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# Association of vitamin D and platelet-to-lymphocyte ratio in treatment escalation risk for newly diagnosed Crohn's disease adults

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## Abstract

**Background** Accumulating research has implicated that vitamin D (VD) may be important in the pathogenesis of Crohn's disease (CD), while the platelet-to-lymphocyte ratio (PLR) is emerging as a biomarker in immune disorders. However, the synergistic effect of VD and PLR on treatment escalation in newly diagnosed CD patients remains unclear. Therefore, this study aims to assess the interaction between PLR and VD on the subsequent use of infliximab and/or immunosuppressants in patients with CD.

**Methods** Newly diagnosed CD patients were selected from the Sir Run Run Shaw Hospital Inflammatory Bowel Disease Biobank (SRRSH-IBC). COX proportional hazards models were employed to assess the association between VD, PLR, and treatment escalation among CD patients.

**Results** Among 108 newly diagnosed CD adult patients, vitamin D deficiency (VDD) was prevalent (78.7%). Compared to CD patients without VDD, those with VDD exhibited a higher risk of treatment escalation, i.e., using infliximab and/or immunosuppressants (HR = 3.22, 95% CI = 1.24–8.35, $P = 0.016$). There is a clear trend of decreasing risk of treatment escalation as VD levels elevating (HR = 0.26, 95% CI = 0.09–0.76, $P$ for trend = 0.014). The stratified analysis revealed a noteworthy interaction between PLR and VD levels concerning treatment escalation. Baseline VDD amplified the risk of treatment escalation among patients with elevated PLR (HR = 4.17, 95% CI = 1.51–11.53, $P_{interaction} = 0.031$). Similar trends were observed when VD levels were stratified into quartiles (highest quartile vs. lowest quartile: HR = 0.18, 95% CI = 0.05–0.62, $P$ for trend = 0.014).

**Conclusion** This study underscores a significant interplay between VD levels and PLR in influencing treatment outcomes in CD. VDD exacerbates the risk of treatment escalation primarily in individuals with heightened PLR levels, highlighting the combined impact of vitamin D status and inflammation on disease progression of CD.

**Keywords** Vitamin D status, Crohn's disease, Platelet-to-lymphocyte ratio, Interplay, Treatment escalation, Inflammation biomarkers

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## Introduction

Inflammatory bowel disease (IBD) is a chronic, recurrent, and lifelong gastrointestinal inflammatory disease that includes mainly two subtypes: Crohn's disease (CD) and ulcerative colitis (UC). IBD is a global disease. While Western populations exhibit IBD prevalence rates approaching 0.5% [1, 2], newly industrialized Asian nations like China demonstrate an accelerating disease burden, with age-standardized prevalence doubling from 25 to 50 per 100,000 within a decade. In previous research, our team predicted that the age-standardized incidence of IBD in China will rise further until a plateau around 2030 with a consistently decreasing age-standardized death rate, bringing China into the Compounding Prevalence stage of IBD [3].

Although the etiology of CD remains unknown, the pathogenesis involves a complex interplay between genetic, environmental, microbiota, and immunological factors. Vitamin D (VD), as a crucial environmental factor, has been suggested to play a role in the pathogenesis of IBD and other immune-mediated diseases [4]. Over 50% of IBD patients exhibit vitamin D deficiency (VDD) [5]. Multiple pathways link VD status with the clinical course of CD, a clinically significant modifier influencing disease relapse rates [6–8], mucosal integrity [9], and therapeutic responses [10]. Mechanistically, VD exerts immunomodulatory effects through maintenance of intestinal epithelial barrier function and suppression of pathogenic inflammatory cascades. Notably, Schäffler et al. demonstrated bidirectional modulation between anti-TNF-α therapy efficacy and VD status in CD management [10], underscoring its therapeutic relevance.

Interactions between blood cells are essential in the pathophysiology of inflammation and immune responses. Neutrophils, lymphocytes, and platelets play roles in regulating inflammation. Previous studies have indicated that platelets and leukocytes may play a pathogenic role in CD, with platelet-leukocyte aggregation contributing to the inflammatory process of CD [11, 12]. The platelet-to-lymphocyte ratio (PLR) has emerged as a robust inflammation biomarker across multiple pathologies — including acute kidney injury, malignancies [13–15], and IBD [16] — offering unique clinical advantages: non-invasive assessment, cost-effectiveness, and stability against diurnal physiological variations. IBD studies demonstrate significant correlations between PLR elevation and inflammatory cytokine levels, effectively mirroring CD disease activity [17, 18]. This investigation systematically evaluates the interplay between baseline VD status and PLR dynamics in predicting therapeutic outcomes among treatment-naïve CD adults.

## Materials and methods

### Participants

All participants were selected from the Sir Run Run Shaw Hospital Inflammatory Bowel Disease Biobank in China (SRRSH-IBC). SRRSH-IBC is a large, ongoing cohort that aims to enroll and follow IBD patients every 3 to 6 months who were diagnosed and treated at SRRSH.

Patient information from admission records between 1999 and 2020 was retrospectively collected and verified by experienced IBD clinicians before being entered into the SRRSH-IBC database. Starting in 2020, SRRSH-IBC began prospectively recruiting IBD patients during their visits to the hospital. All patients are followed up prospectively at intervals of every 3 to 6 months. By the end of June 2024, a total of 10,690 IBD patients had been enrolled in SRRSH-IBC. A comprehensive range of data on demographic and disease characteristics were collected at baseline, including sex, age at symptom onset, age at diagnosis, family history of IBD, history of medical and surgical treatment prior to diagnosis, disease location, disease behavior, perianal involvement, extra-intestinal manifestations (EIMs), pathology reports, endoscopy findings, radiological features, and lifestyle information. Biological samples such as blood, stool, and biopsied tissues were also collected at baseline and at various follow-up time points.

Eligible patients were those aged 18 years or older, newly diagnosed with CD between January 1, 1999, and December 31, 2019, according to the Chinese consensus on diagnosis [19]. Exclusion criteria included (a) uncertain or revised diagnoses during follow-up and (b) diagnosis of CD before the age of 18. All patients were followed up until their most recent hospital visit, or until December 31, 2020, whichever came first. A detailed description of this cohort has been previously published [20].

### Variable definitions

The diagnosis of CD was established based on a combination of clinical judgment and endoscopic, radiological, and histopathological criteria. The date of diagnosis corresponded to the patient's first endoscopic or histopathological examination, where findings were consistent with CD. Patients were categorized by smoking status as either "current smokers" (those smoking at the time of diagnosis) or "former smokers" (those who had quit before diagnosis). The classification of EIMs followed the 2016 European Crohn's and Colitis Organisation (ECCO) consensus guidelines [21]. The Charlson Comorbidity Index, a widely used algorithm for assessing disease burden based on the presence of comorbidities, assigns a severity-based weight to each of 19 different conditions to help predict health outcomes and associated risks [22]. Disease location and behavior were classified according

to the Montreal classification [23]. Patients were specifically categorized based on disease location into four groups: ileal (L1), colonic (L2), ileocolonic (L3), and upper gastrointestinal (L4). Regarding disease behavior, they were classified as non-stricturing, non-penetrating (B1), stricturing (B2), or penetrating (B3). Disease activity was assessed using the Crohn's Disease Activity Index (CDAI) score, which was documented in medical records by IBD nurses at the time of the patients' initial CD diagnosis [24]. Treatment approaches for CD in China are consistent with those employed in Western countries. Patients were categorized as either "users" or "non-users" of 5-aminosalicylic acid (5-ASA), corticosteroids, thiopurines, or infliximab (IFX) based on their medical records since diagnosis. CD-related hospitalization was defined as the need for inpatient care due to relevant symptoms or surgeries, excluding hospital admissions for routine endoscopy surveillance or standard medication prescriptions. CD-related surgery was characterized as small or large bowel resections necessitated by inflammation or complications, including stenosis, fistula formation, perforation, bleeding, carcinogenesis, drug-resistant complications, drainage of intra-abdominal abscesses or fistulas, and perianal surgical interventions. Phenotype progression was defined in patients if: (1) intestinal strictures (B2) developed in individuals with an inflammatory phenotype (B1), or (2) internal fistulas or abscesses (B3) formed in those with either an inflammatory (B1) or stricturing phenotype (B2), as determined through endoscopic, radiological, or surgical pathological evaluation.

### Measurement of plasma 25(OH)D and PLR

Baseline complete blood count and plasma 25-hydroxyvitamin D (25(OH)D) concentrations were quantified using blood samples collected at diagnosis prior to therapeutic interventions. Absolute platelet count and lymphocyte count were automatically analyzed by the automatic hematology analyzer and blood cell counter (XE-2100, Sysmex). PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. PLR was expressed as a unitless ratio. Plasma 25(OH)D analysis was performed via liquid chromatography tandem-mass spectrometry (LC-MS; instruments: ACQUITY UPLC-TQD [Waters Corporation] or API 3200MD™ [Sciex]). Total 25(OH)D levels (ng/mL) were calculated as the sum of $25(OH)D_3$ and $25(OH)D_2$, with VDD defined as concentrations < 20 ng/mL [25].

### Statistical analyses

Continuous variables were expressed as mean values with corresponding standard deviations (SD), while categorical variables were represented as counts with percentages. For comparisons between continuous variables, either the *t*-test or Mann-Whitney U test was utilized, depending on the distribution. Comparisons between categorical variables were made using the $\chi^2$ test or Fisher's exact test, where applicable. To assess the associations between VD, PLR, and treatment escalation among CD patients, multivariate Cox regression analyses were conducted. Survival curves corresponding to these analyses were plotted, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. A two-tailed *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using R software, version 4.3.0. Packages "survival" and "survminer" in R were used to conduct the analyses and visualization.

### Ethical considerations

The study protocol was approved by the ethical review committee of the Sir Run Run Shaw Hospital, School of Medicine Zhejiang University (20210330-42).

## Results

### Baseline characteristics

A total of 108 patients with newly diagnosed CD were included in this study, comprising 71 females and 37 males. Baseline characteristics of patients are given in Table 1. In CD patients with or without VDD, there was no statistically significant difference in sex, age, BMI, region, occupation, smoking status, season of VD measurement, disease behavior, disease location, CDAI, EIMs, and history of perianal surgery.

### Association between vitamin D levels and medication escalation in patients with Crohn's disease

During the follow-up, 8 CD patients without VDD (34.38%) and 46 CD patients with VDD (54.12%) were changing or escalating treatment to infliximab and/or immunosuppressants (Table 2). Our analysis revealed that the risk of subsequent treatment escalation had significantly increased in CD patients with VDD (HR = 3.22, 95% CI = 1.24–8.35) after adjusting for 12 baseline factors, including sex, age, BMI, region, occupation, smoking status, season of VD measurement, disease behavior, disease location, CDAI, EIMs, and history of perianal surgery (Fig. 1A).

The patients were divided into four quartiles based on their varying VD levels, with 17 (63%), 15 (53.6%), 12 (46.2%), and 10 (37%) CD patients in each group eventually using infliximab and/or immunosuppressants. Compared to the first quartiles, the probability of CD patients using infliximab and/or immunosuppressants significantly increased in the fourth quartile and there is a progressive increase in the risk of using infliximab and/or immunosuppressants as VD levels decreased in CD patients (HR = 0.26, 95% CI = 0.09–0.76, *P* for trend = 0.014), indicating an increased likelihood of

**Table 1** Baseline characteristics of CD patients ($n = 108$)

| Variables | Non-Vitamin D Deficiency | Vitamin D Deficiency | *P*-value |
|---|---|---|---|
| | (*N* = 23) | (*N* = 85) | |
| **Sex (*n*, %)** | | | |
| Female | 15 (65.2%) | 56 (65.9%) | 1.000 |
| Male | 8 (34.8%) | 29 (34.1%) | |
| **Age (years)** | | | |
| Mean (SD) | 36.5 (15.5) | 32.8 (12.4) | 0.295 |
| **BMI (kg/m$^2$)** | | | |
| < 18.5 | 12 (52.2%) | 52 (61.2%) | 0.468 |
| 18.5 ~ 23.9 | 10 (43.5%) | 26 (30.6%) | |
| 24 ~ 27.9 | 1 (4.3%) | 7 (8.2%) | |
| **Region (n, %)** | | | |
| Urban | 11 (47.8%) | 36 (42.4%) | 0.816 |
| Rural | 12 (52.2%) | 49 (57.6%) | |
| **Occupation (n, %)** | | | |
| Unemployeed | 7 (30.4%) | 20 (23.5%) | 0.716 |
| Employeed | 13 (56.5%) | 45 (52.9%) | |
| Student | 2 (8.7%) | 12 (14.1%) | |
| Retired | 1 (4.3%) | 8 (9.4%) | |
| **Smoking status (n, %)** | | | |
| Current smoker | 2 (8.7%) | 10 (11.8%) | 0.907 |
| Former smoker | 2 (8.7%) | 8 (9.4%) | |
| Non-smoker | 19 (82.6%) | 67 (78.8%) | |
| **Season of Vitamin D measurement (n, %)** | | | |
| Spring | 3 (13.0%) | 20 (23.5%) | 0.062 |
| Summer | 11 (47.8%) | 18 (21.2%) | |
| Fall | 7 (30.4%) | 29 (34.1%) | |
| Winter | 2 (8.7%) | 18 (21.2%) | |
| **Disease behavior (n, %)** | | | |
| B1-inflammatory disease | 4 (17.4%) | 28 (32.9%) | 0.107 |
| B2-stricturing disease | 12 (52.2%) | 25 (29.4%) | |
| B3-penetrating disease | 7 (30.4%) | 32 (37.6%) | |
| **Disease location (n, %)** | | | |
| L1—ileal location | 7 (30.4%) | 35 (41.2%) | 0.686 |
| L2—colon location | 0 (0%) | 1 (1.2%) | |
| L3—ileocolon location | 15 (65.2%) | 44 (51.8%) | |
| L4—including upper GI location | 1 (4.3%) | 5 (5.9%) | |
| **Disease activity (CDAI) (n, %)** | | | |
| Remission | 1 (4.3%) | 6 (7.1%) | 0.329 |
| Mild | 3 (13.0%) | 11 (12.9%) | |
| Moderate | 19 (82.6%) | 58 (68.2%) | |
| Severe | 0 (0%) | 10 (11.8%) | |
| **Extraintestinal manifestation (n, %)** | | | |
| No | 18 (78.3%) | 67 (78.8%) | 1.000 |
| Yes | 5 (21.7%) | 18 (21.2%) | |
| **History of perianal surgery (n, %)** | | | |
| No | 17 (73.9%) | 62 (72.9%) | 1.000 |
| Yes | 6 (26.1%) | 23 (27.1%) | |

BMI, Body Mass Index; CDAI, Crohn's Disease Activity Index

**Table 2** Association of baseline VD deficiency with Infliximab and/or immunosuppressants usage in newly diagnosed CD patients

| VD status | *n* | person- months | Events | Crude model | | Adjusted model* | |
|---|---|---|---|---|---|---|---|
| | | | (%) | HR (95% CI) | *P* | HR (95% CI) | *P* |
| **VD deficiency** | | | | | | | |
| No | 23 | 89 | 8 (34.8) | Ref | — | Ref | — |
| Yes | 85 | 391 | 46 (54.12) | 1.46 (0.69–3.10) | 0.320 | 3.22 (1.24–8.35) | **0.016** |
| **VD levels** | | | | | | | |
| Q1 | 27 | 88 | 17 (63.0) | Ref | — | Ref | — |
| Q2 | 28 | 78 | 15 (53.6) | 1.08 (0.54–2.17) | 0.830 | 0.65 (0.24–1.75) | 0.392 |
| Q3 | 26 | 179 | 12 (46.2) | 0.50 (0.23–1.07) | 0.072 | 0.55 (0.20–1.56) | 0.263 |
| Q4 | 27 | 135 | 10 (37.0) | 0.51 (0.23–1.13) | 0.099 | 0.26 (0.09–0.76) | 0.014 |
| | | | | *P* for trend = **0.031** | | *P* for trend = **0.014** | |

*Adjusted for age of onset, sex, region, smoking, season of vitamin D measurement, disease location, disease behavior, occupation, BMI, CDAI, EIM and history of perianal surgery

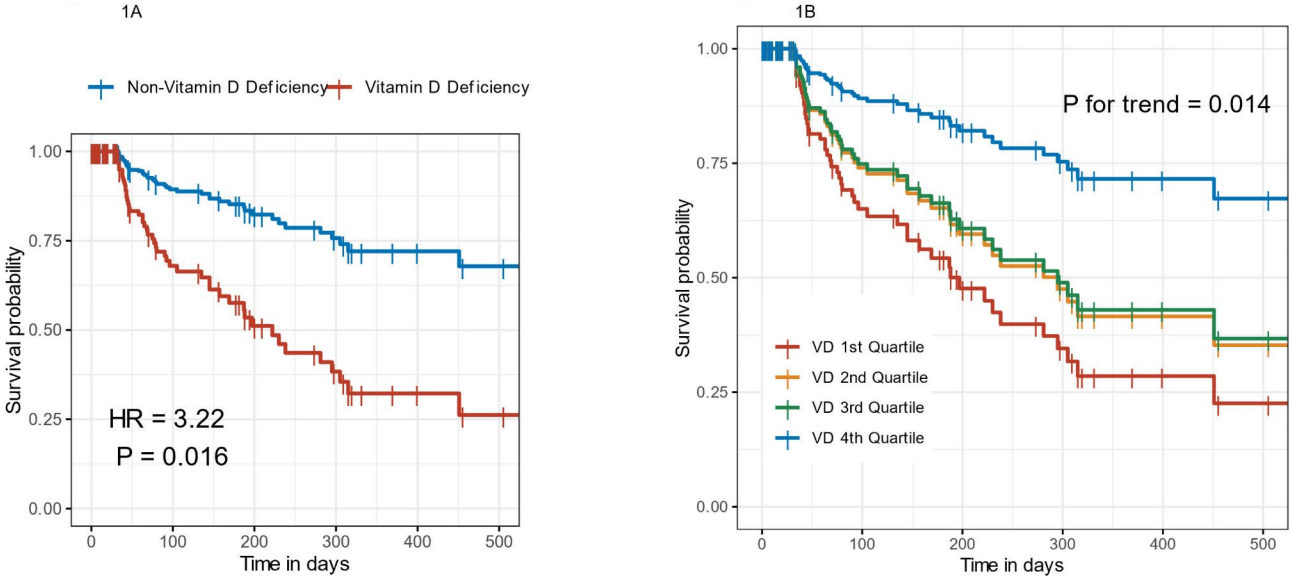


**Fig. 1** Predicted survival curves for drug-free (infliximab and/or immunosuppressant) in newly diagnosed CD patients

treatment escalation in CD patients with low VD levels (Table 2; Fig. 1B).

### Stratified analysis

Since not all patients with VDD ultimately underwent treatment escalation, we suspect a possible interplay between PLR and VD levels in the context of disease progression and treatment response in our cohort of patients with vitamin D deficiency. Thus, stratified analyses were performed based on the PLR. The patients were divided into four quartiles based on their varying PLR levels. Among patients with high baseline PLR levels, infliximab and/or immunosuppressants were required for 7 patients (36.8%) without VDD and 41 patients (61.2%) with VDD. Baseline VDD amplified the risk of treatment escalation particularly among patients with elevated PLR (HR = 4.17, 95%CI = 1.51–11.53, $P_{interaction}$ = 0.031) (Table 3; Fig. 2A). However, this difference was not observed in patients with low baseline PLR levels.

Further categorizing patients into four quartiles based on their VD levels. In the first PLR quartile, there are no significant differences among the four quartiles of VD levels. Among patients with high PLR, however, a trend of increasing risk for treatment escalation in CD patients with low VD levels was observed (highest quartile vs. lowest quartile: HR = 0.18, 95% CI = 0.05–0.62, *P* for trend = 0.014) (Table 4; Fig. 2B).

## Discussion

In this study, we observed an increased likelihood of subsequent use of infliximab and/or immunosuppressants among CD patients with VDD. However, this trend was only identified in patients with high levels of PLR. Conversely, no correlation between VD levels and subsequent treatment escalation emerged in CD patients with low PLR levels.

Associations between CD and VDD have been well-established for a number of years. It is commonly

**Table 3** Interaction between platelet-to-lymphocyte ratio and baseline VD deficiency on Infliximab and/or immunosuppressants usage in newly diagnosed CD patients

| VD deficiency | *n* | person- months | Events (%) | Crude model HR (95% CI) | *P* | Adjusted model* HR (95% CI) | *P* |
|---|---|---|---|---|---|---|---|
| **Platelet-to-lymphocyte ratio < Q1** | | | | | | | |
| No | 4 | 10 | 1 (25.0) | Ref | — | Ref | — |
| Yes | 18 | 100 | 5 (27.8) | 1.20 (0.13–10.79) | 0.871 | ns | ns |
| **Platelet-to-lymphocyte ratio ≥ Q1** | | | | | | | |
| No | 19 | 78 | 7 (36.8) | Ref | — | Ref | — |
| Yes | 67 | 292 | 41 (61.2) | 1.64 (0.73–3.65) | 0.230 | 4.17 (1.51–11.53) | **0.006** |
| | | | | $P^{a}_{interaction}$ = **0.943** | | $P^{a}_{interaction}$ = **0.031** | |

*Adjusted for age of onset, sex, region, smoking, season of vitamin D measurement, disease location, disease behavior, occupation, BMI, CDAI, EIM and history of perianal surgery

[a]*P* value of the interaction between platelet-to-lymphocyte ratio and VD deficiency

ns: non-significant

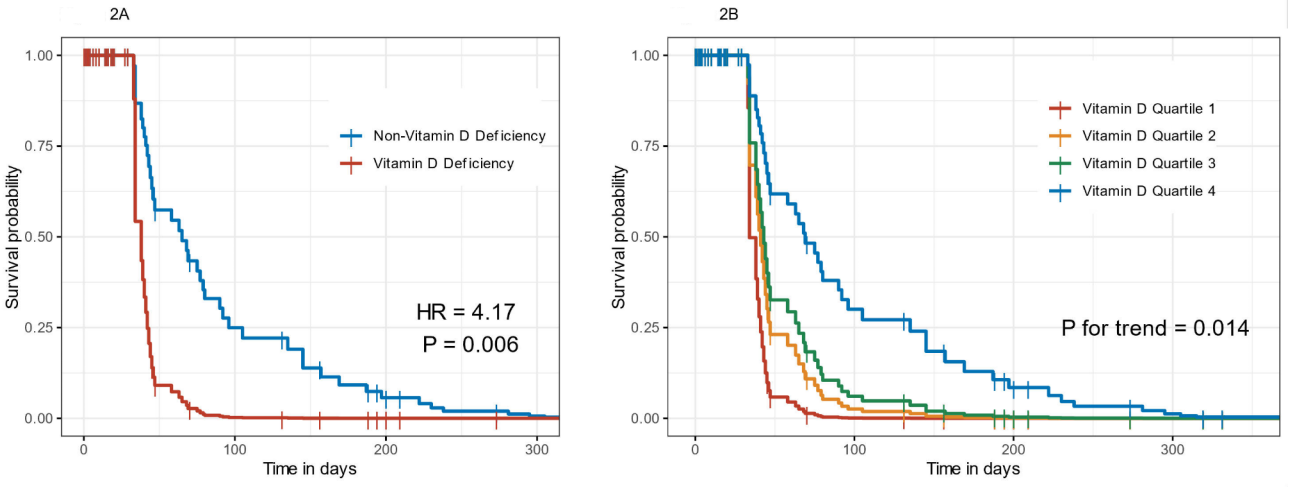


**Fig. 2** Predicted survival curves for drug-free (infliximab and/or immunosuppressant) in newly diagnosed CD patients with an elevated platelet-to-lymphocyte ratio

**Table 4** Interaction between platelet-to-lymphocyte ratio and baseline VD levels on Infliximab and/or immunosuppressants usage in newly diagnosed CD patients

| VD deficiency | *n* | person- months | Events (%) | Crude model HR (95% CI) | *P* | Adjusted model* HR (95% CI) | *P* |
|---|---|---|---|---|---|---|---|
| **Platelet-to-lymphocyte ratio < Q1** | | | | | | | |
| Q1 | 2 | 6 | 1 (50.0) | Ref | — | Ref | — |
| Q2 | 5 | 19 | 0 (0) | ns | ns | ns | ns |
| Q3 | 10 | 40 | 4 (40.0) | 0.89 (0.10–8.03) | 0.915 | ns | ns |
| Q4 | 5 | 46 | 1 (20.0) | 0.33 (0.02–5.35) | 0.432 | ns | ns |
| **Platelet-to-lymphocyte ratio ≥ Q1** | | | | | | | |
| Q1 | 25 | 82 | 16 (64.0) | Ref | — | Ref | — |
| Q2 | 23 | 59 | 15 (65.2) | 1.39 (0.68–2.82) | 0.364 | 0.56 (0.17–1.81) | 0.332 |
| Q3 | 16 | 140 | 8 (50.0) | 0.42 (0.17–1.01) | 0.053 | 0.41 (0.10–1.66) | 0.214 |
| Q4 | 22 | 89 | 9 (40.9) | 0.57 (0.25–1.30) | 0.180 | 0.18 (0.05–0.62) | **0.006** |
| | | | | *P* for trend = **0.045** | | *P* for trend = **0.014** | |
| | | | | $P^{a}_{interaction}$ = 0.750 | | $P^{a}_{interaction}$ = **0.039** | |

*Adjusted for age of onset, sex, region, smoking, season of vitamin D measurement, disease location, disease behavior, occupation, BMI, CDAI, EIM and history of perianal surgery

[a]*P* value of the interaction between platelet-to-lymphocyte ratio and quartiles of VD levels

ns: non-significant

hypothesized that VDD in newly diagnosed CD patients may result from malabsorption and reduced physical activity due to active disease prior to clinical presentation, particularly among those residing in high-latitude regions [26]. Notably, contemporary research paradigms now posit VDD not merely as a clinical consequence, but potentially as a contributory factor in CD pathogenesis through immunomodulatory mechanisms [27].

VD levels are intimately linked with IBD disease activity, including relapses, postoperative recurrence, and efficacy of drug therapy. John Gubatan et al. reported that low $25(OH)D_3$ levels correlate with elevated risks of clinically active CD (pooled OR = 1.66, 95% CI = 1.36–2.02) and disease relapse (pooled OR = 1.35, 95% CI = 1.14–1.59) in CD [8]. VD or vitamin D receptor (VDR) deficiency resulted in severe inflammation of the gastrointestinal tract in animal models of IBD [28, 29]. Notably, CD patients receiving VD supplementation during remission exhibited substantially lower relapse rates (6/46, 13%) compared to placebo controls (14/48, 29%) [30]. A 5-year cohort study of 965 IBD patients by Kabbani et al. further established that VD-deficient individuals required more frequent biological agents, steroids, and analgesics [31]. Consequently, VD therapy may alleviate intestinal inflammatory responses in CD patients, reducing the use of induction-to-remission medications such as corticosteroids and anti-TNF-α therapies. Our data corroborate this pattern, showing higher baseline VDD prevalence (54% vs. 34.8%) among patients eventually requiring infliximab and/or immunosuppressants. In terms of drug efficacy, a single-center observational study demonstrated that low plasma 25(OH)D levels are associated with the discontinuation of anti-TNF-α therapy due to treatment failure, which is more pronounced in CD (HR = 2.38, 95% CI = 0.95–5.99), than UC (HR = 5.84, 95% CI = 0.69–49.62) [32]. This phenomenon may be linked to the synergistic inhibition of peripheral blood mononuclear cell proliferation in CD patients by VD in conjunction with infliximab.

Immunological investigations have shown that CD is a predominantly Th1- and Th17-mediated process, and the Th1 cytokine TNF-α serves as a critical mediator of inflammation in CD patients. Anti-TNF-α agents have proven clinically effective in CD management. Mechanistically, the TNF-α pathway is central to the development of IBD in LI-10 KO mice and serves as a significant target for VD within the body. The VDR binds with the active form of VD, facilitating the transcription of numerous genes involved in immune cell proliferation, cytokine production, and lymphocyte activation. $1,25-(OH)_2D_3$ plays a role in the response to anti-TNF-α therapy by suppressing TNF-α-associated gene expression in colonic tissue [33]. The findings from the above research corroborate the results of this study, indicating a correlation between VD levels and subsequent treatment intensification.

However, only 54% of CD patients with VDD in this study eventually used infliximab and/or immunosuppressants, indicating multifactorial disease progression beyond VDD alone. The interaction between platelets and lymphocytes has been confirmed to reduce pro-inflammatory cytokines [34]. Therefore, this study further explores the potential role of platelets and lymphocytes in CD patients with VDD.

Immune cells such as neutrophils, lymphocytes, and platelets play imperative roles in regulating inflammation and the subsequent changes induced by inflammation. Recent studies have shown that NLR and PLR can serve as predictive indicators of disease activity and complications in CD. These indices demonstrate superior diagnostic performance (sensitivity 75%, specificity 90%) compared to conventional inflammatory markers [17, 35]. Additionally, NLR and PLR are associated with disease activity of CD [16], endoscopic features, and loss of response to biological therapies. Currently, only one study has evaluated the value of NLR during the administration of infliximab in CD patients [36]. The research on predicting the use of infliximab and/or immunosuppressants in CD patients based on PLR remains insufficient, prompting this study to explore VD and PLR as predictive factors for subsequent medication in CD patients.

In this study, 77% of CD patients with higher baseline PLR have VDD, suggesting that PLR-associated bone metabolism abnormalities may stem from chronic inflammation-mediated vitamin D dysregulation. Increased levels of VD can reduce the proliferation of the entire lymphocyte population and CD4 lymphocytes, thus slowing the progression of CD and influencing subsequent medication. Furthermore, VD modulates platelet leukocyte aggregation (PLA) and reduces platelet aggregation by lowering the expression of adhesion molecules required for platelet activation and decreasing the production of pro-inflammatory cytokines [37]. The crosstalk between VD signaling and hematological components (lymphocytes/platelets) critically regulates inflammatory cascades, with pharmacological modulation of these interactions offering therapeutic potential in immune-mediated disorders [38]. Such immune interplay can be quantified through composite biomarkers like PLR.

Our previous study found a significant increase in the use of infliximab and immunosuppressants in Chinese CD patients in the past decades [39], and this study further underscores the interaction between VD levels and PLR that greatly influences treatment outcomes for newly diagnosed adult CD patients. Specifically, VDD exacerbates the risk of treatment escalation primarily in individuals with heightened PLR levels, highlighting the

combined impact of vitamin D status and inflammation on disease progression.

Our study holds several significant implications. Although some research has established a link between VD levels and the clinical course of CD, prior studies have rarely assessed the relationship between VD levels and treatment escalation in CD patients. Moreover, to the best of our knowledge, this is the first research that delves deeper into the interplay between VD levels and PLR concerning treatment escalation in newly diagnosed CD patients. Future larger and prospective studies are warranted to confirm this association and elucidate the underlying mechanisms. We readily acknowledge several limitations to this study. Firstly, it is a single-center study with a relatively small sample size. To accurately estimate the significance of measurement effects and ensure generalizability, larger-scale multicenter studies are needed. Secondly, only baseline measurements of VD and PLR were used; longitudinal variations of these indices may provide more information. Thirdly, only infliximab was assessed as biologic in the study. Future studies should consider a broader range of biologics for a more comprehensive understanding of the role of VD in the progression of CD.

## Conclusions

This study underscores a significant interplay between VD levels and PLR in influencing treatment outcomes in CD patients. Specifically, VDD exacerbates the risk of treatment escalation primarily in individuals with heightened PLR levels, highlighting the combined impact of vitamin D status and inflammation on disease progression.

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Not applicable.

**Author contributions**
Qian Cao and Bule Shao conceived and designed the study. Kan Wang wrote the manuscript. Shichen Zhu wrote the draft, carried out the data analysis and statistical analysis. Lingya Yao designed and draw figures. All authors read and approved the paper.

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**Data availability**
The datasets generated during the current study are not publicly available but obtained from corresponding authors on reasonable requests.

## Declarations

**Ethics approval and consent to participate**
The study protocol was approved by the ethical review committee of the Sir Run Run Shaw Hospital, School of Medicine Zhejiang University (20210330-42).

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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