Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

# A Real-World Study of Upadacitinib in Anti-TNF Refractory Crohn's Disease: Effectiveness, Persistence, and Safety

Yuanyuan Fang, Linlin Zhou, Lingyun Li, Lixue Zhang, Nannan Zhu, Jing Hu, Qiuyuan Liu, Juan Wu, Peipei Zhang, Qiao Mei, Wei Han

Department of Gastroenterology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230022, People's Republic of China

Correspondence: Wei Han; Qiao Mei, Department of Gastroenterology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230022, People's Republic of China, Email yfy114654@fy.ahmu.edu.cn; meiqiao@ahmu.edu.cn



**Purpose:** Real-world evidence on the effectiveness of upadacitinib in Crohn's disease is increasing; however, data from Chinese populations remain limited. This study aimed to evaluate the real-world effectiveness, persistence, and safety of upadacitinib.

**Methods:** This retrospective study included consecutive patients with Crohn's disease treated with upadacitinib at the First Affiliated Hospital of Anhui Medical University who had at least one follow-up visit. Clinical effectiveness was assessed using the Harvey-Bradshaw Index, and endoscopic effectiveness was evaluated using the Simple Endoscopic Score for Crohn's Disease. Logistic regression analysis was performed to identify factors associated with clinical remission at week 12. Kaplan-Meier analysis and Cox regression analysis were used to evaluate upadacitinib persistence.

**Results:** Total of 108 patients with moderate-to-severe Crohn's disease and prior anti-TNF failure or intolerance were included. The clinical remission rates at weeks 12 and 24 were 55.1% and 52.5%, respectively, whereas the biomarker remission rates were 57.3% and 62.5%, respectively. Endoscopic reassessment was available for 32 patients. Endoscopic response was achieved in 16 patients (50.0%), of whom 8 (25.0%) attained endoscopic remission. Pharmacokinetic data from a small subset of 24 patients showed that higher plasma concentrations of upadacitinib were associated with endoscopic remission ($p = 0.023$). Stricturing Crohn's disease (OR = 0.32, 95% CI: 0.12–0.84, $p = 0.021$) and baseline albumin ≤ 35 g/L (OR = 0.22, 95% CI: 0.07–0.62, $p = 0.006$) were associated with a lower likelihood of clinical remission at week 12. Twenty patients discontinued treatment, and baseline albumin ≤ 35 g/L (HR = 3.05, 95% CI: 1.26–7.36, $p = 0.012$) was associated with an increased risk of discontinuation. A total of 22 (20.3%) patients experienced 23 adverse events.

**Conclusion:** This real-world study demonstrates that upadacitinib is effective, with acceptable safety and favorable treatment persistence, in Chinese patients with moderate-to-severe anti-TNF-refractory Crohn's disease. Future studies with larger sample sizes should focus on long-term effectiveness and safety and provide more comprehensive pharmacokinetic characterization.

**Keywords:** upadacitinib, janus kinase inhibitor, crohn's disease, real-world evidence

## Introduction

Crohn's disease is a chronic, relapsing, immune-mediated inflammatory disorder of the gastrointestinal tract, characterized by alternating periods of remission and recurrence. Despite substantial advances in therapeutic development, the management of moderate-to-severe Crohn's disease remains a major clinical challenge. Currently, pharmacological therapies for Crohn's disease can be categorized into traditional therapeutic agents (corticosteroids and immunomodulators), biologics, and small-molecule agents.[1,2] Among patients treated with anti-TNF agents, approximately one-quarter exhibit primary non-response, and nearly one-third of initial responders lose response within 1 year.[3,4] Moreover, patients who fail anti-TNF therapy often show reduced effectiveness with subsequent anti-interleukin or anti-integrin therapies.[5,6] In addition, the immunosuppressive properties of biologic agents may contribute to adverse events (AEs) and treatment discontinuation, further complicating disease management.

https://doi.org/10.2147/JIR.S591249
Received: 2 January 2026
Accepted: 22 April 2026
Published: 5 May 2026

Upadacitinib is an oral, highly selective Janus kinase 1 (JAK1) inhibitor that plays a pivotal role in cytokine signal transduction.[7,8] Phase 3 clinical trials have shown that upadacitinib significantly improves clinical remission and endoscopic response compared with placebo during both 12-week induction therapy and 52-week maintenance therapy in patients with moderate-to-severe Crohn's disease, including those with prior biologic failure.[9,10] However, patients enrolled in clinical trials are often highly selected and may not fully represent those seen in routine clinical practice, particularly with regard to disease complexity, comorbidities, and prior treatment exposure.

Since its approval by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) in 2023 for the treatment of Crohn's disease,[11] an increasing number of real-world studies, including multicenter and nationwide cohorts, have reported its effectiveness and safety. Despite growing clinical interest in JAK1 inhibition, data from Asian populations remain limited.[12,13] Previous studies have shown that susceptibility genes differ between Asian and Western populations, with variants such as TNFSF15 showing stronger associations in Asians, while classical loci such as NOD2 are less prominent.[14,15] In addition, potential predictors of treatment response, as well as the relationship between drug exposure and endoscopic outcomes, have not been well characterized in routine clinical practice.

Therefore, this study aimed to evaluate the real-world effectiveness, persistence, and safety of upadacitinib in Chinese patients with moderate-to-severe Crohn's disease after anti-TNF failure, and to explore potential factors associated with treatment outcomes, including an exploratory analysis of the association between plasma drug concentrations and endoscopic outcomes.

# Methods

## Study Population

This retrospective observational study was based on real-world clinical data. We consecutively enrolled patients with moderate-to-severe Crohn's disease who initiated upadacitinib treatment at the First Affiliated Hospital of Anhui Medical University between December 2023 and August 2025. The Harvey-Bradshaw Index (HBI) was used to assess clinical disease activity, comprising five domains: general well-being (0–4), abdominal pain (0–3), number of liquid stools per day, abdominal mass (0–3), and complications (1 point each). Moderate-to-severe Crohn's disease was defined as HBI $\geq 8$.[16] Eligible patients were aged 18–75 years, had prior failure or intolerance to anti-TNF therapy, and had at least one follow-up visit after initiation of upadacitinib. Exclusion criteria included incomplete baseline data, concurrent use of other biologic therapies, and history of colostomy or ileostomy. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ 2024–05-64).

## Demographic and Clinical Data

Demographic and clinical characteristics before upadacitinib therapy were recorded as baseline data, including age, sex, smoking status, body mass index (BMI), disease location, disease behavior (as defined by the Montreal classification), surgical history, history of perianal disease, prior exposure to biologics, corticosteroids, and immunomodulators, and extraintestinal manifestations (EIMs). The HBI was used to assess clinical activity, and the Simple Endoscopic Score for Crohn's Disease (SES-CD) was used to assess endoscopic activity. Baseline endoscopy data obtained within 2 months before treatment initiation were also accepted. Use of any biologic agent before the start of upadacitinib was defined as a history of biologic exposure. No specific washout period was required before initiating upadacitinib. Biologics used before upadacitinib initiation were defined as those administered within the 2 months preceding the start of upadacitinib therapy.[17] Laboratory parameters, including C-reactive protein (CRP), fecal calprotectin (FC), hemoglobin (HB), and albumin (ALB), were also assessed at baseline.

During follow-up, HBI scores and laboratory parameters were recorded to evaluate clinical and biomarker effectiveness. Endoscopic evaluation was generally performed 6 months after treatment initiation, although the exact timing depended on the physician's discretion and the patient's preference. During follow-up endoscopy, blood samples were collected 24 hours post-administration of the previous upadacitinib dose to determine plasma concentrations and investigate their association with endoscopic outcomes. Plasma upadacitinib concentrations were measured using

a validated liquid chromatography method with mass spectrometric detection.[18] Upadacitinib persistence was calculated as the time elapsed between the first and last doses of upadacitinib.

## Schedule of Upadacitinib Induction and Maintenance Therapy

In this study, patients routinely received an induction dose of 45 mg once daily, followed by a maintenance dose of 30 mg once daily. However, 4 patients reduced the dose to 30 mg once daily during the induction phase because of decreased fibrinogen levels or rash. Patients who achieved endoscopic remission at follow-up endoscopy were switched to 15 mg once daily, whereas those who did not achieve endoscopic remission continued on 30 mg once daily.

## Outcome Measures

The rates of clinical response and remission at weeks 12 and 24, endoscopic remission and response during follow-up, persistence rate and AEs were assessed. Clinical response was defined as a decrease in HBI of $\geq 3$ points. Clinical remission was defined as HBI $\leq 4$. Endoscopic remission was defined as SES-CD $\leq 2$, and endoscopic response was defined as a 50% reduction in SES-CD from baseline.

Secondary endpoints included short-term clinical effectiveness at weeks 4 and 8, the predictors of clinical remission at week 12, and biomaker effectiveness at weeks 12 and 24. CRP remission was defined as CRP $\leq 5$ mg/L, FC remission as FC $\leq 250$ μg/g, and biomarker remission as CRP $\leq 5$ mg/L combined with FC $\leq 250$ μg/g.[19,20]

For safety assessment, all AEs occurring during treatment were recorded and analyzed. AEs were collected through routine clinical follow-up, including outpatient physician assessments, medical record review, and regular follow-up by telephone or text message conducted by clinical research nurses. Patients who discontinued treatment before the assessment time point, whether because of poor effectiveness or AEs, were considered clinical non-responders at all subsequent time points.

## Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data or as median (interquartile range [IQR]) for non-normally distributed data. Categorical variables were summarized as frequencies and percentages. The chi-squared test or Fisher's exact test was used, as appropriate, to compare categorical variables. For group comparisons, the Wilcoxon rank-sum test or Student's *t* test was applied. Clinical effectiveness was assessed at weeks 4, 8, 12, and 24, and logistic regression analysis was used to identify factors associated with clinical remission at week 12.

Cox proportional hazards regression analysis was performed to identify factors associated with treatment discontinuation. Univariate Cox regression analysis included age, sex, disease duration, BMI, EIMs, perianal disease, prior intestinal surgery, prior medication history, and baseline laboratory parameters. Variables with $p < 0.05$ in univariate analysis were entered into the multivariable model using a forward stepwise method. Kaplan-Meier survival analysis was then used to assess treatment persistence, with discontinuation of upadacitinib for any reason defined as the event. Kaplan-Meier curves were stratified according to variables identified as significant in the Cox regression analysis, and differences between groups were compared using the Log rank test. $P < 0.05$ was considered statistically significant. This study protocol strictly adhered to the guiding principles of the Reporting of Studies Conducted Using Observational Routinely-collected Health Data (RECORD) statement.

# Results

## Patient Characteristics

A total of 108 patients with Crohn's disease received upadacitinib therapy and underwent at least one follow-up visit at the First Affiliated Hospital of Anhui Medical University. All patients were classified as having moderate-to-severe Crohn's disease at baseline and had a history of prior anti-TNF treatment failure or intolerance. All 108 patients were included in the persistence and AE analysis. For the effectiveness analysis, 98 patients were eligible for the 12-week analysis, whereas 10 were excluded because they were still receiving treatment but had not yet reached the 12-week

assessment time point. In contrast, 10 patients who discontinued treatment before week 12 because of lack of effectiveness or AEs were retained in the 12-week effectiveness analysis and classified as non-responders. The same approach was applied to the 24-week effectiveness analysis. Seventy-eight patients were included in the 24-week effectiveness analysis, whereas 20 were excluded because they had not yet reached the 24-week assessment time point. In addition, 46 patients were excluded from the endoscopic effectiveness analysis because follow-up endoscopy was unavailable, leaving 32 patients eligible for endoscopic evaluation. The study workflow is presented in Figure 1.

Baseline characteristics are summarized in Table 1. The median follow-up duration was 6 months (IQR: 3–12). Among the patients, 73 (67.5%) were male, and 34 (31.4%) had a BMI ≤ 18.5 kg/m$^2$. The median age was 29 years (IQR: 23–34), and the median disease duration was 4 years (IQR: 3–7). According to the Montreal classification, disease location was ileal (L1) in 22 (20.3%) patients, colonic (L2) in 13 (12.0%), and ileocolonic (L3) in 73 (67.5%). Disease behavior was inflammatory (B1) in 62 (57.4%) patients, stricturing (B2) in 33 (30.5%), and penetrating (B3) in 13 (12.0%). In addition, 5 (4.6%) patients were active smokers, 49 (45.3%) had a history of perianal disease, 10 (9.2%) had EIMs, and 10 (9.2%) had a history of intestinal resection.

Prior treatments were also documented. Forty-three (39.8%) patients had previously received one biologic agent, and 65 (60.1%) had previously received two or more biologic agents. Among the enrolled patients, 38 (35.1%) had a history of immunosuppressive therapy, and 22 (20.3%) had received corticosteroid therapy. All patients had a history of anti-TNF exposure, including 100 (92.5%) who had received infliximab and 36 (33.3%) who had received adalimumab. Within the 2 months before upadacitinib therapy, 46 (42.5%) patients had been treated with infliximab, 22 (20.3%) with adalimumab, 35 (32.4%) with ustekinumab, and 2 (1.8%) with vedolizumab.

## Clinical Effectiveness of Upadacitinib Therapy

At baseline, all patients had an HBI ≥ 8, with a median score of 12 (IQR: 10–14). Clinical remission and clinical response during follow-up are shown in Figure 2A. At week 4, two patients who discontinued upadacitinib were classified as clinical non-responders and were included as such in the subsequent analysis. Overall, 43/108 (39.8%) patients achieved clinical remission and 59/108 (54.6%) achieved clinical response. At week 8, eight patients were classified as clinical non-responders; 49/106 (46.2%) achieved clinical remission and 74/106 (69.8%) achieved clinical response. At week 12, 10 patients were classified as clinical non-responders; 54/98 (55.1%) achieved clinical remission and 75/98 (76.5%)

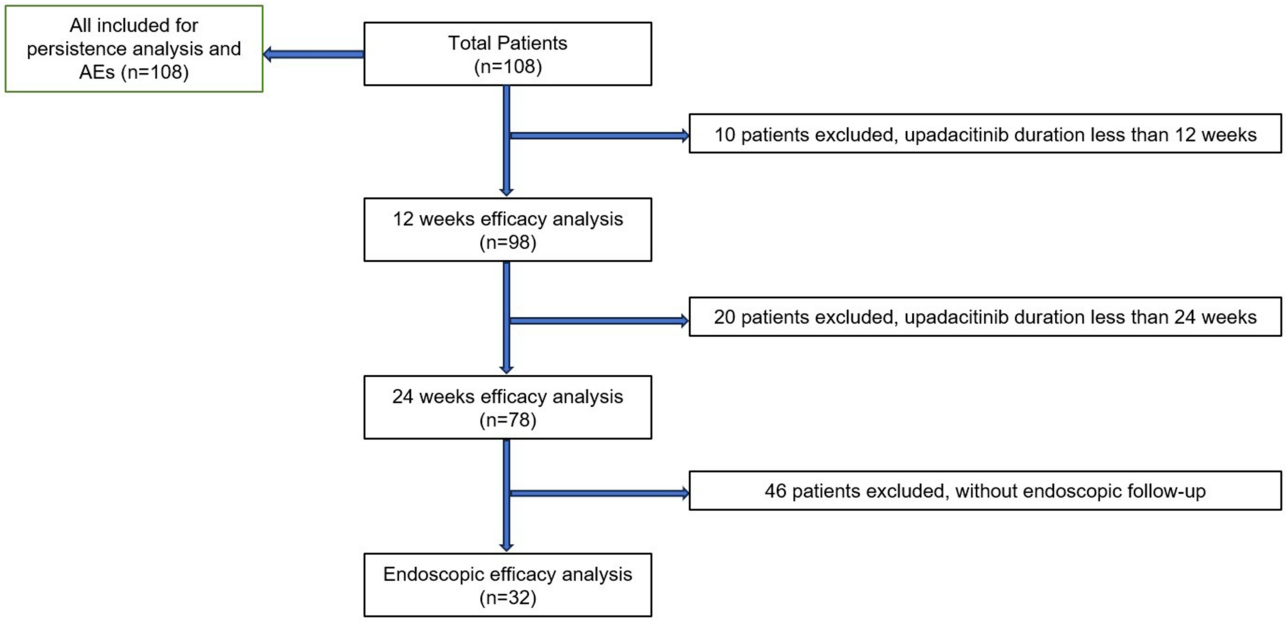


**Figure 1** Flow chart for patient selection.

**Table 1** Baseline Characteristics of the Patients

| Variable | Crohn's Disease (N = 108) |
|---|---|
| Male (n, %) | 73 (67.5) |
| Age (yr), median (IQR) | 29 (23–34) |
| Median time of follow-up (mo) (IQR) | 6 (3–12) |
| Disease duration (yr) (IQR) | 4 (3–7) |
| BMI ≤ 18.5 kg/m2 (n, %) | 34 (31.4) |
| Active smoker, (n, %) | 5 (4.6) |
| Disease location (n, %) | |
| L1 | 22 (20.3) |
| L2 | 13 (12.0) |
| L3 | 73 (67.5) |
| L4 | 0 (0) |
| Disease behavior (n, %) | |
| B1 | 62 (57.4) |
| B2 | 33 (30.5) |
| B3 | 13 (12.0) |
| Perianal disease (n, %) | 49 (45.3) |
| Extraintestinal manifestations (n, %) | 10 (9.2) |
| History of bowel resection, (n, %) | 10 (9.2) |
| Number of Biologic-exposed, (n, %) | |
| 1 | 43 (39.8) |
| 2+ | 65 (60.1) |
| History of Biologic-exposed, n(%) | |
| Infliximab, n(%) | 100 (92.5) |
| Adalimumab, n(%) | 36 (33.3) |
| Ustekinumab, n(%) | 48 (44.4) |
| Vedolizumab, n(%) | 5 (4.6) |
| Biologics prior to upadacitinib start, n(%) | |
| Infliximab, n(%) | 46 (42.5) |
| Adalimumab, n(%) | 22 (20.3) |
| Ustekinumab, n(%) | 35 (32.4) |
| Vedolizumab, n(%) | 2 (1.8) |
| None | 3 (2.7) |
| Prior corticosteroids usage, (n, %) | 22 (20.3) |
| Previous treatment with immunomodulators, (n, %) | 38 (35.1) |
| Fecal calprotectin at baseline (ug/g), median (IQR) | 871.84 (491.73–1800.00) |
| C-reactive protein at baseline (mg/L), median (IQR) | 11.62 (4.62–28.44) |
| Hemoglobin at baseline (g/L), median (IQR) | 115.00 (102.75–128.00) |
| Albumin at baseline (g/L), median (IQR) | 38.85 (35.25–42.20) |
| HBI at baseline, median (IQR) | 12 (10–14) |
| SES-CD at baseline, median (IQR) | 11 (8–14) |

**Abbreviations**: BMI, Body Mass Index; IQR, Interquartile Range; L1, ileal disease; L2, colonic disease; L3, ileocolonic disease; L4, upper gastrointestinal disease; B1, inflammatory; B2: stricturing; B3: penetrating; HBI, Harvey–Bradshaw index; SES-CD, Simple Endoscopic Score for Crohn's Disease.

achieved clinical response. At week 24, 16 patients were classified as clinical non-responders; 41/78 (52.5%) achieved clinical remission and 50/78 (64.1%) achieved clinical response.

## Biomarkers Effectiveness of Upadacitinib Therapy

Median FC and CRP levels at baseline were 871.84 (491.73–1800.00) μg/g and 11.62 (4.62–28.44) mg/L, respectively. Median HB and ALB levels were 115.00 (102.75–128.00) g/L and 38.85 (35.25–42.20) g/L, respectively. Median changes in biochemical indicators are shown in Figure 3. The median CRP level decreased to 1.84 (0.50–6.08) mg/L


https://doi.org/10.2147/JIR.S591249

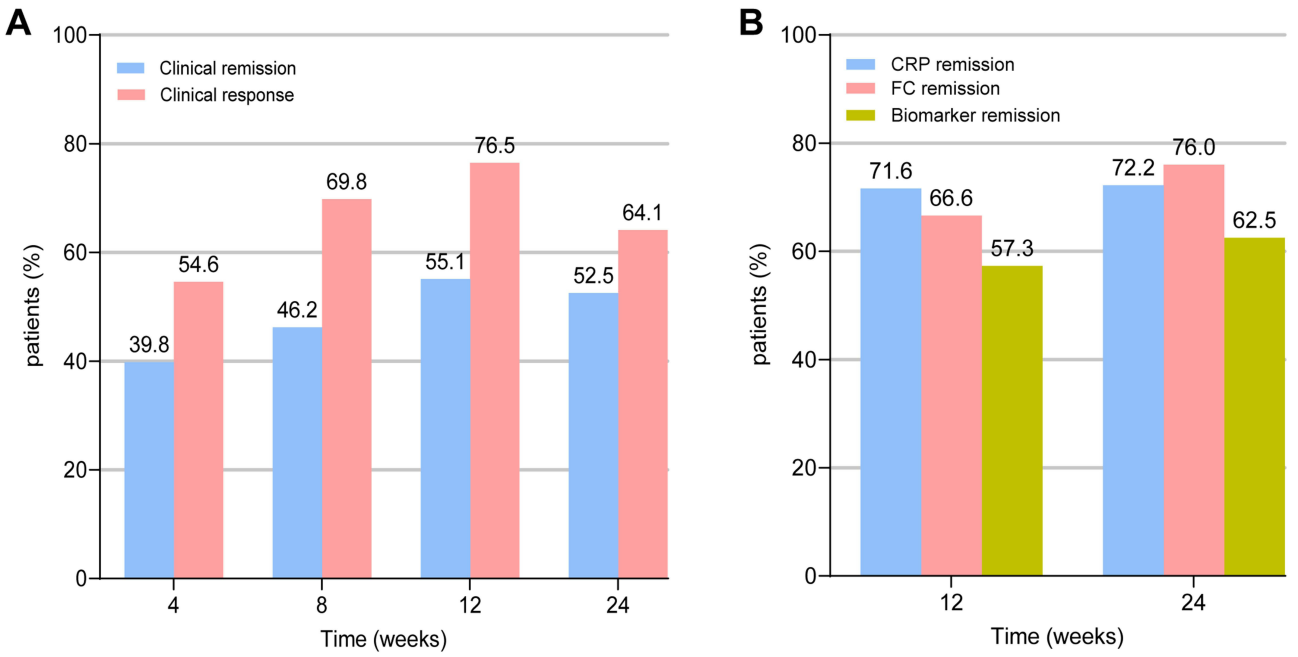


**Figure 2** Effectiveness of upadacitinib therapy in (**A**) Clinical and (**B**) Biomarkers.

at week 12 and to 1.28 (0.50–6.35) mg/L at week 24. The median FC level decreased to 131.32 (43.94–511.44) μg/g at week 12 and to 90.18 (30.00–238.59) μg/g at week 24. The median ALB level increased to 45.00 (41.98–47.72) g/L at week 12 and to 45.80 (42.75–48.30) g/L at week 24. The median HB level increased to 125 (110–135) g/L at week 12 and to 123 (112–136) g/L at week 24. CRP, FC, ALB, and HB changed significantly from baseline to weeks 12 and 24, whereas no significant differences were observed between weeks 12 and 24.

Biomarker effectiveness is shown in Figure 2B. The CRP remission rates were 58/81 (71.6%) at week 12 and 39/54 (72.2%) at week 24. The FC remission rates were 50/75 (66.6%) at week 12 and 38/50 (76.0%) at week 24. The biomarker remission rates were 43/75 (57.3%) at week 12 and 30/48 (62.5%) at week 24.

## Predictors of Clinical Remission at Week 12

In univariate logistic regression analysis, BMI ≤ 18.5 kg/m$^2$ (OR = 0.41, 95% CI: 0.17–0.98, $p$ = 0.048), baseline ALB ≤ 35 g/L (OR = 0.18, 95% CI: 0.06–0.19, $p$ = 0.001), and Crohn's disease behavior (B2 vs B1: OR = 0.27, 95% CI: 0.10–0.66, $p$ = 0.005; B3 vs B1: OR = 0.19, 95% CI: 0.05–0.66, $p$ = 0.012) were inversely associated with clinical remission at week 12 (Table 2). Further multivariable logistic regression analysis showed that baseline ALB ≤ 35 g/L (OR = 0.22, 95% CI: 0.07–0.62, $p$ = 0.006) and stricturing Crohn's disease (B2 vs B1: OR = 0.32, 95% CI: 0.12–0.84, $p$ = 0.021) were associated with clinical remission at week 12, and these associations were statistically significant.

## Endoscopic Effectiveness and Plasma Upadacitinib Concentration

At baseline, 84 patients underwent endoscopy, with a median SES-CD score of 11 (IQR: 8–14). During follow-up, only 32 patients underwent endoscopic evaluation after upadacitinib therapy, and the median time to endoscopic evaluation was 7 months (IQR: 6–9). The follow-up SES-CD score differed significantly from baseline (11 [IQR: 8–15] vs 4 [IQR: 2.75–8.25], $p$ < 0.0001). Endoscopic response was achieved in 16 (50.0%) patients, of whom 8 (25.0%) achieved endoscopic remission. Upadacitinib plasma concentrations were further measured in 24 patients who underwent follow-up endoscopy, of whom 14 (58.3%) achieved endoscopic response and 7 (29.1%) further achieved endoscopic remission. Preliminary exploratory analysis showed no significant difference in plasma concentrations between patients with and without endoscopic response (14.79 ng/mL [IQR: 5.58–72.96] vs 12.37 ng/mL [IQR: 4.45–17.81], $p$ = 0.436)

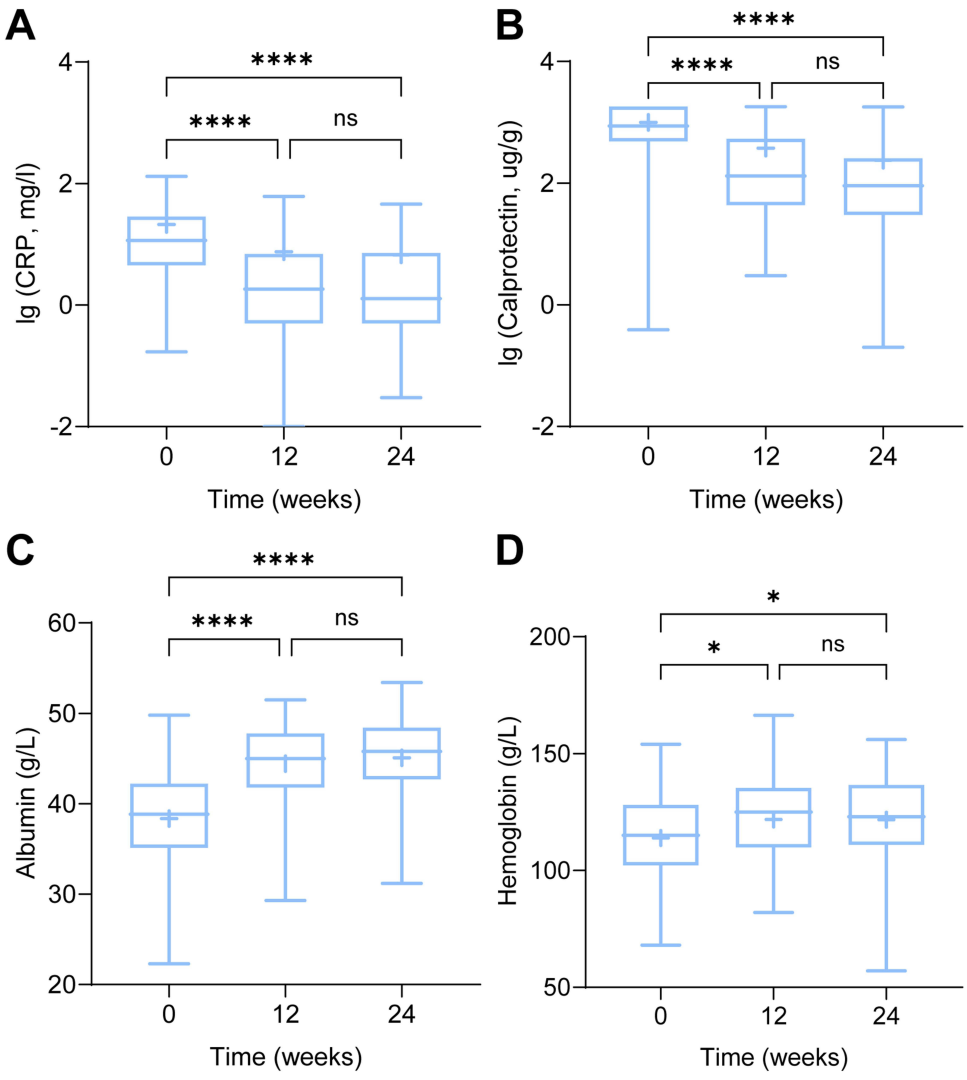


**Figure 3** The changes in biochemical indicators. (**A**) CRP; (**B**) Calprotectin; (**C**) Albumin; (**D**) Hemoglobin. **** indicates $p < 0.0001$;* indicates $p < 0.05$; ns indicates $p > 0.05$.

(Figure 4A). However, patients who achieved endoscopic remission had higher plasma concentrations than those who did not achieve remission (27.15 ng/mL [IQR: 14.79–106.66] vs 10.18 ng/mL [IQR: 3.24–17.86], $p = 0.023$) (Figure 4B).

## Upadacitinib Persistence

A total of 108 patients with Crohn's disease initiated upadacitinib therapy, with a median follow-up duration of 6 months (IQR: 3–12). By the end of follow-up, 20 (18.5%) patients had discontinued upadacitinib, of whom 17 (85.0%) discontinued because of lack of effectiveness and 3 (15.0%) because of severe AEs (rash, zoster infection, and fever, respectively). Univariate Cox analysis showed that baseline BMI ≤ 18.5 kg/m$^2$ (HR = 2.47, 95% CI: 1.03–5.96, $p = 0.042$) and baseline ALB ≤ 35 g/L (HR = 3.25, 95% CI: 1.35–7.82, $p = 0.008$) were associated with upadacitinib discontinuation (Table 3). In the multivariable Cox proportional hazards model, baseline ALB ≤ 35 g/L remained independently associated with an increased risk of discontinuation (HR = 3.05, 95% CI: 1.26–7.36, $p = 0.012$) (Table 3).

The Kaplan-Meier survival curve for upadacitinib persistence in the overall cohort is shown in Figure 5A. The cumulative maintenance rates were 87.50%, 83.7%, 82.06%, and 75.43% at 3, 6, 9, and 12 months, respectively. In addition, the survival curves showed differences in maintenance rates between groups stratified by baseline ALB (> 35 g/L vs ≤ 35 g/L, $p = 0.0055$) and baseline BMI (> 18.5 kg/m$^2$ vs ≤ 18.5 kg/m$^2$, $p = 0.036$) (Figure 5B and C). Patients with


https://doi.org/10.2147/JIR.S591249

**Table 2** Predictors of Clinical Remission at 12 Weeks on Univariate and Multivariable Analyses

| | Clinical Remission at Week 12 (n=98) | | | |
|---|---|---|---|---|
| | Univariate | | Multivariable | |
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Age | 1.51 (0.47–5.07) | 0.488 | | |
| Disease duration, y | 0.96 (0.85–1.08) | 0.513 | | |
| Male sex | 1.80 (0.76–4.30) | 0.180 | | |
| BMI ≤ 18.5, kg/m2 | 0.41 (0.17–0.98) | 0.048 | 0.55 (0.2–1.49) | 0.239 |
| Montreal classification disease location | | | | |
| L2 vs L1 | 2.96 (0.63–16.9 | 0.184 | | |
| L3 vs L1 | 1.33 (0.48–3.74) | 0.587 | | |
| Crohn's disease behavior | | | | |
| B2 vs B1 | 0.27 (0.10–0.66) | 0.005 | 0.32 (0.12–0.84) | 0.021 |
| B3 vs B1 | 0.19 (0.05–0.66) | 0.012 | 0.25 (0.06–1) | 0.055 |
| Prior advanced therapy- exposed 1 vs 2+ | 1.01 (0.45–2.30) | 0.979 | | |
| Perianal disease | 1.34 (0.60–3.02) | 0.474 | | |
| Prior intestinal resection | 0.51 (0.12–1.90) | 0.317 | | |
| Previous corticosteroids usage | 1.29 (0.48–3.61) | 0.622 | | |
| Previous immunosuppressants usage | 1.14 (0.50–2.64) | 0.762 | | |
| Presence of EIMs | 2.04 (0.53–9.92) | 0.325 | | |
| Baseline ALB ≤ 35 g/L | 0.18 (0.06–0.19) | 0.001 | 0.22 (0.07–0.62) | 0.006 |
| Baseline HB ≤ 110 g/L | 0.54 (0.24–1.22) | 0.140 | | |
| Baseline CRP > 5 mg/L | 0.59 (0.23–1.43) | 0.250 | | |
| Baseline FC > 250 ug/g | 0.64 (0.18–2.02) | 0.458 | | |
| Baseline HBI > 12 | 0.49 (0.21–1.11) | 0.092 | | |

**Abbreviations**: BMI, Body Mass Index; L1, ileal disease; L2, colonic disease; L3, ileocolonic disease; B1, inflammatory; B2, stricturing; B3, penetrating; EIMs, extraintestinal manifestations; ALB, albumin; HB, hemoglobin; CRP, C-reactive protein; FC, calprotectin; HBI, Harvey-Bradshaw index.

baseline ALB ≤ 35 g/L had maintenance rates of 71.64%, 67.16%, 67.16%, and 53.73% at 3, 6, 9, and 12 months, respectively, compared with 92.59%, 89.14%, 86.80%, and 83.46% in those with baseline ALB > 35 g/L. Patients with baseline BMI ≤ 18.5 kg/m$^2$ had maintenance rates of 80.25%, 71.55%, 66.44%, and 58.14% at 3, 6, 9, and 12 months, respectively, compared with 90.55%, 88.7%, 82.47%, and 80.25% in those with BMI > 18.5 kg/m$^2$.

## Safety

Among the 108 patients, 22 (20.3%) experienced a total of 23 AEs (Table 4). The most frequently reported AEs were rash (6.4%) and fever (4.6%). Notably, reduced fibrinogen levels were observed in two patients during upadacitinib treatment: in one patient at month 2 (decreasing to 0.91 g/L) and in the other at month 3 (decreasing to 1.55 g/L). After dose reduction to 30 mg once daily, fibrinogen levels normalized in both patients. No serious cardiovascular events or malignancies occurred.

During follow-up, 9 (8.3%) patients underwent Crohn's disease-related surgery. Of these, 6 underwent elective surgery for intestinal fistula, whereas 3 required emergency surgery for intestinal obstruction, intestinal perforation, and massive gastrointestinal bleeding, respectively. The median time from initiation of upadacitinib treatment to surgery was 4 months (IQR: 2.5–8), and 6 of these patients had previously received two or more biologic agents. Imaging findings in patients who underwent surgery for intestinal fistulas showed that intestinal fistulas or penetrating inflammation had already been present before upadacitinib treatment was initiated. Specifically, lesions were located in the ileocecal region in 4 cases and in the ileum in 2 cases.

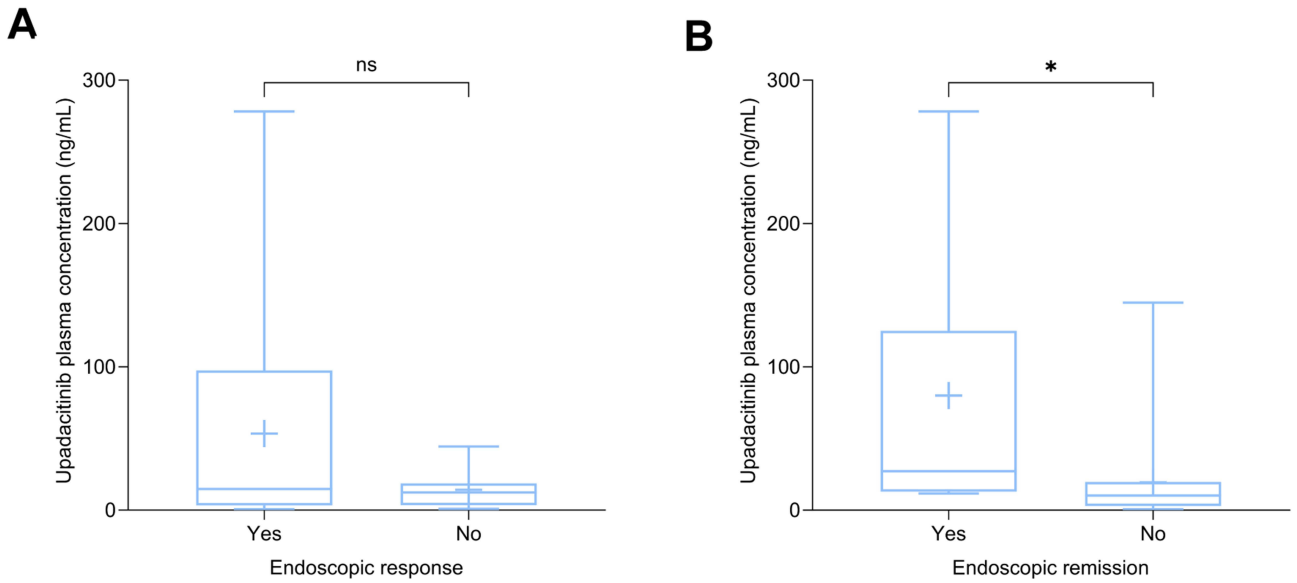


**Figure 4** (**A**) The relationship between endoscopic response and upadacitinib plasma concentrations; (**B**) The relationship between endoscopic remission and upadacitinib plasma concentrations. * indicates $p < 0.05$; ns indicates $p > 0.05$.

## Discussion

This real-world study evaluated the effectiveness of upadacitinib in Chinese patients with moderate-to-severe Crohn's disease. The 100% rate of prior anti-TNF treatment failure or intolerance highlights the refractory nature of the study population. In our cohort, the clinical remission rates were 55.1% at week 12 and 52.5% at week 24, which were slightly higher than those reported in the Phase III U-EXCEL and U-EXCEED trials (49.5% and 38.9%, respectively).[9,21] Our findings are further supported by the consistent week 12 clinical remission rates reported in other real-world studies (56% in Richard et al and 52.1% in Devi et al).[20,22] However, another real-world study from China reported a notably higher remission rate,[13] which may be attributable to two factors: the exclusion of treatment discontinuations from the

**Table 3** Predictors of Upadacitinib Persistence: Univariate and Multivariable Cox Regression

| | Univariate | | Multivariable | |
|---|---|---|---|---|
| | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** |
| Age ≤ 45 years | 1.37 (0.31–5.94) | 0.669 | | |
| Disease duration, y | 1.01 (0.90–1.14) | 0.775 | | |
| Male sex | 1.44 (0.52–3.96) | 0.479 | | |
| BMI ≤ 18.5, kg/m2 | 2.47 (1.03–5.96) | 0.042 | 2.28 (0.94–5.52) | 0.066 |
| Prior advanced therapy exposed 1 vs 2+ | 0.67 (0.26–1.76) | 0.427 | | |
| Perianal disease | 0.78 (0.32–1.93) | 0.605 | | |
| Prior intestinal resection | 2.04 (0.68–6.14) | 0.200 | | |
| Previous corticosteroids usage | 1.40 (0.51–3.88) | 0.509 | | |
| Previous immunosuppressants usage | 0.96 (0.38–2.41) | 0.933 | | |
| Presence of EIMs | 0.40 (0.05–3.05) | 0.382 | | |
| Baseline ALB ≤ 35 g/L | 3.25 (1.35–7.82) | 0.008 | 3.05 (1.26–7.36) | 0.012 |
| Baseline HB ≤ 110 g/L | 0.67 (0.26–1.69) | 0.403 | | |
| Baseline CRP > 5 mg/L | 1.62 (0.54–4.85) | 0.387 | | |
| Baseline FC > 250 ug/g | 1.55 (0.36–6.71) | 0.552 | | |
| Baseline HBI >12 | 0.89 (0.36–2.19) | 0.811 | | |

**Abbreviations**: BMI, Body Mass Index; EIMs, extraintestinal manifestations; HB, hemoglobin; ALB, albumin; CRP, C-reactive protein; FC calprotectin; HBI, Harvey-Bradshaw index.


https://doi.org/10.2147/JIR.S591249

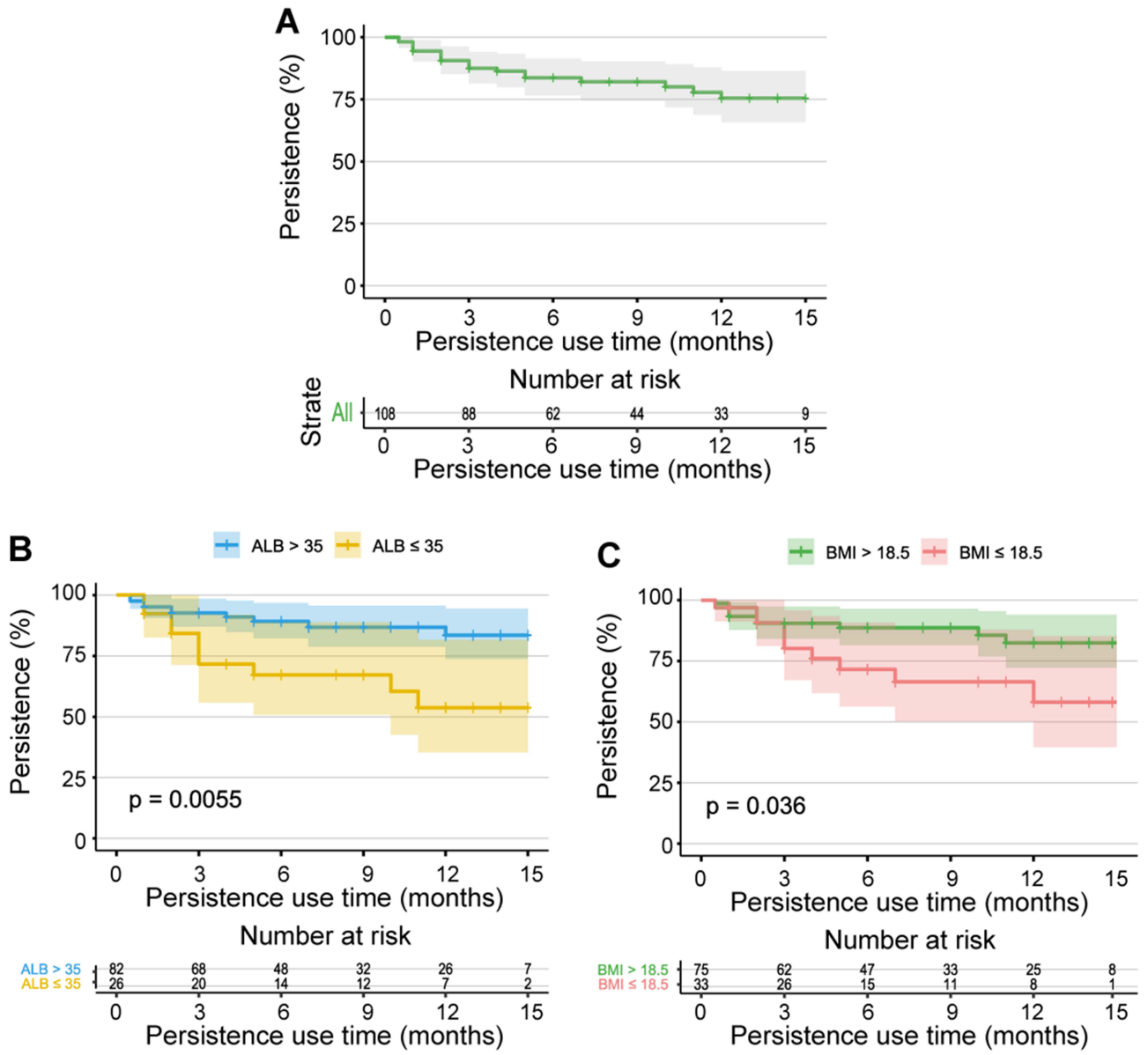


**Figure 5** Kaplan-meier survival curve of upadacitinib therapy over time. (**A**) all patients; (**B**) baseline ALB ≤ 35 g/L and ALB > 35 g/L; (**C**) baseline BMI < 18.5 kg/m$^2$ and BMI ≥ 18.5 kg/m$^2$.

effectiveness analysis and a patient population with milder disease activity at baseline. The inflammatory markers CRP and FC showed marked reductions at weeks 12 and 24, with biomarker remission increasing to 57.3% at week 12 and 62.5% at week 24. A UK multicentre retrospective cohort study by Danso Y et al also demonstrated significant overall reductions in CRP and FC levels at weeks 12 and 24 after upadacitinib treatment.[23] Among the 32 patients who underwent follow-up endoscopy, a significant reduction in SES-CD score was observed, with 25.0% achieving endoscopic remission and 50.0% achieving endoscopic response. Similarly, the study by Chugh et al reported an endoscopic remission rate of 28.6% and an endoscopic response rate of 57.1% at 6 months.[24]

The study preliminarily identified potential predictors of clinical effectiveness. In this real-world study, the stricturing phenotype of Crohn's disease and baseline ALB ≤ 35 g/L were associated with failure to achieve clinical remission at week 12. Similar to other advanced therapies for Crohn's disease, JAK inhibitors primarily target inflammatory pathways and are unlikely to reverse established intestinal fibrosis, which may partly explain the suboptimal clinical efficacy of upadacitinib in patients with stricturing Crohn's disease.[25] Other studies have also explored predictors of clinical

**Table 4** Adverse Events During Upadacitinib Therapy

| Category | Number of Events (n, %) |
|---|---|
| Adverse events, n (%) | |
| Rash | 7 (6.4) |
| Fever | 5 (4.6) |
| Respiratory tract infection | 2 (1.8) |
| Zoster infection | 2 (1.8) |
| Elevated liver enzymes | 2 (1.8) |
| Reduced fibrinogen levels | 2 (1.8) |
| Hypercholesterolemia | 2 (1.8) |
| Leukopenia | 1 (0.9) |
| Adverse events resulting in discontinuation, n (%) | 3 (7.4) |
| Crohn's disease-related surgery, n (%) | 9 (8.3) |

outcomes with upadacitinib. A real-world analysis by Devi J et al identified lower BMI and longer disease duration as factors associated with lower odds of clinical remission at week 12.[22] Another Spanish U-REAL study showed that mild clinical activity at baseline and the absence of previous surgery were associated with clinical remission at week 12.[26]

Upadacitinib was well-tolerated, with no reports of malignant tumors or major adverse cardiovascular events during the study period. Most AEs were mild and did not affect continued treatment. This was consistent with findings from clinical trials, which indicated that upadacitinib has a favorable safety profile.[9,27] Previous studies have suggested that JAK inhibitors may increase the risk of respiratory tract infections. In this study, the incidence of respiratory tract infections was 1.8%, and all cases were mild.[28] A reduction in fibrinogen level, which has not been previously documented, was observed in two patients, and both normalized after dose reduction. Although previous studies have suggested a link between upadacitinib and venous thromboembolism,[29] no definite thrombosis was observed in these two patients. However, the observed decrease in fibrinogen levels may indicate an effect on coagulation function, underscoring the need to monitor hemostatic and coagulation profiles during treatment. This study also found that six patients required surgical intervention for intestinal fistulas during upadacitinib treatment. Notably, all had pre-existing penetrating inflammation in the ileum or ileocecal region before therapy. Given that early surgery for localized ileocecal Crohn's disease is associated with reduced recurrence and improved long-term outcomes,[30,31] clinicians should carefully weigh the choice between initial treatment with small-molecule therapies and direct surgical intervention in such cases.

In this study, we preliminarily explored the association between upadacitinib plasma concentrations and endoscopic outcomes in a real-world setting. For anti-TNF agents, a clear association between plasma drug levels and both clinical and endoscopic outcomes has been well established, whereas such relationships remain less clearly defined for small-molecule therapies.[32–34] In the present study, patients who achieved endoscopic remission tended to have higher plasma concentrations than those who did not achieve remission. However, given the limited sample size of the pharmacokinetic analysis and the fact that plasma concentrations were measured at a single time point approximately 24 hours after dosing, this measurement may not fully reflect overall drug exposure.[18,35] Tissue drug concentration may have greater predictive value than plasma concentration, and subsequent investigations will include a comprehensive analysis of tissue levels.[36]

Among the 108 patients, 20 discontinued treatment, including 17 because of inadequate effectiveness and 3 because of AEs. Our study observed an upadacitinib discontinuation incidence rate of 19 per 100 patient-years. Compared with the rate of 38 per 100 patient-years reported by María et al[26] our study demonstrated better treatment persistence. This finding may be attributable to the fact that our enrolled patients were naive to tofacitinib and may therefore have shown a better response to upadacitinib.[37] Low albumin levels indicated a higher risk of discontinuation, which is consistent with our multivariable logistic regression analysis showing that low albumin levels were associated with poor clinical outcomes.

Our study has several limitations. It was conducted in a relatively small cohort, and further validation in larger populations is warranted. In addition, only a subset of patients underwent endoscopic reassessment and pharmacokinetic analysis, which

may have limited the generalizability of these findings. Furthermore, the regression analysis were based on a limited number of events, which may have affected the stability of the estimates. Nevertheless, this study provides additional real-world evidence supporting the effectiveness, persistence, and safety of upadacitinib in patients with Crohn's disease.

## Conclusion

This real-world study in a Chinese population demonstrates that upadacitinib is effective, with an acceptable safety profile and favorable treatment persistence, in patients with moderate-to-severe Crohn's disease who had previously experienced refractory anti-TNF therapy. In addition, stricturing Crohn's disease and hypoalbuminemia were associated with poorer therapeutic response, whereas exploratory analysis suggested that higher plasma drug concentrations were associated with endoscopic remission. Our findings support the clinical utility of JAK1 inhibition in a real-world setting. Future studies with larger sample sizes should focus on long-term effectiveness and safety and provide more comprehensive pharmacokinetic characterization to support the use of upadacitinib in patients with Crohn's disease.

## Abbreviations

Anti-tumor necrosis factor (anti-TNF); adverse events (AEs); Janus kinase 1 (JAK1); European Medicines Agency (EMA); Food and Drug Administration (FDA); Harvey–Bradshaw Index (HBI); body mass index (BMI); extraintestinal manifestations (EIMs); Simple Endoscopic Score for Crohn's Disease (SES-CD); C-reactive protein (CRP); Fecal calprotectin (FC); hemoglobin (HB); albumin (ALB); standard deviation (SD); interquartile range (IQR).

## Data Sharing Statement

For the protection of patients' privacy, the patient data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. This investigation was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (ID: PJ 2024-05-64). The need for patient consent was waived due to the retrospective nature of the study, and all patient data were fully de-identified.

## Author Contributions

Yuanyuan Fang: writing – review and editing, writing – original draft, validation, conceptualization, methodology, formal analysis, data curation.

Linlin Zhou: formal analysis, visualization, methodology, software, validation.

Lingyun Li: data curation, formal analysis, methodology, investigation, writing – review and editing, validation.

Lixue Zhang: investigation, writing – review and editing.

Nannan Zhu: investigation, writing – review and editing.

Jing Hu: data curation, resources. Qiuyuan Liu: data curation, resources. Juan Wu: data curation, validation. Peipei Zhang: data curation, validation, investigation.

Qiao Mei: conceptualization, methodology, supervision, project administration. Wei Han: conceptualization, methodology, project administration, supervision, funding acquisition. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by the Natural Science Foundation of Anhui Medical University under [Grant No. 2023xkj134].

## Disclosure

The authors declare no conflict of interest.

## References


1. Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing crohn's disease. *Gastroenterology*. 2021;160(7):2496–2508. doi:10.1053/j.gastro.2021.04.022
2. Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in crohn's disease: medical treatment. *J Crohn's Colitis*. 2019;14:4–22. doi:10.1093/ecco-jcc/jjz180
3. Casanova MJ, Chaparro M, Mínguez M, et al. Effectiveness and safety of the sequential use of a second and third Anti-TNF agent in patients with inflammatory bowel disease: results from the Eneida registry. *Inflamm Bowel Dis*. 2020;26:606–616. doi:10.1093/ibd/izz192
4. Chanchlani N, Lin S, Bewshea C, et al. Mechanisms and management of loss of response to anti-TNF therapy for patients with Crohn's disease: 3-year data from the prospective, multicentre PANTS cohort study. *Lancet Gastroenterol Hepatol*. 2024;9:521–538. doi:10.1016/S2468-1253(24)00044-X
5. Yang H, Huang Z, Li M, et al. Comparative effectiveness of ustekinumab vs. vedolizumab for anti-TNF-naïve or anti-TNF-exposed Crohn's disease: a multicenter cohort study. *EClinicalMedicine*. 2023;66:102337. doi:10.1016/j.eclinm.2023.102337
6. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132:52–65. doi:10.1053/j.gastro.2006.11.041
7. Aguilar D, Revilla L, Garrido-Trigo A, et al. Randomized controlled trial substudy of cell-specific mechanisms of janus kinase 1 inhibition with upadacitinib in the crohn's disease intestinal mucosa: analysis from the CELEST study. *Inflamm Bowel Dis*. 2021;27:1999–2009. doi:10.1093/ibd/izab116
8. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov*. 2017;16:843–862. doi:10.1038/nrd.2017.201
9. Loftus EV, Panés J, Lacerda AP, et al. Upadacitinib induction and maintenance therapy for Crohn's Disease. *N Engl J Med*. 2023;388:1966–1980. doi:10.1056/NEJMoa2212728
10. Rogler G. Efficacy of JAK inhibitors in Crohn's Disease. *J Crohns Colitis*. 2020;14:S746–s754. doi:10.1093/ecco-jcc/jjz186
11. Dignass A, Esters P, Flauaus C. Upadacitinib in Crohn's disease. *Expert Opin Pharmacother*. 2024;25:359–370. doi:10.1080/14656566.2024.2333964
12. Fu X, Tu L, Fu Y, et al. Upadacitinib induction therapy in Crohn' s disease: a retrospective real-world study in biologic-refractory patients. *BMC Gastroenterol*. 2025;25:707. doi:10.1186/s12876-025-04305-z
13. Wu H, Xie T, Yu Q, et al. An analysis of the effectiveness and safety of upadacitinib in the treatment of inflammatory bowel disease: a multicenter real-world study. *Biomedicines*. 2025;13:190. doi:10.3390/biomedicines13010190
14. Liu Z, Liu R, Gao H, et al. Genetic architecture of the inflammatory bowel diseases across East Asian and European ancestries. *Nature Genet*. 2023;55:796–806. doi:10.1038/s41588-023-01384-0
15. Smith K. Genetics of IBD in asian populations. *Nat Rev Gastroenterol Hepatol*. 2011;8:598. doi:10.1038/nrgastro.2011.166
16. Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol*. 2010;8:357–363. doi:10.1016/j.cgh.2010.01.001
17. Friedberg S, Choi D, Hunold T, et al. Upadacitinib is effective and safe in both ulcerative colitis and Crohn's Disease: prospective real-world experience. *Clin Gastroenterol Hepatol*. 2023;21:1913–1923.e2. doi:10.1016/j.cgh.2023.03.001
18. Mohamed MF, Klünder B, Lacerda AP, Othman AA. Exposure-Response analyses for upadacitinib efficacy and safety in the Crohn's Disease CELEST study and bridging to the extended-release formulation. *Clin Pharmacol Ther*. 2020;107:639–649. doi:10.1002/cpt.1668
19. Ananthakrishnan AN, Adler J, Chachu KA, et al. AGA clinical practice guideline on the role of biomarkers for the management of Crohn's Disease. *Gastroenterology*. 2023;165:1367–1399. doi:10.1053/j.gastro.2023.09.029
20. Richard N, Amiot A, Seksik P, et al. Effectiveness and safety of upadacitinib induction therapy for 223 patients with Crohn's Disease: a GETAID Multicentre Cohort Study. *Aliment Pharmacol Ther*. 2025;61:1662–1670. doi:10.1111/apt.70073
21. Sandborn WJ, Feagan BG, Loftus EV, et al. Efficacy and safety of upadacitinib in a randomized trial of patients with Crohn's Disease. *Gastroenterology*. 2020;158:2123–2138.e8. doi:10.1053/j.gastro.2020.01.047
22. Devi J, Xu A, Stone M, et al. Real-World effectiveness and safety of upadacitinib in Crohn's Disease: a Multicenter Study. *Clin Gastroenterol Hepatol*. 2025;23:2281–2291.e4. doi:10.1016/j.cgh.2025.01.012
23. Danso Y, Radia C, Elford A, et al. Effectiveness and safety of upadacitinib in a real-world cohort of patients with Crohn's disease in the UK: a multicentre retrospective cohort study. *BMJ Open Gastroenterol*. 2025;12. doi:10.1136/bmjgast-2025-001916
24. Chugh R, Braga-Neto MB, Fredrick TW, et al. Multicentre real-world experience of upadacitinib in the treatment of Crohn's Disease. *J Crohns Colitis*. 2023;17:504–512. doi:10.1093/ecco-jcc/jjac157
25. Lin SN, Mao R, Qian C, et al. Development of antifibrotic therapy for stricturing Crohn's disease: lessons from randomized trials in other fibrotic diseases. *Physiol Rev*. 2022;102:605–652. doi:10.1152/physrev.00005.2021
26. García MJ, Brenes Y, Vicuña M, et al. Persistence, effectiveness, and safety of upadacitinib in Crohn's Disease and ulcerative colitis in real life: results from a Spanish Nationwide Study (Ureal Study). *Am J Gastroenterol*. 2025;120:1593–1604. doi:10.14309/ajg.0000000000003243
27. Colombel JF, Hisamatsu T, Atreya R, et al. Upadacitinib reduces crohn's disease symptoms within the first week of induction therapy. *Clin Gastroenterol Hepatol*. 2024;22:1668–1677. doi:10.1016/j.cgh.2024.02.027
28. Woelfel S, Dütschler J, Junker D, et al. XBB.1.5-Adapted COVID-19 mRNA vaccines but not infections with previous omicron variants boost neutralisation against the SARS-CoV-2 JN.1 variant in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2025;61:299–312. doi:10.1111/apt.18349
29. Clarke B, Yates M, Adas M, Bechman K, Galloway J. The safety of JAK-1 inhibitors. *Rheumatology*. 2021;60:ii24–ii30. doi:10.1093/rheumatology/keaa895

30. Ponsioen CY, de Groof EJ, Eshuis EJ, et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. *Lancet Gastroenterol Hepatol*. 2017;2:785–792. doi:10.1016/S2468-1253(17)30248-0
31. Maruyama BY, Ma C, Panaccione R, Kotze PG. Early laparoscopic ileal resection for localized ileocecal Crohn's Disease: hard sell or a revolutionary new norm? *Inflamm Intest Dis*. 2022;7:13–20. doi:10.1159/000515959
32. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. *Annu Rev Med*. 2015;66:311–328. doi:10.1146/annurev-med-051113-024537
33. Bayoumy AB, Derijks LJJ, Oldenburg B, De Boer NKH. The use of tissue concentrations of biological and small-molecule therapies in clinical studies of inflammatory bowel diseases. *Pharmaceutics*. 2024;16. doi:10.3390/pharmaceutics16121497
34. Hong SN, Song JH, Kim SJ, et al. Subcutaneous infliximab concentration thresholds for mucosal and transmural healing in patients with Crohn's Disease. *Aliment Pharmacol Ther*. 2025;61:313–322. doi:10.1111/apt.18354
35. Klünder B, Mittapalli RK, Mohamed MF, Friedel A, Noertersheuser P, Othman AA. Population pharmacokinetics of upadacitinib using the immediate-release and extended-release formulations in healthy subjects and subjects with rheumatoid arthritis: analyses of phase i-iii clinical trials. *Clin Pharmacokinet*. 2019;58:1045–1058. doi:10.1007/s40262-019-00739-3
36. Verstockt B, Alsoud D, van Oostrom J, et al. Drug tissue concentration and STAT3 modulation as determinants of tofacitinib response in ulcerative colitis. *J Crohn's Colitis*. 2025;19. doi:10.1093/ecco-jcc/jjaf063
37. Bezzio C, Franchellucci G, Savarino EV, et al. Upadacitinib in patients with difficult-to-treat Crohn's Disease. *Crohns Colitis*. 2024;360:6:otae060. doi:10.1093/crocol/otae060