory markers such as erythrocyte sedimentation rate and fecal calprotectin [14-17]. Notably, vitamin D supplementation was found to successfully increase vitamin D levels and subsequently reduce the disease relapse rate in this population, further highlighting the likely protective role of vitamin D in gut inflammation [14]. This is in keeping with the primary result of this study, which indicates that individuals with low vitamin D levels (defined in our study as vitamin D ≤40 ng/mL) were more likely to have more severe diarrhea and colitis (i.e., CTCAE ≥2). Furthermore, it is important to note that, though the difference was not significant, those with ulcerative inflammation on lower endoscopy were found to have numerically lower vitamin D levels.

Additionally, studies have shown that immunosuppressive therapies (ISTs) may be less effective in treating IBD when there is concurrent vitamin D deficiency [18-20]. This is important, because it raises the possibility of standard immunosuppressive therapy being less effective in treating IMC unless the vitamin D deficiency is also addressed. These studies observed vitamin D deficiency to be associated with earlier cessation of anti-tumor necrosis factor (TNF)-α therapy, primarily due to a loss of treatment response [18]. In contrast, those with adequate vitamin D levels at the time of anti-TNF-α therapy were found to have higher odds of remission when compared to those with vitamin D deficiency [19]. This is in keeping with what we found in our sample: that individuals receiving vitamin D supplementation during ICI therapy, presumably as treatment for a vitamin D deficiency that had not yet been corrected, had approximately 2 times higher odds of requiring steroid treatment or a need for immunosuppression, suggesting an inadequate IST response and more severe IMC due to vitamin D deficiency.

Table 6 The role of vitamin D in various immune mediated diseases

Disease	Disease category	Link to vitamin D deficiency	Relevance to disease outcome or phenotype
Immune-mediated colitis	Gastrointestinal, immune-mediated adverse event	This study proposes an association between vitamin D levels and severity of colitis	Lower vitamin D levels may be associated with more severe diarrhea and colitis, greater need for immunosuppressive therapy, and greater clinical burden
Inflammatory bowel disease (ulcerative colitis, Crohn's disease)	Gastrointestinal, immune-mediated	Vitamin D deficiency is common and associated with increased disease activity, elevated inflammatory markers, and higher relapse rates	Vitamin D deficiency is linked to a more severe disease phenotype, more steroid use and hospitalizations, and a poorer response to biologic therapy
Celiac disease	Gastrointestinal, autoimmune	Vitamin D deficiency frequently observed due to malabsorption and chronic intestinal inflammation	Associated with delayed mucosal healing, persistent symptoms, immune system impairment, and increased risk of bone disease
Multiple sclerosis	Systemic autoimmune	Studies outline association between low vitamin D levels and disease activity	Vitamin D influences T-cell differentiation and immune tolerance
Rheumatoid arthritis	Systemic autoimmune	Vitamin D deficiency associated with higher disease activity	Linked to increased inflammatory burden and functional impairment

The potential for vitamin D supplementation as a prophylactic or therapeutic intervention for IMC is significant, as it would also be a better option than treating with immunosuppressive agents for multiple reasons. IST, comprising steroids or biologic therapies, is commonly used for the treatment of IMC, as it is currently the standard of care for this condition. However, ISTs by nature suppress the immune system, and dampen the exaggerated immune response by which ICIs function and treat cancer. In fact, studies have shown that poorer outcomes are associated with steroid use in patients receiving ICIs when compared to steroid-naïve patients on ICIs [21,22]. In contrast to IST, vitamin D supplementation is very safe, avoids negative interactions with other medications, and would be a more ideal option for prophylactic therapy.

In addition to preventing or dampening the severity of IMC, vitamin D may also be a factor in preventing IMC recurrence. IMC recurrence is a common issue, with 1 study finding that of 102 patients who resumed ICI therapy after developing and receiving treatment for IMC, 28 had recurrence of IMC. In this study, those who received IST concurrently with ICI resumption were found to be less likely to have recurrence of IMC, while there was a dose-dependent relationship between doses of IST and a lower risk of IMC recurrence [23]. Interestingly, persistent IMC has also been thought to be a surrogate marker for long-lasting ICI effects, which result in favorable outcomes in terms of cancer prognosis [24,25]. Although our results found no association with vitamin D and recurrence of IMC, we speculate that, given the potential role of vitamin D in IMC, vitamin D supplementation may allow for the effects of ICI therapy to persist without the associated gastrointestinal toxicity. This, in combination with avoiding long term IST, would greatly decrease treatment complications and improve the overall prognosis of this population.

Vitamin D is also a modulator of the gut microbiome, which is heavily implicated in the pathogenesis of gastrointestinal inflammation [5]. The gut microbiome is a diverse environment of microorganisms that plays a significant role in maintaining intestinal homeostasis by promoting the proliferation of beneficial microorganisms and deterring the proliferation of harmful ones [26]. Studies on the topic of gut microbial diversity in those with intestinal inflammation have observed major shifts in microbial populations when compared to those of healthy individuals, and this state of dysbiosis is a finding commonly observed in IBD patients [27]. For example, specific species *Proteobacteria* have even been identified as organisms that thrive in these inflammatory states, while beneficial organisms of the *Bacteroidetes* species, which are abundant in healthy intestinal populations, are scarce [28-30]. Vitamin D has been suggested as a moderator of the gut microbiome in IBD, as studies have shown increases in *Bacteroides* species and *Enterobacteriaceae*, both of which are associated with decreased IBD disease activity [8,31]. Dysregulation of the gut microbiome is implicated in the etiopathogenesis of IMC. Fecal microbiota transplants have also been studied to improve outcomes in IMC through intestinal microbiome modulation [32,33]. Similarly, the gut microbial regulatory effects of vitamin D may exert a beneficial outcome on IMC and need to be explored in detail.

This study had several limitations. First, its retrospective, single-center design introduced potential selection bias and limited generalizability. Vitamin D levels were measured within a period of 6 months before and after ICI initiation, which may not reflect long-term vitamin D status and could lead to misclassification of vitamin D levels. Additionally, we did not assess baseline sun exposure (or factors affecting sun exposure, such as skin pigmentation), dietary intake, or genetic polymorphisms affecting vitamin D metabolism. It should be noted that vitamin D deficiency is typically characterized as vitamin D <20 ng/mL while vitamin D insufficiency is characterized as vitamin D <30 ng/mL. This study used a cutoff of 40 ng/mL to demonstrate the potential benefits of higher baseline levels of vitamin D in this population, but the study is limited in that results from other cutoffs for vitamin D levels are not stated. Endoscopic data were not available for all patients, and the degree of mucosal inflammation may have been

underestimated. Finally, although we observed an association between vitamin D levels and IMC severity, prospective trials are needed to determine whether supplementation can effectively prevent or mitigate IMC in ICI-treated patients.

Future research should include multicenter prospective studies to validate these findings, and should include a larger sample size to further reveal other variables/markers of IMC severity that may be affected by varying vitamin D levels. In addition, the optimal vitamin D threshold for disease regulation and the optimal dose of vitamin D supplementation for prophylactic therapy should be clarified. Without specific guidelines for this population, vitamin D supplementation should follow standard guidelines for treatment of vitamin D deficiency, while prevention of deficiency can be accomplished with daily over-the-counter supplementation.

Another topic of investigation would be to further study the gut microbiome of patients with IMC. By comparing the microbial diversity of those with sufficient and insufficient vitamin D levels, it would be possible to understand the specific microbes that are implicated in the pathogenesis of IMC.

Ultimately, our study shows that there is an association between vitamin D and IMC severity, and our results suggest that there is a role for vitamin D screening and supplementation (if needed) prior to the initiation of ICI therapy. Vitamin D is a safe, easily obtained therapy that has already been shown to be beneficial to patients with malignancy and to patients with IBD. The potential for vitamin D, and other non-IST therapies, to be used to prevent and/or treat IMC is significant, especially given the importance of avoiding immunosuppression in patients receiving ICIs. The goal of all future studies should be to confirm our results and to then implement vitamin D screening and prophylactic supplementation within the management of this patient population.

Summary Box

What is already known:

- Vitamin D is a key modulator of homeostasis in bowel inflammation
- Vitamin D deficiency has been implicated in the pathogenesis of inflammatory bowel disease (IBD)
- There is overlapping immunopathology between IBD and immune-mediated colitis (IMC) suggesting a similar relationship to vitamin D

What the new findings are:

- Patients with vitamin D deficiency experienced more severe IMC
- Patients with vitamin D deficiency and IMC were more likely to require treatment with steroids
- Ultimately, vitamin D may be a protective factor in the development of IMC and severe IMC

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