

# Practical strategy for optimizing the timing of anti-tumor necrosis factor- $\alpha$ therapy in Crohn disease

## A nationwide population-based study

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### Abstract

There is little consensus on the optimal timing of anti-tumor necrosis factor (anti-TNF) therapy to decrease the rates of hospitalization and surgery in Crohn disease (CD). We aimed to assess the real-world outcomes of anti-TNF therapy and estimate the optimal timing of anti-TNF therapy in Korean patients with CD.

Claims data were extracted from the Korean Health Insurance Review and Assessment Service database. Incident patients diagnosed with CD between 2009 and 2016, with at least 1 anti-TNF drug prescription, and with follow-up duration > 6 months were stratified according to the number of relapses prior to initiation of anti-TNF therapy: groups A ( $\leq 1$  relapse), B (2 relapses), C (3 relapses), and D ( $\geq 4$  relapses). The cumulative survival curves free from emergency hospitalization (EH) and surgery were compared across groups.

Among the 2173 patients analyzed, the best and worst prognoses were noted in groups A and D, respectively. The incidences of EH and surgery decreased significantly as the use of anti-TNF agents increased. The 5-year rate of hospitalization was significantly lower in group A than in groups C and D ( $P = .004$  and  $.020$ , respectively), but similar between groups A and B. The 5-year rate of surgery was lower in group A than in group C ( $P = .024$ ), but similar among groups A, B, and D.

In Asian patients with CD, anti-TNF therapy reduces the risk of EH and surgery and should be considered before three relapses, regardless of disease duration.

**Abbreviations:** anti-TNF = anti-tumor necrosis factor, CD = Crohn disease, EH = Emergency hospitalization, HIRA = Health Insurance Review and Assessment Service.

**Keywords:** biological therapy, Crohn's disease, Outcome

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## 1. Introduction

Crohn disease (CD) is a chronic disease with relapsing-remitting course and protracted impact.<sup>[1]</sup> In CD patients, disease flares and complications may result in the need for hospitalization and even surgery,<sup>[2,3]</sup> with high direct healthcare costs.<sup>[4,5]</sup> CD treatment strategies have changed remarkably over the past decades, and the early use of anti-tumor necrosis factor (anti-TNF) therapies is now preferred, with the goal of altering the progressive and destructive course frequently observed in CD.<sup>[6-8]</sup> However, the most substantial improvement in the rate of CD-related hospitalization and surgery has been achieved since the introduction of biological treatments.<sup>[9-12]</sup> Population-based studies are typically required in order to obtain general insight into the natural course of a disease and to subsequently issue recommendations for treatment. However, there is insufficient evidence from population level to clarify the natural course of CD in Asian populations.

The optimal timing of anti-TNF therapy represents another important concern in CD. In current clinical practice, most CD patients who start anti-TNF therapy continue to use anti-TNF therapy for a long time, despite the high cost and ongoing safety concerns. The guidelines issued by the European Crohn and Colitis Organization in 2016 recommend trying corticosteroid treatment before starting anti-TNF agents,<sup>[13]</sup> but no further recommendations are made regarding the timing of anti-TNF

therapy. The Korean guidelines issued in 2017<sup>[14]</sup> also recommend the use of anti-TNF therapy to induce remission of moderate-to-severe CD. However, there is still little agreement on the optimal timing of anti-TNF therapy for CD, especially in Asian populations.

The aim of this nationwide population-based study was to assess the real-world outcomes of anti-TNF treatment in patients with CD, as well as to estimate the optimal timing of anti-TNF therapy to improve the long-term outcomes of CD.

## 2. Patients and methods

### 2.1. Data sources and study population

This was a retrospective nationwide population-based cohort study conducted using the database maintained by the Korean Health Insurance Review and Assessment Service (HIRA), which contains all inpatient and outpatient claims data collected nationwide since 1989.<sup>[15]</sup> HIRA contains the adjusted medical and pharmacy claims for the entire Korean population because all clinics and hospitals in Korea submit claims data to the HIRA in order to obtain reimbursement of medical costs from the Korean Government, which funds public healthcare based on a single-payer system.<sup>[15]</sup> The HIRA provided de-identified data on socio-demographic characteristics (sex, age, and medical-aid program), information related to the healthcare service provided during a given visit (diagnosis, procedures, treatments, prescriptions), type of healthcare service provider (primary, secondary, or tertiary hospital), and the claim date.<sup>[15]</sup> The HIRA database records diagnosis information based on the 6th edition of the Korean Classification of Disease, which is a modified version of the International Classification of Disease, 10th revision, adapted for use within the Korean healthcare system.<sup>[15]</sup>

We extracted all claims data pertaining to incident CD patients and recorded in the HIRA database between 2009 and 2016. Such patients were identified based on the diagnostic code of CD (K50) and a simultaneous prescription of relevant drugs.<sup>[16]</sup> We only included patients followed up for at least 6 months after diagnosis. In South Korea, anti-TNF agents have been covered by insurance for the treatment of patients with CD since October 2010 with strict criteria for reimbursement coverage. An inadequate response to conventional treatment with corticosteroids and/or thiopurines and moderate or severe disease activity are mandatory for government reimbursement coverage.

Our primary goal was to assess the real-world outcomes of treatment with anti-TNF agents such as infliximab and adalimumab. The secondary goal was to determine the optimal timing of anti-TNF therapy for improving the long-term outcomes of CD in Korean patients. This retrospective cohort study was reviewed and approved by the Institutional Review Board of the Kyung Hee University Hospital at Gangdong (KHNMC IRB 2018-01-014). The need for informed consent was waived on account of the fact that all data used in this study were de-identified.

### 2.2. Definition of variables

Relapse was defined as the prescription of  $\geq 30$  mg oral or intravenous prednisone (or equivalent) per day. In this study, CD patients were divided into 4 groups according to the number of relapses before initiation of anti-TNF therapy: group A,  $\leq 1$  relapse; group B, 2 relapses; group C, 3 relapses; and group D,  $\geq 4$  relapses. Emergency hospitalization (EH) was defined as hospitalization via the emergency department for symptoms

associated with a main diagnosis of CD and requiring  $> 30$  mg prednisone (or equivalent) per day.<sup>[17]</sup> Surgery for CD was defined as bowel resection surgery as described within the Current Procedural Terminology code.<sup>[18]</sup> For each month, the rate of EH or surgery was obtained as the ratio between the number of corresponding events and the total number of CD-related claims in that month. Early use of anti-TNF therapy was defined as initiation of anti-TNF agents (ie, first prescription) within 24 months of the initial diagnosis, per the approach used in previous studies.<sup>[19–21]</sup>

The regularity of treatment use was based on the frequency of treatment prescription, per the approach employed in previous studies and pharmacokinetics on immunomodulators<sup>[22,23]</sup> and anti-TNF agents.<sup>[24,25]</sup> During the follow-up periods after a diagnosis of CD, regular and irregular use of immunomodulators was defined if prescriptions for immunomodulatory drugs covered  $\geq 50\%$  or  $< 50\%$ , respectively.<sup>[22,23]</sup> Regarding infliximab therapy, regular and irregular use was defined as the prescription of infliximab at intervals of  $\leq 16$  weeks or  $> 16$  weeks, respectively, during the maintenance phase.<sup>[24]</sup> Regarding adalimumab therapy, regular and irregular use was defined as the prescription of adalimumab at intervals of  $\leq 4$  weeks or  $> 4$  weeks, respectively, during the maintenance phase.<sup>[25]</sup>

### 2.3. Statistical analyses

We used chi-square tests for categorical variables and independent sample *t* tests for continuous variables, as appropriate, in the descriptive analysis comparing patient characteristics among non-matched patients stratified according to the number of relapses (groups A–D). After matching, differences between groups were tested using McNemar test for categorical variables and paired *t* tests for continuous variables.

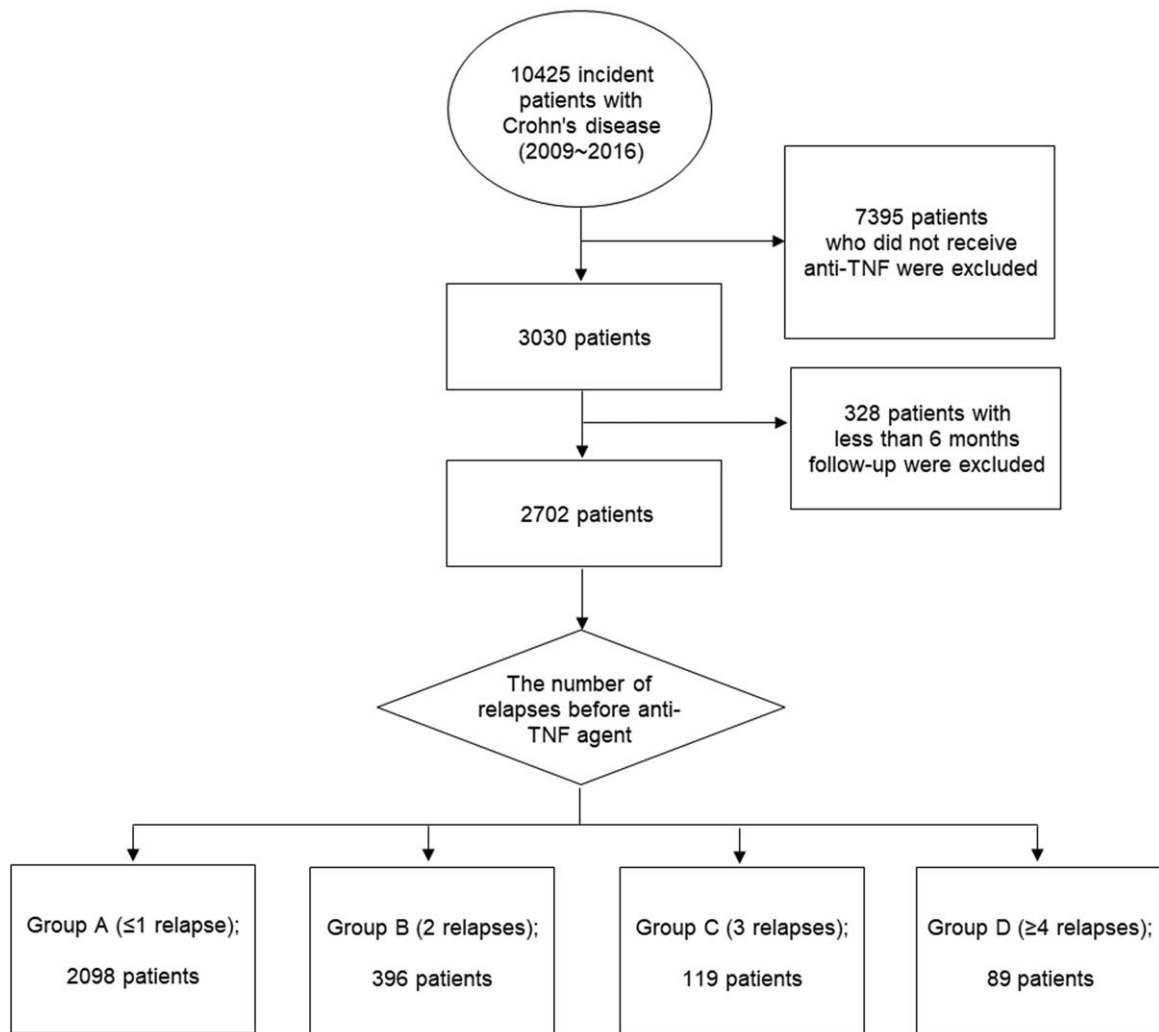
To account for the potential effect of covariates on each outcome, we created a propensity score combining the covariates of age, sex, regularity of medication use, and severity of pre-existing comorbid conditions, which was quantified using the Charlson Comorbidity Index (CCI), an index adapted for use with health administrative data<sup>[26–28]</sup>. The cumulative survival curves were compared across groups A–D using the log-rank test. Correlation analyses were performed to quantify the relationship between the prescription of anti-TNF agents and the rates of CD-related EH and surgery, with the results evaluated using Spearman rank correlation test. The statistical analyses were performed using R version 3.5.1.<sup>[29,30]</sup> All significant thresholds were set at a 2-sided *P*-value of .05.

## 3. Results

Of the 10,425 incident patients diagnosed with CD between January 2009 and December 2016, 3030 patients had at least 1 claim for anti-TNF agents following diagnosis (Fig. 1). After excluding 328 patients followed up for  $< 6$  months, 2702 CD patients were included in this study and stratified into four groups according to the number of relapses prior to initiation of anti-TNF therapy: group A ( $n = 2,098$ ), group B ( $n = 396$ ), group C ( $n = 119$ ), and group D ( $n = 89$ ).

### 3.1. Patient characteristics

In the overall population, the median follow-up duration was 55.7 months (interquartile range, 33.5–77.2 months). The mean



**Figure 1.** Patient selection flowchart. The patients were stratified according to the number of relapses experienced from diagnosis until initiation of anti-TNF therapy. TNF, tumor necrosis factor.

time from diagnosis until initiation of anti-TNF therapy ranged from 16.7 to 48.0 months across groups A–D (Tables 1 and 2). The groups were well matched with respect to major characteristics including age, sex distribution, CCI, and regularity of use of immunomodulatory and anti-TNF therapy.

The effect of medication use on each outcome (EH and surgery rates) was analyzed after propensity score matching with a ratio of 3:3:1:1 for groups A:B:C:D, using group D as reference. The 4 groups were similar in terms of all parameters analyzed, except regarding the effect of regularity of use of anti-TNF therapy on the rate of EH (group A vs group D:  $P = .019$ ). Patients in group D (ie, with  $\geq 4$  relapses) were older and more likely to be men.

### 3.2. Relationship between Anti-TNF agent use and major outcomes

Figure 2 illustrates the time trends for the incidences of EH and surgery, as well as those for the prescription of anti-TNF medication in patients with CD. From 2009 to 2016, the frequency of hospital visits for anti-TNF prescription increased 7.7-fold, from 3.8% to 29.3%, whereas the average annual rates

of EH and surgery decreased by 2.0% (95% confidence interval [CI] for the change: -4.3% to -1.6%) and 3.0% (95% CI for the change: -3.5% to -0.6%), respectively. There was an inverse and significant relationship between the change in the frequency of visits for anti-TNF prescriptions and the change in the annual rates of EH and surgery during the study period (for EH rates:  $r = -0.26$ ,  $P < .001$ ; for surgery rates:  $r = -0.35$ ,  $P = .004$ ).

### 3.3. Relationship between the number of relapses and major outcomes

Figure 3 shows the Kaplan-Meier estimates of the probability of survival free from EH and surgery following a diagnosis of CD. In groups A, B, C, and D, respectively, the mean duration of survival free from EH was  $30.5 \pm 26.3$ ,  $40.0 \pm 20.7$ ,  $55.4 \pm 23.4$ , and  $56.1 \pm 23.8$  months ( $P < .001$ ) (Fig. 3A), whereas the mean duration of survival free from surgery was  $32.0 \pm 24.6$ ,  $33.0 \pm 22.8$ ,  $54.2 \pm 21.8$ , and  $66.0 \pm 19.1$  months ( $P < .001$ ) (Fig. 3B). The 5-year rate of EH was 13.3%, 11.5%, 32.2%, and 25.3% in groups A, B, C, and D, respectively (Fig. 3A), with significantly lower rates in group A than in groups C and D ( $P = .004$  and  $P = .020$ ,

**Table 1**  
**Relationship between patient characteristics and emergency hospitalization in Crohn disease, upon stratification according to the number of relapses.**

Characteristic	Before matching					After matching								
	Group A	P-value	Group B	P-value	Group C	Group D (ref.)	Group A	P-value	Group B	P-value	Group C	Group D (ref.)		
	N=2098		N=396		N=119	N=89	N=267		N=267		N=89	N=89		
Emergency hospitalization	187 (8.9)		42 (10.6)		19 (16.0)	11 (12.4)	19 (7.1)		18 (6.7)		13 (14.6)	11 (12.4)		
Age, yr	21.9±10.9	.409	22.5±10.6	.757	24.0±11.7	.516	22.9±11.3	22.5±9.9	.748	21.8±10.3	.412	22.4±10.9	.751	22.9±11.3
Sex, n (%)														
Male	1466 (69.9)	.770	273 (68.9)	.673	82 (68.9)	.753	64 (71.9)	188 (70.4)	.893	191 (71.5)	1.000	62 (69.7)	.869	64 (71.9)
Female	632 (30.1)		123 (31.1)		37 (31.1)		25 (28.1)	79 (29.6)		76 (28.5)		27 (30.3)		25 (28.1)
Charlson Comorbidity Index	0.3±2.4	.536	0.3±2.4	.558	0.3±1.3	.423	0.5±1.7	0.1±0.6	.049	0.4±2.8	.741	0.4±1.5	.675	0.5±1.7
Time from diagnosis to initiation of anti-TNF therapy, mo	16.7±21.2	<.001	31.7±21.8	<.001	42.0±24.1	.070	48.0±22.7	19.9±22.8	<.001	32.2±22.5	<.001	42.7±24.6	.137	48.0±22.7
Use of immunomodulators, n (%)														
Regular	1095 (52.2)	.840	226 (57.1)	.094	67 (56.3)	.465	45 (50.6)	129 (48.3)	.582	139 (52.1)	.444	51 (57.3)	.549	45 (50.6)
Irregular	789 (37.6)		155 (39.1)		46 (38.7)		36 (40.4)	121 (45.3)		114 (42.7)		33 (37.1)		36 (40.4)
None	214 (10.2)		15 (3.8)		6 (5.0)		8 (9.0)	17 (6.4)		14 (5.2)		5 (5.6)		8 (9.0)
Use of anti-TNF agents, n (%)														
Regular	1748 (83.3)	.019	329 (83.1)	.024	97 (81.5)	.024	83 (93.3)	249 (93.3)	1.000	254 (95.1)	.683	84 (94.4)	1.000	83 (93.3)
Irregular	350 (16.7)		67 (16.9)		22 (18.5)		6 (6.7)	18 (6.7)		13 (4.9)		5 (5.6)		6 (6.7)
Anti-TNF switching, n (%)	158 (7.5)		27 (6.8)		11 (9.2)		7 (7.9)	10 (3.7)		12 (4.5)		4 (4.5)		7 (7.9)

In this analysis, the start point was defined as the date of initiation of anti-TNF therapy, while the end point was defined as the date of the first emergency hospitalization for CD-related symptoms. The patients were stratified according to the number of relapses from the diagnosis of Crohn's disease until initiation of anti-TNF therapy: group A,  $\leq 1$  relapse; group B, 2 relapses; group C, 3 relapses; group D,  $\geq 4$  relapses. Propensity score matching with a ratio of 3:3:1:1 for groups A:B:C:D was conducted based on a combination of the covariates of age, sex, regularity of medication use, and Charlson Comorbidity Index, with group D used as reference. Data represent frequency (percentage) or mean  $\pm$  standard deviation, as appropriate. The *P*-values were obtained using Spearman rank correlation test. TNF = anti-tumor necrosis factor.

respectively), but with similar rates between groups A and B ( $P = .780$ ) (Fig. 3A). The 5-year rate of surgery was 8.3%, 12.9%, 21.4%, and 22.1% in groups A, B, C, and D, respectively (Fig. 3B), with significantly lower rates in group A than in group C ( $P = .024$ ), but with similar rates across groups A, B, and D (A vs B,  $P = .229$ ; A vs D,  $P = .159$ ) (Fig. 3B).

### 3.4. Optimal timing of anti-TNF therapy

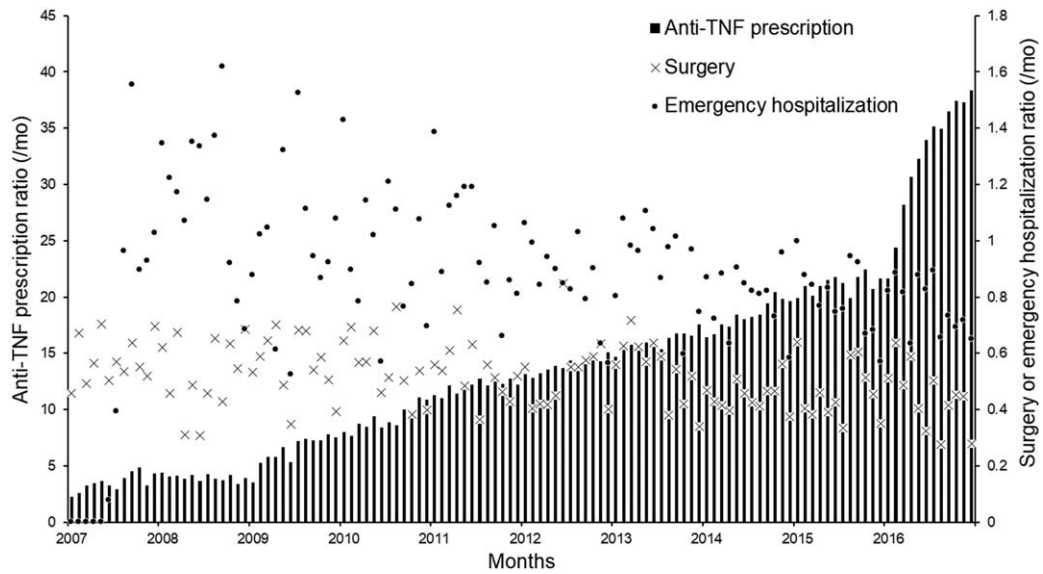
To clarify the efficacy of early anti-TNF therapy, the patients with  $\leq 2$  relapses (ie, groups A and B) were divided into subgroups according to the time interval from diagnosis until

initiation of anti-TNF therapy (early vs late use) (Supplementary Table 1, <http://links.lww.com/MD/D871>). After propensity score matching, most baseline parameters were comparable between the two subgroups. However, regular use of anti-TNF therapy was more common among patients who started anti-TNF therapy at  $> 24$  months after diagnosis than among those who started such therapy early, although the difference did not reach statistical significance. The probability of survival free from EH and surgery did not differ between the 2 subgroups (early vs late initiation of anti-TNF therapy) ( $P = .798$  and  $P = .334$ , respectively) (Supplementary Fig. 1, <http://links.lww.com/MD/D870>).

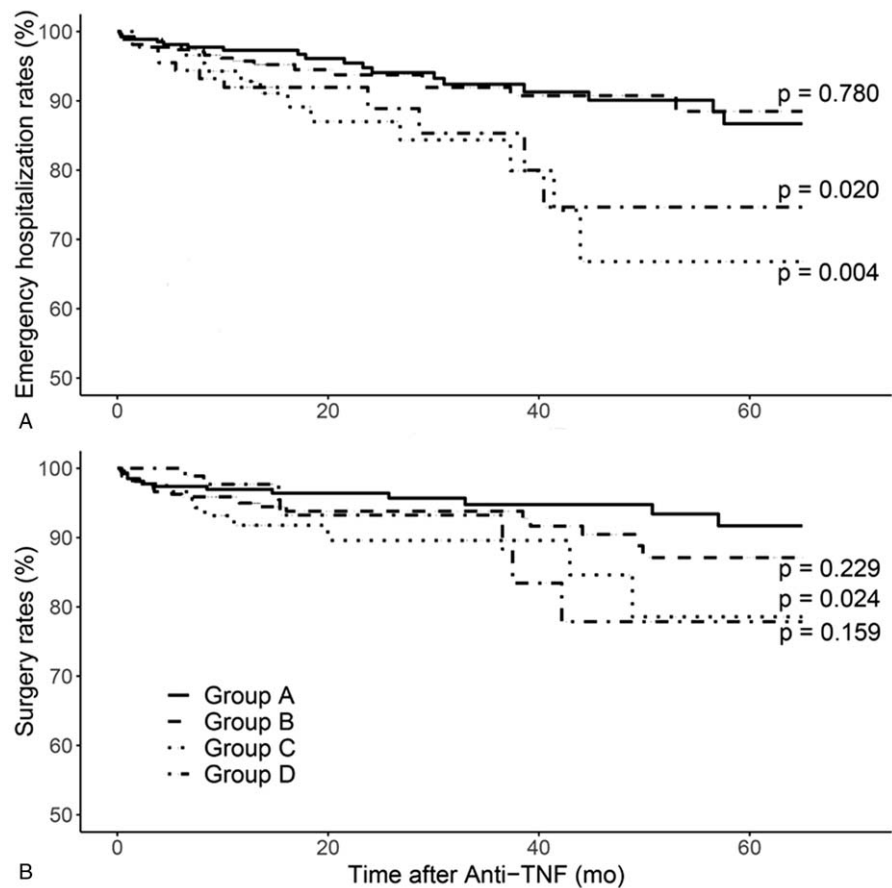
**Table 2**  
**Relationship between patient characteristics and surgery rates in Crohn disease, upon stratification according to the number of relapses.**

Characteristic	Before matching					After matching								
	Group A	P-value	Group B	P-value	Group C	Group D (ref.)	Group A	P-value	Group B	P-value	Group C	Group D (ref.)		
	N=2098		N=396		N=119	N=89	N=267		N=267		N=89	N=89		
Surgery	160 (7.6)		33 (8.3)		16 (13.4)		7 (7.9)	14 (5.2)		20 (7.5)		10 (11.2)		7 (7.9)
Age, yr	21.9±10.9	.409	22.5±10.6	.757	24.0±11.7	.516	22.9±11.3	21.5±9.3	.269	22.0±9.7	.467	22.0±10.7	.583	22.9±11.3
Sex, n (%)														
Male	1466 (69.9)	.770	273 (68.9)	.673	82 (68.9)	.753	64 (71.9)	194 (72.7)	1.000	199 (74.5)	.728	65 (73.0)	1.000	64 (71.9)
Female	632 (30.1)		123 (31.1)		37 (31.1)		25 (28.1)	73 (27.3)		68 (25.5)		24 (27.0)		25 (28.1)
Charlson Comorbidity Index	0.3±2.4	.536	0.3±2.4	.558	0.3±1.3	.423	0.5±1.7	0.3±1.9	.333	0.3±2.2	.511	0.3±1.5	.575	0.5±1.7
Time from diagnosis to initiation of anti-TNF therapy, months	16.7±21.2	<.001	31.7±21.8	<.001	42.0±24.1	.070	48.0±22.7	18.5±21.7	<.001	31.3±22.8	<.001	42.9±24.1	.146	48.0±22.7
Use of immunomodulators, n (%)														
Regular	1088 (51.9)	.773	217 (54.8)	.304	65 (54.6)	.694	46 (51.7)	137 (51.3)	.441	140 (52.4)	.823	50 (56.2)	.757	46 (51.7)
Irregular	800 (38.1)		163 (41.2)		48 (40.3)		36 (40.4)	118 (44.2)		111 (41.6)		34 (38.2)		36 (40.4)
None	210 (10.0)		16 (4.0)		6 (5.0)		7 (7.9)	12 (4.5)		16 (6.0)		5 (5.6)		7 (7.9)
Use of anti-TNF agents, n (%)														
Regular	1747 (83.3)	.222	336 (84.8)	.434	97 (81.5)	.215	79 (88.8)	238 (89.1)	1.000	241 (90.3)	.839	79 (88.8)	1.000	79 (88.8)
Irregular	351 (16.7)		60 (15.2)		22 (18.5)		10 (11.2)	29 (10.9)		26 (9.7)		10 (11.2)		10 (11.2)
Anti-TNF switching, n (%)	156 (7.4)		37 (9.3)		14 (11.8)		8 (9.0)	18 (6.7)		18 (6.7)		9 (10.1)		8 (9.0)

In this analysis, the start point was defined as the date of initiation of anti-TNF therapy, while the end point was defined as the date of the first surgery for CD-related symptoms. The patients were stratified according to the number of relapses from the diagnosis of Crohn disease until initiation of anti-TNF therapy: group A,  $\leq 1$  relapse; group B, 2 relapses; group C, 3 relapses; group D,  $\geq 4$  relapses. Propensity score matching with a ratio of 3:3:1:1 for groups A:B:C:D was conducted based on a combination of the covariates of age, sex, regularity of medication use, and Charlson Comorbidity Index, with group D used as reference. Data represent frequency (percentage) or mean  $\pm$  standard deviation, as appropriate. The *P*-values were obtained using Spearman rank correlation test. TNF = anti-tumor necrosis factor.



**Figure 2.** In Crohn's disease, the use of anti-TNF therapy correlates inversely with the monthly rates of emergency hospitalization and surgery. Data cover the patients diagnosed between 2009 and 2016. TNF= tumor necrosis factor.



**Figure 3.** Kaplan-Meier survival analysis for emergency hospitalization (A) and surgery (B) in patients with Crohn disease. The patients were stratified according to the number of relapses until initiation of anti-tumor necrosis factor therapy: group A,  $\leq 1$  relapse; group B, 2 relapses; group C, 3 relapses; group D,  $\geq 4$  relapses. TNF = tumor necrosis factor.



#### 4. Discussion

To our knowledge, this was the largest nationwide population-based study to assess the natural course of CD and focus on major outcomes such as EH and surgery. Moreover, we covered the period from 2009 to 2016, during which there was a substantial increase in the use of anti-TNF agents in South Korea. Our results suggest that anti-TNF therapy may decrease the risk of EH and surgery. Indeed, during the study period, the rates of EH and surgery decreased despite an increase in the prevalence of CD.<sup>[16]</sup> The present results have also helped us identify a practical strategy for optimal timing of anti-TNF therapy in CD patients, which focuses on the number of relapses rather than on disease duration. These findings can be used to inform clinical decision making, improve patient care, and increase the efficiency of healthcare services provided to CD patients.

Studies conducted after the introduction of biologics have reported inconsistent results regarding hospital utilization among patients with inflammatory bowel disease (IBD), likely because hospital utilization is a multifactorial issue. A report based on a European inception cohort reported an inverse relationship between healthcare utilization and the use of anti-TNF agents in CD patients.<sup>[31]</sup> On the contrary, other studies reported that the emergency department utilization rate among IBD patients increased even after the introduction of biologics.<sup>[11,32]</sup> Similar inconsistencies are noted among reports regarding surgery rates in IBD patients after the introduction of anti-TNF therapy.<sup>[33–37]</sup> These inconsistent findings regarding both emergency department utilization and surgery rates may be influenced by factors other than anti-TNF therapy, such as improved disease detection capabilities, introduction of practice guidelines, continuing medical education on IBD, and a shift in care from surgeons to gastroenterologists.<sup>[33]</sup> The present nationwide cohort study suggests that, in South Korea, both emergency department utilization and surgery rates have decreased significantly since the introduction of anti-TNF therapy. Although the improved clinical outcomes noted in our study can be partly explained by other factors such as improved access to specialized IBD care in tertiary centers,<sup>[12]</sup> the efficacy of anti-TNF therapy is likely the main explanation in the Korean population, in which the prevalence of CD is low. In fact, there was little effort to promote awareness of CD in South Korea before 2010, and no framework for educating the patients in this direction was implemented, yet the rates of EH and surgery have decreased continuously since the introduction of anti-TNF agents, as revealed by our nationwide population-based study.

Current guidelines strongly recommend that, in CD patients, anti-TNF therapy should be used when other medications are either poorly tolerated or insufficiently effective.<sup>[38–40]</sup> Furthermore, continued long-term use of anti-TNF agents is recommended in even those who attain remission, because there is little consensus on when to de-escalate or stop anti-TNF agents.<sup>[41,42]</sup> There is an increasing preference for the early initiation of anti-TNF therapy after diagnosis, with the goal to prevent the development of complications and to decrease corticosteroid exposure.<sup>[6]</sup> However, there is no universal definition for “early anti-TNF use” in the literature. In many studies, “early anti-TNF use” was described either with respect to the disease course (time since diagnosis)<sup>[19–21,43]</sup> or with respect to the treatment course (use in patients naïve to immunomodulators, or earlier use than would be done in the conventional step-up treatment approach).<sup>[6,44–46]</sup> These definitions were mostly based on clinical

trials supporting the role of anti-TNF drugs in improving the natural course of the disease.<sup>[6,47,48]</sup> The current study is the first nationwide population-based study supporting such a claim based on real-world data, especially in an Asian population.

The availability of anti-TNF agents for CD may differ across countries due to differences in healthcare systems and national guidelines. Therefore, the optimal timing for initiation of anti-TNF therapy may also differ across countries. In this context, it is highly desirable to develop a simplified, objective, and practical suggestion for determining the optimal starting time of anti-TNF therapy. Based on our study, which employed real-world data, the optimal outcomes can be obtained when anti-TNF agents are started before three relapses. Basing the decision only on disease duration is not expected to be as effective, as we observed no difference between the outcomes of early and late anti-TNF therapy among patients with  $\leq 2$  relapses. Therefore, the present observations may lay the foundation of a new framework for deciding the optimal timing for starting anti-TNF therapy in CD patients. Nevertheless, prospective clinical trials are warranted to clarify this aspect.

Several limitations of our study merit discussion. First, an important weakness of the study is related to the accuracy of CD diagnosis. Because of the nature of claims data, we could not exclude the bias of inadequate diagnosis. However, the reliability of identifying IBD patients using information from the HIRA database was validated in a previous study.<sup>[16]</sup> Second, we cannot exclude the effect of unmeasured confounders in the descriptive analysis, and cannot clarify the causal relationship between the clinical outcomes and anti-TNF therapy in CD. Third, the lack of clinical information, such as a disease activity, on individual patients represents another major drawback of claims data. Patients with predictors of poor prognosis (extensive small-bowel involvement, perianal involvement, or extra-intestinal manifestations) may have been included in the subgroup with early initiation of anti-TNF therapy.<sup>[6,49]</sup> In the light of these limitations, it is important to establish larger, nationwide prospective registries for CD cohorts in order to address the specific questions raised by the present study.

#### 5. Conclusion

The present study not only confirms the beneficial effects of anti-TNF therapy for reducing the rates of hospitalization and surgery due to CD, but also suggests that the decision to start anti-TNF therapy should take into consideration the number of relapses rather than disease duration. Anti-TNF agents should be considered in patients who have had 2 relapses, regardless of disease duration.

#### Author contributions

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