Original Article

Vitamin D and CRP are associated in hospitalized inflammatory bowel disease (IBD) patients in Shanghai

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Background and Objectives: Patients with inflammatory bowel disease (IBD) are more likely to be confirmed with vitamin D deficiency. However, the association between inflammation and vitamin D remains unclear. The purpose of this study was to evaluate the association between inflammation and vitamin D in hospitalized patients with IBD. **Methods and Study Design:** All the participants were recruited from one teaching hospital from June 2018 to October 2022. Inflammation was evaluated by serum concentration of C-reactive protein (CRP), using an immunoturbidimetric method at admission. We further divided the participants into five groups based on serum CRP levels: <5, 5–9.9, 10–19.9, 20–39.9, and >40mg/L. Serum 25-hydroxy-vitamin D (25-(OH)-D) was assessed by liquid chromatography tandem mass spectrometry. Additional information, including age, sex, body mass index (BMI), IBD (ulcerative colitis vs. Crohn's disease) subtype, was abstracted from medical records. **Results:** This study included 1,989 patients with IBD (average age was 39.4 years, 33.8% of them were women, 1,365 CD and 624 UC patients). The median CRP was 5.49 mg/L (range of quartiles: 1.64~19.5 mg/L) and the prevalence of 25-(OH)-D deficiency was 69.8%. CRP was significantly associated with serum level of 25-(OH)-D. The difference in 25-(OH)-D was -4.28 ng/ml (-5.27 ng/ml, -3.31 ng/ml) between two extremist CRP groups after adjustment of potential covariates (age, sex, BMI, type of IBD, dietary type, season, and lymphocyte count). Subgroup analysis in sex, type of IBD, and age, were similar to the main analysis results. **Conclusions:** There was a negative association between CRP levels and vitamin D in hospitalized patients with IBD.

Key Words: inflammatory bowel disease (IBD), C-reactive protein (CRP), inflammation, vitamin D

INTRODUCTION

Inflammatory bowel disease (IBD) consists of two conditions (Ulcerative colitis, UC and Crohn's disease, CD) that are characterized by chronic inflammation of the gastrointestinal tract.[1] C-reactive protein (CRP) is a biomarker reflecting systemic inflammation, and has been evaluated as a useful marker of IBD activity.[2] Boirivant et al. reported that among patients with CD, elevated CRP levels in the previous year was associated with an increased risk of recurrence in the second year compared to that in patients with normal CRP levels.[3] In a study of 200 Norwegian patients with IBD who were followed for 5 years and the results showed that CRP response was stronger in patients with CD compared to patients with UC, CRP levels increased with the severity of patients with UC at diagnosis.[4]

IBD could result in abnormalities of both absorption and utilization of micronutrients, including vitamin D.[5-7] Previous studies found that the deficiency of vitamin D was prevalence among patients diagnosed with IBD. Low vitamin D, caused by mal-absorption, inadequate dietary intake, and insufficient sunlight exposure,[8,9] would increase the risk of IBD.[7,8,10,11] Pharmacological interventions, including corticosteroids and immunosuppressive drugs could also interfere with vitamin D metabolism and absorption, thereby exacerbating the deficiency.[6] In addition, 25-hydroxyvitamin D [25-(OH)-D] as the active form of vitamin D, is negatively associated with disease activity, regardless of IBD type.[12] Moreover, a longitudinal study demonstrated that low vitamin D was associated with a high incidence and disease severity in IBD.[13] Supplementation with vitamin D has been demonstrated to improve disease activity, quality of life in patients, and

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reduce likelihood of IBD-related complications.[7] A meta-analysis indicated that supplementation with vitamin D considerably reduced the risk of recurrence in patients with CD.[14] Another randomized placebo-controlled trial also proved that daily supplementation of 1200 IU vitamin D could reduce the risk of relapse in 94 patients with CD.[15]

The connection between inflammation and vitamin D remains unclear. A cross-sectional study showed that CRP is one of the useful markers of IBD activity, was inversely associated with serum vitamin D.[2] However, the association was evaluated by correlation without consideration of potential confounding.[16,17] An observational study reported a inversely correlation between serum 25-(OH)-D levels and CRP.[18] One study reported that from mild to moderate to severe inflammation, vitamin D concentration decreased significantly with the increase of CRP concentration.[19] Another two studies reported that CRP in UC patients was associated with vitamin D, but not in CD patients[20,21] while the reverse scenario was found in Germany study.[22] Studies performed in Italy[23] and Switzerland[24] reported CRP was associated with vitamin D by multivariate analysis. However, sample size was small in all above-mentioned studies.

Therefore, we performed the current retrospective study to evaluate the association between inflammation and serum vitamin D levels among 1,989 hospitalized patients with IBD. Inflammation was evaluated by serum level of CRP. We postulated that the increase of CRP level could result in low level of vitamin D.

METHODS

Study participants

All participants in the current study were hospitalized for treatment of IBD who were recruited from Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, from June 2018 to October 2022. In this study, none of the IBD patients used vitamin D dietary supplements. We performed a sequential recruitment as following: Patients with liver disease (n=30), kidney disease (n=18) and cancer (n=24) were excluded. We further excluded individuals with missing (n=634), and those who aged less than 18 years (n=3). Finally, 1,989 adult patients (1,365 cases of CD and 624 cases of UC) with active IBD were included in the study (Figure 1). The protocol (No. LY-2022-057-B) of this study was approved by the Ethical Committee of Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine. As a retrospective study, patients' written consent was waived by the same Ethical Committee.

Serum level of CRP

All measurements in this study were performed in the clinical laboratory of the Ren Ji Hospital. After fasting for at least 8 h, venous blood samples were drawn in the morning and transfused into a vacuum tube containing EDTA. Serum concentration of CRP was measured using an immunoturbidimetric method (PA990 analyzer, Lifotronic Technology, Shenzhen, China). The minimum detectable concentration of CRP was 0.5 mg/L, and the difference between the two groups was 12.5%. All participants were further divided into five groups by CRP levels: <5, 5–9.9, 10–19.9, 20–39.9, and >40 mg/L.[25]

Serum 25-(OH)-D, calcium and phosphate

In this study, serum 25-(OH)-D was the primary outcome while serum level of calcium and phosphorus were secondary outcome. The serum 25-(OH)-D was determined by liquid chromatography tandem mass spectrometry methods and serum concentrations of 25-(OH)-D below

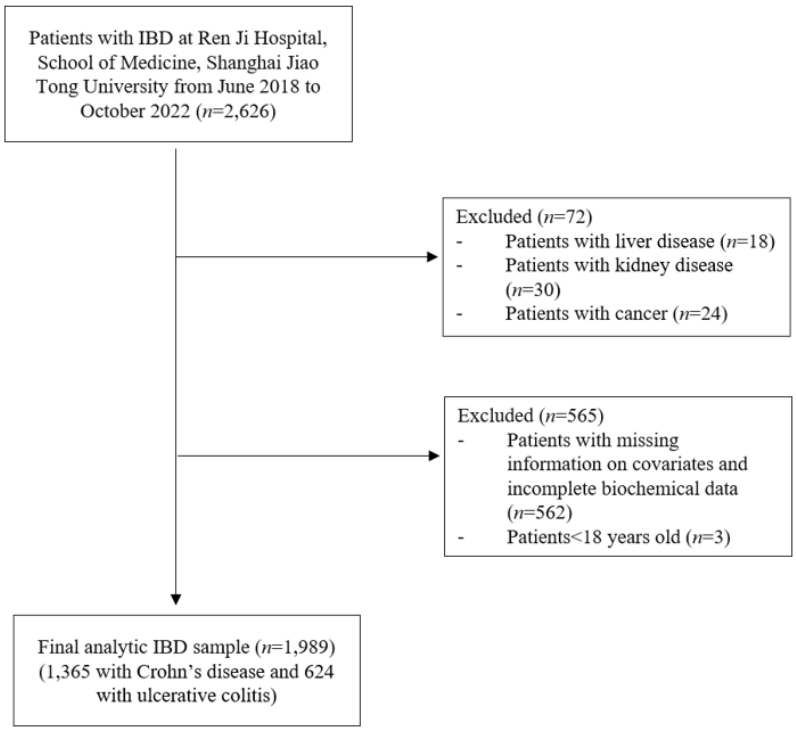


Figure 1. Flowchart of sample recruitment

20ng/ml was defined as low vitamin D level.26 And we also recorded the collection date of serum 25-(OH)-D samples. Serum level of phosphorus and calcium were assessed by chemiluminescent immunoassay method. To avoid the effect of hypoalbuminemia on serum level of calcium, albumin-corrected calcium was applied for further analysis, which was calculated as the following equation: serum total calcium (mmol/L) + 08 x [40-serum albumin(g/L)].[27, 28] Low level of serum calcium and phosphorus were defined as <2.1 mmol/L and <0.81 mmol/L was defined as low level of calcium and phosphorus, respectively.

Other information

Blood samples were prepared according to the above methods. Alanine transferase (ALT), alkaline phosphatase (ALP), glutamyltransferase (GGT), and total bilirubin (TBIL), were assayed by enzyme-linked immunosorbent method. The estimated glomerular filtration rate (eGFR) was calculated from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. All the biochemical markers were measured at admission of IBD patients. Body weight and height were measured by trained nurses upon admission. BMI was calculated by dividing weight (kg) by the square of height (m^2). Age, sex, primary diagnosis, and the history of chronic disease, diet intake, and surgery were abstracted from medical records.

Statistical analysis

All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). The chi-square test was performed to compare the type of IBD in the different CRP groups. Body mass index (BMI), liver and kidney function, and the plasma calcium, 25-(OH)-D, and phosphorus levels were compared using a Kruskal-Wallis analysis of variance and pairwise Mann-Whitney U test. The least square means (LSMs) and their standard for the different CRP group were calculated; subgroups of IBD type were also analyzed (Supplementary Table 1). We screened for risk factors using a one-way analysis of variance before performing multivariate linear regression. Multiple linear regression analysis was conducted in all participants and subgroups using covariables (age, sex, BMI, type of IBD (CD vs. UC), dietary type, season and lymphocyte count) adjusted for covariates to explore whether there were differences in plasma calcium, 25-(OH)-D, and phosphorus concentrations across CRP groups. Multivariable logistic regression analysis was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between CRP concentrations and risk of low levels of calcium (<2.2mmol/L),[29] phosphorus (<1.1mmol/L),[30] and 25-(OH)-D (<20ng/ml) 26 (Supplementary Table 2). Odds ratios (ORs) and 95% confidence intervals (CIs) between CRP concentration and risk of low calcium were calculated using multivariate logistic regression analysis. To test the robustness of main analysis, we performed four subgroup analysis in different sex (men vs. women), IBD type (UC vs. CD), age (<45y vs. ≥45 y), and in different body weight status (low body weight vs. normal body weight vs. overweight). Consider that serum vitamin D fluctuated in different seasons31, we further performed a sensitivity analysis in different seasons (Spring, Summer, Autumn, and Winter) (Supplementary Table 3). A two-tailed and statistical significance was set at *p*-value <0.05.

RESULTS

In this study the mean age of the patients with IBD was 39.4±14.3 years, 33.8% of them were women, and the median CRP was 5.49 mg/L (interquartile range: 1.64-19.5 mg/L). Age, sex, and IBD type differed significantly among the CRP groups. Compared to the group with the lowest CRP concentrations, BMI, TBIL, calcium, and 25-(OH)-D levels were significantly lower in the highest CRP group (all $p<0.001$). In contrast, ALP, GGT, eGFR and LYC were significantly increased in the highest CRP group (all $p<0.001$). And with the increase of CRP, the days in hospital of patients with IBD were also increased ($p<0.001$) (details were shown in Table 1). Most patients with IBD follow a semi-liquid diet type during their hospital stay (Table 1 and Supplementary Table 4).

The association between CRP and 25-(OH)-D are listed in Table 2. After adjusting for age, sex, BMI, type of IBD, dietary type, season and lymphocyte count, CRP was significantly associated with serum level of 25-(OH)-D (Table 2, model 2). The difference in 25-(OH)-D was -4.28 ng/ml (95% CI: -5.27 ng/ml, -3.31 ng/ml) between two extremist CRP groups (<5mg/L vs. ≥40 mg/L). Similarly, CRP was shown to be associated with the risk of low 25-(OH)-D. The adjusted odd ratio was 10.72 (95% CI: 6.84, 16.81) in CRP level ≥40 mg/L group patients, compared with low level of CRP (<5mg/L) group (Supplementary Table 2). CRP was also associated with serum level of calcium but not with serum level of phosphorus (Supplementary Table 4, model 2).

The results of subgroup analysis are shown in Table 3. The correlation between CRP and 25-(OH)-D was stronger in patients with CD, in older patients (≥45 y), and in patients with overweight (BMI ≥24 kg/m^2), compared to their counterparts. The association was similar in women with that in men. In addition, the highest CRP group (CRP ≥40 mg/L) was showed significant negative association with 25-(OH)-D in different seasons (spring, summer, autumn and winter) ($p<0.001$).

DISCUSSION

Our study analyzed the data on inpatients with IBD from a single central hospital and found that CRP was associated with serum 25-(OH)-D and calcium, but not phosphorus. The strengthen of this study had a large sample size and adjusted for potential confounding factors including age, sex, BMI, type of IBD, dietary type, season, and lymphocyte count.

Vitamin D belongs to a fat-soluble steroid hormone that has immunoregulatory functions in patients with IBD.[32] A higher incidence of vitamin D deficiency has been observed in IBD patients compared to the general population,[33,34] with high rates of deficiency ranging from 22% to 63%.[35] This is similar to our result, the prevalence of 25-(OH)-D deficiency was 69.8% in this study (Supplementary Table 5). However, in one study including 60 patients with IBD, 95% of whom were confirmed have

Table 1. Baseline characteristics in 1,989 adult hospitalized patients with IBD by CRP groups

	CRP (mg/L) groups					*p* value
	CRP<5 1.91±0.05 (n=939)	5≤CRP<10 7.08±0.09 (n=285)	10≤CRP<20 14.5±0.18 (n=280)	20≤CRP<40 28.0±0.36 (n=244)	CRP≥40 73.8±2.27 (n=241)	
Age	40.4±0.5	39.4±0.9	38.1±0.8	37.4±0.9	39.1±1.0	0.0122
Sex, M/F	614/325	190/85	200/80	160/84	143/98	<0.0001
Disease type						
CD	635 (31.93)	207 (10.41)	191 (9.60)	176 (8.82)	156 (7.84)	<0.0001
UC	304 (15.28)	78 (3.92)	89 (4.47)	68 (3.42)	85 (4.27)	
BMI	21.9±0.65	20.8±0.23	20.3±0.19	20.5±0.30	19.5±0.24	<0.0001
ALT (U/L)	19.4±0.55	15.8±0.75	18.9±2.62	12.5±0.59	16.5±1.32	<0.0001
ALP (U/L)	81.7±1.65	83.8±1.58	94.2±9.14	79.6±1.61	92.6±3.20	0.0030
TBIL (μmol/L)	9.46±0.20	7.23±0.24	8.15±0.36	7.14±0.26	7.49±0.24	0.0001
GGT (U/L)	27.1±1.3	24.0±1.3	32.2±4.4	27.4±1.7	38.4±2.9	<0.0001
eGFR (ml/min)	116±0.9	116±1.7	117±2.1	115±2.1	123±2.4	0.0391
LYC ($x10^9$/L)	1.49±0.02	1.35±0.03	1.32±0.03	1.28±0.04	1.26±0.04	<0.0001
Calcium (mmol/L)	1.07±0.004	1.10±0.01	1.12±0.01	1.14±0.01	1.16±0.01	<0.0001
Phosphorus (mmol/L)	1.17±0.01	1.23±0.03	1.21±0.03	1.18±0.03	1.20±0.04	0.0672
25-(OH)-D (ng/ml)	18.3±0.24	16.7±0.41	16.4±0.42	14.1±0.42	12.7±0.41	<0.0001
Days in hospital	7.8±5.9	8.7±5.6	10.3±7.6	13.3±7.8	15.4±8.0	<0.0001
Examine season						
Spring	140 (7.02)	36 (1.8)	53 (2.7)	42 (2.1)	48 (2.5)	<0.061
Summer	310 (15.55)	107 (5.4)	101 (5.1)	79 (4.0)	70 (3.5)	
Autumn	307 (15.4)	73 (3.7)	77 (3.9)	72 (3.6)	69 (3.5)	
Winter	182 (9.1)	69 (3.5)	49 (2.5)	54 (2.8)	51 (2.6)	
Dietary type						
General diet	40 (4.26)	11 (3.86)	12 (4.29)	5 (2.05)	5 (2.07)	<0.002
Semi-solid diet	404 (43.02)	110 (38.60)	145 (51.79)	109 (44.67)	117 (48.55)	
Soft diet	81 (8.63)	24 (8.42)	17 (6.07)	14 (5.74)	19 (7.88)	
Others	414 (44.09)	140 (49.12)	106 (37.86)	116 (47.54)	100 (46.73)	

CD: Crohn's disease; UC: ulcerative colitis; BMI, body mass index; ALT, alanine transferase; ALP, alkaline phosphatase; TBIL, total bilirubin; GGT, glutamyltransferase; eGFR, estimated glomerular filtration rate; LYC, Lymphocyte count.
Chi-square tests for age, gender, disease type, examine season and dietary type; LSM (Lease Square Mean) ± standard by different CRP groups.

Table 2. Multiple linear regression for the association of calcium, phosphorus and vitamin D in different CRP groups

Parameters	Model	CRP (mg/L) groups					*p* trend
		<5 mg/L 1.91±0.05 (n=939)	5≤CRP<10mg/L 7.08±0.09 (n=285)	10≤CRP<20mg/L 14.5±0.18 (n=280)	20≤CRP<40mg/L 28.0±0.36 (n=244)	≥40 mg/L 73.8±2.27 (n=241)	
All subjects							
Concentration of calcium, mmol/L	Model 1	ref.	0.01 (-0.003, 0.03)	-0.01 (-0.03, 0.01)	-0.06 (-0.08, -0.04)	-0.12 (-0.14, -0.10)	<0.0001
	Model 2	ref.	0.02 (-0.002, 0.03)	-0.01 (-0.03, 0.01)	-0.06 (-0.08, -0.04)	-0.12 (-0.14, -0.10)	<0.0001
Concentration of phosphorus, mmol/L	Model 1	ref.	0.05 (-0.01, 0.11)	0.03 (-0.03, 0.09)	-0.01 (-0.07, 0.05)	0.01 (-0.05, 0.08)	0.0782
	Model 2	ref.	0.05 (-0.003, 0.11)	0.03 (-0.03, 0.09)	-0.001 (-0.06, 0.06)	0.02 (-0.04, 0.08)	0.2135
Concentration of 25-(OH)-D, ng/ml	Model 1	ref.	-0.03 (-0.94, 0.89)	-0.24 (-1.17, 0.68)	-2.83 (-3.81, -1.86)	-4.32 (-5.29, -3.34)	<0.0001
	Model 2	ref.	0.03 (-0.88, 0.95)	-0.26 (-1.18, 0.66)	-2.77 (-3.74, -1.79)	-4.28 (-5.27, -3.31)	<0.0001

Model 1: adjustment of age, sex, BMI and type of IBD (CD vs. UC)
Model 2: adjustment of age, sex, BMI, type of IBD (CD vs. UC), dietary types (general diet, semi-solid diet, soft diet, or others), season (spring, summer, autumn, or winter), and lymphocyte count

Table 3. Multiple linear regression (standardized β, 95% CI) results for the association of calcium, vitamin D and phosphorus in different CRP groups: subgroups analysis

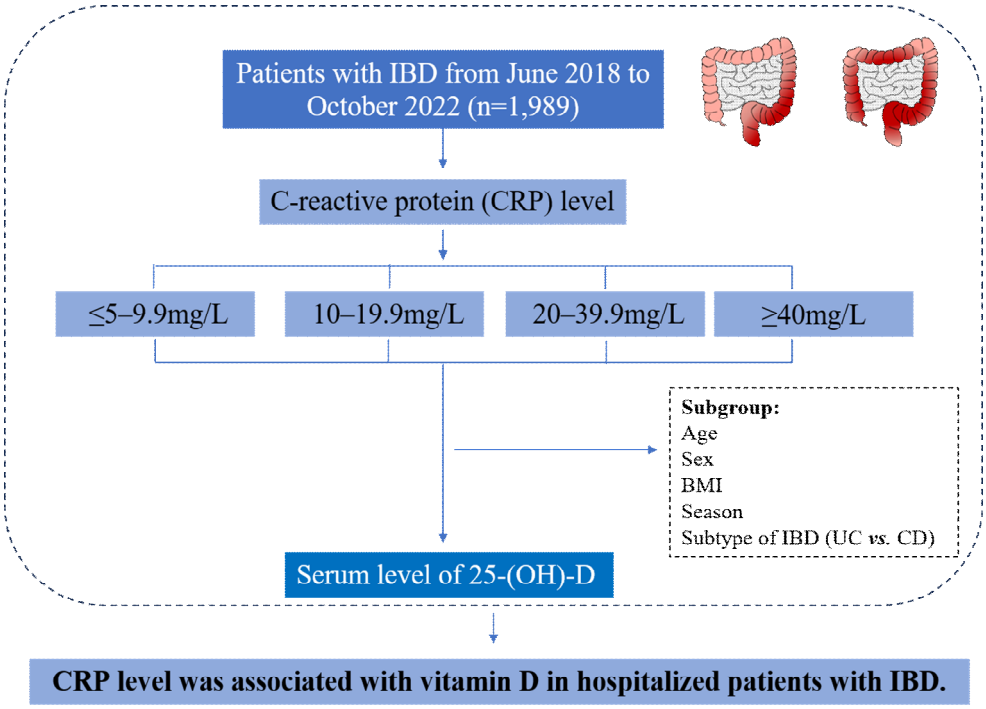
	CRP (mg/L) groups					*p* trend
	<5 mg/L 1.91±0.05 (n=939)	5≤CRP<10mg/L 7.08±0.09 (n=285)	10≤CRP<20mg/L 14.5±0.18 (n=280)	20≤CRP<40mg/L 28.0±0.36 (n=244)	≥40 mg/L 73.8±2.27 (n=241)	
Concentration of calcium, mmol/L						
Male	ref.	-0.01 (-0.02, 0.01)	0.08 (0.01, 0.04)	0.14 (0.03, 0.07)	0.21 (0.06, 0.10)	<0.0001
Female	ref.	-0.05 (-0.04, 0.01)	0.06 (-0.01, 0.04)	0.13 (0.02, 0.06)	0.16 (0.03, 0.07)	<0.0001
CD	ref.	-0.04 (-0.03, 0.004)	0.08 (0.10, 0.04)	0.17 (0.04, 0.07)	0.23 (0.06, 0.10)	<0.0001
UC	ref.	0.01 (-0.02, 0.03)	0.04 (-0.01, 0.04)	0.06 (-0.01, 0.05)	0.10 (0.01, 0.06)	<0.0001
Age<45y	ref.	-0.02 (-0.02, 0.01)	0.06 (0.002, 0.04)	0.15 (0.03, 0.07)	0.22 (0.06, 0.09)	<0.0001
≥45y	ref.	-0.03 (-0.01, 0.05)	0.03 (0.02, 0.06)	0.11 (0.01, 0.07)	0.13 (0.02, 0.07)	<0.0001
Low BW	ref.	-0.05 (-0.04, 0.01)	-0.02 (-0.02, 0.03)	0.15 (0.02, 0.06)	0.27 (0.05, 0.09)	<0.0001
Normal BW	ref.	0.005 (-0.02, 0.02)	0.10 (0.01, 0.05)	0.10 (0.02, 0.06)	0.16 (0.04, 0.08)	<0.0001
Overweight	ref.	-0.11 (-0.06, -0.001)	0.11 (0.001, 0.07)	0.21 (0.03, 0.10)	0.07 (-0.02, 0.08)	<0.0001
Concentration of phosphorus, mmol/L						
Male	ref.	0.03 (-0.04, 0.10)	0.02 (-0.06, 0.03)	-0.02 (-0.09, 0.06)	0.12 (0.03, 0.20)	0.0114
Female	ref.	0.08 (-0.005, 0.17)	0.04 (-0.05, 0.14)	0.01 (-0.08, 0.11)	-0.13 (-0.22, -0.04)	0.0539
CD	ref.	0.04 (-0.02, 0.10)	0.06 (-0.10, 0.12)	-0.02 (-0.09, 0.05)	0.03 (-0.04, 0.10)	0.1694
UC	ref.	0.08 (-0.05, 0.20)	-0.04 (-0.15, 0.08)	0.04 (-0.09, 0.17)	-0.006 (-0.13, 0.12)	0.7986
Age<45y	ref.	-0.003 (-0.07, 0.06)	0.02 (-0.04, 0.08)	0.02 (-0.05, 0.09)	0.05 (-0.02, 0.12)	0.3379
≥45y	ref.	0.17 (0.05, 0.28)	0.06 (-0.06, 0.18)	-0.06 (-0.19, 0.07)	-0.05 (-0.07. 0.07)	0.6160
Low BW	ref.	0.02 (-0.06, 0.12)	0.04 (-0.04, 0.13)	-0.07 (-0.15, 0.01)	-0.004 (-0.08, 0.07)	0.5124
Normal BW	ref.	0.02 (-0.06, 0.11)	0.02 (-0.06, 0.11)	0.02 (-0.06, 0.13)	0.03 (-0.05, 0.16)	0.2436
Overweight	ref.	0.13 (0.03, 0.27)	0.01 (-0.12, 0.16)	0.02 (-0.11, 0.17)	-0.07 (-0.32, 0.06)	0.2143

CD, Crohn's disease; UC, ulcerative colitis; BW, body weight.
low BW: BMI<18.5; Normal BW: 18.5≤BMI<24; overweight: BMI≥24
Male, female: adjustment of age, BMI and type of IBD (CD vs. UC); CD, UC: adjustment of age, sex and BMI; age<45, age≥45: adjustment of sex, BMI and type of disease (CD vs. UC); low BW, Normal BW: 18.5≤BMI<24, overweight: BMI≥24: adjustment of age, sex, and type of IBD (CD vs. UC); spring, summer, autumn and winter: adjustment of age, sex, BMI and type of IBD (CD vs. UC).

Table 3. Multiple linear regression (standardized β, 95% CI) results for the association of calcium, vitamin D and phosphorus in different CRP groups: subgroups analysis (cont.)

	CRP (mg/L) groups					*p* trend
	<5 mg/L 1.91±0.05 (n=939)	5≤CRP<10mg/L 7.08±0.09 (n=285)	10≤CRP<20mg/L 14.5±0.18 (n=280)	20≤CRP<40mg/L 28.0±0.36 (n=244)	≥40 mg/L 73.8±2.27 (n=241)	
Concentration of 25-(OH)-D, ng/ml						
Male	ref.	0.60 (-0.54, 1.75)	0.04 (-1.09, 1.16)	-3.35 (-4.58, -2.12)	-4.38 (-5.66, -3.09)	<0.0001
Female	ref.	-1.45 (-2.97, 0.08)	-0.84 (-2.48, 0.80)	-1.83 (-3.44, -0.23)	-4.20 (-5.70, -2.70)	<0.0001
CD	ref.	0.26 (-0.82, 1.34)	0.07 (-1.05, 1.19)	-2.69 (-3.85, -1.54)	-4.63 (-5.83, -3.43)	<0.0001
UC	ref.	-0.97 (-2.69, 0.76)	-0.62 (-2.27, 1.03)	-3.23 (-5.05, -1.41)	-3.33 (-5.02, 1.63)	<0.0001
Age<45y	ref.	-0.06 (-1.13, 1.01)	0.15 (-0.91, 1.20)	-2.70 (-3.80, -1.59)	-4.16 (-5.31, -3.01)	<0.0001
≥45y	ref.	-0.04 (-1.76, 1.69)	-1.10 (-2.93, 0.73)	-3.21 (-5.17, -1.25)	-4.63 (-6.46, -2.80)	<0.0001
Low BW	ref.	0.02 (-1.42, 2.23)	-0.01 (-1.50, 2.01)	-0.13 (-4.44, -1.10)	-2.21 (-5.58, -2.55)	<0.0001
Normal BW	ref.	-0.01 (-1.33, 1.04)	-0.02 (-1.59, 0.79)	-0.10 (-3.88, -1.19)	-0.17 (-5.44, -2.67)	<0.0001
Overweight	ref.	-0.01 (-2.54, 2.03)	-0.02 (-3.17, 1.93)	-0.14 (-6.07, -0.90)	-0.18 (-9.51, -2.63)	<0.0001
Spring	ref.	0.13 (-0.08, 5.01)	-0.04 (-2.63, 1.25)	-0.21 (-6.42, -2.07)	-0.14 (-4.63, -0.55)	<0.0001
Summer	ref.	-0.001 (-1.49, 1.44)	-0.001 (-1.52, 1.50)	-0.14 (-5.00, -1.61)	-0.19 (-6.28, -2.80)	<0.0001
Autumn	ref.	-0.06 (-3.11, 0.48)	-0.04 (-2.66, 0.87)	-0.07 (-3.43, 0.20)	-0.21 (-6.64, -3.04)	<0.0001
Winter	ref.	0.01 (-1.58, 2.08)	0.03 (-1.55, 2.68)	-0.09 (-3.85, 0.17)	-0.19 (-6.29, -2.08)	<0.0001

CD, Crohn's disease; UC, ulcerative colitis; BW, body weight.
low BW: BMI<18.5; Normal BW: 18.5≤BMI<24; overweight: BMI≥24
Male, female: adjustment of age, BMI and type of IBD (CD vs. UC); CD, UC: adjustment of age, sex and BMI; age<45, age≥45: adjustment of sex, BMI and type of disease (CD vs. UC); low BW, Normal BW: 18.5≤BMI<24, overweight: BMI≥24: adjustment of age, sex, and type of IBD (CD vs. UC); spring, summer, autumn and winter: adjustment of age, sex, BMI and type of IBD (CD vs. UC).



Graphical abstract

vitamin D deficiency.[36] In a retrospective cohort study of United States, about 50% patients with IBD (n=504) were deficient in vitamin D and 10.9% were severely deficient (25-(OH)-D is 10 ng/mL). Vitamin D deficiency depends on a variety of factors, such as study location and season of measurement.[37] We analyzed serum 25-(OH)-D samples collected from patients with IBD in this study by different seasons (spring, summer, autumn, and winter), it showed that 25-(OH)-D collected in summer were significantly higher than in other three seasons (Supplementary Table 3). This may be related to the amount of sunlight exposure that IBD patients get in the summer, however it still showed low levels of 25-(OH)-D (<20ng/ml). Otherwise, in a cohort of 79,719 individuals in the Nurses' Health Study, women with the highest vitamin D had a significantly lower risk of developing CD.34 Older adults were diagnosed with IBD is a clinical predictor of lower vitamin D. Vitamin D deficiency has been found in both CD and UC.37 Similar results were found in our subgroup analysis of age (<45y vs. ≥45 y) and IBD type (UC vs. CD). These results may be influenced by seasonal variations in vitamin D levels, meanwhile, may be associated with elevated CRP concentrations, chronic disease, differences in baseline CRP levels, gender, age, and supplemental dose of vitamin D.[38]

Several studies have reported the results on the effects of vitamin D supplementation on CRP levels. The cohort study of Framingham Offspring showed that no significant relationship between vitamin D and CRP (n=1,381).[39] A recent meta-analysis using randomized controlled trials reported that vitamin D therapy had a favorable effect on marker inflammation.[40] In a meta-analysis study that included 10 randomized controlled trials, the effect of vitamin D supplementation on CRP was analyzed, and the results showed that vitamin D supplementation can significantly reduce CRP levels by 1.08 mg/L.[41] However, most current studies have focused on the effects of vitamin D on CRP, and conversely, there are few results on the effects of CRP on vitamin D. Our findings indicate that participants with elevated CRP exhibit significantly lower vitamin D levels compared to those with lower CRP. In addition, Bellia, et al. reported that CRP levels in 147 morbidly obese patients ranged from 1.88-4.01 mg/L, and supplementation of vitamin D for one year in overweight and obese participants resulted in a decrease in serum IL-6 concentration and a significant increase in serum CRP concentration.[42] Meanwhile, one study showed that high BMI was positively associated with vitamin D deficiency.[43] There may be a correlation between inflammation, BMI, and vitamin D, which is supported by our results. In the subgroup analysis, our results showed that overweight IBD patients with high levels of CRP showed a more pronounced negative association with vitamin D. We also found that older (≥45 years) or overweight IBD patients had higher CRP levels and a more pronounced association with vitamin D. Ngo et al. studied 253 adults aged 51 to 77 years with an average CRP level of 3.6±4.0 mg/mL and a significant negative correlation between serum vitamin D and CRP levels,[44] which was similar to our result. The mechanism between inflammation and vitamin D might be multifactorial, including the changes in metabolism related enzymes, intestinal calcium absorption and urinary calcium excretion.[19] Furthermore, inflammation can influence the production and availability of vitamin D-binding protein (DBP). Hence, our findings also need to be re-examined in larger randomized controlled trials designed specifically to investigate the association between inflammation levels and vitamin D in the future.

Our study also found that IBD patients with high CRP concentrations showed lower plasma calcium levels, which has rarely been reported. Individuals with IBD often experience diarrhea, which can further affect nutrient absorption and lead to malnutrition. A meta-analysis

of 19 studies has reported inadequate calcium intake in all adults with IBD.[45] Low plasma vitamin D concentrations in IBD patients might be one possible reason for plasma calcium. Meanwhile, it may also be related to the type of diet of the patients, many patients maintain a semi-liquid diet during the hospital stay. Chronic malnutrition can lead to reduced immunity and increased inflammation. Increasing age is related to decreased immunity and increased inflammation, which is why people over 45 years of age in our study showed a higher correlation coefficient than those under 45 years of age. Therefore, more attention should be paid to inflammation levels and micronutrient status in low-weight older populations.

Our study also had some limitations. First, the cross-sectional study design made it impossible to establish casual association between inflammation and vitamin D. Further, the data was from single center, and thus the generalizability is limited. Second, the information of extent or localization of patients with IBD were not collected in the analysis. This information will be collected in future prospective studies. Third, antibiotics and steroids, which were reported to be closely associated with CRP 6 were deficient. A well-designed prospective study is needed to duplicate our results.

Conclusion

CRP was associated with vitamin D and calcium in hospitalized patients with IBD. Micronutrient concentrations of patients, especially vitamin D and calcium should be routinely tested in IBD patients with high CRP.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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Supplementary Table 1. Characteristics of the sample stratified by CRP groups of CD and UC

	CRP (mg/L) groups					*p* value
	CRP<5	5≤CRP<10	10≤CRP<20	20≤CRP<40	CRP≥40	
	1.91±0.05	7.08±0.09	14.5±0.18	28.0±0.36	73.8±2.27	
	(n=939)	(n=285)	(n=280)	(n=244)	(n=241)	
CD (n=1365)						
ALT (U/L)	18.6±0.59	15.6±0.92	19.1±3.74	11.3±0.61	14.7±1.49	<0.0001
ALP (U/L)	80.5±1.27	82.5±1.79	86.6±3.33	80.1±1.95	95.3±4.32	<0.0001
TBIL (μmol/L)	9.62±0.26	7.73±0.26	8.25±0.46	7.19±0.31	7.25±0.29	0.0001
GGT (U/L)	24.3±1.17	23.0±1.33	29.3±3.27	25.4±1.72	39.4±3.67	<0.0001
eGFR (ml/min)	118±1.11	119±1.98	118±1.96	118±2.16	126±3.07	<0.0001
LYC ($x10^9$/L)	1.41±0.02	1.29±0.03	1.23±0.04	1.23±0.04	1.13±0.05	<0.0001
Calcium (mmol/L)	2.16±0.01	2.19±0.01	2.23±0.07	2.25±0.01	2.28±0.01	<0.0001
Phosphorus (mmol/L)	1.16±0.01	1.22±0.03	1.23±0.04	1.17±0.03	1.21±0.04	0.0003
25-(OH)-D (ng/ml)	18.5±0.29	17.16±0.50	16.8±0.51	14.6±0.51	12.8±0.47	<0.0001
UC (n=624)						
ALT (U/L)	20.7±1.16	14.9±1.32	19.1±2.33	15.4±1.35	20.8±2.64	0.0016
ALP (U/L)	84.3±4.76	89.0±3.55	112±28.75	78.0±3.05	85.2±5.03	0.0941
TBIL (μmol/L)	9.08±0.28	7.77±0.58	8.08±0.59	7.07±0.47	7.91±0.46	<0.0001
GGT (U/L)	32.4±3.38	26.9±3.10	39.6±12.20	32.4±4.20	37.0±4.91	0.2730
eGFR (ml/min)	113±1.53	110±3.10	112±3.44	109±5.24	116±4.05	<0.0001
LYC ($x10^9$/L)	1.65±0.04	1.49±0.07	1.53±0.07	1.43±0.09	1.50±0.08	0.0642
Calcium (mmol/L)	2.18±0.01	2.20±0.01	2.21±0.01	2.22±0.02	2.23±0.02	<0.0001
Phosphorus (mmol/L)	1.18±0.02	1.26±0.07	1.17±0.05	1.23±0.06	1.19±0.09	0.8849
25-(OH)-D (ng/ml)	17.7±0.43	15.1±0.66	15.3±0.75	13.0±0.73	13.0±0.80	<0.0001

CD, Crohn's disease; UC, ulcerative colitis; BMI, body mass index; ALT, alanine transferase; ALP, alkaline phosphatase; TBIL, total bilirubin; GGT, glutamyltransferase; eGFR, estimated glomerular filtration rate; LYC, Lymphocyte count. LSM ± standard deviation adjusted by age, sex and BMI.

Supplementary Table 2. Odd ratios (95% CI) for low calcium, 25-(OH)-D and phosphorus according to the different CRP groups

	CRP (mg/L) groups					*p* trend
	<5 mg/L	5≤CRP<10mg/L	10≤CRP<20mg/L	20≤CRP<40mg/L	≥40 mg/L	
	1.91±0.05	7.08±0.09	14.5±0.18	28.0±0.36	73.8±2.27	
	(n=939)	(n=285)	(n=280)	(n=244)	(n=241)	
All subjects						
Number of cases of low calcium	595	152	113	77	48	
Multivariate model	ref.	1.47 (1.12, 1.92)	2.45 (1.86, 3.23)	3.62 (2.66, 4.93)	6.03 (4.25, 8.56)	<.0001
Number of cases of low phosphorus	168	52	51	53	68	
Multivariate model	ref.	1.03 (0.73, 1.47)	1.02 (0.72, 1.46)	1.30 (0.95, 1.92)	1.87 (1.32, 2.64)	0.0010
Number of cases of low 25-(OH)-D	21	8	6	17	27	
Multivariate model	ref.	1.35 (0.59, 3.10)	0.88 (0.34, 2.29)	3.20 (1.63, 6.29)	4.20 (2.16, 8.14)	<.0001

Low calcium: <2.1 mmol/L; low phosphorus: <0.81 mmol/L; low vitamin D: <20 ng/mL

Multivariate model adjustment of age, sex, BMI, type of IBD (CD vs. UC), dietary types (general diet, semi-solid diet, soft diet, or others), season (spring, summer, autumn, or winter), and lymphocyte count.

Supplementary Table 3. 25-(OH)-D (ng/mL) in different seasons

	Spring n=320	Summer n=663	Autumn n=599	Winter n=407	*p* value
25-(OH)-D	14.3±0.37	18.4±0.28	17.7±0.30	13.9±0.35	<0.0001

Supplementary Table 2. Dietary type and biochemical examination season of patients with IBD during hospitalization by CRP groups (n, %)

	CRP (mg/L) groups					Total (n=1,989)
	CRP<5 (n=939)	5≤CRP<10 (n=285)	10≤CRP<20 (n=280)	20≤CRP<40 (n=244)	CRP≥40 (n=241)	
Dietary type						
General diet	40 (4.26)	11 (3.86)	12 (4.29)	5 (2.05)	5 (2.07)	73 (3.67)
Semi-liquid diet	404 (43.0)	110 (38.6)	145 (51.8)	109 (44.7)	117 (48.6)	885 (44.5)
Soft diet	81 (8.63)	24 (8.42)	17 (6.07)	14 (5.74)	19 (7.88)	155 (7.79)
Others	414 (44.1)	140 (49.1)	106 (37.9)	116 (47.5)	100 (46.7)	876 (44.0)
Season						
Spring	140 (7.02)	36 (1.8)	53 (2.7)	42 (2.1)	48 (2.5)	319 (16.1)
Summer	310 (15.6)	107 (5.4)	101 (5.1)	79 (4.0)	70 (3.5)	667 (33.5)
Autumn	307 (15.4)	73 (3.7)	77 (3.9)	72 (3.6)	69 (3.5)	598 (30.0)
Winter	182 (9.1)	69 (3.5)	49 (2.5)	54 (2.8)	51 (2.6)	405 (20.4)

Supplementary Table 5. Deficiency of serum calcium, phosphorus and 25-(OH)-D

	Standard range	Deficiency rate (n, %)
Calcium	2.2-2.7 mmol/L	985 (49.5)
Phosphorus	1.1-1.5 mmol/L	418 (21.0)
25-(OH)-D	20-50 ng/mL	1389 (69.8)