

ORIGINAL ARTICLE

Initial medical and surgical management of inflammatory bowel disease in the biologic era: A comparison between the United States and China

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Key words

biologics, Crohn's disease, inflammatory bowel disease, inflammatory bowel disease (IBD)-related surgery, ulcerative colitis.

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Abstract

Background and Aims: We compared the initial medical and surgical management of Crohn's disease (CD) and ulcerative colitis (UC) between the United States and China, with aims to better characterize the global variation in the treatment patterns of inflammatory bowel disease (IBD).

Methods: Participants from the United States and China completed a questionnaire on demographic and clinical characteristics, medications (biologics, immunomodulators, aminosaliculates, steroids), and IBD-related surgical history. Patients diagnosed in 2006 and later were eligible. Analysis was restricted to treatment patterns within 1 year of diagnosis. Multivariable logistic regressions examined differences by country.

Results: We recruited 202 CD (US: 49%, China: 51%) and 133 UC (US: 63%, China: 37%) participants. Median age at survey was 31 years (range: 18–76) and at diagnosis was 28 years (range: 12–70). Biologics were commonly used in the United States for CD (66%) and UC (28%) and less commonly in China for CD (19%) and UC (0%). On regression, US CD participants were more likely to receive biologics (odds ratio [OR] 23.82 [95% confidence interval [CI] 8.98–63.14]), aminosaliculates (OR 4.93 [2.00–12.15]), and steroids (OR 4.36 [1.87–10.16]). US UC participants were more likely to receive immunomodulators (OR 3.45 [1.09–10.90]) and steroids (OR 3.31 [1.55–7.06]). There existed minimal differences regarding undergoing surgery for CD (US: 16%, China: 16%) and UC (US: 5%, China: 2%). A proportion (US: 12%, China: 19%) underwent IBD-related surgery prior to diagnosis (median: 5 years; range: 1–39).

Conclusion: US, relative to Chinese, participants were more likely to report early biologic use. There were no differences between countries in undergoing early surgery. Evaluating global practice variation is integral to optimizing early pharmacological therapy and timing of surgery for patients with IBD.

Introduction

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC), which are chronic relapsing and remitting immune-related diseases of multifactorial etiologies. IBD is traditionally considered a “Western” disease, with the highest incidence rates in North America, Europe, Australia, and New Zealand.¹ However, increasing numbers of IBD cases have been documented in Asia since the 1990s, specifically in China.²

While there is reported global heterogeneity of disease activity, most strategies for treatment have largely followed Western guidelines, and guidelines are similar across the world.^{3–8} Medical treatment is chosen according to the patient's

risk profile and disease severity, with aims of controlling inflammation and associated symptoms. The primary goals of therapy are induction and maintenance of remission, with surgical intervention as needed for disease that is refractory to medication. Corticosteroids and aminosaliculates (ASAs) are largely advised to induce remission in most guidelines, while immunomodulators (IMMs) are recommended for maintenance. Furthermore, ASAs are also recommended for the maintenance of UC in many cases. Western guidelines have more recently suggested early biologic use for the induction and maintenance of moderate-to-severe IBD; in contrast, the Asia-Pacific guidelines recommended biologics specifically for steroid-refractory disease.^{7,8}

Infliximab is the most commonly used antitumor necrosis factor (anti-TNF) agent approved for IBD induction and maintenance of remission.^{4,7–9} Infliximab was first approved by the US Food and Drug Administration (FDA) in 1998 and by the China FDA (CFDA) in 2006. Recently published management guidelines (May 2018) approve the use of infliximab for UC.¹⁰ One-fourth of all new pharmacological entities launched in the United States have been biologics, with the market growing rapidly.¹¹ Importantly, the adoption of biologics is costly and requires policy shifts to provide access, all while controlling health-care budgets. The differential introduction of biologics across the globe may account for dissimilarities and obstacles related to the availability and use for IBD management.

Given the rising incidence and prevalence of IBD worldwide, it is important to understand how the treatment patterns may differ by region to ensure management equity across the globe. There are few previous studies that directly compare the management of IBD between Eastern and Western countries. Therefore, we aimed to examine the treatment patterns, including use of medications and surgery within 1 year of diagnosis, among CD and UC patients in the United States and China, diagnosed in 2006 and beyond, when biologics were available in both countries.

Methods

Participants and study design. We recruited patients with either CD or UC and administered a questionnaire regarding IBD and related history. The questionnaire was completed online (bit.ly/IBD-MIMAS) or with a researcher asking the questions in the clinics. In China, patients with IBD were recruited at the Sixth Affiliated Hospital of Sun Yat-Sen University (SYSU, a statewide referral center for IBD patients) in Guangdong, China, during a clinic visit from May 2014 to March 2018. In the United States, patients were recruited from Johns Hopkins Medicine (May 2015 to March 2018), University of California Irvine (March 2016 to March 2018), or through the participant recruitment website ResearchMatch (March 2016 to August 2017). ResearchMatch is a disease-neutral, institution-neutral, online volunteer recruitment platform designed to match volunteers with researchers.¹² Inclusion criteria included participants aged 18 years or older at the time of survey completion with IBD for at least 1 year, diagnosed in 2006 or later, and full completion of modules of the questionnaire with information on demographics and treatment history. Only 97 of 432 eligible participants were excluded because of incomplete questionnaires.

Demographics and clinical characteristics.

Information regarding demographics included age at survey, age at IBD diagnosis, gender, and race (white, black, Asian, other). Duration of disease was assessed by calculating the time between the dates of survey initiation and IBD diagnosis. Questions regarding risk factors or disease-modifiable factors included smoking status at time of diagnosis (current, former, never), family history of IBD (0 members, 1–2 members, 3+ members), diet at time of survey (vegetarian, nonvegetarian, other), employment history at time of survey (ever worked on farm or factory, office worker, never worked, missing), and physical activity levels in the year prior to survey completion (sedentary, light activity,

moderate activity, vigorous activity, very vigorous activity). The physical activity levels were determined using the Stanford Brief Activity survey, which is a validated physical activity questionnaire.^{13,14} History and year of diagnosis of other autoimmune diseases or extraintestinal manifestations, which may require the use of IBD-related medications, was also assessed (arthritis, erythema nodosum, psoriasis, systemic lupus erythematosus, uveitis or episcleritis, and multiple sclerosis).

IBD-related disease activity and symptom severity.

Participants were asked to report their subjective assessment of disease activity during the 6 months prior to the survey. Disease activity was categorized as: severe (symptoms every day or most days), moderate (symptoms 1–2 days per week or month), mild (symptoms for a few days in past 6 months), and remission (absence of symptoms). Questions were also inquired about the severity of abdominal pain, diarrhea, bloody stools, and pus drainage near anus over the year prior to questionnaire completion using the same frequency-based categories of severity.

Medical and surgical management of IBD.

We included participants who were diagnosed with CD or UC in 2006 and later given that biologics were first approved in China in 2006¹⁵; this ensured a homogenous population with regard to each respective country's access to all medications. Moreover, we focused on treatment within 1 year of diagnosis given the importance of the early initiation of appropriate medications and to account for the effect of early treatment choices. Participants were asked to identify medications and the time that they first used the medication. IBD medications included biologics (infliximab, adalimumab, certolizumab, natalizumab, ustekinumab, golimumab, vedolizumab), IMMs (mercaptopurine, methotrexate, azathioprine, cyclosporine, tacrolimus), ASAs (mesalamine or sulfasalazine), and steroids (bethamethasone, budesonide, dexamethasone, fludocortisone, hydrocortisone, methylprednisone, prednisolone, prednisone).

Participants were asked to provide a surgical history. We categorized the following as IBD-related: small bowel resection, large bowel resection, stricturoplasty, diversion, stoma, gastroenterostomy, abdominal fistula repair, abdominal abscess drainage, perianal fistula repair, and perianal abscess drainage. Time to surgery was assessed by calculating time between the month and year of diagnosis and month and year of surgery, and patients were categorized as having surgery either before diagnosis or within 1 year after diagnosis.

Statistical analysis. We compared the participant characteristics between the United States and China using frequencies for categorical variables and medians with ranges for continuous variables. Analyses for CD and UC participants were performed separately. We used multivariable logistic regression models to compare the prevalence of medication use and undergoing surgery within 1 year of diagnosis between the United States and China. We applied two approaches to address confounding: one was based on adjusting for study site, age at diagnosis, gender, and smoking status at time of diagnosis (model 1; minimal adjustment); the second adjusted for study site, age at diagnosis, gender, smoking status at time of diagnosis, use of medications by class within 1 year of diagnosis (including all other

medication classes for each medication analysis and for surgery analysis), and history of surgery within 1 year of diagnosis (for medication analyses; model 2; full adjustment). In this way, regressions also adjusted for use of medications prior to surgery and surgery prior to specific drugs. All analyses were performed using Stata version 15 (College Station, TX, USA).

Ethical considerations. Consent was assumed by completion of the questionnaire if completed online or with written informed consent if completed in the clinic. The Institutional Review Boards of each recruiting site reviewed and approved this study.

Results

Demographic, clinical, and disease characteristics. We recruited a total of 335 individuals who met inclusion

criteria and completed the relevant questionnaire modules. There were 202 participants with CD (US: 49%, China: 51%) and 113 participants with UC (US: 63%, China: 37%). Relevant demographic and clinical characteristics are shown in Table 1.

All participants reported having moderate-to-severe disease activity at the time of the survey, with no difference between countries (Table 2). Chinese participants were more likely to report being severely affected by anal abscesses for both CD (22%) and UC (16%) and bloody stools for UC (35%). However, there were more Chinese participants who reported having remission of abdominal pain (CD: 27%, UC: 45%) and diarrhea (CD: 27%, UC: 31%) secondary to IBD relative to US participants.

Initial medical management. While biologics were commonly used in the United States for both CD (66%) and UC (28%), there were few Chinese participants who received

Table 1 Demographic and clinical characteristics of participants in the United States and China ($N = 335$)

	United States		China	
	CD ($N = 99$)	UC ($N = 85$)	CD ($N = 103$)	UC ($N = 49$)
Age at survey completion, <i>median (range)</i>	31 (18–75)	35 (19–76)	28 (18–51)	33 (18–60)
Age at diagnosis, <i>median (range)</i>	27 (13–68)	31 (17–70)	27 (15–48)	32 (16–56)
Female	73%	67%	41%	59%
Race				
White	87%	81%	0%	0%
Black	4%	6%	0%	0%
Asian	5%	7%	98%	100%
Other	4%	6%	2%	0%
Smoking status at time of diagnosis				
Current	14%	19%	11%	14%
Former	12%	18%	6%	14%
Never	74%	64%	84%	71%
Family history of IBD				
0 members	60%	54%	94%	100%
1–2 members	26%	35%	6%	0%
3+ members	14%	11%	0%	0%
Diet				
Nonvegetarian	92%	95%	92%	98%
Vegetarian	2%	0%	1%	0%
Other	6%	5%	7%	2%
Employment				
Ever farm	5%	11%	1%	6%
Ever factory	3%	11%	34%	27%
Ever office	78%	71%	43%	55%
Never	10%	6%	20%	12%
Missing	4%	2%	2%	0%
Physical activity				
Sedentary	34%	22%	70%	63%
Light activity	27%	26%	23%	31%
Moderate activity	15%	27%	3%	6%
Vigorous activity	20%	20%	4%	0%
Very vigorous activity	3%	5%	0%	0%
History of other autoimmune diseases/manifestations				
Before IBD diagnosis	31%	14%	1%	2%
Within 1 year of IBD diagnosis	14%	5%	1%	2%
>1 year after IBD diagnosis	9%	5%	0%	0%
>1 year after IBD diagnosis	8%	5%	0%	0%

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Table 2 Subjective disease activity and symptom severities of participants in the United States and China (*N* = 335)

	United States		China	
	CD (<i>N</i> = 99) (%)	UC (<i>N</i> = 85) (%)	CD (<i>N</i> = 103) (%)	UC (<i>N</i> = 49) (%)
Disease activity				
Severe	47	53	48	37
Moderate	53	47	52	63
Mild	0	0	0	0
Remission	0	0	0	0
Abdominal pain				
Severe	21	12	26	16
Moderate	44	49	31	18
Mild	25	27	16	20
Remission	9	12	27	45
Diarrhea				
Severe	19	19	24	33
Moderate	54	44	31	16
Mild	20	22	17	20
Remission	7	14	27	31
Bloody stools				
Severe	2	12	3	35
Moderate	28	32	17	29
Mild	26	39	17	16
Remission	43	18	63	20
Anal abscesses				
Severe	8	7	22	16
Moderate	15	18	14	16
Mild	11	31	8	10
Remission	66	45	56	57

CD, Crohn's disease; UC, ulcerative colitis.

biologics for CD (19%) and no participants who received biologics for UC (0%) (Figs 1, 2). Data with regard to IMM, ASA, and steroid use are shown in Figures 1 and 2. A total of 40 participants received no medications within the first year of IBD diagnosis. Fewer CD participants from the United States (1%) relative to China (23%) received no treatment within the first year; however, similar proportions of UC participants received no medications (US: 11%, China: 12%). Thirty-two participants received ASAs, IMMs, and biologics within the first year, with a greater proportion being from the United States (CD: 21%, UC: 8%) compared to China (CD: 4%, UC: 0%).

CD participants from the United States were more likely to receive biologics (Table 3, Model 2: Odds Ratio [OR] 23.82, [95% confidence interval [CI] 8.98–63.14)), ASAs (OR 4.93 [2.00–12.15]), and steroids (4.36 [1.87–10.16]) relative to those from China. UC participants in the United States were more likely to receive IMMs (Model 2: OR 3.45, 95% CI [1.09–10.90]) and steroids (OR 3.31, 95% CI [1.55–7.06]).

Initial surgical management. Similar proportions of participants underwent early surgery for CD (US: 16%, China: 16%) and UC (US: 5%, China: 2%) (Figs 3, 4; Table 3). Many CD patients had an IBD-related surgery before diagnosis (US: 12%, China: 19%), where the median number of years between

the first IBD-related surgery and IBD diagnosis was 6 years (range: 1–39 years) for the United States and 2.5 years (range: 1 to 14 years) for China. The most common types of surgery before diagnosis in the United States were colectomy, followed by small bowel resection and perianal fistula repair. The most common types of surgery before diagnosis in China were perineal abscess drainage, followed by colectomy and small bowel resection. No UC participants underwent surgery before diagnosis.

Discussion

We found differences in initial medical, but not surgical, management between the United States and China for IBD patients. Specifically, those in the United States were more likely to use biologics within the first year of diagnosis. While the proportion of those who underwent surgery early was similar between countries, there was a larger proportion of Chinese participants who underwent surgery for CD prior to diagnosis. Despite these differences, the majority of participants from both countries reported moderate-to-severe disease activity. Such practice variation may be due to several factors, including less experience or access to the growing options for medical management, delays in diagnosis, costs to the national health-care systems and individual patients, differences in utilization of step-up *versus* top-down treatment, or greater periods of time allowed before escalating therapy.

Our findings are in concordance with other comparative studies, which have shown that Eastern patients are less likely to receive biologic therapy for IBD than their Western counterparts.^{16,17} One study showed that 40% of CD patients received biologics in Melbourne compared to 11% in Hong Kong. A 2009 survey study of Asian IBD specialists (*N* = 87) reported that no specialists considered biologics the first choice for the treatment of CD and UC, and only 20% of physicians considered biologics a second choice for CD and 15% for UC.^{17,18} Furthermore, a review of Chinese medication literature reported that 90% of patients used concomitant traditional Chinese medications, suggesting that perhaps cultural perceptions may also confound the treatment of disease.¹⁹ Indeed, later adoption of biologics, limited evidence regarding use in Asian populations, and physician preference and experience may all play a role in choice of therapeutics.

The use of biologics is generally conceived to impose a considerable burden on Asian national health-care systems compared to conventional therapies. The nonnegligible costs associated with biologic therapy include expensive acquisition, increased health resource utilization, and inflexible hospital-based reimbursement policies.^{20–22} A Chinese study aimed to identify barriers to biologic use and identified limitations in China's production, R&D capabilities, and resource allocation.^{15,23} Contrary to these findings, cost-effectiveness analyses have shown that improved quality of life, mental health, physical function, overall health benefits, and economic benefits may outweigh the health-care costs associated with use of biologics.^{24–26} The development of biosimilars has been shown to drive down treatment costs to address the affordability challenge and is thought to benefit countries like China.^{16,27} Future studies delineating the effect of biosimilars on disease rates and remission are warranted.

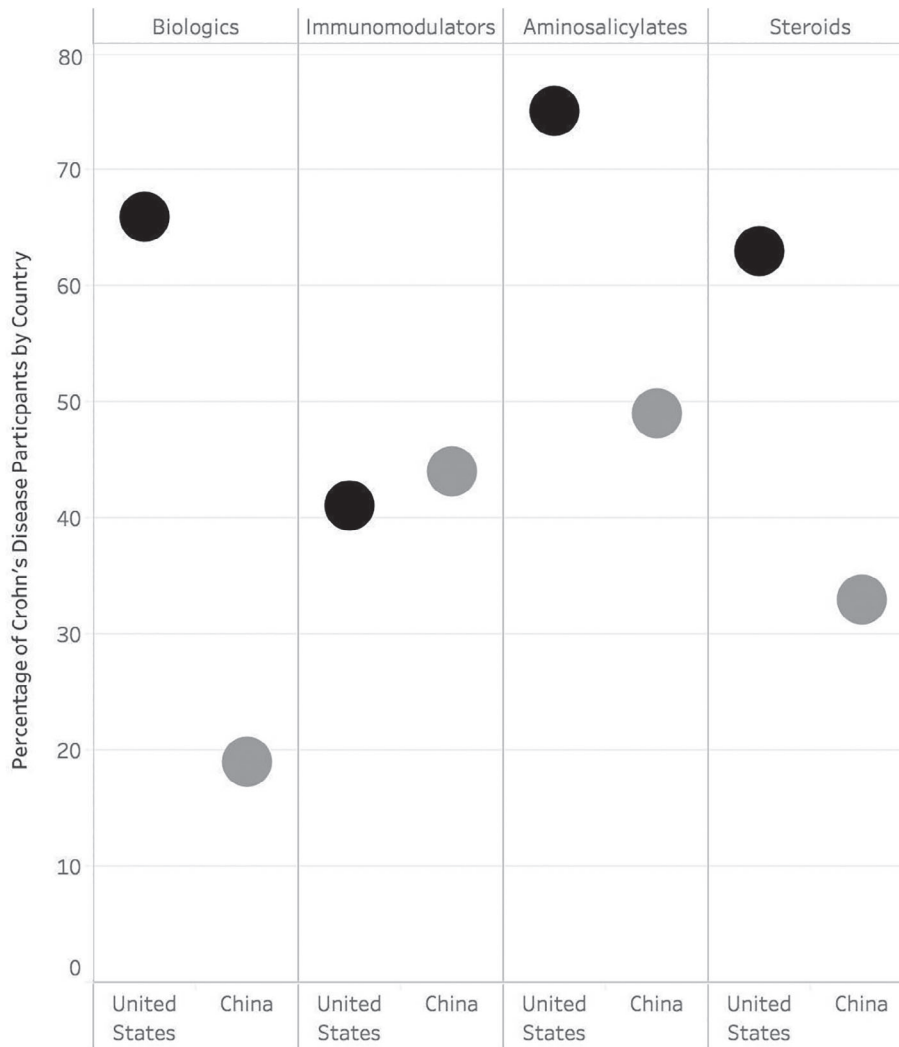


Figure 1 Prevalence of medication use within 1 year of Crohn's disease diagnosis by country.

Costs to individual patients should also be considered. Known differences in the public health insurance systems among Asian countries affect the number of patients able to receive biologics. For example, the percentage of IBD patients receiving biologics is reportedly the highest in Japan, where the payment for diagnosis, treatment, and disease follow-up is entirely covered by the government. On the other hand, there is an annual \$15 000–20 000 out-of-pocket fee for biologics in China, where patients cover their own medical expenses.²⁸ The US health system can be best described as a hybrid. While the passage of the Affordable Care Act in 2010 increased the proportion of the US population that had some type of health insurance to 90%, many patients may still have high out-of-pocket deductibles for biologics.²⁹ Indeed, socioeconomic differences may influence the choice of treatment largely due to options that are available.³⁰ Policies that drive down costs for biologics among patients in the United States, China, and other Asian countries are pivotal.

We found that a number of Chinese participants underwent surgery for CD prior to diagnosis. Physicians' understanding of IBD in China is undergoing rapid and dynamic progress, where familiarity has been growing in the past two decades.³¹ It is possible that those presenting with a combination of either acute abdominal pain, diarrhea, bloody stools, or abscesses were previously misdiagnosed with more prevalent causes of acute abdomen, including appendicitis, diverticulitis, cholecystitis, or acute pancreatitis.³² Reasons for misdiagnosis include low awareness of the differential diagnosis, inadequate radiological and pathological examinations, and a relatively high rate of infections such as intestinal tuberculosis, which may mimic IBD.^{33,34} However, evolving care patterns over time have led to earlier disease detection, endoscopic and radiographic support, and improved access to tertiary-level institutions.³⁵ A systematic review evaluating surgical treatment of IBD in China between 1990 and 2014 found that larger centers and studies performed in later years had

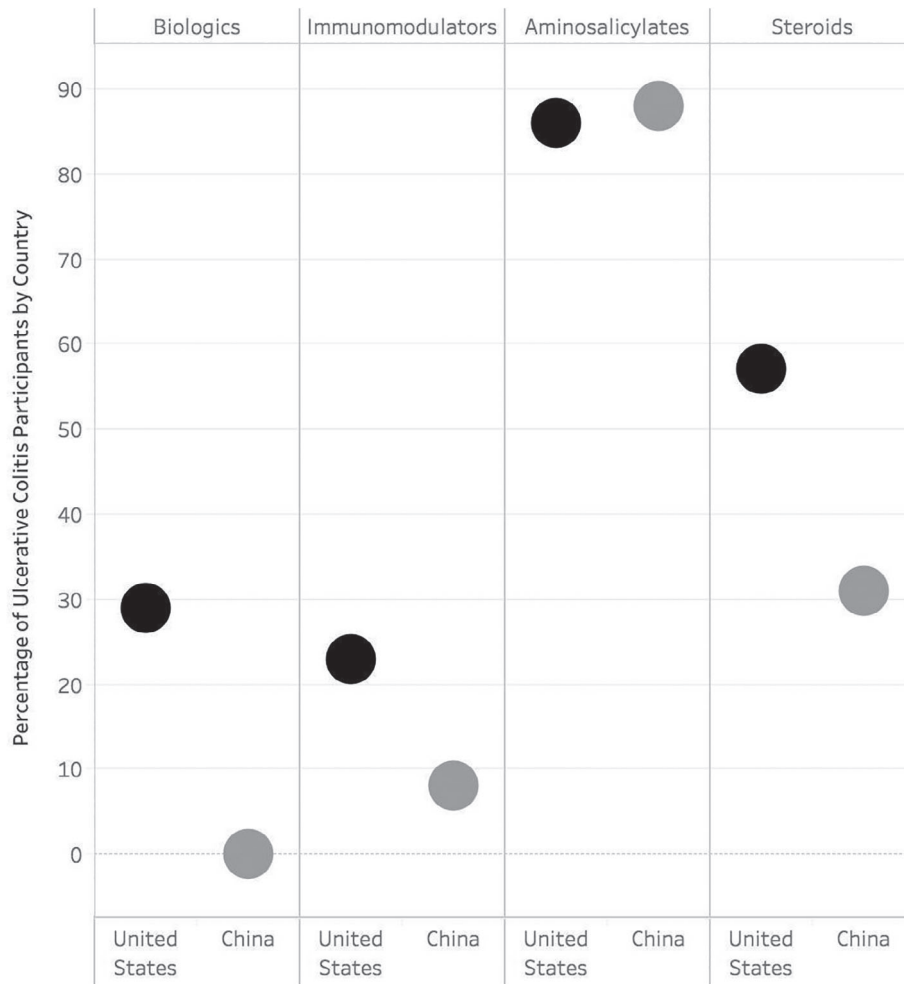


Figure 2 Prevalence of medication use within 1 year of ulcerative colitis diagnosis by country.

Table 3 Odds of selected outcomes within first year of inflammatory bowel disease (IBD) diagnosis in the United States relative to China (reference)

	Crohn's disease			Ulcerative colitis		
	Unadjusted model	Adjusted model 1	Adjusted model 2	Unadjusted model	Adjusted model 1	Adjusted model 2
Surgery	1.04 (0.49–2.23)	1.41 (0.63–3.18)	1.60 (0.56–4.58)	2.37 (0.26–21.83)	2.31 (0.24–21.81)	0.76 (0.04–13.44) [†]
Biologic use	7.93 (4.18–15.06)	12.63 (5.91–27.02)	23.82 (8.98–63.14)	—	—	—
IMM use	0.91 (0.52–1.59)	0.92 (0.50–1.67)	0.32 (0.14–0.73)	2.02 (1.03–10.16)	3.45 (1.09–10.90)	2.10 (0.57–7.70) [‡]
ASA use	3.14 (1.73–5.69)	2.93 (1.56–5.53)	4.93 (2.00–12.15)	0.85 (0.30–2.43)	1.00 (0.34–2.97)	0.81 (0.23–2.86)
Steroid use	3.40 (1.91–6.06)	3.58 (1.91–6.70)	4.36 (1.87–10.16)	3.09 (1.47–6.50)	3.31 (1.55–7.06)	1.88 (0.77–4.59)

[†]Smoking and IMM use were not included in this regression because no UC surgical patients were smokers at time of diagnosis and did not use IMM within the first year.

[‡]Smoking and surgery were not included in this regression because no UC IMM users were smokers at time of diagnosis, and none had undergone surgery within the first year.

Model 1 multivariable regressions adjusted for site, age at diagnosis, and gender. Model 2 multivariable regressions adjusted for site, age at diagnosis, gender, smoking status at time of survey, history of other autoimmune diseases/complications diagnosed within first year of IBD diagnosis, and use of medications by class and history of surgery within 1 year of diagnosis.

95% CI, 95% confidence interval; ASA, aminosalicylates, IMM, immunomodulators; OR, odds ratio.

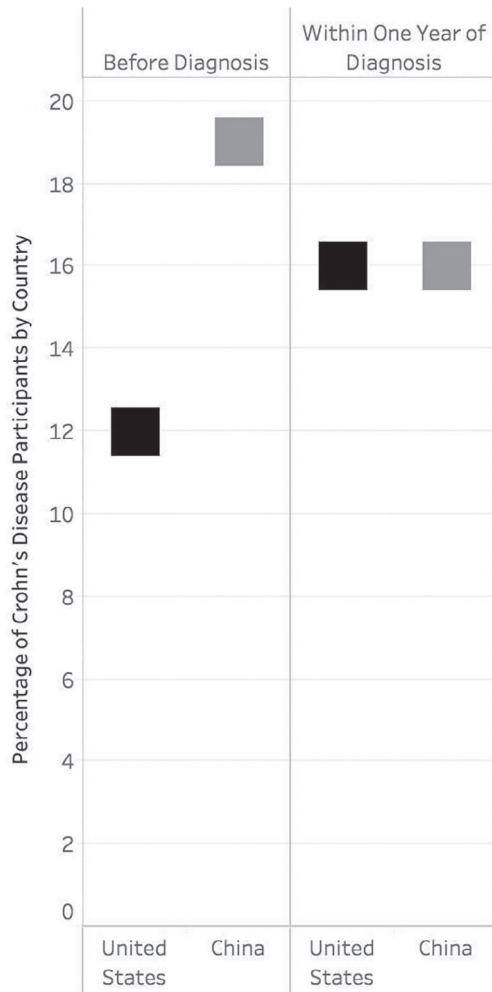


Figure 3 Prevalence of surgery for Crohn's disease by country.

relatively lower rates of CD misdiagnosis and lower postoperative complications for UC.³⁶ Future studies should assess the probable declining rates of IBD-related surgery prior to diagnosis, especially as Chinese physicians and patients become more familiar with the disease process and aim to optimize medical therapy to achieve better control of IBD.

We acknowledge several limitations in this study. First, we analyzed a convenience sample as the study population included patients recruited from tertiary referral centers. While this sample may not be generalizable to all IBD patients in both the United States and China, acquiring patients who received care from tertiary referral centers provided us with granular information related to their medical and surgical management. Second, as patients provided their own responses, our data may be subject to recall bias; however, this provided us with the unique opportunity to obtain patient-level symptoms in the last 6 months. Finally, while a patient's severity of disease may affect their recall of prior symptoms, we sought to address this potential limitation by asking for severity at the time of completing the questionnaire. The ECCO-EpiCom inception cohort supports that differences in disease management may be related to

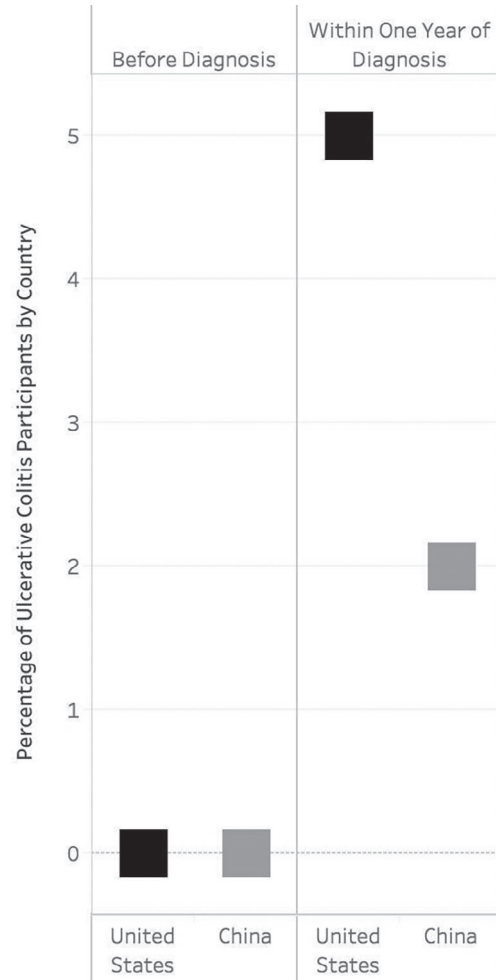


Figure 4 Prevalence of surgery for ulcerative colitis by country.

factors outside of the medical or disease severity realms and complicated by significant differences in the health systems across regions.³⁰

In conclusion, participants with IBD from the United States were more likely to have received biologics relative to their Chinese counterparts, although without differences in undergoing surgical management. Importantly, a significant number of participants underwent surgery for CD prior to its diagnosis. Similar disease activities and symptomatology were reported between the two countries, suggesting that management differences may be related to practice variation. With the increasing global incidence and prevalence of IBD, it is imperative to further characterize the differences in IBD management for future standardization and equality in achieving disease control.

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