Gastroenterology 2024;166:815–825

Early Initiation of Biologics and Disease Outcomes in Adults and Children With Inflammatory Bowel Diseases: Results From the Epidemiology Group of the Nationwide Israeli Inflammatory Bowel Disease Research Nucleus Cohort

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BACKGROUND & AIMS: In this nationwide study, we explored whether early initiation of biologics is associated with improved outcomes in children and adults with Crohn's disease (CD) and ulcerative colitis (UC). **METHODS:** All patients diagnosed with CD or UC in Israel (2005–2020) were included in the Epidemiology Group of the Israeli Inflammatory Bowel Disease Research Nucleus cohort, encompassing 98% of the population. We compared disease duration at biologics initiation (ie, 0–3 months, >3–12 months, >1–2 years, and >2–3 years) using the cloning, censoring, and weighting by inverse probabilities method to emulate a target trial, adjusting for time-varying confounders and selection bias. **RESULTS:** Of the 34,375 included patients (of whom 5240 [15%] were children), 7452 of 19,264 (39%) with CD and 2235 of 15,111 (15%) with UC received biologics. In CD, by 10 years postdiagnosis, the probability of CD-related surgery decreased gradually but modestly with earlier initiation of biologics; a significant difference was noted between >2–3 years (31%) and 0–3 months (18%; $P = .02$; number needed to treat, 7.7), whereas there was no difference between the 0–3-month and >3–12-month periods. The 10-year probability of steroid dependency for the 0–3-month period (19%) differed both from the >2–3-year (31%; $P < .001$) and 1–2-year periods (37%; $P < .001$). In UC, no significant differences in colectomy or steroid dependency rates were observed between the treatment initiation periods. Similar trends were noted in the pediatric population. **CONCLUSIONS:** Very early initiation of biologics was not associated with some outcomes except for a modest risk reduction of surgery and steroid dependency for CD, which requires confirmation in future studies. In UC, early introduction of biologics was not associated with reduced risk of colectomy or steroid dependency.

Keywords: Ulcerative Colitis; Crohn's Disease; Biologics Initiation; Surgery; Steroid Dependency.

Although biologics have revolutionized the treatment of inflammatory bowel diseases (IBDs), their effectiveness in improving long-term outcomes remains controversial, as reported in population-based studies of adults[1,2] and children.[3,4] In the epidemiology group of the nationwide Israeli IBD Research Nucleus (epi-IIRN) cohort, we previously showed that despite a sharp increase in the use of biologics since 2005, outcomes for adults and children with Crohn's disease (CD) improved only modestly.[5] In ulcerative colitis (UC), only hospitalization rates decreased in association with the increasing use of biologics, and colectomy and steroid dependency rates remained unchanged.[6]

It has been argued often that the effect of biologics on the natural history of CD may be diminished if they have been initiated too late during the disease course. This notion led to the "top-down" approach, in which biologics are initiated early in those who are judged to be at risk for a complicated disease course. Several studies, mostly retrospective or post hoc analyses of randomized controlled trials (RCTs) with limited sample sizes, have explored the effectiveness of early vs late introduction of anti–tumor necrosis factor (TNF) in CD, suggesting that earlier treatment leads to better outcomes.[7,8] However, these studies were from referral centers, and most dichotomized early treatment as 2 years from diagnosis,

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Abbreviations used in this paper: **CD, Crohn's disease; CI, confidence interval; epi-IIRN, epidemiology group of the Israeli IBD Research Nucleus; HMO, health maintenance organization; IBD, inflammatory bowel disease; IQR, interquartile range; NNT, number needed to treat; RCT, randomized controlled trial; SMD, standardized mean difference; TNF, tumor necrosis factor; TTE, target trial emulation; UC, ulcerative colitis.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2024.01.041

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Two administrative studies explored the effectiveness of early (ie, <2 years from diagnosis) introduction of biologics while controlling for baseline characteristics by propensity score, which does not address time-varying confounders.

NEW FINDINGS

Early initiation of biologics was associated with modest risk reduction of surgery and steroid dependency for CD, which requires confirmation in future studies, but not in UC.

LIMITATIONS

Our study lacked variables that could influence the decision to initiate biologics at certain time periods, such as endoscopic activity, symptom assessment, and imaging results.

CLINICAL RESEARCH RELEVANCE

Our data may support initiation of biologics during the first year after diagnosis of CD in patients who are at particular risk for complicated disease, but further studies are required to verify this. In UC, step-up treatment with mesalamine, thiopurines, and then biologics may be appropriate because earlier introduction of biologics does not change the natural disease course.

BASIC RESEARCH RELEVANCE

This is the first study, to our knowledge, to use a target trial emulation approach to address time- related biases (eg, lead time bias and immortal time bias) in addition to confounding by indication. The successful implementation of this advanced strategy may serve as a model for other administrative studies exploring similar research questions.

thus missing the potential effect of truly "early" treatment. Moreover, the short follow-up periods in these studies may have led to erroneous positive associations in cases where early initiation of biologics merely delayed the inevitable.

To date, only 2 population-based studies explored the association between early biologic treatment and disease outcomes while adjusting for baseline characteristics, one in CD and UC[9] and the other in UC.[10] Both studies used propensity score matching, which in retrospective analyses may alleviate confounding by indication bias to some extent but not the time-varying confounding effect. The latter may bias the results when time-varying variables are associated both with the exposure and the outcome, such as when exploring the timing of biologics initiation.[11] A third population-based administrative study compared the effectiveness of anti-TNF treatment initiated within 30 days of disease onset or later in children and young adults but without adjusting for baseline severity and reported inconclusive results.[12]

The ideal design for studying the optimal timing of biologics initiation would randomize patients at diagnosis to different time-to-biologics periods and include several years of follow-up. While awaiting such a trial, real-world administrative data can attempt to emulate it using the target trial emulation (TTE) approach.[13] This uses observational data to mimic a target trial through a structured process of selecting patients and defining the exposure and outcome with weights assigned at different timepoints of the follow-up.[13]

We thus aimed to use unselected nationwide data from the epi-IIRN cohort to explore whether early initiation of biologics treatment is associated with improved disease outcomes in CD and UC while adjusting for both confounding by indication and time-dependent biases through advanced modeling of TTE. We also compared the results for childhood-onset vs adult-onset disease.

Methods

This study used the epi-IIRN cohort, which includes all IBD patients in Israel (n = 53,161 as of June 2020) as derived from the country's 4 health maintenance organizations (HMOs), which insure 98% of the population. The electronic medical records of the HMOs contain detailed data on health contacts, medication purchases, procedure codes, blood test results, and use of other ambulatory health services. Medication purchase records are accurate because they are dispensed and subsidized by the HMOs. To identify patients with IBD, we applied a previously developed case ascertainment algorithm, which was validated with high accuracy (99% specificity, 89% sensitivity, 92% positive predictive value, and 99% negative predictive value).[14] Data obtained from the HMOs were linked by a deterministic approach to the Israeli Ministry of Health's national registries, which maintain prospective validated records on surgeries and admissions.

The HMOs made the transition from paper to electronic records between 2000 and 2003, and subsequently, 2005 was validated as the cutoff for determining incidence, which corresponds to a look-back period of 2 to 5 years.[14] We excluded those with medication/code before 2005 because it was unknown whether the first code/medication was simply the first record in the newly established computerized system. After 2005, the first IBD-related code/medication was taken as the diagnosis date as previously validated.[14] As more time passes since the establishment of the computerized system in 2000, the accuracy of the algorithm is improving as the average look-back period of our cohort increases. Nonetheless, for a sensitivity analysis, we have added the diagnostic delay for each patient to our model to account for possible bias in technical and real delays in the diagnosis date. We estimated the diagnostic delay from the first gastrointestinal-related International Classification of Diseases–9th Revision code during the 5-year period before diagnosis in accordance with Benchimol et al[15] and, in addition, from the presence of anemia or hypoalbuminemia.

We included patients with CD and UC who initiated biologics between January 2005 and June 2020. In a classic TTE, we would have included all patients in the target trial from the earliest date they were eligible to receive biologics (ie, date of diagnosis). However, that approach might have biased our analysis because patients diagnosed with mild disease would never be eligible to receive such treatment. Nonetheless, we added a sensitivity analysis that included all patients (ie, those who did and did not receive biologics).

We compared 4 biologics initiation periods determined a priori based on clinical judgment: disease onset (ie, first 3

months from diagnosis), very early initiation (3–12 months), early initiation (1–2 years), and late initiation (2–3 years). Biologics treatments that began after 3 years were excluded to minimize a potential bias arising from the fact that the practice of initiating biologics >3 years from diagnosis was mainly seen during the first years of our cohort. However, we also included a sensitivity analysis with patients initiating biologics after 3 years of diagnosis. CD and UC were analyzed separately, and subgroup analysis was conducted for the pediatric population. The primary outcomes were time to steroid dependency (ie, cumulative steroid treatment for >90 days in any given year), IBD-related surgery for CD, and colectomy for UC (Supplementary Table 1). Patients were followed until discontinuing biologics (ie, no treatment for at least 90 days), death, emigration, or end of follow-up. Switching between biologics within the 90-day timeframe was considered as continuous biologic treatment. Socioeconomic status was determined using a standardized system provided by Points Location Intelligence, which uses Israel Central Bureau of Statistics socioeconomic data with additional variables and was scored from 1 (lowest) to 10 (highest).

To account for the considerable heterogeneity in the frequency and timing of routine laboratory tests in an administrative database, we grouped all patients in severity groups according to the available tests combined (hemoglobin, white blood cell count, platelets, albumin, C-reactive protein, erythrocyte sedimentation rate, and fecal calprotectin) by hierarchical clustering. This method was previously validated and used in the epi-IIRN cohort to account for disease severity[16] (see Supplementary Methods for more details). If considered individually, the large amount of missing data would have led to the exclusion of many patients from the models because only the minority of patients had all tests available at a given time before diagnosis (Supplementary Tables 2 and 3).

Analytic Approach

The framework of a TTE design proposes that time-dependent modeling can account for differences that may change between groups of patients in observational databases during the follow-up period and thus compare them as if they were randomized. (Detailed descriptions of this method can be found in the Supplementary Methods, Supplementary Table 4, and Supplementary Figures 1 and 2). Briefly, the framework uses the cloning, censoring, and weighting method,[17] which can mitigate not only confounding by indication but also time-varying confounding for confounders at baseline, time-varying confounders, immortal time bias, and lead time bias. Immortal time bias occurs when studies fail to align the start of follow-up and treatment assignment, which can be seen in cases where information on time to treatment is used to classify patients into exposure groups[18] (Supplementary Figure 3). Lead time bias may favor early initiators, lending to an artificial survival advantage because they are earlier in their disease progression than late initiators[19] (Supplementary Figure 3).

The first step of the TTE method, cloning, allows for patients to be assigned to all 4 treatment strategies when treatment allocation is still unknown. We can assume that all patients are potentially eligible to receive biologics at baseline (ie, time of diagnosis). Therefore, initially, all patients enter all treatment strategies (ie, treatment periods). Practically, we created 4 identical replicates of each patient's record corresponding to each of the 4 treatment strategies, making the new dataset 4 times larger than the original one. At this point, baseline confounding is eliminated because all baseline characteristics are identical for all strategies. Next, we assessed whether replicates adhered to their assigned treatment strategy at quarterly intervals. Replicates were eliminated from further analyses as soon as they were censored from their assigned treatment strategy (ie, starting biologics or not). This process ensured that the event (ie, surgery or steroid dependency) accounted for the relevant treatment strategy of each patient. Time-varying inverse probability weighting was used to balance the impact of potential confounders between the treatment initiation periods and to adjust for potential selection bias.[17,19] Essentially, the weight of the censored replicates is redistributed among the remaining replicates with similar characteristics (Supplementary Figure 4). Baseline

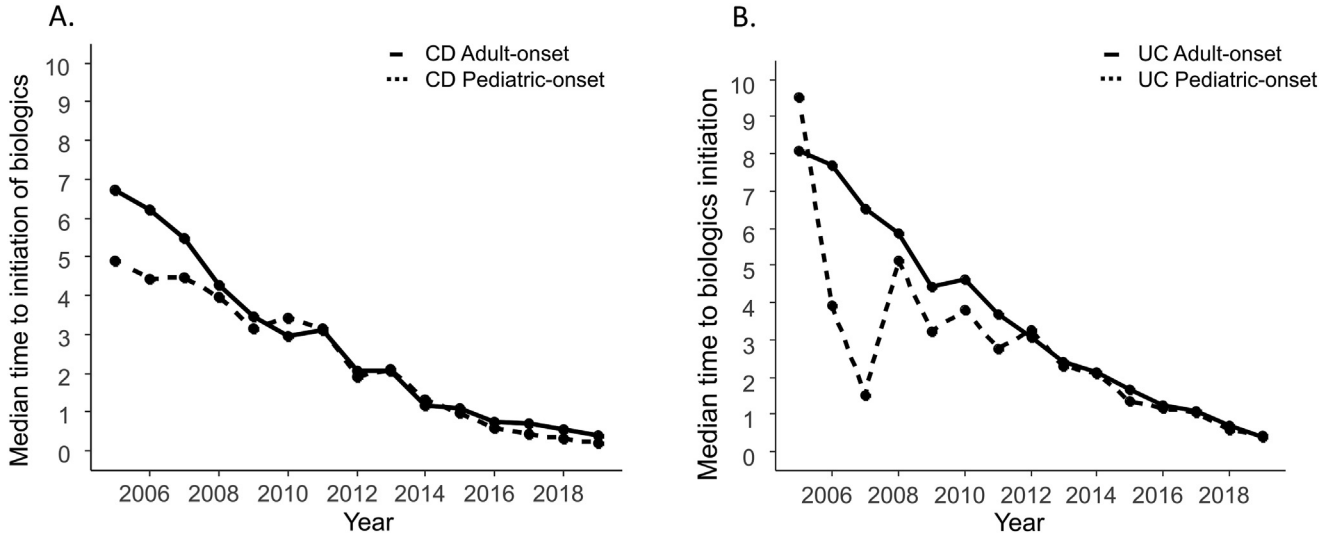

Figure 1. Median time to biologics from 2005 to 2019 in Crohn's disease (CD) (*A*) and ulcerative colitis (UC) (*B*) stratified by adults and children.

Table 1. Basic Characteristics of Patients Initiating Biologics in the epi-IIRN Cohort

Variables	CD (n = 7242)	UC (n = 2235)
Age at diagnosis, *y*, mean ± SD	29 ± 16	31 ± 17
Pediatric onset (<18 y), n (%)	2112 (29)	561 (25)
Adult onset (18–65 y), n (%)	4866 (67)	1569 (70)
Elder onset (>65 y), n (%)	264 (4)	105 (5)
Male sex, n (%)	3984 (55)	1093 (55)
Year of diagnosis, n (%)		
2005–2010	2317 (32)	772 (35)
2010–2015	2529 (35)	613 (27)
2015–2020	2396 (33)	850 (38)
Follow-up period, *y*, median (IQR)	6.9 (3.5–9.9)	7 (4–11)
Time to initiating biologics, median (IQR)	1.3 (0.4–4.0) y	2.2 (0.8–5.1) y
0–3 mo, n (%)	1115 (15)	206 (9)
>3–12 mo, n (%)	2050 (28)	450 (20)
>1–2 y, n (%)	1129 (16)	396 (18)
>2–3 y, n (%)	704 (10)	271 (12)
>3 y, n (%)	2244 (31)	912 (41)
First biologic, n (%)		
Anti-TNF	6738 (93)	1682 (75)
Ustekinumab	42 (1)	4 (0)
Vedolizumab	457 (6)	534 (24)
Tofacitinib	5 (0)	15 (0)
SES points, median (IQR)	6 (5–7)	6 (4–7)
District of residence, n (%)		
Central	5501 (76)	1632 (73)
Northern	824 (11)	332 (15)
Southern	917 (13)	272 (12)
Perianal disease before IBD diagnosis, n (%)	554 (8)	—
Clusters of disease severity by blood tests at diagnosis, n (%)		
Minimal	1524 (21)	—
Mild	2895 (40)	334 (15)
Moderate	1622 (22)	736 (33)
Severe	686 (9)	952 (43)
Extreme	514 (7)	213 (10)

NOTE. Baseline characteristics are identical for all four time periods (see Methods for details).
SD, standard deviation; SES, socioeconomic status.

variables included in the model were age, year of diagnosis, district of residence, sex, socioeconomic status, diagnostic delay, laboratory severity clusters, and perianal disease. Time-varying variables per quartile, starting after the baseline period and until the end of follow-up, were added, including the use of mesalamine and immunomodulators, as well as laboratory test results (C-reactive protein, platelets, albumin, white blood cell count, and hemoglobin), hospitalizations with gastrointestinal-related diagnoses, gastroenterologist visits, IBD-related comorbidity (Supplementary Table 5), and subsequent diagnosis of perianal disease. Time-varying weights were assigned to all replicates for each disease quarter. These weights, estimated by fitting a pooled logistic model for quarterly probabilities, represented the probability that a replicate would remain uncensored during follow-up. We truncated the weights at the 99th percentile to avoid the influence of outlying values.[19] Pairwise standardized mean differences (SMDs) were used to assess whether the weighted groups constructed by the model at baseline were indeed balanced across the time period groups. This analysis was repeated for all models; SMD of <0.1 was considered well balanced.[20]

Baseline characteristics were well balanced between treatment periods (ie, SMD < 0.1) in all models described hereafter except for year of diagnosis in CD (Supplementary Tables 6–13). We therefore added the variable "year of diagnosis" to all models, and, in addition, we stratified the data by year of diagnosis (before 2010 and after 2010) in a sensitivity analysis to ensure similarity. Subsequently, Kaplan-Meier survival curves weighted by the previously obtained inverse probability weightings were estimated to assess the effect of time-to-biologics initiation periods on disease outcomes. To estimate the long-term effects of early biologics initiation, we estimated the pointwise 7- and 10-year probabilities of the outcome from the curve. The complexity of the statistical methods used in this study, including time-dependent weights, prevented analyzing trends between initiation periods. The 95% confidence intervals (CIs) for survival probabilities were obtained through a nonparametric bootstrap procedure with 500 replicates. $P < .05$ was considered significant, and all analyses were made in R version 4.0.0 (R Core Team).

Results

Of the 34,375 patients diagnosed with IBD during the study period, 7452 of 19,264 (39%) CD patients received biologics (2112 [29%] children and 5130 [71%] adults), as did 2235 of 15,111 (15%) UC patients (561 [25%] children and 1674 [75%] adults) (Supplementary Figure 2). For CD, the median time to biologics was 1.3 years (interquartile range [IQR], 0.44–4.0] (1 year [IQR, 0.3–3.6] in children and 2.8 years [IQR, 0.5–4.2] in adults), and for UC, the median time to biologics was 2.19 years (IQR, 0.82–5.07) (1.58 years [IQR, 0.59–3.74] in children and 2.41 years [IQR, 0.92–5.43 in adults]). The median follow-up duration was 6.8 years (IQR, 3.5–10.6) for CD and 7 years (IQR, 4–11) for UC, translating to a total of 69,767 patient-years (Figure 1). Among the CD and UC patients, respectively, 1115 and 206 received biologics during the first 3 months after diagnosis; 2050 and 450 during the 3–12-month period; 1129 and 396 during the >1–2-year period; and 704 and 271 during the >2–3-year period. Most of the eligible patients (93% in CD and 75% in UC) initiated anti-TNF as the first biologic (Table 1).

Crohn's Disease

There was a gradual, albeit modest, decrease in CD-related surgeries when biologics were initiated earlier (Figure 2). The difference was significant only when comparing the 2 extreme groups (<3 months vs >2–3 years after diagnosis) but not when comparing >3–12 months to >1–2 years (Figure 2). The probability of IBD-related surgery at 10 years was 18% (95% CI, 11–26) for those

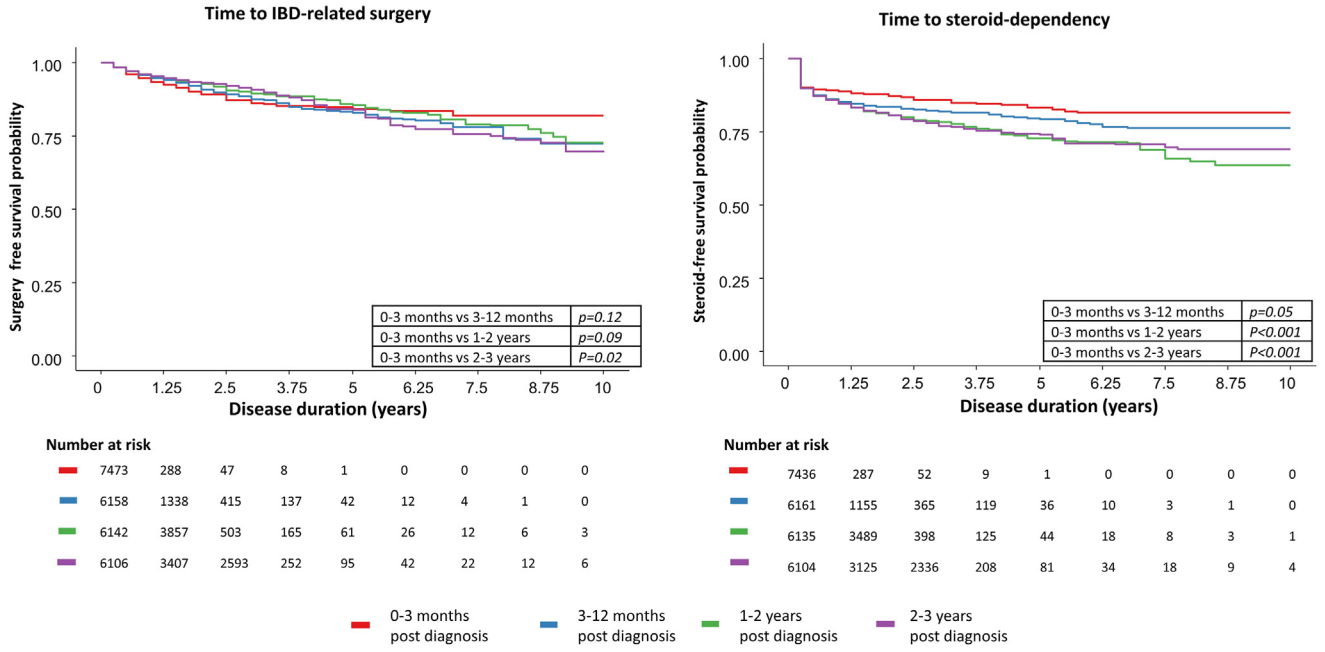

Figure 2. Time to disease outcomes in CD stratified by time to biologics treatment.

starting biologics at 0–3 months postdiagnosis and 31% (95% CI, 24–38) for those starting in the >2–3-year period ($P = .02$; number needed to treat [NNT], 7.7). (The 7-year probabilities are presented in Table 2). The same observation, but with a larger and earlier effect, was apparent for steroid dependency, with a statistical difference seen for those initiating biologics earlier than 12 months from diagnosis but with no significant difference between initiation in the 0–3-month and >3–12-month periods (Figure 2). The probability of steroid dependency (ever) by 10 years was 19% (95% CI, 14–23) for those starting biologics during the 0–3-month period compared with 31% (95% CI, 27–35) for those starting biologics during the >2–3-year period ($P < .001$; NNT, 8.3) (Table 2).

A similar trend was noted in subgroup analysis of the pediatric cohort, although the advantage of early initiation of biologics did not reach statistical significance given the smaller sample size (Supplementary Figure 5 and Table 3). By 10 years, the probability of surgery in children initiating biologics during the first 3 months was 14% (95% CI, 0–29) compared with 32% (95% CI, 21–43) in the 2–3-year period (Supplementary Figure 5, Table 3). The 10-year probability for steroid dependency for those in the 0–3-month period was 22% (95% CI, 13–32) vs 26% (95% CI, 20–31) in the 2–3-year period (Supplementary Figure 5 and Table 3).

Ulcerative Colitis

There was no decrease in colectomy rates for those initiating biologics early during the disease course compared to later initiation (Figure 3). The probability of colectomy at 10 years was 4% (95% CI, 1–8) for those initiating biologics within the first 3 months postdiagnosis vs 5% (95% CI, 1–10) for those starting in the 2–3-year period ($P = .71$). (The 7-year probabilities are presented in Table 2.) Although there was a numeric decrease for steroid dependency, the advantage of early biologics initiation did not reach statistical significance (Figure 3). The probability of steroid dependency (ever) by 10 years was 25% [95% CI, 0–54] for those initiating biologics during the 0–3-month period vs 56% (95% CI, 42–70) in the latest period ($P = .06$) (Table 2).

Similar nonsignificant results were observed in the pediatric population (Supplementary Figure 6 and Table 3). By 10 years postdiagnosis, the probability for colectomy in children initiating biologics in the 0–3-month period was 6% (95% CI, 0–12) vs 8% (95% CI, 0–17) in the >2–3-year period ($P = .74$) (Supplementary Figure 6 and Table 3). The corresponding 10-year probabilities for steroid dependency were 26% (95% CI, 18–34) vs 58% (95% CI, 51–65), respectively ($P < .001$) (Supplementary Figure 6 and Table 3).

These results were similar in sensitivity analyses that included all patients rather than only those who eventually received biologics and, separately, when also including patients who received biologics after 3 years from diagnosis (Supplementary Figure 7 and Supplementary Tables 14 and 15), when stratifying patients by year of diagnosis (Supplementary Figure 8 and Supplementary Table 16), and when including the diagnostic delay variable to the models (data not shown).

Discussion

In this nationwide study, which, to our knowledge, is the largest to date to explore the effect of the timing of biologics initiation on disease outcomes, we show that early initiation of biologics may be associated with a modest improvement in long-term outcomes for patients with CD. The absolute risk reduction in the 10-year probability for surgical

Table 2. Disease Outcomes in CD and UC, Comparing Between Disease Duration Periods Before Biologics Initiation

Disease outcomes	Probability, % (95% CI)	0–3 mo	3–12 mo	1–2 y	2–3 y
CD					
7-year probability for surgery					
0–3 mo	18 (11–25)	—	—	—	—
3–12 mo	22 (18–26)	$P = .35$	—	—	—
1–2 y	20 (15–24)	$P = .75$	$P = .38$	—	—
2–3 y	24 (19–30)	$P = .17$	$P = .48$	$P = .16$	—
10-year probability for surgery					
0–3 mo	18 (11–26)	—	—	—	—
3–12 mo	28 (18–37)	$P = .12$	—	—	—
1–2 y	27 (20–35)	$P = .09$	$P = .9$	—	—
2–3 y	31 (24–38)	$P = .02$	$P = .62$	$P = .50$	—
7-year probability for steroid dependency					
0–3 mo	19 (14–23)	—	—	—	—
3–12 mo	24 (21–27)	$P = .05$	—	—	—
1–2 y	31 (27–36)	$P < .001$	$P < .01$	—	—
2–3 y	29 (26–33)	$P < .01$	$P = .02$	$P = .52$	—
10-year probability for steroid dependency					
0–3 mo	19 (14–23)	—	—	—	—
3–12 mo	24 (21–27)	$P = .05$	—	—	—
1–2 y	37 (29–44)	$P < .001$	$P < .01$	—	—
2–3 y	31 (27–35)	$P < .001$	$P < .01$	$P = .21$	—
UC					
7-year probability for colectomy					
0–3 mo	4 (1–8)	—	—	—	—
3–12 mo	10 (3–17)	$P = .17$	—	—	—
1–2 y	7 (3–11)	$P = .34$	$P = .52$	—	—
2–3 y	5 (1–10)	$P = .71$	$P = .31$	$P = .62$	—
10-year probability for colectomy					
0–3 mo	4 (1–8)	—	—	—	—
3–12 mo	10 (3–17)	$P = .17$	—	—	—
1–2 y	7 (3–11)	$P = .34$	$P = .52$	—	—
2–3 y	5 (1–10)	$P = .71$	$P = .30$	$P = .62$	—
7-year probability for steroid dependency					
0–3 mo	25 (0–66)	—	—	—	—
3–12 mo	54 (26–82)	$P = .24$	—	—	—
1–2 y	42 (37–47)	$P = .41$	$P = .41$	—	—
2–3 y	56 (42–70)	$P = .16$	$P = .90$	$P = .07$	—
10-year probability for steroid dependency					
0–3 mo	25 (0–54)	—	—	—	—
3–12 mo	54 (28–80)	$P = .15$	—	—	—
1–2 y	42 (37–47)	$P = .25$	$P = .38$	—	—
2–3 y	56 (42–70)	$P = .06$	$P = .90$	$P = .07$	—

NOTE. *P* values denote comparisons between periods.

resection between those initiating biologics within 3 months of diagnosis vs after 2–3 years was 13%, translating to an NNT of 7.7. The lack of statistical significance for periods earlier than 2 years for surgery and 1 year for steroid dependency allows for early initiation to be defined as 1–2 years from diagnosis, which is in line with the time period recommended by the Paris definition for early CD trials.[21] However, although not statistically significant, we observed a further gradual decrease in surgery rates and steroid dependency when biologics were initiated in earlier time periods. In UC, early initiation of biologics was not associated with reduced rates of colectomy and steroid dependency. Similar trends were noted in the pediatric-onset disease subgroup. The lack of association between the timing of biologics initiation and colectomy in UC is in agreement with 2 smaller population-based studies,[9,10] both of which stratified patients into before and after 2-year periods without further categorization, and a recent meta-analysis of 9 RCTs showing that the timing of biologics initiation was not associated with colectomy rates.[22]

Surprisingly, few CD studies have directly examined the association between timing of biologics initiation and disease course. The only other population-based administrative study to do so was a propensity score-adjusted analysis of 742 patients, which showed that initiation earlier than 2 years was associated with superior outcomes.[9] Three additional studies of CD patients, 2 retrospective and 1 of registry data, similarly suggested that early initiation of anti-

Table 3. Disease Outcomes in CD and UC *Pediatric Patients*, Comparing Between Disease Duration Periods Before Initiation of Biologics

Disease outcomes	Probability, % (95% CI)	0–3 mo	3–12 mo	1–2 y	2–3 y
CD					
7-year probability for surgery					
0–3 mo	14 (0–29)	—	—	—	—
3–12 mo	19 (13–26)	$P = .51$	—	—	—
1–2 y	16 (9–23)	$P = .85$	$P = .45$	—	—
2–3 y	29 (18–41)	$P = .11$	$P = .15$	$P = .05$	—
10-year probability for surgery					
0–3 mo	14 (0–29)	—	—	—	—
3–12 mo	22 (13–31)	$P = .40$	—	—	—
1–2 y	25 (12–38)	$P = .27$	$P = .66$	—	—
2–3 y	32 (21–43)	$P = .06$	$P = .16$	$P = .44$	—
7-year probability for steroid dependency					
0–3 mo	22 (13–31)	—	—	—	—
3–12 mo	23 (19–27)	$P = .84$	—	—	—
1–2 y	26 (20–33)	$P = .44$	$P = .40$	—	—
2–3 y	24 (21–26)	$P = .75$	$P = .84$	$P = .43$	—
10-year probability for steroid dependency					
0–3 mo	22 (13–31)	—	—	—	—
3–12 mo	23 (19–27)	$P = .83$	—	—	—
1–2 y	35 (18–53)	$P = .18$	$P = .18$	—	—
2–3 y	26 (20–31)	$P = .49$	$P = .45$	$P = .29$	—
UC					
7-year probability for colectomy					
0–3 mo	6 (0–12)	—	—	—	—
3–12 mo	20 (1–39)	$P = .17$	—	—	—
1–2 y	3 (0–6)	$P = .39$	$P = .08$	—	—
2–3 y	8 (0–17)	$P = .74$	$P = .26$	$P = .33$	—
10-year probability for colectomy					
0–3 mo	6 (0–12)	—	—	—	—
3–12 mo	20 (2–38)	$P = .14$	—	—	—
1–2 y	3 (0–6)	$P = .38$	$P = .07$	—	—
2–3 y	8 (0–17)	$P = .74$	$P = .24$	$P = .33$	—
7-year probability for steroid dependency					
0–3 mo	26 (18–34)	—	—	—	—
3–12 mo	44 (33–55)	$P < .05$	—	—	—
1–2 y	54 (43–66)	$P < .001$	$P = .22$	—	—
2–3 y	57 (49–66)	$P < .001$	$P = .06$	$P = .64$	—
10-year probability for steroid dependency					
0–3 mo	26 (18–34)	—	—	—	—
3–12 mo[a]	—[a]	—	—	—	—
1–2 y[a]	—[a]	—	—	—	—
2–3 y	58 (51–65)	$P < .001$	—	—	—

NOTE. *P* values denote comparisons between periods.
[a]Follow-up was insufficient to calculate these outcomes at 10 years.

TNF (defined as <2 years of disease duration without other stratification) was associated with improved disease outcomes.[23–25] In this study, we also showed an advantage to biologics initiation earlier than 2 years. Hitherto, only a small analysis from the RISK cohort directly explored time periods earlier than 2 years. In a propensity score–matched analysis of 68 children with CD, anti-TNF initiation during the first 3 months from diagnosis yielded higher 1-year steroid-free remission rates than immunomodulators or no treatment despite later addition of biologics.[26] The effectiveness of early introduction of biologics in CD may be also remotely inferred from a recent retrospective cohort study of 1037 CD patients who underwent ileocecal resection, which showed that initiating anti-TNF within 4 weeks of surgery resulted in a lower postoperative recurrence rate than later introduction but, in accordance with our results, with only a modest effect.[27]

Investigators often base their argument that early biologics initiation results in beneficial effects in CD on several types of studies that do not directly address this question. For instance, the "top-down" trials in adults[28] and children[29] with CD showed that early initiation of infliximab was superior to other treatment alternatives but did not address the main question of our study: whether earlier initiation of biologics—within the group of patients who will ultimately require it—improves long-term outcomes. The

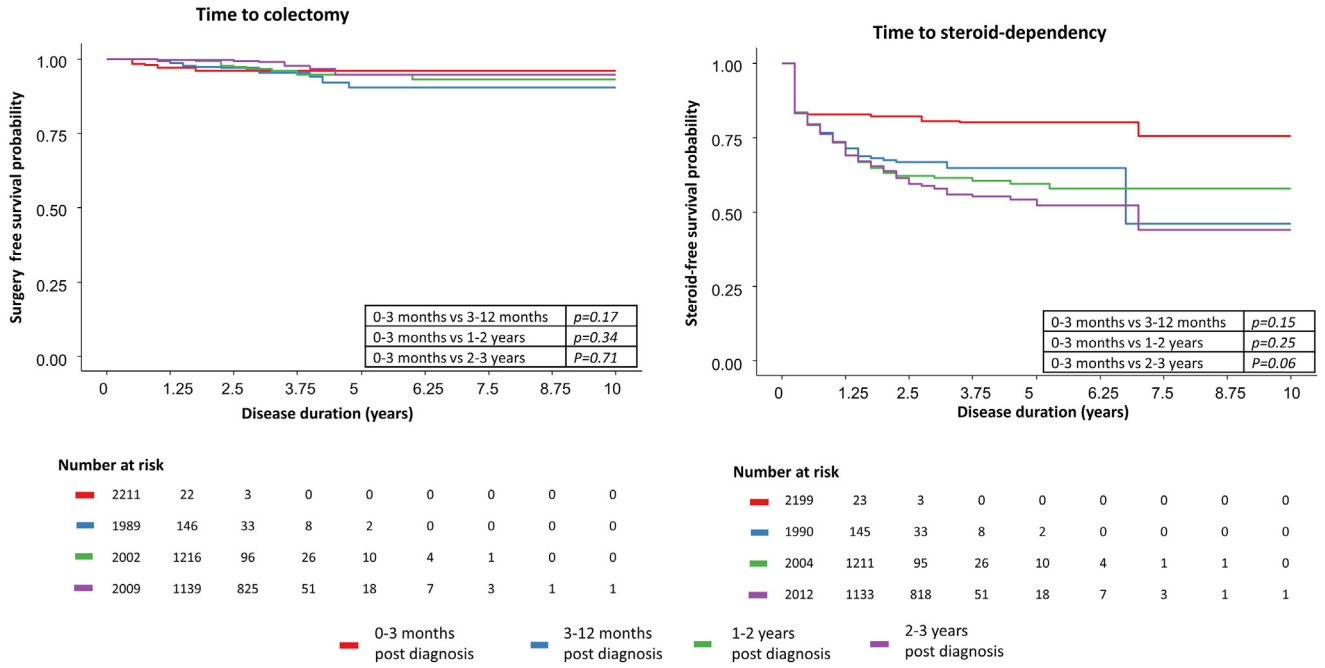

Figure 3. Time to disease outcomes in UC stratified by time to biologics treatment.

same applies to the SONIC trial,[30] which showed that early treatment with a combination of infliximab and thiopurines is superior to either alone but did not assess different timings for the initiation of this therapy. Treat-to-target trials, such as CALM, which showed that early treatment escalation based on biomarkers is superior to a clinical symptoms-based strategy, have not directly addressed the significance of treatment delay in those who will eventually require biologics.[31] Other sets of data arguing for early introduction of biologics in CD are based on post hoc stratification of patients with different disease durations randomized in clinical trials of biologics. These have repeatedly shown a reverse association between disease duration and therapeutic success, as reported for the CHARM[32] and PRECISE[33] trials. However, these analyses compare different patients at different timepoints with multiple possible time-dependent biases. The presumed positive effect of early intervention may be apparent in cases where such intervention merely delays inevitable adverse outcomes, as illustrated in Figure 4. Indeed, in the aforementioned meta-analysis of disease duration strata from different RCTs, although patients with shorter disease duration enrolled in CD trials had higher remission rates, the same trend was apparent in the placebo groups. Hence, treatment effect seemed independent of disease duration.[22]

Analyzing intervention initiation timing on unselected administrative data presents the statistical challenge of

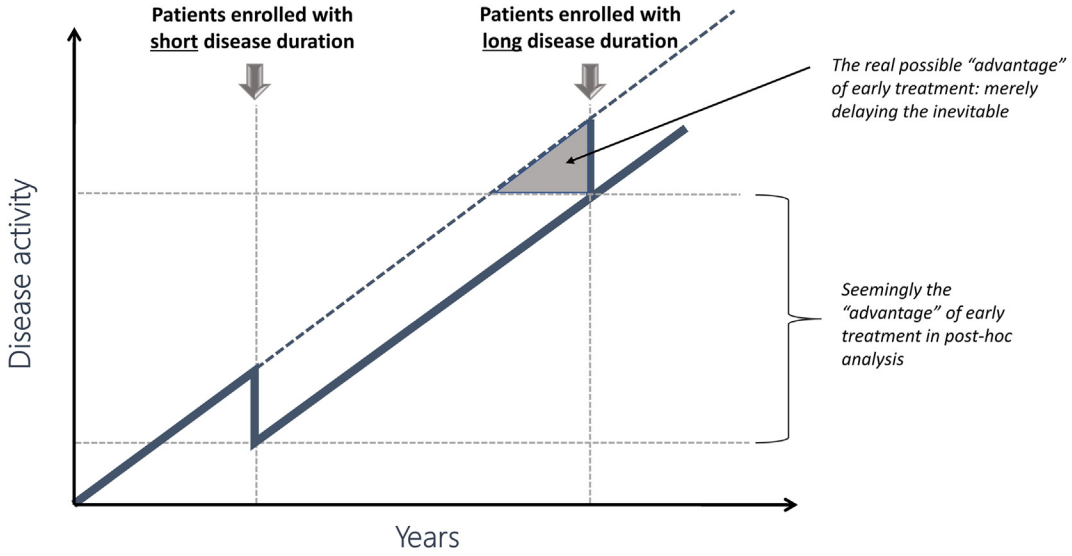

Figure 4. Possible time bias in comparing different patients at different timepoints in post hoc analyses of RCTs.

needing to account for 2 time-dependent variables—mean time from diagnosis to biologics and from biologics to outcome—while controlling for numerous confounding factors at diagnosis and thereafter. Researchers often turn to propensity score matching to evaluate treatment effects in retrospective analyses of observational data. However, this approach is insufficient when assessing the effects of early vs late interventions because it cannot control for time-varying factors in the presence of confounding and immortal time biases. Although we attempted to overcome these challenges through advanced TTE modeling that mimics a clinical trial setting, we acknowledge the limitations of this approach. Our study lacked variables that could influence the decision to initiate biologics at certain time periods, such as endoscopic activity, symptom assessment, and imaging results. Although we tried to account for the effect of these through proxy variables (eg, hospitalizations, diagnosis codes, clustering of laboratory results, number of physician visits, etc), residual confounding effects could not be excluded. Therefore, the actual effect of early biologics may be larger than we found, as biologics are typically administered to patients with more severe disease. Reassuringly, all measured baseline variables were balanced across the groups in all 8 models, except for year of diagnosis. We thus included this variable in all models. Indeed, in a sensitivity analysis that stratified patients diagnosed before and after 2010, the overall findings remained similar. Any analysis of time to treatment in IBD may also be affected by diagnostic delay, the median of which may reach almost 1 year in CD.[34] However, the results also remained similar in a sensitivity analysis that attempted to account for this delay. Finally, most patients had a follow-up period shorter than 5 years, which may be insufficient to fully evaluate the effect of the interventions on surgical rates.

In conclusion, early initiation of biologics was not associated with several IBD outcomes, with the exception of a modest reduced risk of surgery and steroid dependency for CD, which requires confirmation in future studies. In UC, early introduction of biologics was not associated with reduced risk of colectomy or steroid dependency. Taken together, although our data may support initiating biologics early in CD patients, expectations regarding the added benefit of this strategy should be realistic, with an NNT of 7.7. Therefore, it may be reasonable to use a very early treatment strategy in high-risk CD patients. In UC, step-up treatment with mesalamine, thiopurines, and biologics thereafter may be appropriate in most patients, because our results, supported by previous studies, suggest that earlier initiation of biologics does not change the natural course of the disease. An RCT comparing very early, early, and late introduction of biologics may be difficult to conduct but is urgently needed to confirm the results of this administrative study.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2024.01.041.

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Received March 13, 2023. Accepted January 26, 2024.

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Conflicts of interest

These authors disclose the following: Shomron Ben Horin has served as an advisory board member of and/or received consulting and/or speaker fees from AbbVie, BMS, Celltrion, Eli Lilly, Evinature, Falk, Ferring, Galmed, Gilead, GSK, Janssen, Medial Earlysign, NeoPharm, Novartis, Pfizer, Predicta Med, Roche, and Takeda; holds options/stocks in Evinature, Galmed, and Predicta Med; and has received research support from AbbVie, Celltrion, Galmed, Janssen, Medtronic, OutSense, Pfizer, and Takeda. Iris Dotan, in the last 3 years, has received consulting fees, research grants, or honoraria from Abbott, AbbVie, Altman Health, Arena, Athos, Cambridge Healthcare, Celgene/BMS, Celltrion Healthcare, Dr. Falk Pharma, Eli Lilly, Ferring, Food Industries Association, Galapagos, Gilead, Integra Holdings, Janssen, Neopharm, Pfizer, Rafa Laboratories, Roche/Genentech, Sandoz, Sangamo, Sublimity, Takeda, Wildbio, Altman Research, Pfizer, and BMS. Dan Turner, in the last 3 years, has received consulting fees, research grants, royalties, or honoraria from AbbVie, Atlantic Health, BMS, Celgene, Eli Lilly, Ferring, Janssen, Pfizer, Roche, and Takeda. The remaining authors disclose no conflicts.

Funding

This Epidemiology Group of the Israeli Inflammatory Bowel Disease Research Nucleus project was funded by a grant from the Leona M. and Harry B. Helmsley Charitable Trust.

Data Availability

Access to the data underlying this article will be granted on reasonable request to the corresponding author.

Supplementary Materials

Emulating a Target Trial Through Cloning, Censoring, and Weighting

Time-varying bias, lead time bias, and immortal time bias. Comparing observational data to determine treatment effect requires the implementation of methods that can appropriately adjust for confounding by indication, time-varying bias, lead time bias, and immortal time bias. [e1]

Treatment-confounder feedback occurs when the confounder affects the treatment and the treatment affects the confounder.[e2] In the presence of treatment-confounder feedback, propensity score–adjusted analysis may address confounding by indication but not time-varying biases. Cox proportional hazards models are standard approaches for modeling time to outcomes, but their use may generate biased results when time-varying confounders are affected by previous exposures, such as the different timings of biologics initiation.[e3] As such, adjusting for past covariate history using standard approaches may produce biased results when (1) there is a time-dependent variable that is both a risk factor for the outcome and a predictor of the subsequent exposure and (2) past exposure history can predict the risk factor.[e3] For example, current laboratory test results will influence or promote the next treatment intervention decision. Then, in light of that decision, future laboratory test results will influence the outcome and continuation or change of treatment (Supplementary Figure 1). Additionally, immortal time bias occurs when studies fail to align the start of follow-up, study eligibility, and treatment assignment, such as in cases where future information is used to classify patients into exposure groups.[e1] In other words, all patients need to survive until the initiation of biologics; otherwise, they cannot be classified. The immortal period will be longer for those initiating biologics later, favoring late biologics initiation because patients would need to survive long enough to initiate biologics at a later time, that is, not experience a disease outcome that would qualify them to initiate biologics (Supplementary Figure 2). Similarly, lead time bias occurs because patients who initiate biologics early will be earlier in their disease course than patients who initiate biologics later. Therefore, it may seem like patients who initiate early have worse outcomes than those initiating later when, in fact, the period where outcomes are observed (follow-up) starts earlier in their disease course[e4] (Supplementary Figure 2).

Cloning and assigning replicates to treatment strategies. At diagnosis, we cannot know what treatments a given patient will receive and when, and thus patients at this point must be assigned to all possible treatment options.[e4–e6] For example, considering the 4 treatment strategies in our study (initiating biologics during 0–3 months, 3–12 months, 1–2 years, and 2–3 years), we will examine a hypothetical patient A who receives biologics at 1.5 years postdiagnosis and has an event (eg, surgery) at 2 years postdiagnosis. During the first 3-month period of disease (quarter), this patient is compatible with all 4 strategies. After 1 quarter, this patient is not eligible for the "initiating biologics at 0–3 months" strategy anymore but is still eligible for the 3 remaining strategies. After reaching the 1-year mark, the patient's data are no longer consistent with "0–3 months" or "3–12 months" treatment strategies, although they can still be considered eligible for the remaining 2 strategies. At 1.5 years, the patient initiates biologics, which defines him or her as a "1–2 year" initiator. From that point, the patient is not eligible for the "2–3 years" category.

Censoring replicates when deviating from assigned strategy. Practically, the time-dependent contribution from each patient can be adjusted by expanding the risk sets in each quarter so that patients who are still at risk contribute 1 replicate observation for each treatment strategy that the patient is presently compatible with.[e4–e6] For example, our aforementioned patient A will be artificially censored from strategies 0–3 and 3–12 at disease quarters 2 and 5, respectively. During the 4th and 5th quarters, the patient will contribute 2 replicates to each risk set following strategies "1–2 years" and "2–3 years," respectively. In the 6th quarter (1.5 years), the replicates assigned to "2–3 years" are artificially censored. For strategy "1–2 years" and from the 6th quarter until the end of follow-up, patient A remains uncensored because his or her data are consistent with the "1–2 years" strategy. Note that once a patient is censored from a treatment strategy, his or her future outcome data do not count for that strategy.

See example of patient A below:

Patient A

Patient ID	Replicate	Assigned strategy	Disease quarter	Biologics treatment start	Failure outcome	Censoring
A	A.1	0–3 mo	1	0	0	0
A	A.1	0–3 mo	2	0	0	1
A	A.2	3–12 mo	1	0	0	0
A	A.2	3–12 mo	2	0	0	0
A	A.2	3–12 mo	3	0	0	0
A	A.2	3–12 mo	4	0	0	0
A	A.2	3–12 mo	5	0	0	1
A	A.3	1–2 y	1	0	0	0
A	A.3	1–2 y	2	0	0	0

Patient A. Continued

Patient ID	Replicate	Assigned strategy	Disease quarter	Biologics treatment start	Failure outcome	Censoring
A	A.3	1–2 y	3	0	0	0
A	A.3	1–2 y	4	0	0	0
A	A.3	1–2 y	5	0	0	0
A	A.3	1–2 y	6	1	0	0
A	A.3	1–2 y	7	1	0	0
A	A.3	1–2 y	8	1	1	0
A	A.4	2–3 y	1	0	0	0
A	A.4	2–3 y	2	0	0	0
A	A.4	2–3 y	3	0	0	0
A	A.4	2–3 y	4	0	0	0
A	A.4	2–3 y	5	0	0	0
A	A.4	2–3 y	6	1	0	1

Inverse probability weighting to adjust for selection bias. The next step is to use inverse probability weighting to adjust for selection bias introduced by the artificial censoring. To do this, we created a "pseudo-expanded risk set" at each disease quarter by assigning each patient with a time-varying weight, up-weighting uncensored replicates who have similar characteristics as censored replicates.[e4–e6] Therefore, a pseudo-population is created in which censoring is no longer informative. For each dataset representing a different treatment strategy, a pooled logistic regression model was fit to estimate the inverse probability of censoring weights where "remaining uncensored" is the outcome. For each timepoint and assuming the patient is still at risk (not censored), the denominator represents the probability of initiating biologics treatment conditional on previous treatment history, time-varying confounding variables, and baseline variables.[e4–e6] Note that a patient who has initiated biologics treatment is considered to continue treatment until censoring due to discontinuing biologics, undergoing a disease-related event, or death. Mathematically, for a patient i, let $C_i(k)$ be the artificial censoring indicator at time k, $Y_i(k)$ the occurrence of the event of interest at time k, $A_i(k)$ the biologics indicator, X_i the assigned strategy, V_i a vector of baseline covariates, and $\overline{L}_i(k)$ the history of all time-varying covariates up to time k.

$$w_i(t) = \prod_{k=0}^{t} \frac{\Pr_{EXP}\{C_i(k) = 0 | Y_i(k) = C_i(k-1) = 0, X_i, V_i\}}{\Pr\{A_i(k) | Y_i(k) = C_i(k) = 0, \overline{A}_i(k-1), \overline{L}_i(\mathrm{k}), V_i\}}$$

Once a patient initiated biologics, each element of the denominator was set to 1 as their probability to remain uncensored, per definition. According to Cain et al,[e6] given the treatment arm X_i, each element in the denominator is equivalent to the probability of remaining uncensored in the expanded dataset given fixed and time-varying covariates $\Pr_{EXP}\{C_i(\mathrm{k}) = 0 | Y_i(k) = C_i(k-1) = 0, \overline{A}_i(k-1), \overline{L}_i(\mathrm{k}), V_i, X_i\}$. We modeled the latter probability to obtain the probability estimators of the denominator. We truncated the weights at the 99th percentile to avoid the influence of very large weights.

To estimate the per-protocol effect, we performed an additional censoring 90 days after the last biologics course date if there was a gap of >90 days without any biologic purchase. Additional time-varying weights were computed on the long, unexpanded data to account for this type of censoring as follows, this time denoting by $C_i^B(k)$ the indicator of being censored at time k due to nonadherence or withdrawal as described earlier.

$$w_i^B(t) = \prod_{k=0}^{t} \frac{\Pr\{C_i^B(k) = 0 | Y_i(k) = C_i^B(k-1) = 0, V_i\}}{\Pr\{C_i^B(k) = 0 | Y_i(k) = C_i^B(k-1) = 0, \overline{A}_i(k-1), \overline{L}_i(k), V_i\}}$$

Then the censoring due to biologics withdrawal was performed. After that, cloning and weighting were performed as described earlier. Finally, these weights were multiplied with the former weights for each patient in each observed disease quarter to obtain the final weights $w_i(t) \times w_i^B(t)$ that were used for the analysis.

Main model. Next, we stacked the 4 datasets and used a weighted nonparametric Kaplan-Meier estimator to measure the effect of the different biologics initiation treatment strategies.[e7] The 95% CIs for 7- and 10-year survival were calculated using nonparametric bootstrap with 500 replicates.

Clustering Analysis

Hierarchical clustering analysis was used to divide our cohort into groups based on laboratory test result

abnormalities at diagnosis. Hierarchical clustering is an unsupervised method for partitioning patient data into clusters where elements are grouped according to their similarities.[25] The advantage of this method is that it enables categorization of all patients despite some missing tests, which is typical in administrative databases. Laboratory test results included in the clustering analysis were C-reactive protein (CRP), erythrocyte sedimentation rate, platelets, hemoglobin, albumin, and white blood cell count. Each laboratory test result was standardized, as appropriate, by dividing the test result by the age- and sex-adjusted upper/lower normal limit.

To include all patients in the final analysis, we used imputation of the most commonly performed laboratory tests (platelets, white blood cell count, and hemoglobin), based on demographic and other clinical variables. The predictive mean method for imputation was used to impute missing values for those without any laboratory data and was computed in R package MICE.[26] The predictive mean method was chosen because it works well with large datasets and imputes values taken from the original data, maintaining the original distribution of the variables.

The clustering analysis created a severities group that demonstrated intuitive increases in severity for each blood test, as we previously reported and validated on the epi-IIRN.[19]

A dissimilarity matrix was computed on the standardized laboratory test result variables for each dataset with Gower's distance using the R package *cluster*.[27] The dissimilarity matrix measures whether units (here, patients) can be clustered based on how similar or dissimilar they are from one another.[28] The *cluster* package was chosen for its ability to handle missing data.[28] Next, a bottom-up process, agglomerative hierarchical clustering, was performed using Ward's method, which was chosen because it produces clusters that minimize within-group dispersion[29] and a large agglomerative coefficient (0.99), thus describing the strength of the clustering structure. The optimal number of clusters was chosen using the elbow method.[30] The order of the clusters, from mild to extreme disease activity, was determined by observing the mean values of the laboratory results while considering the percentage of missing data in each group. Additionally, the contribution of each laboratory test in determining the disease activity category was assessed by comparing the ratio between the standardized values in the clusters. Importantly, the outcome data were not used in the process; thus, the statistical assessment of differences in outcomes between the clusters remained independent.

The clustering process was repeated separately for UC and CD, yielding disease-specific clusters. In CD, the 19,263 patients included in the current study were grouped into 5 distinct clusters of disease severity (minimal, mild, moderate, severe, and extreme) (Supplementary Table 2). In UC, the 15,111 included patients were grouped into 4 clusters (mild, moderate, severe, and extreme) (Supplementary Table 3). As shown in the tables and lending support for internal validity, there was a gradual worsening in the median values across all clusters. For instance, CD patients in the extreme cluster had CRP values almost 10 times greater than those of the minimal cluster (median CRP values, 5.9 [IQR, 2.6–10.7] vs 0.6 [IQR, 0.1–1.8], respectively). UC patients in the extreme cluster had ESR values 6 times greater than those of the mild cluster (median ESR values, 8 [IQR, 4–16] vs 50 [IQR, 28-73]) and CRP values almost 4 times greater than those of the mild cluster (median CRP values, 0.28 [IQR, 0–0.98] vs 1.14 [IQR, 0.34–4.37]). In a predictive validity analysis for CD and UC, we found that the clusters significantly predicted surgery, steroid dependency, and use of biologics with a gradual increase in the proportions of patients with the poor outcome among the disease severity clusters (data not yet published).

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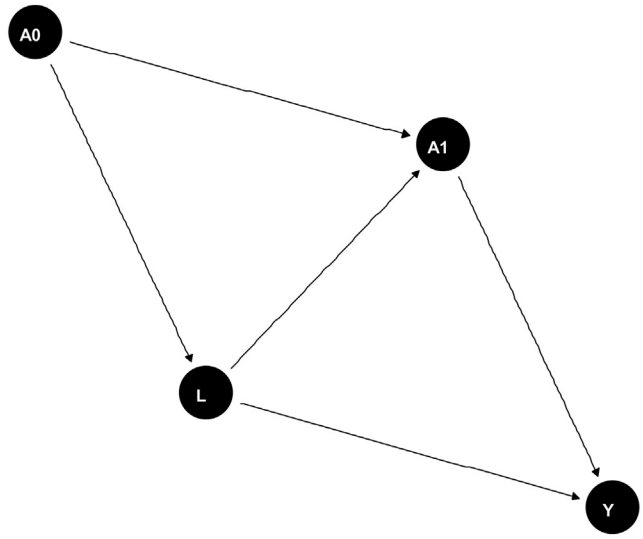
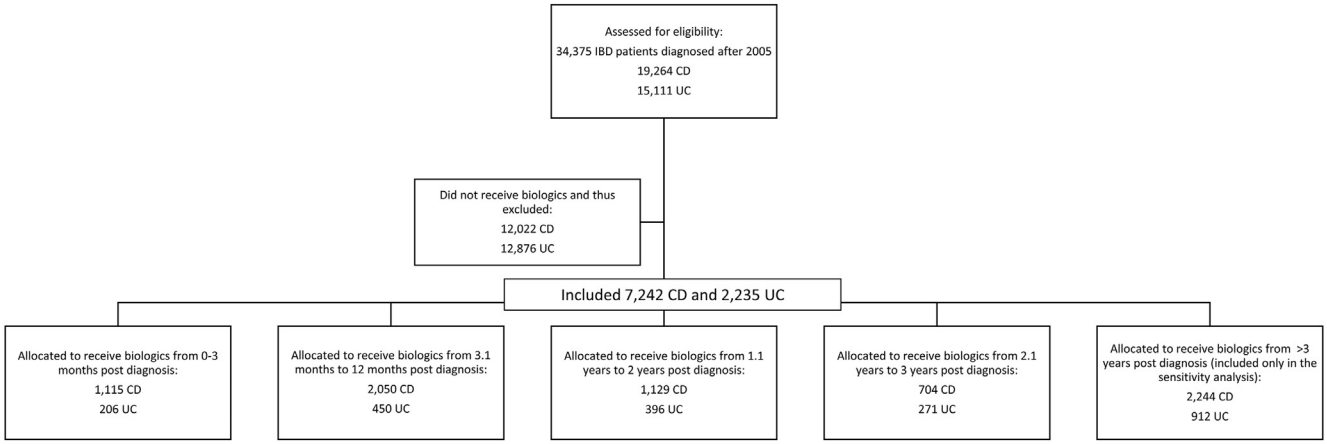
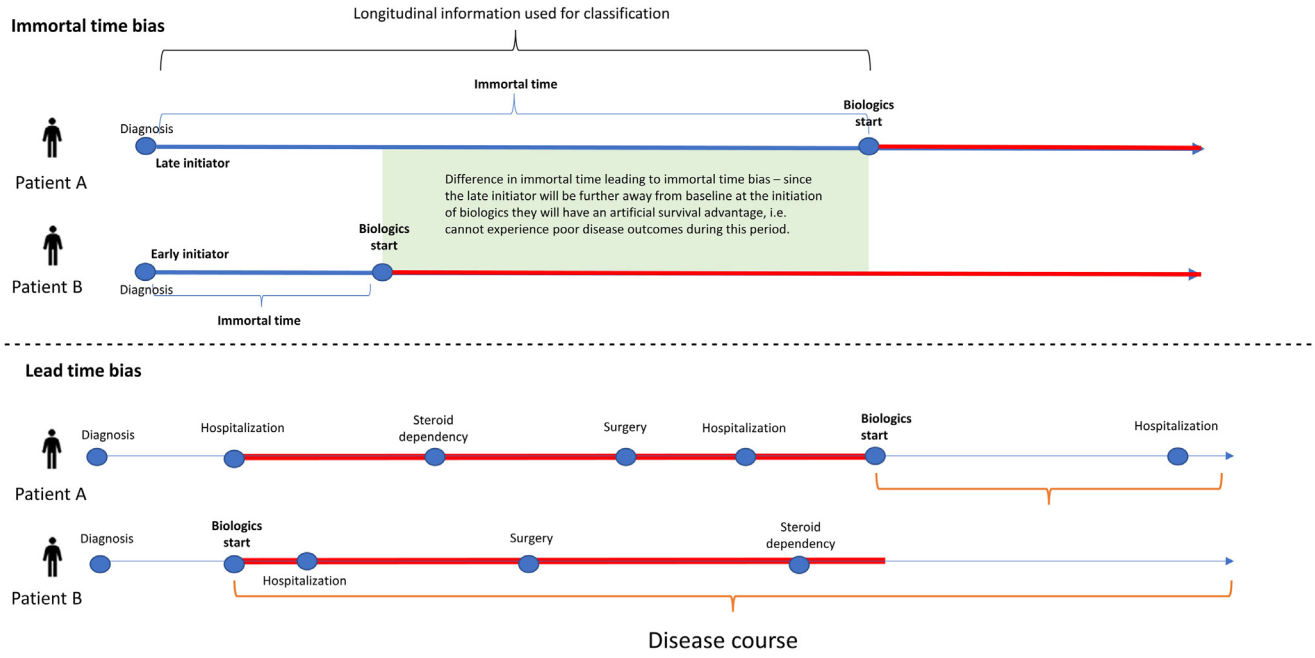


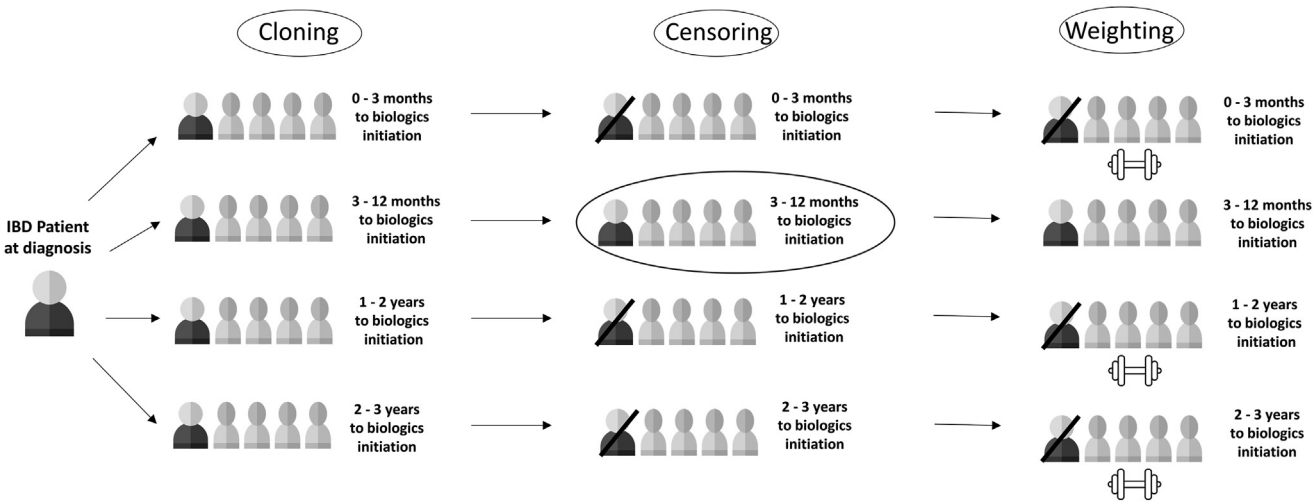
Supplementary Figure 1. Casual diagrams (directed acyclic graph [DAGs]) depicting relationships between exposure and outcome variables while demonstrating the issue of time-dependent confounding. A0 is the treatment decision (to initiate biologics or not) at time 0 and A1 is the treatment decision at time 1. L is the time-varying confounder (eg, laboratory test results), and Y is the outcome variable. The decision to initiate biologics or not at A0 affects the subsequent decision period, A1, while also affecting laboratory test result levels (L). L affects the decision to initiate biologics at A1 while also affecting outcomes. Note that the classical DAG will also have a component of unmeasured common cause of L and Y, not shown in this diagram for simplicity.



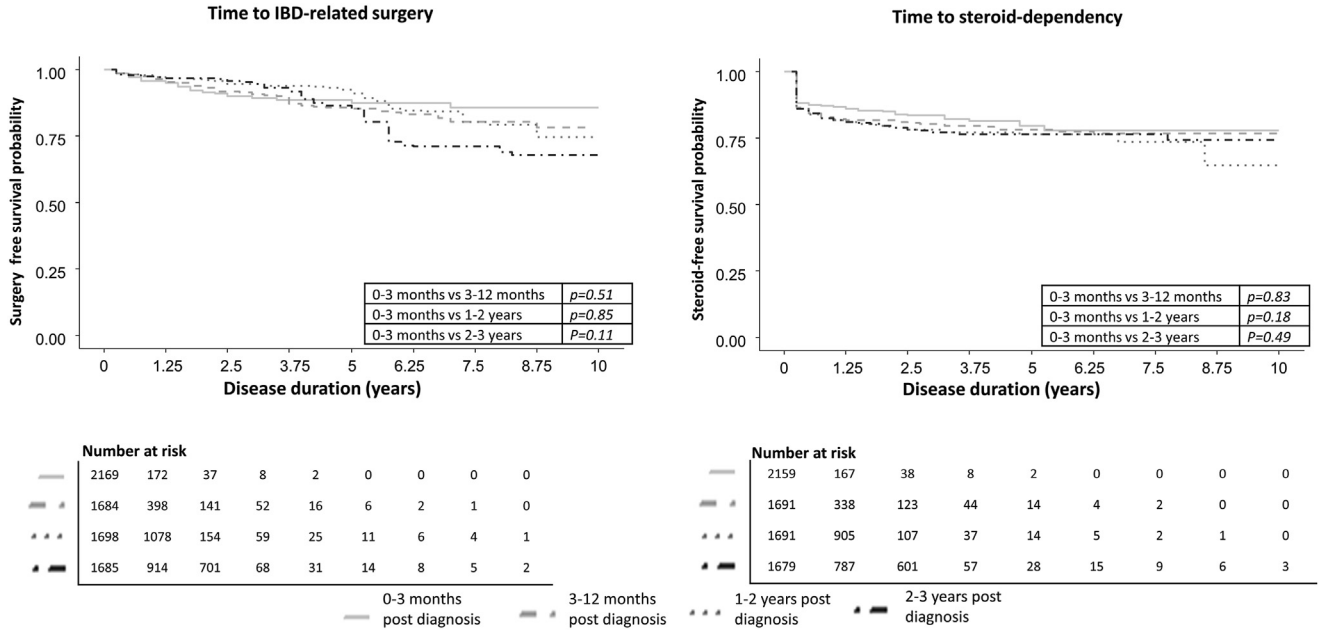
Supplementary Figure 2. Consort flow diagram.



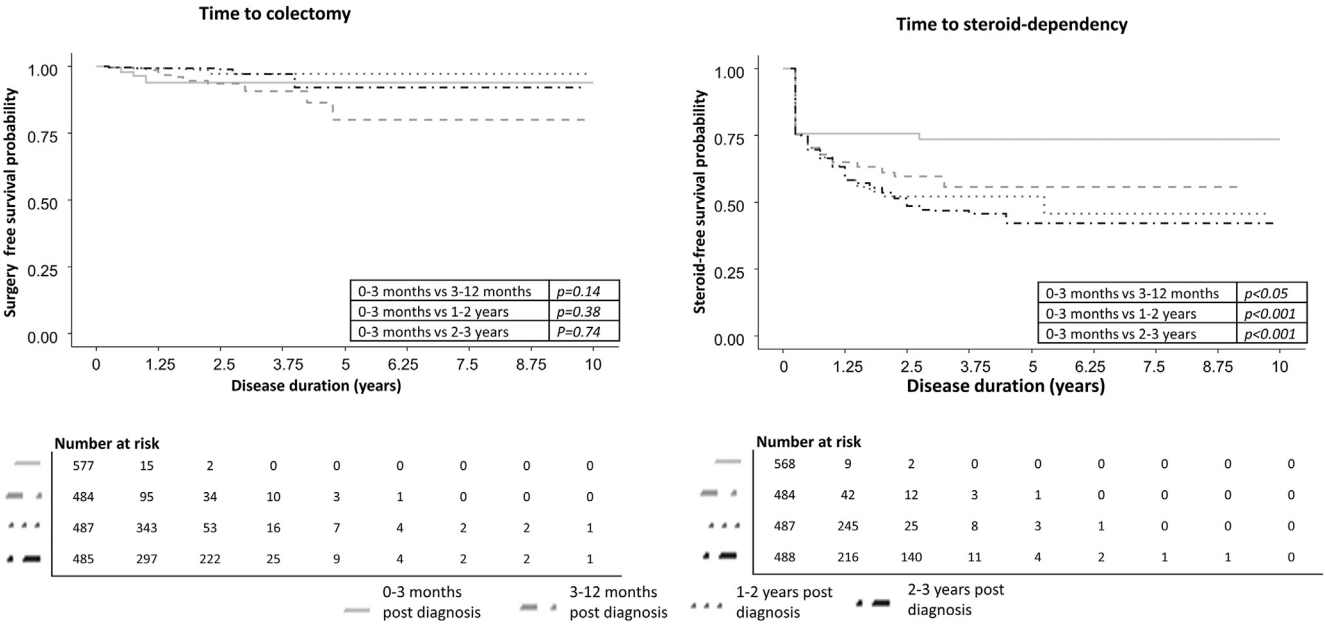
Supplementary Figure 3. Illustration of immortal time bias and lead time bias. Immortal time bias: To be classified into one of the assignment groups, all patients need to survive (ie, be in an event-free status that qualifies the patient to initiate biologics) until treatment start. All patients will be "immortal" until biologics initiation. Immortal time will be longer for those who begin treatment later, thus favoring late-exposure patients. Lead time bias: Disease outcomes may be similar for early and late initiators of biologics, but time to these outcomes may only seem longer for the former because they had longer follow-up periods within the study. Patient A might or might not be event free for longer than patient B; only biologics initiation in the former is earlier in the disease course.



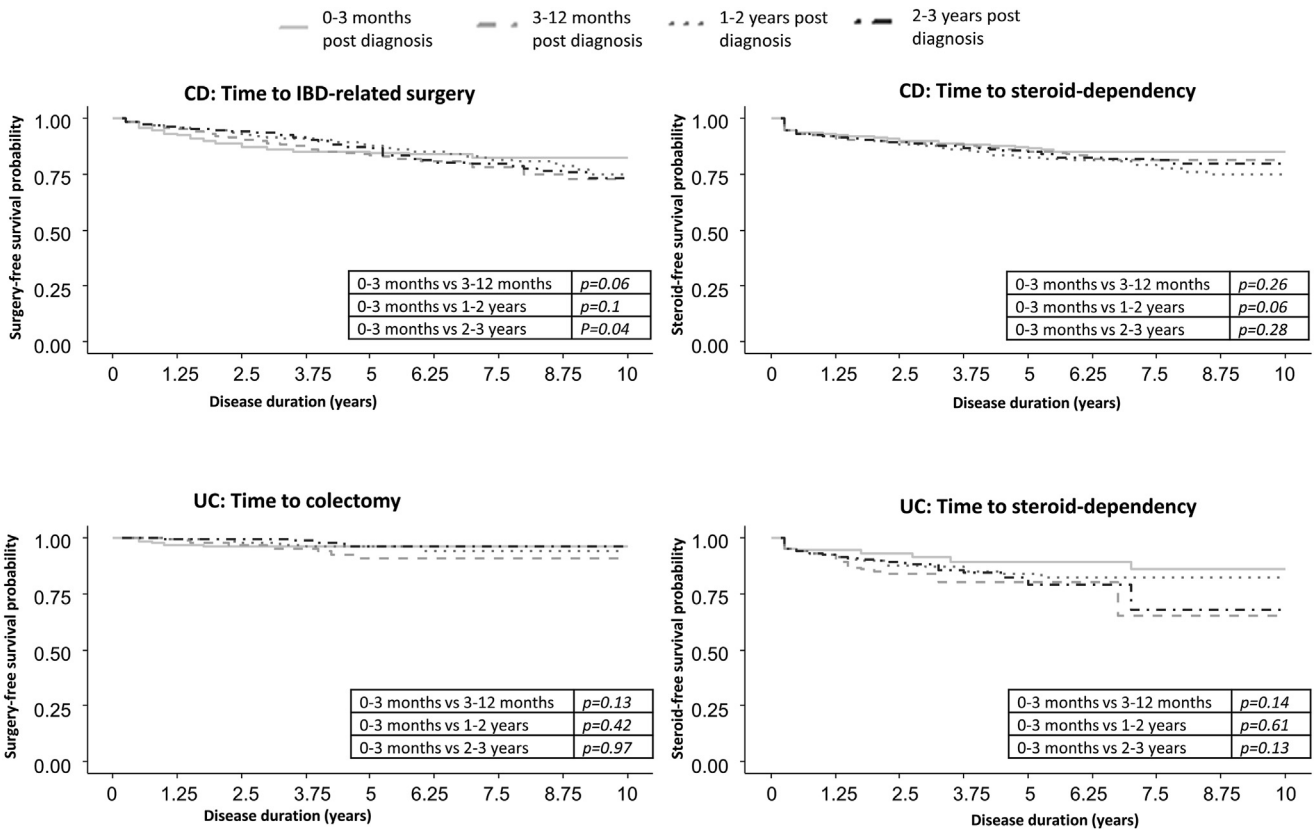
Supplementary Figure 4. A diagram explaining the cloning, censoring, and weighting process. Take a hypothetical patient at the time of diagnosis. This patient is potentially eligible to initiate biologics at any time and therefore is entered into each treatment arm (cloning), mimicking clinical trials before randomization. Then the patient is followed. When the patient initiates biologics in the 3–12-month period, he or she is then censored from the remaining treatment strategies because he or she is no longer eligible to initiate at those times (censoring). Finally, the weights of the censored patient are now distributed among the remaining patients.



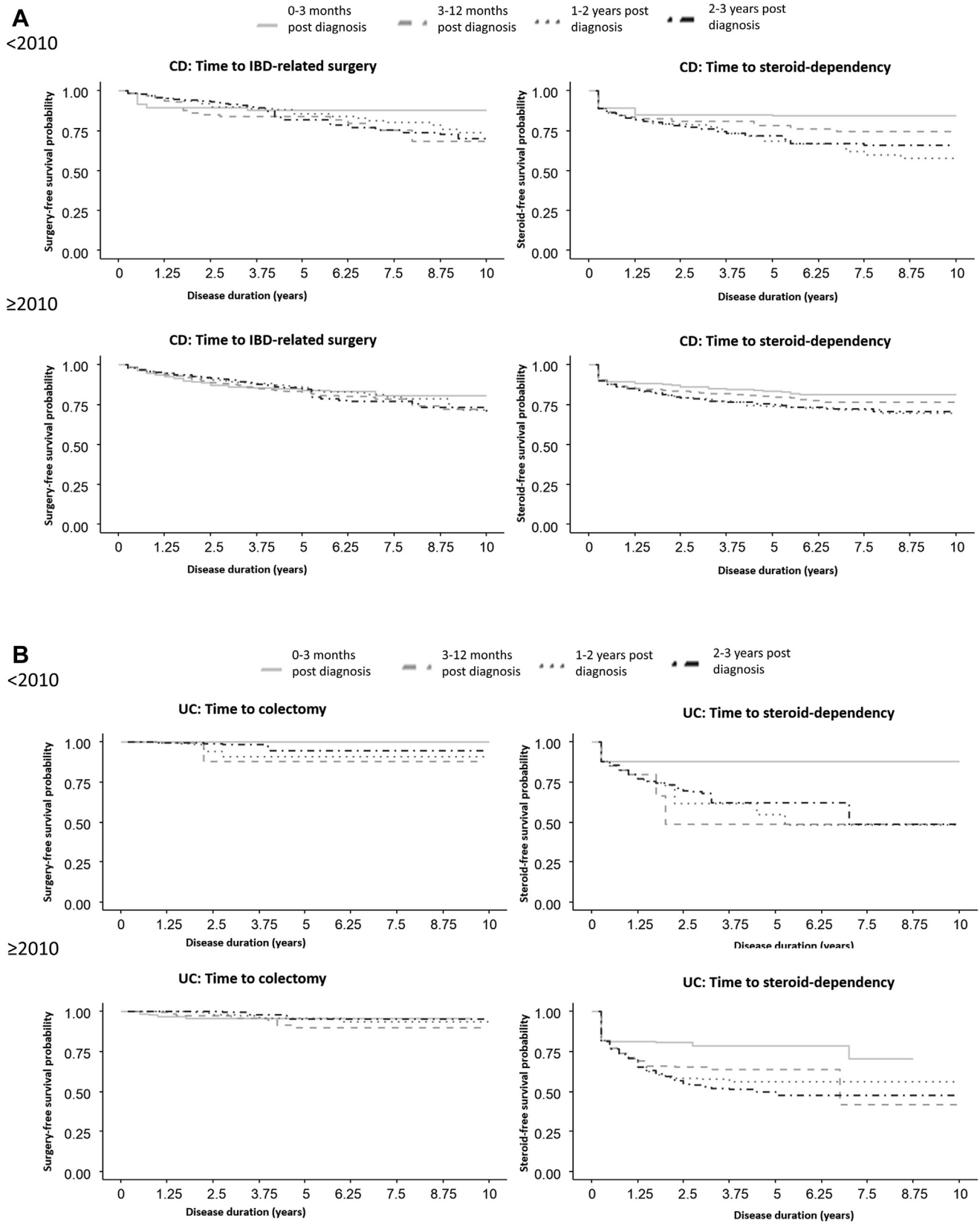
Supplementary Figure 5. Time to disease outcomes in pediatric-onset CD stratified by time to biologics treatment.



Supplementary Figure 6. Time to disease outcomes in pediatric-onset UC stratified by time to biologics treatment.



Supplementary Figure 7. Time to disease outcomes in CD and UC stratified by time to biologics, calculated for all IBD patients (ie, including those who never received biologics).



Supplementary Figure 8. Time to disease outcomes in (*A*) CD and (*B*) UC stratified by year of diagnosis (before and after 2010).

Supplementary Table 1. List of GI-Related Surgeries From the International Classification of Diseases, 9th Revision

Code name	Code number
Gastrotomy	43/43.4/43.41/43.42/43.49/43.9/43.91/43.99
Partial gastrotomy	43.5/43.6/43.7/43.8/43.81/43.89
Other stomach surgeries	43.3/44.63/44.69/44.9/44.92/44.99
Incision of the intestine	45/45.01/45.02/45.03/45.3/45.31/45.32/45.33/45.34/45.41/45.43/ 45.49/45.5/45.51/45.52/45.6/ 45.61/45.62/45.63/45.7/45.71/45.72
Hemicolectomy	45.73/45.74/45.75/45.76/45.79
Total colectomy	45.8/45.81/45.82/45.83
Intestinal anastomosis	45.9/45.91/45.92/45.93/45.94/45.95
Exteriorization of the intestine	46.01/46.02/46.03/46.04
Colostomy	46.1/46.11/46.13/46.14
Ileostomy	46.2/46.21/46.22/46.23/46.24
Other enterostomy	46.3/46.31/46.32/46.39/46.4/46.41/46.43
Closure of intestinal stoma	46.4/46.51/46.52/48.72/48.74
Fixation of intestine	46.6/46.61/46.62/46.63/46.64/46.7/46.72/46.73/46.74/46.75/46.76/ 46.79/46.8/46.81/46.82/46.91/ 46.99
Operation of rectum	48/48.1/48.3/48.31/48.32/48.33/48.34/48.35/48.4/48.42/48.43/48.49/ 48.5/48.51/48.52/48.59/ 48.6/48.61/48.62/48.63/48.64/48.65/48.69/ 48.75/48.76/48.79/48.91/48.92/48.99
Perianal surgeries	48.73/48.8/48.81/48.82/48.93/49/49.01/49.02/49.04/49.1/49.11/49.12/ 49.3/49.31/49.39/49.6/ 49.7/49.73/49.9/49.93/49.99
Other abdomen operations	54/54.1/54.11/54.12/54.19/54.21/54.3/54.4/54.5/54.51/54.59/54.72/ 54.73/54.74/54.75/54.9/ 54.93/54.95

Supplementary Table 2. Clusters of Laboratory Test Results From Hierarchical Clustering in CD, Median (IQR)

Test name	Minimal (n = 5086)	Mild (n = 8593)	Moderate (n = 3366)	Severe (n = 1315)	Extreme (n = 903)
CRP, mg/dL	0.6 (0.1–1.8)	1.0 (0.3–2.38)	2.6 (1.0–5.2)	4.7 (2.05–8.2)	5.9 (2.6–10.7)
ESR, mm/h	12 (6–21)	25 (15–39)	44 (30–61)	58 (36–74)	63 (41–87)
Platelets, $10^3/\mu$L	241 (204–291)	288 (249–331)	386 (336–434)	462 (394–519)	581 (505–658)
WBC, $10^3/\mu$L	7.6 (6.2–9.6)	7.6 (6.4–8.9)	8.6 (7.0–10.2)	9.9 (7.5–12.3)	10.8 (8.6–14)
Hemoglobin, g/dL	14.8 (14.2–15.4)	12.8 (12.2–13.5)	11.4 (10.8–12.0)	10.8 (10.1–11.6)	10.0 (9.2–11)
Albumin, g/dL	4.4 (4.2–4.6)	4.2 (3.9–4.4)	3.8 (3.6–4.1)	3.5 (3.2–3.9)	3.4 (3.0–3.7)
Calprotectin, μg/g	172 (70–441)	278 (110–714)	657 (285–2015)	1270 (618–2610)	1,380 (418–3093)

NOTE. CRP was available in 9017 (47%); ESR was available in 7286 (38%); platelets were available in 19,263 (100%); WBC count was available in 19,263 (100%); albumin was available in 10,857 (56%); hemoglobin was available in 19,263 (100%); and calprotectin was available in 705 (4%).
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

Supplementary Table 3. Clusters of Laboratory Test Results From Hierarchical Clustering in UC, Median (IQR)

Test name	Mild (n = 2820)	Moderate (n = 5718)	Severe (n = 5672)	Extreme (n = 901)
CRP, mg/dL	0.28 (0–0.98)	0.25 (0–0.8)	0.55 (0.1–1.6)	1.14 (0.34–4.37)
ESR, mm/h	8 (4–16)	12 (8–21)	27 (16–41)	50 (28–73)
Platelets, $10^3/\mu$L	238 (198–296)	244 (213–275)	291 (245–346)	454 (379–532)
WBC, $10^3/\mu$L	7 (6–8.28)	6.8 (5.8–7.9)	6.98 (5.8–8.26)	9.7 (7.2–12.51)
Neutrophils, $10^3/\mu$L	3.88 (3.12–4.75)	3.7 (2.99–4.47)	3.87 (3.01–4.91)	6.08 (4.23–8.24)
Hemoglobin, g/dL	15.4 (14.9–15.8)	13.8 (13.3–14.3)	12.2 (11.5–12.7)	10.0 (8.94–11)
Albumin, g/dL	4.53 (4.36–4.7)	4.3 (4.15–4.5)	4.17 (3.92–4.34)	3.7 (3.34–4.75)
Calprotectin, μg/g	475 (108–1166)	419 (105–1192)	590 (176–1890)	694 (359–1753)

NOTE. CRP was available in 5259 (35%); ESR was available in 4586 (30%); platelets were available in 15,111 (100%); WBC count was available in 15,111 (100%); neutrophils were available in 4979 (33%); albumin was available in 8139 (54%); hemoglobin was available in 15,111 (100%); and calprotectin was available in 322 (2%).
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

Supplementary Table 4. Specification and Emulation of a Target Trial of Early vs Late Initiation of Biologics Treatment Among CD and UC Patients

Component	Target trial	Emulated trial using real-world data
Aim	Estimate the effect of early biologics initiation on disease outcomes at 7 and 10 years post-CD/UC diagnosis	Same
Eligibility	Patients newly diagnosed with CD or UC	Patients diagnosed with CD or UC after 2005 and received biologics
Exclusions	Patients already diagnosed with CD or UC	CD and UC patients diagnosed before 2005. CD and UC patients who did not receive biologics ever during follow-up
Treatment strategies	1. Received biologics in first 3 months from diagnosis 2. Received biologics in the first 3 months to 1 year from diagnosis 3. Received biologics in the 1–2-year period from diagnosis 4. Received biologics in the 2–3-year period from diagnosis	Same
Treatment assignment	Patients are randomly assigned to either strategy	Patients are nonrandomly assigned to a treatment strategy. Randomization is emulated via cloning of patients in all 4 arms.
Outcome	IBD-related surgery Steroid dependency	Same
Causal contrast	Intention to treat	Per protocol when the protocol is without discontinuation greater than 90 days; that is, in each arm of the emulated trial, patients who deviate from the protocol are censored at their time of deviation.
Statistical analysis	Estimation of time to event using Kaplan-Meier curve. Survival probabilities at 7 and 10 years postdiagnosis will be reported.	We created an expanded dataset including 4 replicates for each included patient and assigned 1 replicate to each treatment strategy. We adjusted for the following baseline and time-varying variables: Baseline: age, year of diagnosis, district of residence, sex, socioeconomic status, and variable for laboratory tests reflecting disease activity and perianal diagnosis. Time-varying variables: mesalamine and immunomodulators, as well as laboratory test results (CRP, platelets, albumin, white blood cell count, and hemoglobin), hospitalizations, gastroenterologist visits, and subsequent diagnosis of perianal disease. Estimation of time to event using Kaplan-Meier curve. Survival probabilities at 7 and 10 years postdiagnosis will be reported.

CRP, C-reactive protein.

Supplementary Table 5. List of International Classification of Diseases, 9th Revision Code Numbers of IBD-Related Comorbidity

Code name	Code number
Arthritis	716.9
Erythema nodosum	695, 695.0, 695.01, 695.10, 695.11, 695.12, 695.19, 695.2, 695.3, 695.31
Pyoderma gangrenosum	686.0, 686.00, 686.01, 686.09, 686.1, 686.81, 686.9
Osteoporosis	733.0/730.01/733.02/733.03
Osteopenia	733.9
Iridocyclitis	364.0, 364.00, 364.002, 364.01, 364.02, 364.03, 364.04, 364.1, 364.10, 364.11, 364.110, 364.2, 364.21, 364.22, 364.23, 364.76, 364.77, 364.8, 364.81, 364.82, 364.89, 364.9, 379
Episcleritis	379.0, 379.00, 379.002, 379.009, 379.01, 379.02, 379.03, 379.04, 379.05, 379.07, 379.09, 379.1, 379.11, 379.19, 379.2, 379.21, 379.210, 379.211, 379.212, 379.22, 379.220, 379.23, 379.24, 379.25, 379.26, 379.27, 379.29, 379.3, 379.31, 379.32, 379.33, 379.34, 379.39, 379.391, 379.4, 379.40, 379.41, 379.60, 379.61, 379.8, 379.9, 379.90, 379.99
Primary sclerosing cholangitis	576, 576.0, 576.1, 576.16, 576.2, 576.3, 576.4, 576.8, 576.9
Uveitis	363.202, 364, 364.000, 364.05, 364.3, 364.30, 364.4, 364.41, 364.42, 364.5, 364.51, 364.53, 364.531, 364.56, 364.59, 364.6, 364.60, 364.61, 364.62, 364.7, 364.70, 364.71, 364.72

Supplementary Table 6. Covariate Balance for CD Surgery Model

Variables	0–3 mo vs 3–12 mo	0–3 mo vs 1–2 y	0–3 mo vs 2–3 y	3–12 mo vs. 1–2 y	3–12 mo vs 2–3 y	1–2 y vs 2–3 y
Male sex	–0.01	–0.009	–0.009	0	0	0
District						
Southern	–0.001	–0.001	–0.001	0	0	0
Central	–0.005	–0.005	–0.005	0	0	0
Northern	0.006	0.005	0.005	0	0	0
Age at diagnosis	0.041	0.039	0.039	–0.002	–0.002	0
Year of diagnosis	–0.127	–0.126	–0.127	0.002	0.001	–0.001
SES points	–0.009	–0.009	–0.01	–0.001	–0.001	0
Mesalamine use	0.017	0.004	0.002	–0.013	–0.015	–0.002
IMM use	–0.034	–0.029	–0.028	0.006	0.006	0.001
Number of gastroenterology visits	0.021	0.04	0.047	0.019	0.026	0.007
CRP,[a] mg/dL						
<1	0	0.002	0.005	0.001	0.004	0.003
1–3	–0.005	–0.004	–0.004	0.001	0.001	0
3–6	–0.007	–0.006	–0.005	0	0.001	0.001
6–10	–0.003	–0.003	–0.003	0.001	0.001	0
>10	–0.009	–0.007	–0.006	0.002	0.003	0.001
Not available	0.023	0.018	0.013	–0.005	–0.01	–0.005
Platelets,[a] $10^3/\mu$L						
<1	–0.013	–0.009	–0.007	–0.005	0.007	0.002
1–1.5	–0.008	–0.009	–0.008	0	0	0
1.5–2	–0.001	–0.001	–0.001	0	0	0
>2	0	0	0	0	0	0
Not available	0.023	0.019	0.016	–0.004	–0.007	–0.003
Albumin,[a] g/dL						
>1	–0.013	–0.009	–0.005	0.004	0.008	0.004
0.8–1	–0.005	–0.002	–0.001	0.003	0.004	0.001
<0.8	0.001	0	0.001	–0.001	0	0.001
Not available	0.018	0.011	0.006	–0.007	–0.012	–0.005
Hemoglobin,[a] g/dL						
>1	0.089	0.078	0.088	–0.012	–0.002	0.01
0.8–1	–0.021	–0.02	–0.017	0.001	0.004	0.003
<0.8	–0.003	–0.002	–0.002	0.001	0.001	0
Not available	0.023	NA	0.016	–0.004	NA	–0.003
White blood cell count,[a] $10^3/\mu$L						
<1	–0.015	–0.015	–0.012	0	0.002	0.003
1–1.5	–0.008	–0.003	–0.003	0.005	0.005	0
1.5–2	–0.001	–0.001	0	0	0	0
2–3	0	0	0	0	0	0
>3	0	0	0	0	0	0
Not available	0.023	NA	NA	NA	NA	NA
Disease activity by blood markers						
Minimal	0.003	0.002	0.002	0	0	0
Mild	0.008	0.007	0.006	–0.001	–0.001	0
Moderate	–0.002	–0.002	–0.001	0.001	0.001	0
Severe	–0.004	–0.003	–0.003	0	0	0
Extreme	–0.005	–0.004	–0.004	0	0.001	0
Hospitalization	–0.005	0	0.002	0.005	0.007	0.002
Perianal diagnosis before IBD diagnosis	–0.005	–0.005	–0.005	0	0	0
Perianal diagnosis after IBD diagnosis	–0.007	–0.006	–0.006	0.001	0.001	0
IBD-related comorbidities	0.011	0.013	0.015	0.002	0.004	0.001

NOTE. Numbers in all cells represent standardized mean difference (SMD), where SMD < 0.1 reflects good balance.
[a]The categories of the laboratory tests represent times their normal limit. Therefore, abnormal test is reflected by values <1 for albumin and hemoglobin and by >1 for CRP, platelets, and white blood cell.
CRP, C-reactive protein; IMM, immunomodulators; NA, not applicable; SES, socioeconomic status.

Supplementary Table 7. Covariate Balance for CD Steroid Dependency Model

Variables	0–3 mo vs 3–12 mo	0–3 mo vs 1–2 y	0–3 mo vs 2–3 y	3–12 mo vs 1–2 y	3–12 mo vs 2–3 y	1–2 y vs 2–3 y
Male sex	–0.01	–0.009	–0.009	0	0	0
District						
Southern	0	0	0	0	0	0
Central	–0.006	–0.005	–0.005	0	0	0
Northern	0.006	0.006	0.005	0	0	0
Age at diagnosis	0.039	0.038	0.038	–0.001	–0.001	0.001
Year of diagnosis	–0.127	–0.127	–0.128	0.001	0	–0.001
SES points	–0.01	–0.01	–0.01	0	–0.001	0
Mesalamine use	0.018	0.006	0.003	–0.013	–0.015	–0.003
IMM use	–0.025	–0.02	–0.02	0.005	0.005	0
Number of gastroenterology visits	0.022	0.042	0.049	0.02	0.027	0.007
CRP,[a] mg/dL						
<1	0.001	0.003	0.005	0.002	0.004	0.002
1–3	–0.004	–0.004	–0.004	0	0	0
3–6	–0.005	–0.004	–0.003	0.001	0.002	0.001
6–10	–0.003	–0.003	–0.003	0	0	0
>10	–0.007	–0.006	–0.006	0.001	0.002	0
Not available	0.019	0.015	0.011	–0.005	–0.008	–0.003
Platelets,[a] $10^3/\mu$L						
<1	–0.012	–0.008	–0.006	0.004	0.006	0.002
1–1.5	–0.005	–0.006	–0.007	–0.001	–0.001	0
1.5–2	0	–0.001	0	0	0	0
>2	0	0	0	0	0	0
Not available	0.018	0.015	0.013	–0.003	–0.005	–0.002
Albumin,[a] g/dL						
>1	–0.009	–0.005	–0.002	0.004	0.007	0.003
0.8–1	–0.004	–0.001	–0.001	0.002	0.003	0
<0.8	0	0	0	–0.001	0	0.001
Not available	0.012	0.007	0.003	–0.006	–0.01	–0.004
Hemoglobin,[a] g/dL						
>1	0.001	0.003	0.004	0.003	0.003	0
0.8–1	–0.016	–0.016	–0.015	0	0.002	0.002
<0.8	–0.003	–0.002	–0.002	0	0	0
Not available	0.018	NA	NA	–0.003	NA	NA
White blood cell count,[a] $10^3/\mu$L						
<1	–0.016	–0.016	–0.013	0	0.003	0.003
1–1.5	–0.002	0.001	0	0.003	0.003	–0.001
1.5–2	0.001	0	0	–0.001	–0.001	0
2–3	0	NA	0	0	0	0
>3	0	0	0	0	0	0
Not available	NA	NA	NA	0.006	NA	NA
Disease activity by blood markers						
Minimal	0.002	0.002	0.002	0	0	0
Mild	0.007	0.006	0.006	–0.001	–0.001	0
Moderate	–0.002	–0.002	–0.001	0	0	0
Severe	–0.003	–0.003	–0.003	0	0	0
Extreme	–0.004	–0.004	–0.004	0	0	0
Hospitalization	0	0.003	0.004	0.003	0.004	0.001
Perianal diagnosis before IBD diagnosis	–0.006	–0.006	–0.006	0	0	0
Perianal diagnosis after IBD diagnosis	–0.008	–0.006	–0.006	0.001	0.002	0
IBD-related comorbidities	0.011	0.014	0.014	0.002	0.003	0.001

NOTE. Numbers in all cells represent standardized mean difference (SMD), where SMD < 0.1 reflects good balance.
[a]The categories of the laboratory tests represent times their normal limit. Therefore, abnormal test is reflected by values <1 for albumin and hemoglobin and by >1 for CRP, platelets, and white blood cell.
CRP, C-reactive protein; IMM, immunomodulators; NA, not applicable; SES, socioeconomic status.

Supplementary Table 8. Covariate Balance for UC Colectomy Model

Variables	0–3 mo vs 3–12 mo	0–3 mo vs 1–2 y	0–3 mo vs 2–3 y	3–12 mo vs 1–2 y	3–12 mo vs 2–3 y	1–2 y vs 2–3 y
Male sex	–0.005	–0.005	–0.004	0	0.001	0
District						
Southern	0	0	0	0	0	0
Central	–0.003	–0.002	–0.002	0	0	0
Northern	0.002	0.002	0.002	0	0	0
Age at diagnosis	0.023	0.021	0.022	–0.002	–0.002	0
Year of diagnosis	–0.073	–0.076	–0.077	–0.003	–0.003	0
SES points	0	0	0.001	0	0.001	0.001
Mesalamine use	0.003	–0.004	–0.005	–0.007	–0.008	–0.001
IMM use	–0.013	–0.013	–0.009	0.001	0.004	0.004
Number of gastroenterology visits	0.04	0.06	0.068	0.02	0.028	0.008
CRP,[a] mg/dL						
<1	–0.001	0	0.001	0.001	0.002	0.001
1–3	–0.01	–0.008	–0.008	0.002	0.002	0.003
3–6	0.001	0.001	0.004	0	0.003	0.003
6–10	–0.003	–0.004	–0.003	–0.001	–0.001	0
>10	–0.004	–0.004	–0.003	0	0.001	0.001
Not available	0.016	0.014	0.009	–0.002	–0.007	–0.005
Platelets,[a] $10^3/\mu L$						
<1	–0.014	–0.014	–0.012	0	0.002	0.002
1–1.5	–0.011	–0.01	–0.009	0.002	0.002	0.001
1.5–2	0.001	0	0.001	0	0	0
>2	NA	NA	NA	NA	NA	NA
Not available	0.024	0.023	0.02	–0.001	–0.004	–0.003
Albumin,[a] g/dL						
>1	–0.007	–0.005	–0.002	0.003	0.005	0.003
0.8–1	–0.007	–0.006	–0.004	0.001	0.003	0.002
<0.8	–0.001	–0.001	0	0	0.001	0.001
Not available	0.016	0.012	0.006	–0.004	–0.01	–0.006
Hemoglobin,[a] g/dL						
>1	0.008	0.006	0.005	–0.002	–0.003	–0.001
0.8–1	–0.03	–0.026	–0.025	0.004	0.005	0.001
<0.8	–0.002	–0.003	0	–0.001	0.003	0.003
Not available	0.024	NA	NA	–0.001	NA	–0.003
White blood cell count,[a] $10^3/\mu L$						
<1	–0.01	–0.012	–0.012	–0.003	–0.002	0
1–1.5	–0.012	–0.009	–0.008	0.003	0.005	0.002
1.5–2	–0.001	0	0.001	0.001	0.002	0.001
2–3	–0.002	–0.002	–0.002	0	0	0
>3	0	0	0	0	0	0
Not available	0.025	NA	0.02	–0.001	NA	NA
Disease activity by blood markers						
Mild	0.004	0.004	0.004	0	0	0
Moderate	0.006	0.005	0.004	–0.001	–0.001	0
Severe	–0.004	–0.004	–0.004	0	0	0
Extreme	–0.005	–0.005	–0.004	0	0.001	0.001
Hospitalization	–0.011	–0.009	–0.003	0.003	0.008	0.005
IBD-related comorbidities	0.005	0.006	0.007	0.002	0.002	0.001

NOTE. Numbers in all cells represent standardized mean difference (SMD), where SMD < 0.1 reflects good balance.
[a]The categories of the laboratory tests represent times their normal limit. Therefore, abnormal test is reflected by values <1 for albumin and hemoglobin and by >1 for CRP, platelets, and white blood cell.
CRP, C-reactive protein; IMM, immunomodulators; NA, not applicable; SES, socioeconomic status.

Supplementary Table 9. Covariate Balance for UC Steroid Dependency Model

Variables	0–3 mo vs 3–12 mo	0–3 mo vs 1–2 y	0–3 mo vs 2–3 y	3–12 mo vs 1–2 y	3–12 mo vs 2–3 y	1–2 y vs 2–3 y
Male sex	–0.004	–0.003	–0.003	0.001	0.001	0
District						
Southern	0.001	0.001	0	0	0	0
Central	–0.004	–0.003	–0.003	0	0.001	0
Northern	0.003	0.003	0.003	0	–0.001	0
Age at diagnosis	0.025	0.024	0.024	–0.001	–0.001	0
Year of diagnosis	–0.076	–0.077	–0.077	–0.001	–0.001	0
SES points	0	–0.001	0	0	0.001	0.001
Mesalamine use	0.002	–0.002	–0.005	–0.004	–0.007	–0.002
IMM use	–0.001	–0.001	0.003	0.001	0.004	0.003
Number of gastroenterology visits	0.044	0.064	0.071	0.02	0.027	0.007
CRP,[a] mg/dL						
<1	0.001	0.001	0.001	–0.001	0	0.001
1–3	–0.01	–0.009	–0.009	0.001	0.001	0.003
3–6	0.004	0.003	0.006	–0.001	0.002	0.003
6–10	–0.002	–0.003	–0.003	–0.001	–0.001	0
>10	–0.001	0	–0.001	0.001	0.001	0
Not available	0.007	0.009	0.005	0.001	–0.002	–0.003
Platelets,[a] $10^3/\mu L$						
<1	0.109	0.146	0.162	0.037	0.053	0.016
1–1.5	–0.008	–0.007	–0.007	0.001	0.002	0
1.5–2	0.002	0.001	0.001	0	–0.001	0
>2	0	0	0	0	0	0
Not available	0.014	0.016	0.016	0.002	0.001	–0.001
Albumin,[a] g/dL						
>1	–0.001	–0.001	0	0	0.001	0.001
0.8–1	–0.004	–0.002	–0.001	0.001	0.002	0.001
<0.8	0	0	0	–0.001	0	0.001
Not available	0.004	0.004	0.001	0	–0.003	–0.003
Hemoglobin,[a] g/dL						
>1	0.005	0.001	0.001	–0.004	–0.004	0
0.8–1	–0.02	–0.017	–0.017	0.003	0.003	–0.001
<0.8	0	–0.001	0.001	–0.001	0.001	0.002
Not available	NA	0.017	NA	0.002	0.001	–0.001
White blood cell count,[a] $10^3/\mu L$						
<1	–0.01	–0.016	–0.018	–0.005	–0.007	–0.002
1–1.5	–0.003	0.001	0.001	0.004	0.005	0.001
1.5–2	0.001	0	0.002	–0.001	0.001	0.002
2–3	–0.002	–0.002	–0.002	0	0	0
>3	0	0.001	0.001	0	0	0
Not available	0.015	NA	NA	NA	NA	NA
Disease activity by blood markers						
Mild	0.003	0.004	0.003	0.001	0	0
Moderate	0.005	0.004	0.004	–0.001	–0.001	0
Severe	–0.003	–0.003	–0.003	0	0	0
Extreme	–0.005	–0.005	–0.004	0	0.001	0
Hospitalization	–0.001	–0.003	0.002	–0.002	0.003	0.004
IBD-related comorbidities	0.004	0.006	0.006	0.001	0.001	0

NOTE. Numbers in all cells represent standardized mean difference (SMD), where SMD < 0.1 reflects good balance.
[a]The categories of the laboratory tests represent times their normal limit. Therefore, abnormal test is reflected by values <1 for albumin and hemoglobin and by >1 for CRP, platelets, and white blood cell.
CRP, C-reactive protein; IMM, immunomodulators; NA, not applicable; SES, socioeconomic status.

Supplementary Table 10. Covariate Balance for CD PIBD Surgery Model

Variables	0–3 mo vs 3–12 mo	0–3 mo vs 1–2 y	0–3 mo vs 2–3 y	3–12 mo vs 1–2 y	3–12 mo vs 2–3 y	1–2 y vs 2–3 y
Male sex	0	0.001	0.001	0.001	0.001	0
District						
Southern	–0.007	–0.008	–0.007	–0.001	0	0
Central	–0.002	–0.002	–0.003	0	–0.001	–0.002
Northern	0.009	0.009	0.01	0	0.001	0.001
Age at diagnosis	–0.033	–0.034	–0.033	–0.001	0	0.001
Year of diagnosis	–0.212	–0.204	–0.204	0.008	0.007	0
SES points	0.004	0.008	0.007	0.003	0.003	–0.001
Mesalamine use	0.046	0.032	0.026	–0.013	–0.019	–0.006
IMM use	–0.033	–0.028	–0.028	0.005	0.005	0
Number of gastroenterology visits	0.052	0.066	0.065	0.013	0.012	–0.001
CRP,[a] mg/dL						
<1	–0.005	–0.007	–0.003	–0.002	0.002	0.004
1–3	–0.011	–0.01	–0.01	0.001	0.001	0
3–6	0	0	0.001	0	0.001	0.001
6–10	–0.007	–0.007	–0.007	0	0	0
>10	–0.012	–0.008	–0.006	0.005	0.006	0.001
Not available	0.036	0.031	0.025	–0.004	–0.011	–0.007
Platelets,[a] $10^3/\mu$L						
<1	–0.023	–0.021	–0.016	0.002	0.006	0.005
1–1.5	–0.01	–0.008	–0.011	0.002	–0.002	–0.003
1.5–2	–0.003	–0.002	–0.001	0.001	0.002	0.001
>2	–0.001	–0.001	0	0	0.001	0.001
Not available	0.037	0.032	0.029	–0.005	–0.007	–0.003
Albumin,[a] g/dL						
>1	–0.01	–0.008	–0.007	0.001	0.003	0.001
0.8–1	–0.021	–0.021	–0.02	0	0	0.001
<0.8	0.001	–0.001	0	–0.002	–0.001	0.001
Not available	0.036	0.029	0.022	–0.007	–0.014	–0.007
Hemoglobin,[a] g/dL						
>1	0.089	0.078	0.088	–0.012	–0.002	0.01
0.8–1	–0.01	–0.001	–0.003	0.009	0.007	–0.002
<0.8	–0.007	–0.003	–0.002	0.004	0.005	0
Not available	NA	0.032	NA	NA	NA	–0.003
White blood cell count,[a] $10^3/\mu$L						
<1	–0.041	–0.043	–0.039	–0.002	0.002	0.004
1–1.5	0.004	0.011	0.009	0.007	0.006	0.001
1.5–2	0.001	0.002	0.002	0.001	0	0
2–3	–0.001	–0.001	–0.001	0	0	0
>3	0	0	0	0	0	0
Not available	0	0	0	NA	NA	NA
Disease activity by blood markers						
Minimal	0.007	0.007	0.007	–0.001	0	0
Mild	0.011	0.009	0.008	–0.002	–0.002	–0.001
Moderate	–0.003	–0.003	–0.002	0	0.001	0.001
Severe	–0.009	–0.008	–0.008	0	0	0
Extreme	–0.006	–0.005	–0.005	0.001	0.001	0
Hospitalization	–0.002	0.008	0.019	0.01	0.021	0.011
Perianal diagnosis before IBD diagnosis	–0.006	–0.006	–0.006	0	0	0
Perianal diagnosis after IBD diagnosis	–0.009	–0.008	–0.008	0.001	0.001	0
IBD-related comorbidities	0.009	0.011	0.012	0.002	0.003	0.001

NOTE. Numbers in all cells represent standardized mean difference (SMD), where SMD < 0.1 reflects good balance.
[a]The categories of the laboratory tests represent times their normal limit. Therefore, abnormal test is reflected by values <1 for albumin and hemoglobin and by >1 for CRP, platelets, and white blood cell.
CRP, C-reactive protein; IMM, immunomodulators; NA, not applicable; PIBD, pediatric inflammatory bowel diseases; SES, socioeconomic status.

Supplementary Table 11. Covariate Balance for CD PIBD Steroid Dependency Model

Variables	0–3 mo vs 3–12 mo	0–3 mo vs 1–2 y	0–3 mo vs 2–3 y	3–12 mo vs 1–2 y	3–12 mo vs 2–3 y	1–2 y vs 2–3 y
Male sex	0.001	0.001	0.001	0.001	0.001	0
District						
Southern	–0.007	–0.007	–0.007	0	0	0
Central	–0.002	–0.002	–0.004	0	–0.001	–0.001
Northern	0.009	0.01	0.011	0	0.001	0.001
Age at diagnosis	–0.035	–0.037	–0.037	–0.002	–0.002	0
Year of diagnosis	–0.21	–0.205	–0.205	0.005	0.005	–0.001
SES points	0.002	0.005	0.004	0.004	0.002	–0.001
Mesalamine use	0.045	0.032	0.025	–0.013	–0.019	–0.006
IMM use	–0.017	–0.016	–0.016	0.001	0.001	0
Number of gastroenterology visits	0.05	0.062	0.061	0.012	0.012	–0.001
CRP,[a] mg/dL						
<1	–0.004	–0.004	–0.001	0	0.003	0.004
1–3	–0.008	–0.007	–0.007	0.001	0.001	0
3–6	0.003	0.002	0.002	–0.001	–0.001	0
6–10	–0.009	–0.008	–0.008	0.001	0.001	0
>10	–0.011	–0.008	–0.008	0.003	0.003	0
Not available	0.29	0.027	0.023	–0.003	–0.006	–0.004
Platelets,[a] $10^3/\mu L$						
<1	–0.023	–0.021	–0.017	0.002	0.006	0.004
1–1.5	–0.003	–0.004	–0.008	–0.002	–0.006	–0.004
1.5–2	–0.002	–0.001	0	0.001	0.002	0.001
>2	–0.001	–0.001	0	0	0.001	0.001
Not available	0.029	0.027	0.026	–0.002	–0.003	–0.001
Albumin,[a] g/dL						
>1	–0.021	–0.02	–0.015	0.001	0.006	0.005
0.8–1	–0.005	0	–0.002	0.006	0.004	–0.002
<0.8	–0.001	–0.002	–0.001	–0.002	0	0.001
Not available	0.027	0.022	0.018	–0.005	–0.009	–0.004
Hemoglobin,[a] g/dL						
>1	–0.009	–0.007	–0.005	0.002	0.004	0.002
0.8–1	–0.013	–0.016	–0.018	–0.003	–0.005	–0.002
<0.8	–0.007	–0.004	–0.003	0.003	0.004	0
Not available	0.03	0.027	NA	–0.002	NA	NA
White blood cell count,[a] $10^3/\mu L$						
<1	–0.04	–0.041	–0.038	–0.002	0.001	0.003
1–1.5	0.008	0.013	0.012	0.005	0.004	–0.001
1.5–2	0.003	0.002	0.002	–0.001	–0.002	–0.001
2–3	–0.001	–0.001	–0.001	0	0	0
>3	0	0	0	NA	NA	NA
Not available	NA	0.027	NA	NA	–0.004	NA
Disease activity by blood markers						
Minimal	0.006	0.006	0.006	0	0	0
Mild	0.009	0.008	0.007	–0.001	–0.002	–0.001
Moderate	–0.003	–0.003	–0.002	0.001	0.001	0
Severe	–0.007	–0.007	–0.007	0	0	0
Extreme	–0.006	–0.005	–0.005	0.001	0.001	0
Hospitalization	0.003	0.011	0.018	0.008	0.016	0.007
Perianal diagnosis before IBD diagnosis	–0.007	–0.007	–0.007	0	0	0
Perianal diagnosis after IBD diagnosis	–0.01	–0.008	–0.009	0.002	0.001	0
IBD-related comorbidities	0.012	0.014	0.014	0.002	0.002	0

NOTE. Numbers in all cells represent standardized mean difference (SMD), where SMD < 0.1 reflects good balance.
[a]The categories of the laboratory tests represent times their normal limit. Therefore, abnormal test is reflected by values <1 for albumin and hemoglobin and by >1 for CRP, platelets, and white blood cell.
CRP, C-reactive protein; IMM, immunomodulators; NA, not applicable; PIBD, pediatric inflammatory bowel diseases; SES, socioeconomic status.

Supplementary Table 12. Covariate Balance for UC PIBD Colectomy Model

Variables	0–3 mo vs 3–12 mo	0–3 mo vs 1–2 y	0–3 mo vs 2–3 y	3–12 mo vs 1–2 y	3–12 mo vs 2–3 y	1–2 y vs 2–3 y
Male sex	–0.005	–0.006	–0.008	–0.001	–0.002	–0.001
District						
Southern	–0.005	–0.006	–0.006	–0.001	–0.001	0
Central	–0.001	0	–0.001	0	0	–0.001
Northern	0.005	0.007	0.007	0.001	0.002	0.001
Age at diagnosis	–0.008	–0.007	–0.006	0	0.001	0.001
Year of diagnosis	–0.092	–0.094	–0.092	–0.003	0	0.002
SES points	–0.024	–0.024	–0.029	–0.001	–0.005	–0.005
Mesalamine use	–0.033	–0.034	–0.036	0	–0.002	–0.002
IMM use	–0.028	–0.024	–0.018	0.004	0.01	0.006
Number of gastroenterology visits	0.026	0.041	0.053	0.015	0.027	0.012
CRP,[a] mg/dL						
<1	0.006	0.008	0.008	0.002	0.001	–0.001
1–3	–0.005	–0.005	–0.003	0	0.001	0.001
3–6	0	–0.004	0.002	–0.004	0.001	0.005
6–10	0.001	0	–0.001	–0.001	–0.002	–0.001
>10	–0.009	–0.008	–0.009	0.001	0.001	0
Not available	0.007	0.009	0.004	0.007	–0.003	–0.005
Platelets,[a] $10^3/\mu L$						
<1	0.013	0.012	0.014	–0.001	0.001	0.002
1–1.5	–0.03	–0.028	–0.026	0.002	0.004	0.002
1.5–2	0.002	0.002	0.003	0	0.001	0.001
>2	0	0	0	0	0	0
Not available	0.015	0.015	0.009	–0.001	–0.006	–0.005
Albumin,[a] g/dL						
>1	0.003	0.006	0.013	0.004	0.01	0.007
0.8–1	–0.025	–0.021	–0.02	0.005	0.006	0.001
<0.8	–0.002	–0.002	–0.002	0	0	0.001
Not available	0.019	0.015	0.007	–0.004	–0.012	–0.008
Hemoglobin,[a] g/dL						
>1	0.019	0.019	0.021	–0.001	0.002	0.002
0.8–1	0.001	–0.002	–0.003	–0.003	–0.005	–0.001
<0.8	–0.009	–0.012	–0.01	–0.003	–0.001	0.002
Not available	NA	–0.138	NA	–0.025	–0.038	–0.013
White blood cell count,[a] $10^3/\mu L$						
<1	0.009	0.006	0.01	–0.003	0.001	0.004
1–1.5	–0.024	–0.021	–0.02	0.003	0.004	0.001
1.5–2	–0.001	0	0	0.001	0.001	0
2–3	0	0	0	0	0	0
>3	0	0	0	0	0	0
Not available	NA	NA	NA	NA	NA	NA
Disease activity by blood markers						
Mild	0.004	0.003	0.003	0	0	0
Moderate	0.007	0.008	0.008	0.001	0.002	0.001
Severe	–0.006	–0.007	–0.009	–0.001	–0.002	–0.002
Extreme	–0.004	–0.004	–0.003	0	0.001	0.001
Hospitalization	–0.026	–0.019	–0.01	0.007	0.016	0.009
IBD-related comorbidities	0.005	0.008	0.008	0.003	0.003	–0.001

NOTE. Numbers in all cells represent standardized mean difference (SMD), where SMD < 0.1 reflects good balance.
[a]The categories of the laboratory tests represent times their normal limit. Therefore, abnormal test is reflected by values <1 for albumin and hemoglobin and by >1 for CRP, platelets, and white blood cell.
CRP, C-reactive protein; IMM, immunomodulators; NA, not applicable; PIBD, pediatric inflammatory bowel diseases; SES, socioeconomic status.

Supplementary Table 13. Covariate Balance for UC PIBD Steroid Dependency Model

Variables	0–3 mo vs 3–12 mo	0–3 mo vs 1–2 y	0–3 mo vs 2–3 y	3–12 mo vs 1–2 y	3–12 mo vs 2–3 y	1–2 y vs 2–3 y
Male sex	–0.006	–0.005	–0.004	0.001	0.002	0.001
District						
Southern	–0.005	–0.006	–0.007	–0.002	–0.002	–0.001
Central	–0.002	–0.001	–0.001	0	0.001	0
Northern	0.006	0.007	0.008	0.001	0.002	0
Age at diagnosis	–0.013	–0.011	–0.009	0.001	0.004	0.003
Year of diagnosis	–0.091	–0.096	–0.093	–0.005	–0.002	0.003
SES points	–0.024	–0.025	–0.028	–0.001	–0.005	–0.004
Mesalamine use	–0.015	–0.021	–0.029	–0.006	–0.014	–0.008
IMM use	–0.011	–0.004	0.003	0.007	0.014	0.006
Number of gastroenterology visits	0.013	0.032	0.036	0.018	0.023	0.004
CRP,[a] mg/dL						
<1	0.01	0.009	0.007	–0.002	–0.003	–0.001
1–3	0.002	0.002	0.005	0	0.003	0.003
3–6	–0.002	–0.004	–0.001	–0.002	0.001	0.003
6–10	0.001	0	–0.002	–0.001	–0.003	–0.002
>10	–0.008	–0.007	–0.008	0.001	0.001	–0.001
Not available	–0.003	0	–0.002	0.004	0.001	–0.003
Platelets,[a] $10^3/\mu L$						
<1	0.109	0.146	0.162	0.037	0.053	0.016
1–1.5	–0.023	–0.022	–0.021	0.003	0.003	0.001
1.5–2	0.002	0.001	0.002	–0.001	0	0
>2	0	0	0	0	0	0
Not available	0.005	0.007	0.004	0.002	–0.001	0.003
Albumin,[a] g/dL						
>1	0.015	0.017	0.023	0.002	0.008	0.005
0.8–1	–0.018	–0.02	–0.019	–0.002	–0.002	0
<0.8	–0.002	–0.002	–0.002	0	0	0
Not available	0.005	0.005	–0.001	0	–0.006	–0.006
Hemoglobin,[a] g/dL						
>1	0.012	0.009	0.011	–0.003	–0.001	0.002
0.8–1	–0.012	–0.006	–0.01	0.006	0.002	–0.004
<0.8	–0.005	–0.01	–0.004	–0.00	0	0.005
Not available	NA	–0.114	NA	–0.028	NA	–0.012
White blood cell count,[a] $10^3/\mu L$						
<1	0.007	0	0.002	–0.007	0.005	0.002
1–1.5	–0.026	–0.034	–0.039	–0.008	–0.013	–0.005
1.5–2	–0.011	–0.008	–0.007	0.004	0.004	0
2–3	0	0.001	0.002	0.001	0.002	0.001
>3	0	0	0	0	0	0
Not available	NA	NA	NA	NA	NA	NA
Disease activity by blood markers						
Mild	0.001	0.001	0.001	0	–0.001	–0.001
Moderate	0.008	0.009	0.01	0.001	0.002	0.001
Severe	–0.005	–0.006	–0.006	–0.001	–0.001	0
Extreme	–0.004	–0.004	–0.005	0	0	0
Hospitalization	–0.004	–0.002	0.007	0.002	0.01	0.008
IBD-related comorbidities	0.003	0.007	0.008	0.004	0.005	0.001

NOTE. Numbers in all cells represent standardized mean difference (SMD), where SMD < 0.1 reflects good balance.
[a]The categories of the laboratory tests represent times their normal limit. Therefore, abnormal test is reflected by values <1 for albumin and hemoglobin and by >1 for CRP, platelets, and white blood cell.
CRP, C-reactive protein; IMM, immunomodulators; NA, not applicable; PIBD, pediatric inflammatory bowel diseases; SES, socioeconomic status.

Supplementary Table 14. The 7- and 10-Year Probability of Surgery and Steroid Dependency in CD and UC Patients (Including Patients Who Never Received Biologics), Comparing Between Disease Duration Periods Before Biologics Initiation

Disease outcomes	Probability, % (95% CI)	0–3 mo	3–12 mo	1–2 y	2–3 y
CD					
7-y probability for surgery					
0–3 mo	18 (11–24)	—	—	—	—
3–12 mo	22 (18–26)	$P = .24$	—	—	—
1–2 y	17 (14–20)	$P = .89$	$P = .07$	—	—
2–3 y	21 (16–25)	$P = .43$	$P = .64$	$P = .21$	—
7-y probability for steroid dependency					
0–3 mo	18 (11–24)	—	—	—	—
3–12 mo	27 (19–35)	$P = .06$	—	—	—
1–2 y	25 (19–32)	$P = .1$	$P = .72$	—	—
2–3 y	28 (21–35)	$P = .04$	$P = .9$	$P = .6$	—
10-y probability for surgery					
0–3 mo	15 (10–20)	—	—	—	—
3–12 mo	19 (15–23)	$P = .26$	—	—	—
1–2 y	21 (17–25)	$P = .06$	$P = .42$	—	—
2–3 y	18 (15–22)	$P = .28$	$P = .88$	$P = .30$	—
10-y probability for steroid dependency					
0–3 mo	15 (10–20)	—	—	—	—
3–12 mo	19 (15–23)	$P = .26$	—	—	—
1–2 y	25 (19–31)	$P < .01$	$P = .08$	—	—
2–3 y	20 (16–25)	$P = .12$	$P = .61$	$P = .19$	—
Ulcerative colitis					
7-y probability for colectomy					
0–3 mo	4 (1–7)	—	—	—	—
3–12 mo	9 (3–15)	$P = .13$	—	—	—
1–2 y	6 (1–11)	$P = .42$	$P = .46$	—	—
2–3 y	4 (0–7)	$P = .97$	$P = .14$	$P = .43$	—
7-y probability for steroid dependency					
0–3 mo	4 (1–7)	—	—	—	—
3–12 mo	9 (3–15)	$P = .13$	—	—	—
1–2 y	6 (1–11)	$P = .42$	$P = .46$	—	—
2–3 y	4 (0–7)	$P = .97$	$P = .14$	$P = .43$	—
10-y probability for colectomy					
0–3 mo	14 (0–48)	—	—	—	—
3–12 mo	35 (7–62)	$P = .35$	—	—	—
1–2 y	18 (12–23)	$P = .84$	$P = .23$	—	—
2–3 y	32 (12–52)	$P = .37$	$P = .87$	$P = .17$	—
10-y probability for steroid dependency					
0–3 mo	14 (1–27)	—	—	—	—
3–12 mo	35 (10–60)	$P = .14$	—	—	—
1–2 y	18 (12–23)	$P = .61$	$P = .19$	—	—
2–3 y	32 (12–52)	$P = .13$	$P = .86$	$P = .17$	—

Supplementary Table 15. The 7- and 10-Year Probabilities of Surgery in Patients With CD and UC Who Initiated Biologics From 3 Years Postdiagnosis, Comparing Between Disease Duration Periods Before Biologics Initiation

Disease outcomes	Probability, % (95% CI)	Number of outcomes	0–3 mo	3–12 mo	1–2 y	2–3 y
7-year probability for surgery in CD, >3 y	20 (18–22)	103	$P = .64$	$P = .26$	$P = .9$	$P = .11$
7-year probability for colectomy in UC, >3 y	3 (1–4)	5	$P = .33$	$P = .06$	$P = .06$	$P = .23$
10-year probability for surgery in CD, >3 y	30 (28–32)	113	$P < .01$	$P = .63$	$P = .46$	$P = .87$
10-year probability for colectomy in UC, >3 y	4 (2–5)	6	$P = .84$	$P = .12$	$P = .21$	$P = .53$

Supplementary Table 16. The 10-Year Probabilities for Surgery and Steroid Dependency for CD and UC Stratified by Year of Diagnosis (Before 2010 and After 2010)

Disease outcomes	Year of diagnosis < 2010 probability, %	Year of diagnosis ≥ 2010 probability, %	NNT prior to 2010	NNT after 2010
CD				
10-year probability for surgery				
0–3 mo	12	20	—	—
3–12 mo	31	28	—	—
1–2 y	26	28	—	—
2–3 y	30	32	5.6	8.3
10-year probability for steroid dependency				
0–3 mo	15	19	—	—
3–12 mo	26	24	—	—
1–2 y	42	31	—	—
2–3 y	34	30	5.3	9.1
UC				
10-year probability for colectomy				
0–3 mo	0	5	—	—
3–12 mo	13	11	—	—
1–2 y	9	7	—	—
2–3 y	5	5	—	—
10-year probability for steroid dependency				
0–3 mo	12	—	—	—
3–12 mo	—	58	—	—
1–2 y	52	44	—	—
2–3 y	51	52	—	—