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# Changes in the clinical course and prognosis of ulcerative colitis in Chinese populations: a retrospective cohort study

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**Background/Aims:** Data on the natural course of Chinese patients with ulcerative colitis (UC) was lacking. This study aimed to evaluate the natural history and prognosis of patients with UC in the past 15 years in China. **Methods:** This cohort study included patients with UC in a tertiary hospital in southern China from 2007 to 2021 (cohort I: 2007–2011, cohort II: 2012–2016, cohort III: 2017–2021). Patients' clinical characteristics and natural history were analyzed retrospectively. **Results:** Of 1,139 included patients, 683 patients presented with proctitis or left-sided colitis at diagnosis and 38.5% of them (263/683) developed proximal disease extension. Fifty-eight percent of patients experienced relapse, chronic continuous and intermittent active course. Five patients (0.4%) developed colorectal tumors/dysplasia. The overall surgery rate was 8.6%, and the rates were 14.2%, 7.8%, and 8.0% in the 3 cohorts, respectively ($P=0.059$). Average time from diagnosis to surgery decreased from cohorts I to III (144 months vs. 36 months, $P<0.001$), so did the use of glucocorticoids (58.2% vs. 43.5%, $P<0.001$) and immunosuppressants (14.1% vs. 13.4%, $P=0.016$), and days of hospitalization (13 days vs. 9 days, $P<0.001$). Biologics were used more frequently during the first year (0.8%, 2.1%, and 13.7% for cohorts I to III, respectively; $P<0.001$). The rate of mucosal healing increased over time. **Conclusions:** In Chinese UC patients, one-third of patients experienced proximal disease extension. The rates of malignancy and mortality were low. More biologics were used, while use of immunosuppressants and glucocorticoids were reduced over time. Early biologics use seemed to promote mucosal healing, but the rate of colectomy has not dramatically decreased. **(Intest Res 2024;22:357-368)**

**Key Words:** Ulcerative colitis; Disease course; Epidemiology; Drug therapy; Prognosis

## INTRODUCTION

Ulcerative colitis (UC), a subtype of inflammatory bowel disease (IBD), is a chronic inflammatory disease that affects the gastrointestinal tract and is characterized by a progressive course.[1] IBD has typically been referred to as a disease of the West.[2] However, in some Asian nations and other newly industrialized nations, the prevalence of UC is rising quickly.[3-5] The incidence rate of UC dramatically rose in the mid to late twentieth century.[6]

Treatment objectives for UC have changed over the past 10 years, moving from clinical remission to mucosal healing and even the modification of clinical course. Innovative medications have shed light on the treat to target strategy, but it is still unknown if they can alter the natural course of UC. Understanding the natural history of disease is crucial considering the progressive nature of UC and the burden of illness. Previ-

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ously, information on the natural course of patients with UC was mostly dominated by Western populations. Although researches including Asian populations have been reported in recent years, there was large data gap on the typical course of UC patients in China. The present study aimed to assess the natural course of patients with UC in China. We also wanted to look into how treatment patterns have changed over time.

## METHODS

### 1. Study Population and Design

This was a hospital-based cohort study. All diagnosed cases of UC were from a tertiary IBD center in southern China from 2007 to 2021. Patients were diagnosed based on a comprehensive analysis of clinical, laboratory, imaging, endoscopic, and histopathological manifestations.[7] Patients who lacked clinical data, had gastrointestinal tumors at diagnosis, lost to follow-up or followed up for less than half a year were excluded. Clinical demographics was collected, including sex, age, diagnosis year, disease phenotype, smoking status, family history, disease extension categorized by Montreal classification and medical therapy.

### 2. Definitions

The date of the initial endoscopic examination was regarded as date of diagnosis. When the diagnosis changed from IBD unclassified or Crohn's disease to UC, the date at diagnosis was defined as the date of the first IBD diagnosis.[8] The clinical types of UC were classified into initial onset and chronic relapse.[9] According to the Montreal classification, the extent of UC was classified into 3 categories: ulcerative proctitis (E1, proximal extent of inflammation distal to the rectosigmoid junction), left-sided colitis (E2, involvement limited to a portion of the colorectum distal to the splenic flexure), and extensive colitis (E3, involvement extending proximally to the splenic flexure).[10] Disease extension was defined as proximal progression from the initial extent of diagnosis as defined by endoscopy.[11] Former smokers were defined as those who had abstained from smoking for more than 3 months. Early use of corticosteroids was defined as the usage within 3 months of being diagnosed with UC.[8] Different disease activity patterns were defined as follows: (1) remission or mild severity of intestinal symptoms after initial high activity; (2) relapse, increase in the severity of intestinal symptoms after a period of remission; (3) chronic continuous, persistent symptoms; (4) chronic intermittent, intermittent symptoms; and (5) continuous remission, basically inactive.[12,13] Mucosal healing was defined as Mayo endoscopic subscore (MES) of 0.

### 3. Treatment Strategy

5-Aminosalicylates (5-ASA) was the principal medications utilized to induce and maintain remission in mild-to-moderate UC. Glucocorticoids were given to patients with moderate-to-severe and 5-ASA resistance. Prednisone was administered at a dose of 0.75 to 1 mg/kg/day (the doses of other types of systemic hormones were equivalent to that of prednisone).[7] Glucocorticoids were weaned off till withdrawal after symptom relief. Patients who were reliant on glucocorticoids were advised to take thiopurines such azathioprine and 6-mercaptopurine. Thalidomide was used to treat refractory UC but was not the first choice. For individuals with severe UC, intravenous glucocorticoids were the first-line of treatment. For patients who did not response to appropriate intravenous glucocorticoid treatment, biological agents and intravenous cyclosporine were tried. Treatments, such as colectomy, were carried out according to shared decision-making by doctors and patients. Although the anti-tumor necrosis factor agent, infliximab (Janssen-Cilag International N.V., Raritan, NJ, USA), was originally authorized in China in May 2007, the approval for UC treatment was not until 2019. The anti-integrin biologic, vedolizumab was approved for the treatment of UC in March 2020.

### 4. Follow-up

We employed a standard case report form to gather data and frequently updated the outpatient department data. Two authors (X.L. and K.C.) thoroughly examined the data. The disease extent was determined by full colonoscopy at diagnosis and during follow-up. In case of the some severely active disease, flex sigmoidoscopy plus abdominal imaging were performed to determine the disease extent. Evaluation of endoscopic severity using the MES. From the time of diagnosis until death or the end of follow-up (June 30, 2022) for all patients, whichever came first.

### 5. Statistical Analysis

Continuous variables were expressed as medians and interquartile ranges (IQRs), whereas categorical variables were expressed as percentages[14] and relevant 95% confidence intervals (CIs) were calculated. The one-way analysis of variance was used to compare continuous variables of 3 or more groups, while the chi-square test and Fisher exact test were used to compare categorical variables. Cumulative risks for proximal

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extension, mucosal healing and colectomy, were calculated using the Kaplan-Meier method. Log-rank was employed for comparisons of values between the groups. Univariate and multivariate Cox regression was used to determine predictive factors. A 2-sided test was conducted in all cases, and *P*-value of <0.05 was used to denote statistical significance. Bonferroni correction was used to adjust for multiple comparisons. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) was used for data analysis.

### 6. Ethical Considerations

We conducted this study in compliance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (No. E2022287). Informed consent was waived.

## RESULTS

### 1. Baseline Characteristics

A total of 1,139 participants were included in the study. We classified the patients into cohort I (2007–2011, n=127), cohort II (2012–2016, n=486), and cohort III (2017–2021, n=526) according to the year of diagnosis. The patients were followed up for 6,945 person-years. The median age at UC diagnosis was 39 years (IQR, 29–51 years), and 41.3% of patients were female. Fifteen patients (1.3%) had a family history of IBD. At diagnosis, 251 patients (22.0%) and 888 patients (78.0%) were initial onset and chronic relapse, respectively. There were 962 non-smokers (84.5%), 14 former smokers (1.2%), and 125 smokers (11.0%). A total of 63 patients (5.5%) were elderly-onset UC, with 2 (1.6%), 30 (6.2%) and 31 (5.9%) in the cohorts I, II and III, respectively. No significant differences were found

**Table 1.** Characteristics of Patients with 1,139 Patients with UC during 2007 to 2021 by Year of Diagnosis

| Clinical characteristics | Year of diagnosis | | |
|---|---|---|---|
| | Cohort I (2007–2011) | Cohort II (2012–2016) | Cohort III (2017–2021) |
| No. of patients | 127 | 486 | 526 |
| Male sex | 81 (63.7) | 276 (56.8) | 312 (59.3) |
| Age at diagnosis | | | |
| ≤ 16 yr | 2 (1.6) | 13 (2.7) | 23 (4.4) |
| 17–40 yr | 71 (55.9) | 246 (50.6) | 255 (48.5) |
| > 40 yr | 54 (42.5) | 227 (46.7) | 248 (47.1) |
| Clinical classification | | | |
| Initial onset | 1 (0.8) | 130 (26.7) | 120 (22.8) |
| Chronic relapse | 126 (99.2) | 356 (73.3) | 406 (77.2) |
| Montreal classification[a] | | | |
| E1 | 34 (26.8) | 140 (28.8) | 128 (24.3) |
| E2 | 41 (32.3) | 174 (35.8) | 166 (31.6) |
| E3 | 52 (40.9) | 172 (35.4) | 232 (44.1) |
| Family history | | | |
| No | 105 (82.7) | 463 (95.3) | 486 (92.4) |
| Yes | 2 (1.6) | 7 (1.4) | 6 (1.1) |
| Unknown | 20 (15.7) | 16 (3.3) | 34 (6.5) |
| Smoking | | | |
| Never smoker | 109 (85.8) | 378 (77.8) | 475 (90.3) |
| Current smoker | 16 (12.5) | 67 (13.8) | 42 (8.0) |
| Former smoker | 1 (0.7) | 5 (1.0) | 8 (1.5) |
| Unknown | 1 (0.7) | 36 (7.4) | 1 (0.2) |

Values are presented as number (%).
[a]Disease extension was categorized according to the Montreal classification.

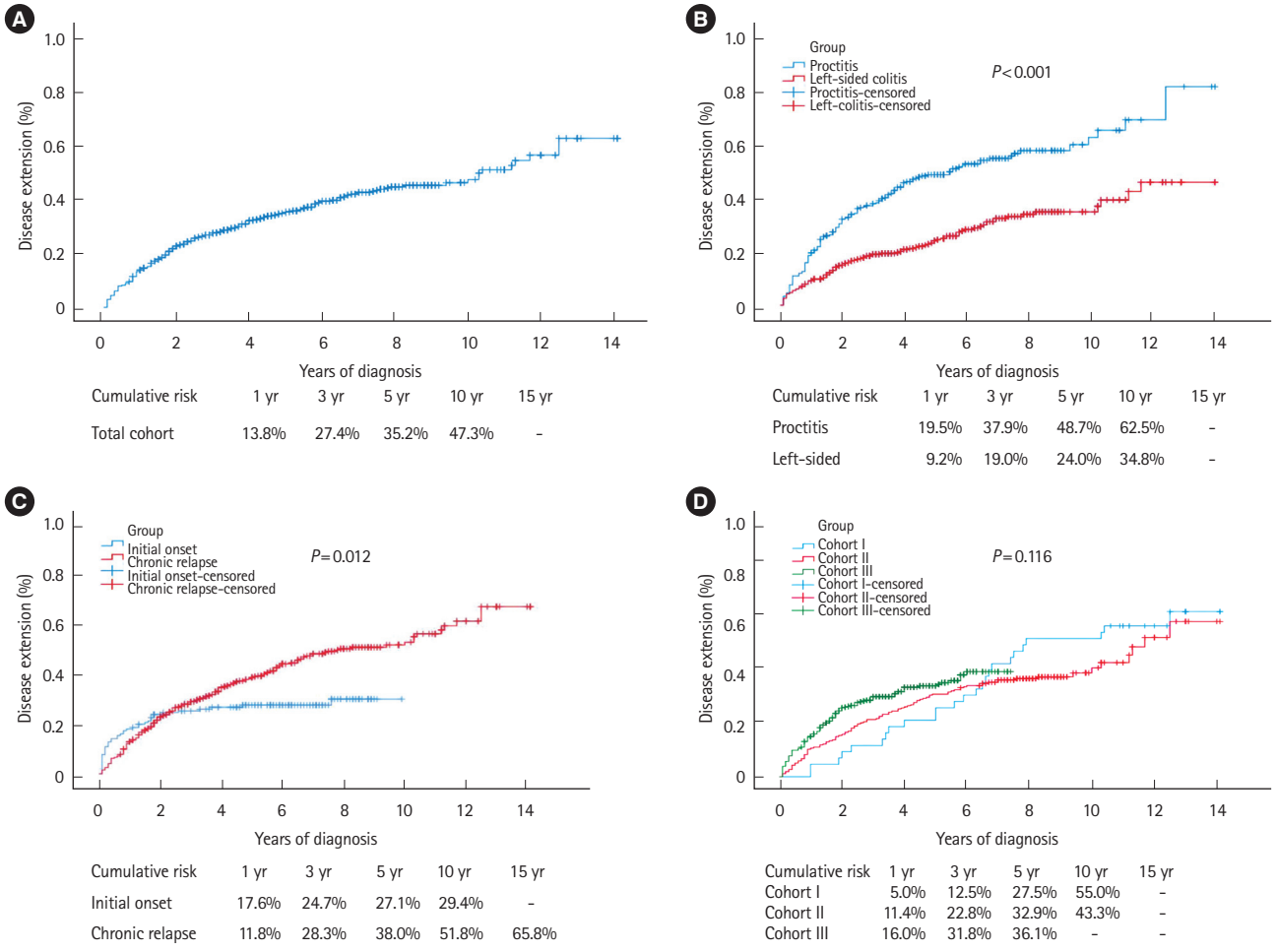


**Fig. 1.** Cumulative risk of proximal disease extension in patients with UC: (A) in the total cohort, (B) according to the disease extent at diagnosis, (C) according to clinical classification, and (D) in the 3 temporal cohorts.

among the 3 cohorts in terms of sex, age and Montreal classification. The demographic and clinical characteristics of the 3 cohorts are listed in Table 1.

### 2. Proximal Disease Extension

At diagnosis, 302 (26.5%), 381 (33.5%), and 456 (40.0%) patients had proctitis, left-sided colitis and extensive colitis, respectively. Among 683 patients diagnosed with proctitis or left-sided colitis, 263 (38.5%) had proximal disease extension (Supplementary Fig. 1), with a median time to extension of 49.0 months (IQR, 21.5–83.0 months). The cumulative risks of proximal extension were 13.8%, 27.4%, 35.2%, and 47.3% for all patients diagnosed with proctitis or left-sided colitis after 1, 3, 5, and 10 years, respectively (Fig. 1A). The cumulative risk of proximal disease extension in patients with proctitis at diagnosis was significantly higher than in those diagnosed with left-sided colitis ($P<0.001$) (Fig. 1B). At 1, 3, 5, and 10 years, the cumulative proximal extension risks for proctitis were 19.5%, 37.9%, 48.7%, and 62.5%, while those for left-sided colitis were 9.2%, 19.0%, 24.0%, and 34.8%, respectively. Compared to the patients with initial onset, the cumulative risk of proximal disease extension was higher in patients with chronic relapse ($P=0.012$) (Fig. 1C). No significant differences were observed in the cumulative risk of proximal extension among the temporal cohorts ($P=0.116$) (Fig. 1D). According to multivariate Cox analysis, cohort III (hazard ratio [HR], 1.762; 95% CI, 1.169–2.657), type of chronic relapse (HR, 1.639; 95% CI, 1.172–2.290), and disease extent upon diagnosis ($HR_{E2}$, 0.438; 95% CI, 0.342–0.562) were all independent predictors of proximal disease extension (Supplementary Table 1).

### 3. Temporal Trends in Therapy

The temporal trends in medical therapy for UC were depicted in Table 2. A 5-ASA use within 1 year after diagnosis was in-

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**Table 2.** Temporal Trends in Medical Therapy of Ulcerative Colitis between 2007 and 2021

| | All periods (2007–2021) | *P*-value[a] | Cohort I (2007–2011) | *P*-value[b] | Cohort II (2012–2016) | *P*-value[c] | Cohort III (2017–2021) |
|---|---|---|---|---|---|---|---|
| 5-Aminosalicylic acid therapy within the first yr of diagnosis | 96.7 (95.5–97.6) | 0.016 | 92.9 (87.1–96.2) | 0.098 | 96.3 (94.2–97.7) | 0.125 | 97.9 (96.3–98.8) |
| 5-Aminosalicylic acid therapy within 5 yr of diagnosis | 97.7 (96.8–98.6) | <0.001 | 92.9 (88.4–97.4) | 0.104 | 97.9 (96.7–99.2) | 0.754 | 98.6 (97.7–99.7) |
| Early corticosteroid use (within 3 mo of diagnosis) | 29.5 (26.9–32.2) | 0.141 | 32.3 (24.8–40.8) | 0.933 | 31.9 (27.9–36.2) | 0.065 | 26.6 (23.0–30.6) |
| Corticosteroid therapy within 5 yr of diagnosis | 49.6 (46.7–52.5) | <0.001 | 58.2 (49.6–67.0) | 0.379 | 53.9 (49.5–58.4) | 0.001 | 43.5 (39.3–47.8) |
| Immunosuppressant therapy within the first yr of diagnosis | 9.7 (8.1–11.5) | 0.835 | 11.0 (6.7–17.7) | 0.548 | 9.3 (7.0–12.2) | 0.813 | 9.7 (7.5–12.5) |
| Immunosuppressant therapy within 5 yr of diagnosis | 16.3 (14.2–18.5) | 0.016 | 14.1 (8.0–20.3) | 0.293 | 19.9 (16.4–23.5) | 0.018 | 13.4 (10.6–16.4) |
| Biologics therapy within 1 yr of diagnosis | 7.3 (5.9–9.0) | <0.001 | 0.8 (0.1–4.3) | 0.475 | 2.1 (1.1–3.8) | <0.001 | 13.7 (11.0–16.9) |
| Biologics therapy within 5 yr of diagnosis | 15.2 (13.2–17.4) | <0.001 | 7.1 (3.8–12.9) | 0.726 | 8.0 (5.9–10.8) | <0.001 | 23.8 (20.3–17.6) |

Values are presented as percent (95% confidence interval). All comparisons are performed by chi-square test, both overall and pairwise.
[a]Overall comparison of all 3 study periods.
[b]Pairwise comparison of cohort I (2007–2011) and cohort II (2012–2016) (Bonferroni correction was used to adjust for multiple comparisons).
[c]Pairwise comparison of cohort II (2012–2016) and cohort III (2017–2021) (Bonferroni correction was used to adjust for multiple comparisons).

**Table 3.** Disease Activity Patterns in Patients with Ulcerative Colitis According to Temporal Cohort

| Disease activity pattern | Cohort I (2007–2011) | Cohort II (2012–2016) | Cohort III (2017–2021) | *P*-value[a] | *P*-value[b] |
|---|---|---|---|---|---|
| Remission | 22 (17.3) | 116 (23.9) | 245 (46.6) | <0.001 | <0.001 |
| Relapse | 40 (31.5) | 121 (24.9) | 163 (31.0) | | |
| Chronic continuous | 17 (13.4) | 10 (2.1) | 7 (1.3) | | |
| Chronic intermittent | 40 (31.5) | 207 (42.6) | 55 (10.5) | | |
| Continuous remission | 8 (6.3) | 32 (6.6) | 56 (10.6) | | |

Values are presented as number (%). All comparisons are performed by chi-square test, both overall and pairwise.
[a]Pairwise comparison of cohort I (2007–2011) and cohort II (2012–2016) (Bonferroni correction was used to adjust for multiple comparisons).
[b]Pairwise comparison of cohort II (2012–2016) and cohort III (2017–2021) (Bonferroni correction was used to adjust for multiple comparisons).

creased from cohort I to cohort II, and kept stable afterwards ($P$=0.016). The use of glucocorticoids gradually decreased over time. There was a tendency of decline in early glucocorticoid use from 32.3% in 2007–2011 to 26.6% in 2017–2021 ($P$=0.141). In the last 2 cohorts, the use of glucocorticoids dropped from 53.9% to 43.5% within 5 years of diagnosis ($P$=0.001). The use of immunosuppressive medications within 1 year of diagnosis did not differ among the 3 cohorts ($P$=0.835), the probability of receiving immunosuppressive medications within 5 years after diagnosis decreased from 19.9% in cohort II to 13.4% in cohort III ($P$=0.018). A discernible increase in the probability of receiving biological agents has been observed in cohorts II and III. In total, 2.1% and 8.0% of patients diagnosed from 2012 to 2016 received biologic therapy within 1 and 5 years after diagnosis, while the rates were 13.7% and 23.8% of patients diagnosed from 2017 to 2021, respectively (both $P$<0.001).

### 4. Disease Activity Patterns

In all temporal cohorts (2007–2021), 383 patients (33.6%) reported remission or mild severity of intestinal symptoms after the initial activity, 324 patients (28.4%) reported a relapse pattern, 34 patients (3.0%) reported a chronic continuous, 302 patients (26.5%) reported a chronic intermittent, and 96 patients (8.4%) reported a continuous remission pattern, respectively. Compared with cohort I and cohort II, the proportion of patients in "remission" and "continuous remission" in the co-

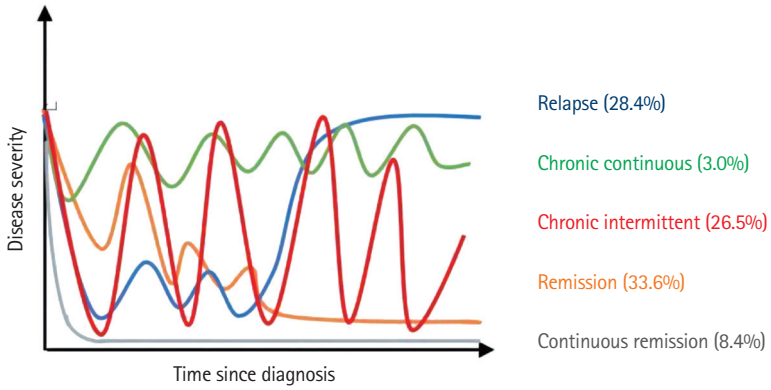


**Fig. 2.** Patient distribution based on disease activity patterns since diagnosis.

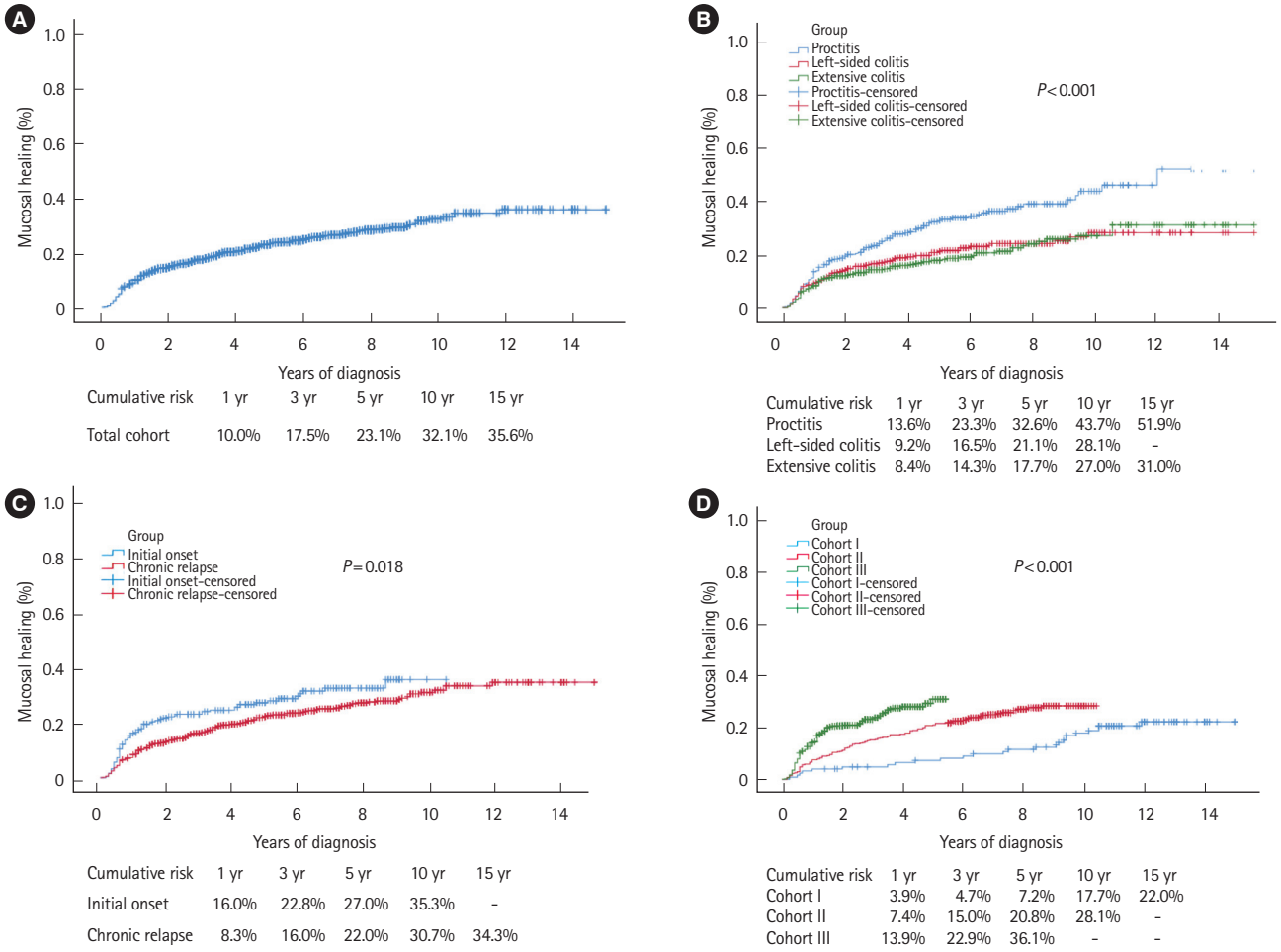


**Fig. 3.** Cumulative risk of mucosal healing in patients with UC: (A) in the total cohort, (B) according to the disease extent at diagnosis, (C) according to clinical classification, and (D) in the 3 temporal cohorts.

hort III group showed an increasing trend (17.3% vs. 23.9% vs. 46.6%, $P<0.001$; 6.3% vs. 6.6% vs. 10.6%, $P<0.001$) (Table 3). Fig. 2 depicts the distribution of disease activity patterns in patients with UC.

### 5. Hospitalization

The average number of hospitalizations per patient was 1 (IQR, 1–3), and the longest medium hospitalization stay was 11 days (IQR, 7–19 days). The medium longest hospitalization

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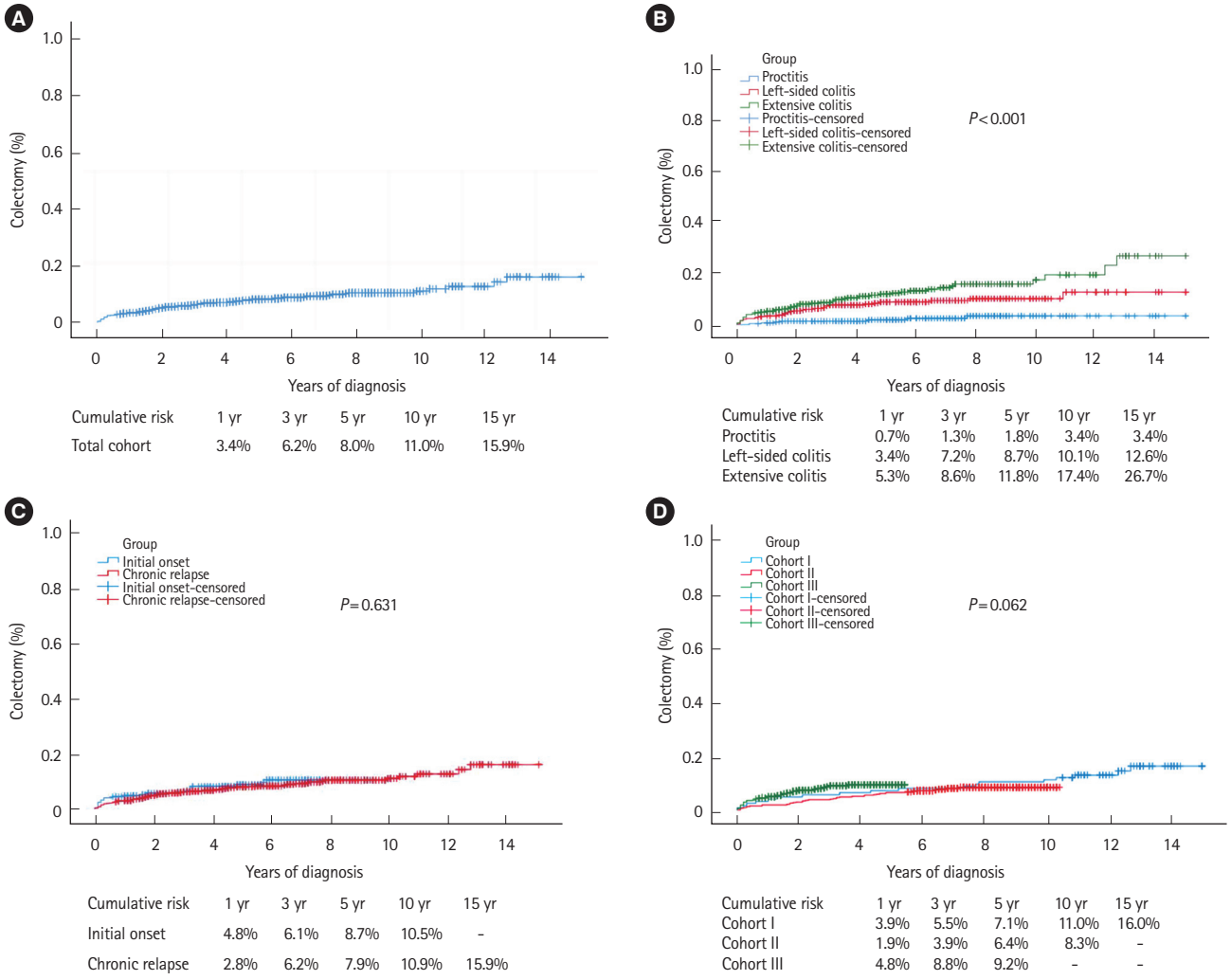


**Fig. 4.** Cumulative risk of colectomy in patients with UC: (A) in the total cohort, (B) according to the disease extent at diagnosis, (C) according to clinical classification, and (D) in the 3 temporal cohorts.

stays decreased over time (Supplementary Table 2).

### 6. Mucosal Healing

A total of 276 patients (24.2%) had at least 1 mucosal healing during the follow-up. The cumulative risks of mucosal healing at 1, 3, 5, 10, and 15 years after diagnosis were 10.0%, 17.5%, 23.1%, 32.1%, and 35.6%, respectively (Fig. 3A). The cumulative risks of mucosal healing at 1, 3, 5, 10, and 15 years in patients diagnosed with proctitis were 13.6%, 23.3%, 32.6%, 43.7%, and 51.9%, respectively. The rates in patients diagnosed with left-sided colitis were 9.2%, 16.5%, 21.1%, 28.1%, and 28.1%, respectively. The rates in patients diagnosed with extensive colitis were 8.4%, 14.3%, 17.7%, 27.0%, and 31.0%, respectively ($P<0.001$) (Fig. 3B). The cumulative risks of mucosal healing at 1, 3, 5, and 10 years were 16.0%, 22.8%, 27.0%, and 35.3% for initial onset, while the cumulative risks of chronic relapse were 8.3%, 16.0%, 22.0%, and 30.7% ($P=0.018$) (Fig. 3C). The cumulative risks of mucosal healing increased significantly over time ($P<0.001$) (Fig. 3D). Multivariate Cox analysis showed that disease extent at diagnosis ($HR_{E2}$, 0.571; 95% CI, 0.427–0.763; $HR_{E3}$, 0.515; 95% CI, 0.386–0.687), the use of biologics within 1 year after diagnosis (HR, 1.792; 95% CI, 1.139–2.820) and last 2 cohorts ($HR_{cohort\ II}$, 1.876; 95% CI, 1.164–3.026; $HR_{cohort\ III}$, 3.166; 95% CI, 1.922–5.216) were independent predictors of mucosal healing (Supplementary Table 3).

### 7. Colectomy

Among the 1,139 patients, 98 patients (8.6%) underwent colectomy. Interval between diagnosis and colectomy decreased significantly from 144 months (IQR, 132–157 months) in

2007–2011 to 36 months (IQR, 22–51 months) in 2017–2021 ($P<0.001$). The indications for colectomy were refractory to treatment in 88 patients (89.8%), colorectal dysplasia/cancer in 3 patients (3.1%), colon perforation in 3 patients (3.1%), obstruction in 2 patients (2.0%), and toxic megacolon in 2 patients (2.0%). In cohort I, 1 patient (0.8%) underwent surgery immediately after diagnosis for concurrent toxic megacolon. In cohort II, 3 patients (0.6%) underwent surgery immediately after diagnosis for gastrointestinal perforation or uncontrolled hemorrhage. In cohort III, 2 patients (0.4%) underwent immediate surgery for intestinal obstruction and hemorrhagic shock. At 1, 3, 5, 10, and 15 years after diagnosis, the cumulative risks for colectomy were 3.4%, 6.2%, 8.0%, 11.0%, and 15.9%, respectively (Fig. 4A). For proctitis, the risks were 0.7%, 1.3%, 1.8%, 3.4%, and 3.4%, respectively. For left-sided colitis, the risks were 3.4%, 7.2%, 8.7%, 10.1%, and 12.6%, respectively. For extensive colitis, the risks were 5.3%, 8.6%, 11.8%, 17.4%, and 26.7%, respectively. The cumulative risks of colectomy in patients with extensive colitis at diagnosis were significantly higher than that in patients with proctitis or left-sided colitis at diagnosis ($P<0.001$) (Fig. 4B). The cumulative risk of colectomy did not differ significantly between initial onset and chronic relapse ($P=0.631$) (Fig. 4C). In the 3 temporal cohorts, the cumulative risks of colectomy showed no difference ($P=0.062$) (Fig. 4D). Of 224 patients receiving biological agents, 27 (12.1%) underwent colectomy at a median of 4 months (IQR, 2–8 months) following the administration of biological agents. Colectomy was independently predicted by disease extent at diagnosis ($HR_{E2}$, 3.131; 95% CI, 1.376–7.124; $HR_{E3}$, 4.810; 95% CI, 2.183–10.601) and ever glucocorticoid usage (HR, 3.359; 95% CI, 1.915–5.891) using multivariate Cox analysis (Supplementary Table 4).

**8. Colitis-Associated Colorectal Cancer**

Five patients (0.4%) developed colorectal tumors/dysplasia. Patient 1 was diagnosed with villous tubular adenoma of the colon 99 months after diagnosis, patient 2 with moderately differentiated adenocarcinoma of the rectum 24 months after diagnosis, patient 3 with highly differentiated adenocarcinoma of the ileocecal region 49 months after diagnosis, patient 4 with sigmoid colon carcinoma 62 months after diagnosis, and patient 5 with tumor of the right colon 22 months after diagnosis. The cumulative risks of colitis-associated colorectal cancer (CAC) occurrence within 1, 3, 5, 10, and 15 years after UC diagnosis were 0%, 0.1%, 0.2%, 0.4%, and 0.4%, respectively.

**9. Mortality**

In general, 4 patients (0.4%) died during the follow-up period. Patient 1 died of liver metastasis of a pancreatic malignant tumor at 53 months after diagnosis. Patient 2 died of hemorrhagic shock and abdominal infection at 86 months after diagnosis after ileal pouch-anal anastomosis. Patient 3 died of septic shock and respiratory failure at 84 months after diagnosis. Patient 4 died of cerebral infarction at 15 months after diagnosis.

## DISCUSSION

In this hospital-based study, we investigated the natural history of UC patients in China. To the best of our knowledge, this is the first study to assess the long-term prognosis and natural course of UC in mainland China.

In the present cohort, 38.5% of patients experienced proximal extension. It was similar as the previous studies. According to a British study,[15] proximal extension can happen at any point following the original diagnosis, and that 31.1% of patients had it within 10 years of diagnosis. In East Asia, this figure was 33.8% in Japan[16] and 30.2% in South Korea.[14] Another study from mainland China reported, that the 5-year cumulative probability of disease extension was 30.5%.[17]

Similar to the previous data,[8] 5-ASA remained to be the most frequently used medication in our cohort. Compared to cohort I, a significant increase in 5-ASA use within 1 year after diagnosis was observed in cohort II, which may reflect the evaluated consciousness of standardized treatment. In light of recurrence and remission characteristics of UC, patients who used glucocorticoids within 5 years after diagnosis still reported to be 49.6%.[18] Our data was similar. However, the use of glucocorticoids has gradually decreased over time, particularly in the last 2 cohorts. It may be partly due to an improved understanding of glucocorticoid use, more standardized early treatment after diagnosis, close surveillance of disease recurrence, or the blooming of emerging therapies.[19] Our research also revealed a more aggressive treatment in UC treatment, with a marked rise in early biologic use. After the policy of reimbursement of biologics in China for UC patients, the tendency was more clear.

It was also the first study among Chinese patients to examine the disease activity patterns of patients with UC. More than half of the patients experienced "chronic active" or "intermittent active" disease patterns, while 33.6% and 8.4% of patients had patterns of "remission" and "continuous remission,"

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respectively, which reflecting the heterogeneity of UC. Surprisingly, the proportion of patients with remission and continuous remission patterns in the cohort III group exhibited a growing tendency when compared to cohort I and cohort II. We must admit that this difference may be partially due to the difference in follow-up time (the first cohort had longer follow-up time than the last 2 cohorts), the potential effect of more aggressive treatment should be considered. Longer follow-up was needed to provide solid evidence.

Mucosal healing is an emerging primary endpoint of UC treatment. Our results showed that only 24.2% of patients have experienced mucosal healing at least once throughout the entire course of the disease. This was relatively lower than the previous data. According to a multicenter study involving 6 Asian nations,[20] 38.2% of patients achieved mucosal healing within 1 year of diagnosis and the cumulative risks of mucosal healing at 12, 18, and 24 months after diagnosis were 22.2%, 44.5%, and 83.9%. The results of inception cohort study in the IBSEN study showed that within 1 year of diagnosis, 50% of patients achieved endoscopic mucosal healing.[21] However, the definition of mucosal healing in UC patients was still controversial,[22] MES = 0 or 1 can be defined as mucosal healing. Since we set a stricter standard for mucosal healing, that is, MES = 0. The proportion of patients with endoscopic scores ranging from 3 to 1 and from 2 to 1 were excluded from our analysis, which may result in a lower mucosal healing rate. Interestingly, we found that the cumulative risk of mucosal healing increased significantly over time. This result may be associated with changes in drug therapy. Although the proximal disease extension rate of proctitis was higher than left-sided colitis, the mucosal healing rate was also higher. There were several studies indicating that proctitis seemed to have better prognosis,[23-26] which might be related to the higher mucosal healing rate. Multivariate Cox regression analysis showed that the disease extent at diagnosis ($HR_{E2}$, 0.571; 95% CI, 0.427–0.763; $HR_{E3}$, 0.515; 95% CI, 0.386–0.687), the use of biologics within 1 year after diagnosis (HR, 1.792; 95% CI, 1.139–2.820) and last 2 cohorts ($HR_{cohort\ II}$, 1.876; 95% CI, 1.164–3.026; $HR_{cohort\ III}$, 3.166; 95% CI, 1.922–5.216) were independent predictors of mucosal healing.

In our group, the 10-year cumulative risk of colectomy was 11.0%, which was higher than that of other Asian cohorts,[14,27,28] comparable to that of European cohorts,[8,13,29] and lower than that of the American cohorts.[30] This may be caused by the variation of included population. In a tertiary hospital, more extensive and refractory patients would be included. The rate of surgery remained stable throughout the study period. However, we found that the interval between diagnosis and surgery was decreased over time. There were several potential explanations for this outcome. Firstly, it may reflect the changes about knowledge and acceptance about surgery of the IBD doctors and patients. Even in the biologic era, surgery for severely ill patients may only be postponed, it cannot be avoided.[31] Postponing surgery can result in increased postoperative complications, mortality and a higher percentage of colostomies.[32-34] The current guideline suggested that it is essential to identify at early-stage patients likely to require colectomy.[35] As a result, to do surgery at the proper time but not as the last choice was gradually accepted. As shown in Supplementary Table 5, refractory UC was the primary reason for surgery, which was consistent to the previous studies.[8,14] In these patients, IBD doctors were prone to do surgery early. At the meantime, the patients' knowledge of the disease has increased over time, which helped them to make the decision of early surgery. Secondly, although the rate of surgery was comparable among the 3 cohorts, a slightly higher proportion (9.4% and 9.5%, respectively, compared to cohorts I and II) of moderate-to-severe patients in cohort III, which may result in higher incidence of surgery in the short term. It was partially caused by the limitation of hospital based and the retrospective nature of the study. Considering the short application time of biologics, we cannot prove a causal relationship between the introduction of biologics and the changes in colectomy. The effect of biologics on medium- and long-term prognosis requires further clinical researches and longer time follow-up.

The incidence rate of CAC varies significantly from one region to another. Geographically, Americans and Britons were at a larger risk than Scandinavians and people living in other nations.[36] There was little available data on CAC in Chinese patients. It was important to note that the CAC incidence in the present study was still lower than that of other Chinese research.[37,38] Given the relatively short duration of our research for malignancy, long-term follow-up was required to elucidate the CAC incidence in patients with UC. We also found that the mortality rate associated with UC was lower than earlier studies,[14,39] which may be due to the improvement of patients' awareness of disease and close monitoring during the follow-up.

Several limitations existed in this research. Firstly, as was already indicated, the longest follow-up period for the latest cohort was only 5 years, which resulted in a shorter follow-up time when we analyzed long-term outcomes as colectomy,

disease activity pattern and trends in therapy, compared to that in the first 2 cohorts. Secondly, limited by the collection of retrospective data, we could investigate the patients' disease activities using each follow-up record, but we could not evaluate the frequency of all disease flares. Finally, population-based studies should be done to further confirm the results.

In conclusion, about 40% of patients developed disease extension and about a half of patients experienced active disease pattern in the current hospital-based cohort study. Colectomy, CAC, and mortality rates continued to be low over time. Biologics were used earlier and more frequently, which may reduce the need for immunosuppressants and glucocorticoids. These changes may increase the rate of clinical remission and mucosal healing. However, the rate of surgery seemed to be stable. Prospective, population-based studies should be conducted to confirm our results and further clarify the changes of natural course of UC in the biologics era.

## ADDITIONAL INFORMATION

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### Conflict of Interest

Gao X is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

### Data Availability Statement

Not applicable.

### Author Contributions

Conceptualization: Gao X. Data curation: Liu X, Chao K. Formal analysis: Liu X, Yang Q, Chao K. Funding acquisition: Diao N, Gao X, Chao K. Investigation: Liu X. Methodology: Chao K. Project administration: Gao X, Chao K. Resources: Gao X, Chao K. Software: Liu X, Yang Q. Supervision: Gao X. Validation: Diao N, Tang J. Visualization: Huang Z. Writing-original draft: Liu X. Writing-review & editing: all authors. Approval of final manuscript: all authors.

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### Supplementary Material

Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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