Development of a Novel Predictive Model for the Clinical Course of Crohn's Disease: Results from the CONNECT Study

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Background: A considerable number of patients with Crohn's disease (CD) develop irreversible intestinal damage, although the early administration of immunomodulatory or biological therapies might prevent this. The aims of our study were to develop and validate a novel predictive model that can be used to predict the risk of surgical intervention in Korean patients with CD.

Methods: The prognostic model was derived from the multicenter longitudinal CONNECT (CrOhn's disease cliNical NEtwork and CohorT) study cohort consisting of 1338 patients with CD, who were split into training and validation sets. The Korean Crohn's Disease Prediction (KCDP) model was developed with the training set data using the Cox proportional hazards model and multivariate analysis, and was then validated using the validation set.

Results: A total of 1271 patients with CD were analyzed. During the follow-up period of 10,188 patient-years (median 7.1 yrs), 361 patients (28.4%) underwent CD-related surgery. Age at diagnosis, jejunal involvement, initial disease behavior, and perianal disease at diagnosis were associated with a poor prognosis and included in the KCDP model, which showed a modest discrimination ability with a Harrel's c-index of 0.731 at 5 years, and was well calibrated (Hosmer–Lemeshow $\chi^2 = 8.230$, $P = 0.511$).

Conclusions: This is the first validated surgery risk prediction model for Korean patients with CD; it provides accurate individualized estimates of the probability of surgery using clinical parameters collected at diagnosis. This model might guide appropriate patient selection for the early intensive treatment of CD.

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Key Words: Crohn's disease, natural course, prediction model, prognosis risk factors, surgery

Crohn's disease (CD) is a chronic inflammatory gastrointestinal disorder characterized by a progressive and destructive course, resulting in irreversible bowel damage and ultimately affecting the patient's quality of life. Many studies have reported a change in disease behavior over time, from initial inflammatory lesions to stricturing or fistulizing lesions that may eventually require bowel resection surgery.[1–3] The conventional step-up therapy for moderate-to-severe CD is based on the treatment of acute flares using corticosteroids, followed by maintenance of clinical remission.[4–6] Although this strategy is highly effective in the short term, it has not been shown to alter the natural history of the disease, with increased risk of serious infections and mortality.[7,8] Beyond, treating symptoms, the ultimate goal of medical therapy in CD would be to change its natural disease course and prevent progression, bowel damage, and disability. This goal might be achieved with a top–down strategy using tumor necrosis factor antagonists early in the disease, either as monotherapy or in combination with immunomodulators. Randomized trials evaluating the use of combined tumor necrosis factor antagonists and immunomodulators revealed that this strategy induced mucosal healing more frequently, and could modify the course of CD with higher rates of corticosteroid-free remission and lower rates of hospitalization and surgery.[9–14] However, long-term studies are needed to confirm whether such early combined therapy can prevent disease progression. In addition, potential toxicities and the high cost of top–down strategy preclude its use in all patients, and the analysis of population-based data from the prebiological era suggested that approximately 50% of patients had noncomplicated diseases more than 10 years after their diagnosis.[15] Overtreatment of these low-risk patients will result in a poor

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therapeutic index; to achieve better outcomes with a top–down strategy, it would be important to make an accurate selection of patients who are either at high risk of disease progression or developing disease-related complications. Therefore, identifying factors that can predict a poor prognosis and developing disease course models should be the initial steps for achieving this goal.

Previously identified predictors of advanced CD include the following: a younger age at diagnosis[15,16]; small bowel involvement[3,15,17,18]; perianal disease[3,16,19]; the need for systemic steroids[16]; tobacco smoking[20,21]; and serologic markers, such as anti–*Saccharomyces cerevisiae* antibody.[22,23] However, CD has a wide clinical spectrum, and its course has often been difficult to predict based on a single prognostic factor. To this date, only a few studies have evaluated combinations of these predictors for CD outcomes,[16,18,19] and further development is required for an integrative prediction model for an adverse disease course using factors at diagnosis. Moreover, CD phenotypes differ considerably between East Asians and whites,[24,25] and therefore, it is crucial to understand the natural history of CD as well as the predictors of its course in different populations. As of now, this has not been addressed in Korean patients with CD.

Our study aimed to develop and validate a novel prediction model that can be used to predict the risk of surgical intervention to guide appropriate patient selection for early intensive therapy in Korean patients with CD.

PATIENTS AND METHODS

This study population was from the CrOhn's disease cliNical NEtwork and CohorT (CONNECT) study in Korea, which is a multicenter longitudinal cohort, enrolled from 2008. The cohort data are both retrospective (for patients enrolled before 2009) and prospective (for patients enrolled during and after 2009). Patients in the latter group were enrolled using a novel web-based electronic case report form system (www.cdcohort.org). A study coordinator monitored the submission and quality of electronic case report form data to ensure it was well recorded and of high quality. Further information concerning the study cohort is described in more detail in our previous report.[26]

Study Population

A total of 1338 patients diagnosed with CD between July 1982 and July 2010 at 29 secondary and tertiary referral centers were included in this study. Patients with less than 6-month follow-up or incomplete data were excluded.

Definitions

Patients were diagnosed with CD according to the internationally accepted criteria.[6,27] Diagnosis was based on a combination of clinical presentation, endoscopic findings, or macroscopic appearance at surgery, radiology, histology, or serology. Patients with CD were classified according to the Montreal classification using data including age at diagnosis, disease behavior, and location of disease.[28] The extent of disease and possible strictures were established by endoscopic and radiological examinations or surgical findings. Stricturing disease was defined as the occurrence of constant luminal narrowing with prestenotic dilatation or obstructive signs/symptoms without penetrating disease. Penetrating disease was defined as the presence of intra-abdominal fistulas, inflammatory masses, or abscesses. CD-related surgery was defined as any surgical procedure for CD to treat complications or medically refractory disease during the follow-up period, excluding surgery within 30 days of diagnosis.

Outcome Measures

The main outcome variable was CD-related surgery, and a prediction model for the 5-year probability of undergoing CD-related surgery was developed. If there were more than 1 CD-related surgery events during the follow-up period from July 1982 to November 2013, we included only the first event in our statistical analyses.

Statistical Analysis

Development of Prediction Model

Continuous variables were reported as median and range, whereas categorical variables were reported as proportions and percentages. We randomly stratified the cohort data into 2 equal groups, each at a 1:1 ratio: a training set for model development and a validation set. The Cox proportional hazards model was used to model CD-related surgery, after testing the assumptions underlying its use. The model for predictive risk of undergoing CD-related surgery was then fitted, in which the average probabilities of remaining "surgery-free at follow-up" time points were estimated using a baseline hazard function with the mean values of potential predictors. Both hazard ratio and 95% confidence interval of each risk factor were also estimated. Based on the univariate analysis performed for available variables, potential predictors were applied for building the full multivariate model.

The individual risk of undergoing CD-related surgery was estimated using the baseline hazard function of the Cox regression model derived from training data set, by a method similar to one previously described.[29] The model for the 5-year risk of undergoing CD-related surgery was as follows: $P = 1-\mathrm{S}(t)^{\exp(f[x,M])}$ and $f(x, M) = \beta_1(x_1-M_1) + \cdots + \beta_p(x_p-M_p)$. $\beta_1, \ldots, \beta_p$ are the regression coefficients; $x_1, \ldots, x_p$ represent an individual's risk factors; $M_1, \ldots, M_p$ are the mean values of risk factors in the cohort; and S (t) is the event-free rate of subjects with the mean values of risk factors at time t ($t = 5$ yrs in this study). Therefore, the predicted 5-year risk of undergoing surgery was estimated using the baseline hazard function of training set cohort, with the mean value of each predictor at the time of 5-year follow-up.

Validation of a Prediction Model

Discrimination, the ability of a predictive model to distinguish individuals more likely to experience an event from those less likely to experience an event, was assessed using the concordance statistic (c-statistic) that corresponds to the area under a receiver operating characteristic curve.[30] The overall c-statistics were calculated using

logistic regressions. Calibration, another performance measure of a predictive model, assesses how closely the predicted risk agrees with the actual risk.[31] Calibration was conducted using the validation set with the β coefficients, the mean of each risk factor, and the average survival rate at 5-year from the training set. Participants in the validation set cohort were divided into deciles of individual predicted risk, and in each decile, the expected events were the sum of individual predicted risks. The predicted and actual risks in each decile were compared using the Hosmer–Lemeshow χ^2 test.[32]

Simple Point Score Model

A simple point score model for surgery in CD was developed based on the original predictive factors and a Cox regression model in which age was changed from a continuous to a categorical variable based on the median age. The β coefficients were newly fitted using this Cox regression model by first multiplying the regression coefficients by 1.5 and rounding them,[33] and then the risk score of each participant was calculated as the sum of the points from each risk factor. The cumulative risk of surgery was analyzed using the Kaplan–Meier curve according to the total score and was categorized by score group.

All analyses were conducted using SAS version 9.01 (SAS Institute Inc., Cary, NC) or SPSS 20.0 for Windows (SPSS Inc., Chicago, IL).

ETHICAL CONSIDERATIONS

The study was approved by the institutional review board of each participating center. Written informed consent was obtained from all patients. Patient confidentiality was maintained in accordance with the guidelines from the Korean Ministry of Health, Welfare, and Family Affairs.

RESULTS

Baseline and Follow-Up Characteristics

Figure 1 shows a flowchart of the study cohort. A total of 1271 patients with CD in the cohort were analyzed. The median age at diagnosis was 24 years (range, 7–87 yrs), and 80% of patients showed small bowel involvement. At diagnosis, 1008 patients (79.3%) had inflammatory disease and 554 patients (43.6%) had perianal disease. During the follow-up period of 10,188 patient-years (median, 7.1 yrs; range, 0.5–31.1 yrs), 361 patients (28.4%) underwent CD-related surgery. The cumulative probability of CD-related surgery analyzed using the Kaplan–Meier method was 21.0% at 5 years and 34.7% at 10 years (Fig. 2). The patient characteristics at diagnosis (baseline) and follow-up of the entire study cohort are shown in Table 1.

Development and Validation of a Cox Regression Model

The results from univariate and multivariate Cox regression analyses of possible predictors of CD-related surgery in the training set cohort are shown in Table 2. Four variables were significantly associated with CD-related surgery: younger age at diagnosis, jejunal involvement, initial stricturing or penetrating disease behavior, and perianal disease at diagnosis. These variables were included in the prediction model for 5-year risk of CD-

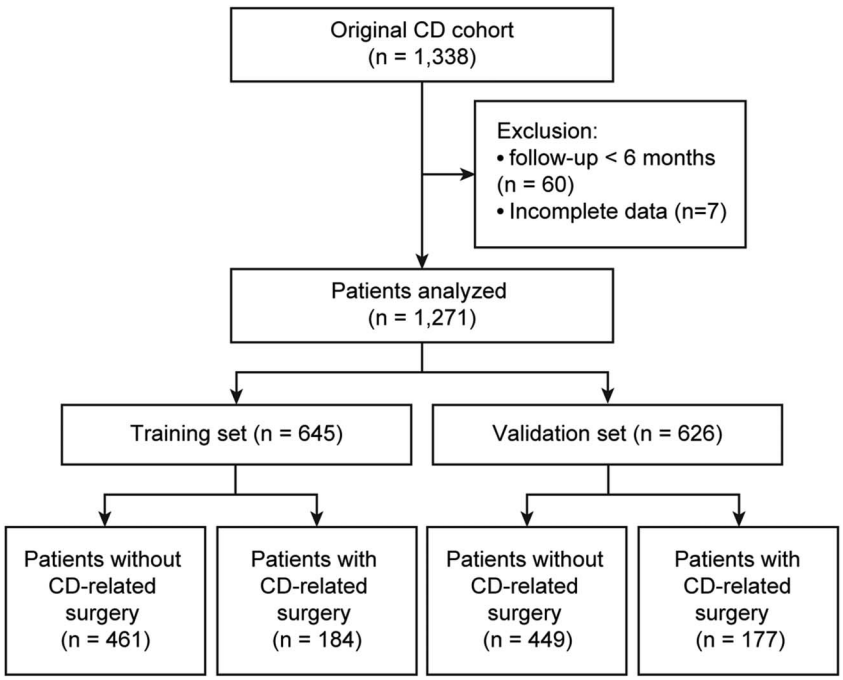

FIGURE 1. Study cohort flowchart.

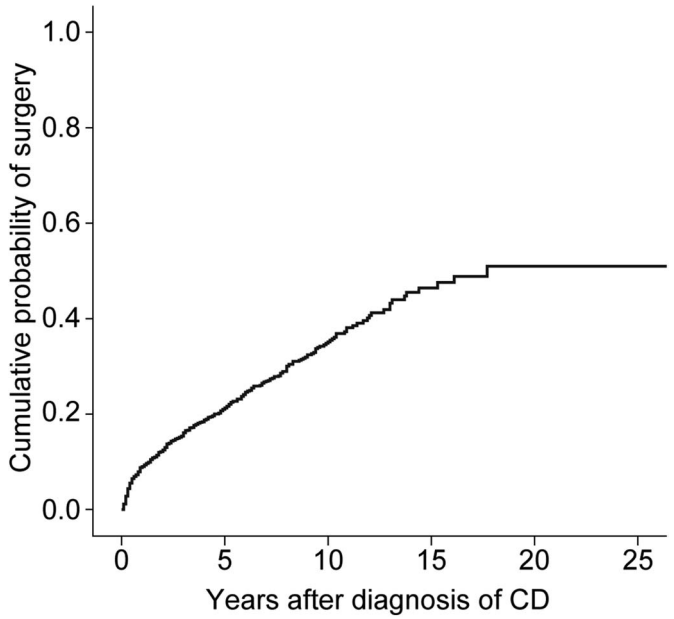

FIGURE 2. Cumulative probability of CD-related surgery from diagnosis among 1271 Korean patients with CD diagnosed between 1982 and 2010.

related surgery, which we named the Korean Crohn's Disease Prediction (KCDP) model, described as follows:

$$P_{\text{CD-related surgery at 5 years}} = 1 - 0.803^{\exp(\text{Prognostic index})},$$

where

$$\begin{aligned}\text{Prognostic index} = {} & -0.018 \times (\text{age} - 27) \\ & + 0.682 \times (\text{jejunum involvement } [0: \text{No}; 1: \text{Yes}] - 0.15) \\ & - 0.597 \times (\text{initial behavior } [0: \text{stricturing or penetrating}; \\ & 1: \text{inflammatory}] - 0.79) + 0.609 \times (\text{perianal disease} \\ & [0: \text{No}; 1: \text{Yes}] - 0.46).\end{aligned}$$

In the discrimination analysis using the KCDP model for the training set cohort, the c-statistics was 0.73, showing a good ability to distinguish high-risk from low-risk patients with regard to CD-related surgery. In the validation cohort, the c-statistics was 0.65, showing a modest ability to distinguish high- and low-risk patients.

In the calibration analysis, χ^2 was 8.23 ($P = 0.511$) in the training cohort, showing that the actual rates of CD-related surgery in the training set were similar to those predicted by the KCDP model (Fig. 3A). However, the KCDP model fitted less well with the validation set ($\chi^2 = 24.2$; $P = 0.004$) (Fig. 3B).

Secondary Model Development with Simple Point Score

The KCDP model was too complicated for use in daily clinical practice, and we therefore developed a simple point score model for CD-related surgery (simplified-KCDP; S-KCDP) based on the original predictive factors of the KCDP model by rounding the newly fitted β coefficients for 4 categorical variables (age at diagnosis ≤24 yrs, jejunum involvement, stricturing or penetrating behavior, and perianal lesions at diagnosis). The S-KCDP model was the sum of the scores of these variables, and patients were classified into low-risk (score

TABLE 1. Baseline Characteristics of the Study Cohort

Characteristics	CD Cohort (n = 1271)
Baseline characteristics at diagnosis	
Demographic data	
Age, years, median (range)	24.0 (7–87)
Male sex, n (%)	882 (69.4)
Body mass index, kg/m^2, median (range)	19.0 (12–41)
Family history of IBD, n (%)	27 (2.1)
Presence of granuloma, n (%)	409 (32.2)
Location (involvement), n (%)	
Jejunum	198 (15.6)
Ileum	997 (78.4)
Colorectal	934 (73.5)
Upper GI tract	91 (7.2)
Montreal classification	
Age at diagnosis, n (%)	
<16 yrs (A1)	121 (9.5)
17–40 yrs (A2)	972 (76.5)
>40 yrs (A3)	178 (14.0)
Location, n (%)	
Ileal (L1)	291 (22.9)
Colonic (L2)	228 (17.9)
Ileocolonic (L3)	706 (55.5)
Isolated upper disease (L4)	15 (1.2)
Behavior, n (%)	
Inflammatory (B1)	1008 (79.3)
Stricturing (B2)	120 (9.4)
Penetrating (B3)	143 (11.3)
Perianal lesions, n (%)	554 (43.6)
Stenosis, n (%)	144 (11.3)
Perforation, n (%)	53 (4.2)
Follow-up	
Median follow-up, yrs (range)	7.1 (0.5–31.1)
CD-related surgery, n (%)	361 (28.4)
1 time	251 (69.5)
2 times	78 (21.6)
≥3 times	32 (8.9)
Duration for surgery, yrs, median (range)	2.5 (0.1–17.7)
Biological agent use, n (%)	411 (32.3)
Duration for biological agent use, yrs, median (range)	5.0 (0, 23.1)
CD-related death, n (%)	7 (0.6%)

GI, gastrointestinal; IBD, inflammatory bowel disease.

TABLE 2. Univariate and Multivariate Predictors of CD-Related Surgery in the Training Set Using a Cox Regression Model (n = 645)

	Univariate Analysis			Multivariate		
Characteristics	Hazard Ratio	95% Confidence Interval	*P*	Hazard Ratio	95% Confidence Interval	*P*
Demographic data						
Age at diagnosis, yrs	0.980	0.965–0.995	**0.009**	0.982	0.966–0.998	**0.028**
Male sex, n (%)	0.752	0.560–1.009	0.057			
Body mass index, kg/m^2	0.958	0.896–1.024	0.210			
Family history of inflammatory bowel disease, n (%)	0.880	0.281–2.757	0.827			
Presence of granuloma at diagnosis, n (%)	1.289	0.955–1.739	0.097			
Location (involvement)						
Jejunum	2.069	1.486–2.881	**<0.001**	1.977	1.411–2.770	**<0.001**
Ileum	1.264	0.875–1.827	0.212			
Colorectal	1.237	0.880–1.740	0.221			
Upper GI tract	1.418	0.836–2.405	0.195			
Montreal classification						
Age at diagnosis						
<16 yrs (A1)	1	—				
17–40 years (A2)	0.744	0.479–1.155	0.187			
>40 yrs (A3)	0.539	0.288–1.009	0.053			
Location						
Ileal (L1)	1	—				
Colonic (L2)	0.964	0.592–1.568	0.881			
Ileocolonic (L3)	1.361	0.939–1.973	0.103			
Isolated upper disease (L4)	2.897	0.892–9.405	0.077			
Behavior						
Inflammatory (B1)	1	—		0.551	0.401–0.757	**<0.001**
Stricturing (B2)	1.753	1.142–2.691	**0.010**			
Penetrating (B3)	1.878	1.275–2.767	**0.001**			
Perianal lesions at diagnosis, n (%)	2.042	1.518–2.747	**<0.001**	1.839	1.356–2.495	**<0.001**
Stenosis at diagnosis, n (%)	1.474	0.997–2.180	0.052			
Perforation at diagnosis, n (%)	1.166	0.597–2.280	0.653			

Bold indicates a P value < 0.05.

0–1), intermediate-risk (score 1.5–2), and high-risk (score ≥2.5) groups for surgery (Table 3). Kaplan–Meier plots stratified by the S-KCDP classification showed a significantly greater surgery rate in the high-risk group compared with the low-risk group (log-rank $P < 0.001$) in both the training and validation sets (Fig. 4).

Risk Stratification According to S-KCDP Classification

The 5- and 10-year surgery rates and hazard ratios for S-KCDP classification in the training and validation sets are summarized in Table 4. The 5-year surgery rates in low-, intermediate-, and high-risk patients were 13.7%, 25.5%, and 50.6%, respectively, in the training set, and 15.0%, 26.9%, and 39.7%, respectively, in the validation set (Table 4). In addition, the 5- and 10-year risks of surgery by S-KCDP classification showed a significant tendency to increase as the classification moved from low- to high-risk group by Cox regression analyses (all $P < 0.05$) (Table 4).

Predictive Performance of S-KCDP Classification

The area under a receiver operating characteristic curve values using the S-KCDP score for 5- and 10-year predictions of surgery were 0.677 and 0.671, respectively, in the training set, and 0.654 and 0.616, respectively, in the validation set (Table 5).

DISCUSSION

This is the first study to develop a validated risk prediction model of surgery for Korean patients with CD. The model was derived from a large, well-characterized population of patients

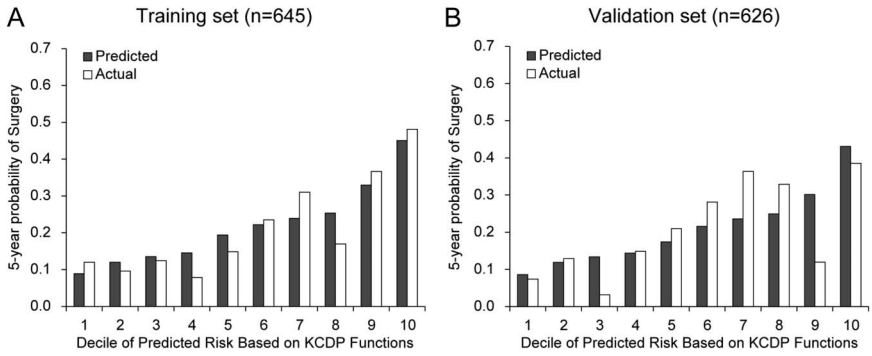

FIGURE 3. Performance plots for the 5-year prediction of surgery events in the CONNECT cohort using the KCDP model. A, Training set; (B) validation set.

followed at 29 different centers, and it provides individualized estimates for the probability of undergoing CD-related surgery using readily collected clinical parameters at diagnosis.

There is growing evidence that early intensive therapy in CD, using immunomodulators and biologics, increases the probability of mucosal healing and early sustained remission.[9,10,14] Accordingly, composite predictor index is increasingly needed to identify patients who are more likely to develop either severe or complicated disease at the time of their diagnosis, given the complex benefit–risk balance of top–down management strategies. Although individual clinical predictors of advanced CD have been previously identified, very few currently available composite models have combined these predictors.[16,18,19] The first such model was based on a study of 1123 patients from a tertiary center in France,[16] where the authors developed a scoring system using 3 risk factors at diagnosis that were independently associated with a disabling 5-year disease course: age <40 years, perianal disease, and an initial requirement for steroid use. Although this study was performed in the prebiological era, the rate of disabling disease was 85% at 5 years after diagnosis, which was too high for considering early aggressive treatments. This phenomenon may have resulted from the relatively high proportion of severe disease cases treated in a tertiary center, and the cohort might not represent all types of CD. In another study investigating 361 patients from a tertiary center in Belgium,[19] a model developed for the prediction of severe CD in a 5-year period used 2 factors at diagnosis: stricturing behavior and weight loss >5 kg. However, predictive performances were low. In a more recent study in Norway, on a population-based cohort of 237 patients,[18] risk matrixes for prediction of advanced CD for 5- and 10-year courses were developed using anti–*Saccharomyces cerevisiae* antibody status, age, and the need for systemic steroids for both 5- and 10-year analyses, together with disease location for the 5-year analysis and disease behavior for the 10-year analysis. The matrix provided the actual risk estimate and showed substantial differences in the probability of developing advanced disease. However, the matrixes were built with relatively few patients (132 and 190 patients) and were preliminary, without any reported predictive performance or validation. None of these previous studies generated a sufficiently robust model, using clinical factors at diagnosis, for both predicting the disease course and selecting patients for early aggressive treatment.

Our KCDP model is particularly useful for providing objective prognostic information that aids clinical decision making. It may also be useful for informing patients of their risk of future complications, increasing their understanding of the disease course, and improving their treatment adherence. Furthermore, with the S-KCDP model, we can categorize the risk of a future complication (surgery), and consider a top–down treatment strategy for patients classified as high risk. For example, when considering the management of a 20-year-old patient who was newly diagnosed with inflammatory CD involving the

TABLE 3. The β Coefficients and Hazard Ratios of Risk Factors for CD-Related Surgery from a Multivariate Cox Proportional Hazards Model and the Corresponding Rounded Risk Score for the S-KCDP Model in the Training Set

Variables	Adjusted HR (95% CI)	*P*	β	Scoring
Age at diagnosis ≤24 yrs	1.424 (1.049–1.932)	0.023	0.353	0.5
Jejunum involvement	2.013 (1.436–2.822)	<0.001	0.699	1
Stricturing or penetrating behavior	1.839 (1.336–2.533)	<0.001	0.609	1
Perianal lesions at diagnosis, n (%)	1.892 (1.399–2.559)	<0.001	0.638	1

S-KCDP Classification	Total Score
Low risk	0–1
Intermediate risk	1.5–2
High risk	≥2.5

CI, confidence interval; HR, hazard ratio; S-KCDP, Simplified Korean Crohn's Disease Prediction.

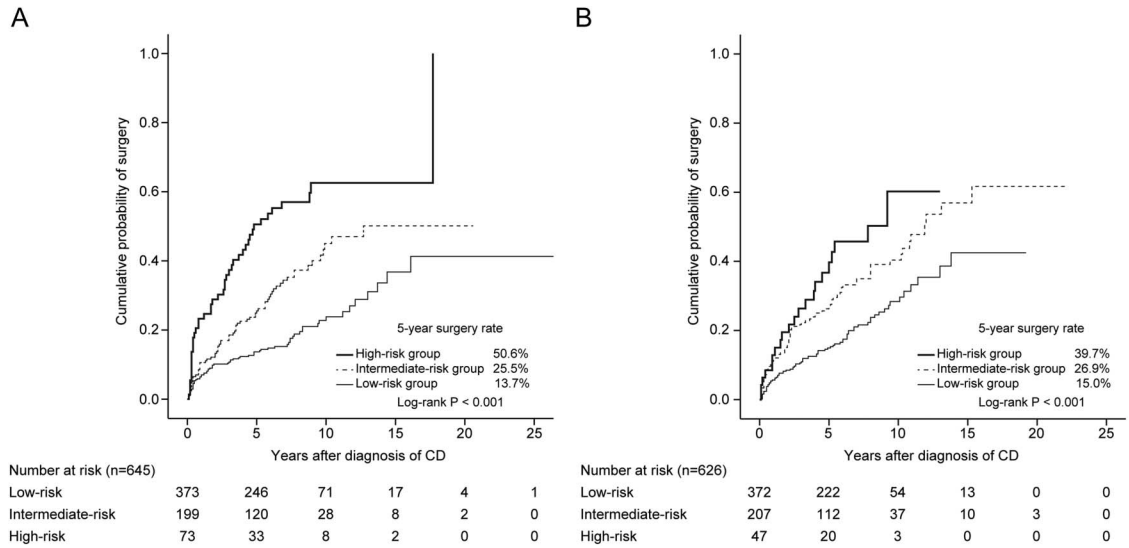

FIGURE 4. Kaplan–Meier curves according to S-KCDP classification in the training set (A) and the validation set (B). Patients defined as high risk based on S-KCDP classification had a significantly higher likelihood of surgery than those defined as low risk (log-rank test, $P < 0.001$). S-KCDP, Simplified Korean Crohn's Disease Prediction.

jejunum with perianal disease, the estimated 5-year risk of CD-related surgery could be 42% and the S-KCDP score would be 2.5, classifying the patient as high risk. We can consider this risk stratification, in conjunction with other risks and the costs of using immunomodulators or biologics, when we decide whether to treat patients with a top–down or accelerated step-up strategy. Furthermore, the proportions of patients categorized as high risk by the S-KCDP model were 11% and 7.5% for the training and validation sets, respectively, which is a reasonable finding for an optimal benefit–risk balance in early aggressive treatment strategy.

Our cohort included patients from 29 representative secondary and tertiary referral centers nationwide; therefore, it was representative of the entire population. Indeed, similar to a recent population-based study in Korea,[34] the following factors were observed in our study: younger age at diagnosis (median 24 years), male patient predominance (male-to-female ratio of 2.3:1), more frequent ileocolonic location (55.5%), more frequent perianal disease (43.6%), and lower rate of surgery compared with previous Western population-based studies.[35–37] Moreover, the cumulative risk of CD-related surgery was 21.0% at 5 years and 34.7% at 10 years, which is in correspondence to the findings of the recent population-based study.[15]

Some of the clinical parameters, which were previously identified as predictors for CD-related surgery and incorporated

TABLE 4. Risk Stratification According to the S-KCDP Risk Group

Risk Group	5-yr Surgery rate, %	10-yr Surgery rate, %	HR (95% CI)	*P*
Training set (n = 645)				
Low risk (score 0–1) (n = 373)	13.7	23.8	1	
Intermediate risk (score 1.5–2) (n = 199)	25.5	45.1	1.95 (1.40–2.72)	<0.001
High risk (score ≥2.5) (n = 73)	50.6	62.6	3.84 (2.63–5.61)	<0.001
Validation set (n = 626)				
Low risk (score 0–1) (n = 372)	15.0	28.4	1	
Intermediate risk (score 1.5–2) (n = 207)	26.9	40.4	1.78 (1.30–2.44)	<0.001
High risk (score ≥2.5) (n = 47)	39.7	60.2	2.59 (1.60–4.20)	<0.001
Overall (n = 1271)				
Low risk (score 0–1) (n = 745)	14.3	26.0	1	
Intermediate risk (score 1.5–2) (n = 406)	25.6	42.6	1.88 (1.50–2.36)	<0.001
High risk (score ≥2.5) (n = 120)	46.4	60.9	3.26 (2.43–4.37)	<0.001

CI, confidence interval; HR, hazard ratio; S-KCDP, Simplified Korean Crohn's Disease Prediction.

TABLE 5. Predictive Performance of the S-KCDP Model for CD-Related Surgery in the Training and Validation Sets

	Training Set		Validation Set	
Time Point	Surgery/No. of Patients Analyzed[a]	AUROC (95% Confidence Interval)	Surgery/No. of Patients Analyzed[a]	AUROC (95% Confidence Interval)
5 yrs	132/538	0.677 (0.623–0.731)	121/482	0.654 (0.600–0.708)
10 yrs	174/286	0.671 (0.608–0.734)	163/259	0.616 (0.545–0.686)

AUROC, area under a receiver operating characteristic curve.
[a]Patients who were surgery-free and followed up for less than five years were excluded from the five year AUROC analysis. The same was applied in ten year analysis.

into the KCDP model, were modified to better fit our data. Although age younger than 40 years at diagnosis was a risk factor for disabling CD in previous studies,[15,16] our S-KCDP model used age ≤24 years instead, because the median age at diagnosis was 24 years, which was less than that used in Western cohorts.[35,38,39] Small bowel involvement was a risk factor for surgery, recurrence, and changes in behavior[3,15,17,18]; in particular, jejunal involvement was shown to be associated with a higher risk of complications[2] and surgery.[40,41] In our cohort, jejunal involvement was observed in 15.6% of patients at diagnosis, which was also more frequent than in Western studies,[40,41] and it was an independent risk factor for surgery. The relative frequency of jejunal disease in the Korean population compared with other populations was consistent with the previous study with other Korean patients, which showed jejunal involvement in 198 of the 1403 (14.1%) at diagnosis of the CD and 19.5% before the first resection.[42] In previous studies, perianal disease and phenotype at diagnosis were associated with complications,[3] a disabling course,[16,19] subsequent surgery,[15,18] and recurrence[17]; these were also independent predictors for CD-related surgery in our cohort.

The strengths of this study include the fact that it is the first Asian study to develop a risk prediction model for surgery derived from a nationwide, large population of patients with CD who have similar characteristics to that of the whole population. We presented and validated the actual equation derived from the Cox proportional hazard model that includes 4 simple but important clinical factors that can be routinely and readily collected. Furthermore, we simplified the model for use in daily clinical practice. Because our model used clinical parameters that can be generally and easily collected, it has the potential to be used in other populations widely. Considering that the characteristics of Western and Asian patients with inflammatory bowel disease differ in terms of epidemiology and phenotypes, our model might fit better in Asian populations, but further validation of the model in other Asian and Western populations would be warranted.

However, several limitations of this study must be considered. The predictive performance of KCDP and S-KCDP models, as assessed by the discrimination and calibration for KCDP, and the area under a receiver operating characteristic curve for S-KCDP are not entirely satisfactory. Moreover, CD is a multifactorial disease with heterogeneous phenotypes, and thus, a consistent prediction of its natural course using a limited number of clinical factors would be difficult. Also, we only evaluated clinical factors and not serological markers (including anti–*Saccharomyces cerevisiae* antibody), fecal calprotectin, nor genetic predictors (such as *NOD2*), although the value of these markers has not yet been shown to accurately predict the course of CD at diagnosis. To increase the predictive accuracy of CD models, further model development needs to be achieved through a collective evaluation of various potential predictors, including the previously mentioned serological and genetic markers along with novel fecal markers. Another limitation of our study could be the use of retrospective patient data of those diagnosed before 2009, as it did not mention the specific types of surgery for these patients.

We used "CD-related surgery" as the study endpoint, as it is a marker of adverse outcome; however, many other endpoints, described as "severe," "advanced," or "disabling" disease, with varying definitions have been used previously. It is not clear which endpoint is the best for selecting patients who can benefit the most from a top–down treatment strategy. Further development and validation of predictive models for other endpoints are needed. Such models could be generated by combining various outcomes such as surgical resection, phenotypic progression, development of steroid dependency, need for thiopurines or biologics, and further hospitalization after disease flare-up. Also, it remains unknown whether treatment decisions based on these factors can actually change the disease outcome.

In conclusion, we have developed and validated a novel prediction model for the 5-year probability of CD-related surgery for Korean patients with CD (the KCDP model). Our model provides objective prognostic information to aid clinical decision making and empowers patients by helping them understand the relative merits of top–down therapy. We believe that this model may guide selection of appropriate patients for early intensive treatment of CD.

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