Development of Time-Aggregated Machine Learning Model for Relapse Prediction in Pediatric Crohn's Disease

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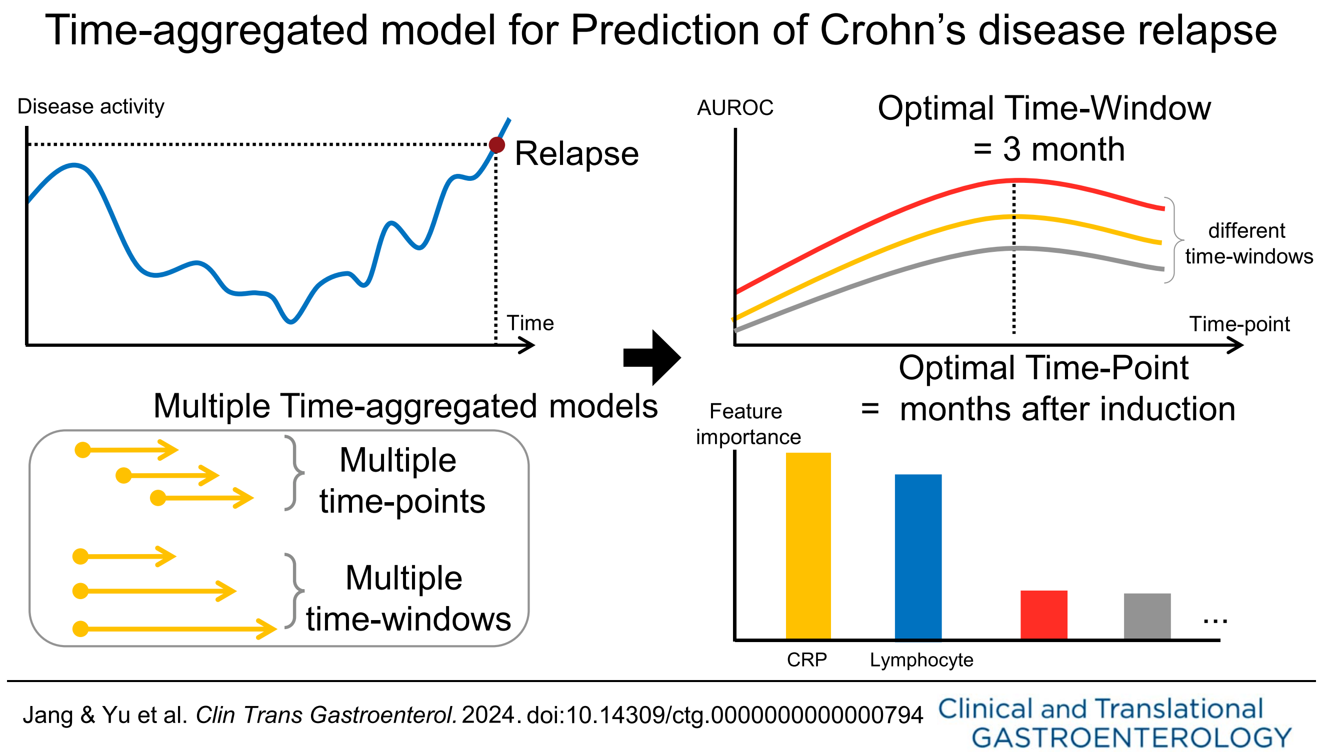
INTRODUCTION: **Pediatric Crohn's disease (CD) easily progresses to an active disease compared with adult CD, making it important to predict and minimize CD relapses. However, prediction of relapse at various time points (TPs) during pediatric CD remains understudied. We aimed to develop a real-time aggregated model to predict pediatric CD relapse in different TPs and time windows (TWs).**

METHODS: **This retrospective study was conducted on children diagnosed with CD between 2015 and 2022 at Severance Hospital. Laboratory test results and demographic data were collected starting at 3 months after diagnosis, and cohorts were formed using data from 6 different TPs at 1-month intervals. Relapse—defined as a pediatric CD activity index ≥ 30 points—was predicted, and TWs were 3–7 months with 1-month intervals. The feature importance of the variables in each setting was determined.**



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RESULTS: **Data from 180 patients were used to construct cohorts corresponding to the TPs. We identified the optimal TP and TW to reliably predict pediatric CD relapse with an area under the receiver operating characteristic curve score of 0.89 when predicting with a 3-month TW at a 3-month TP. Variables such as C-reactive protein levels and lymphocyte fraction were found to be important factors.**

DISCUSSION: **We developed a time-aggregated model to predict pediatric CD relapse in multiple TPs and TWs. This model identified important variables that predicted relapse in pediatric CD to support real-time clinical decision making.**

KEYWORDS: Crohn's disease; prediction of relapse; time-aggregated study; machine learning

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B220, http://links.lww.com/CTG/B221, http://links.lww.com/CTG/B222, http://links.lww.com/CTG/B223

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INTRODUCTION

Crohn's disease (CD) is a type of inflammatory bowel disease and is considered an incurable condition, often requiring lifelong management. The natural course of CD involves recurrent relapses and remissions, leading to the accumulation of intestinal damage (1). In particular, childhood-onset CD progresses more easily to active disease than does adult-onset CD (2–5). Childhood-onset CD is particularly concerning owing to its potential to disrupt the growth and development (2,6–8). In pediatric CD, the relapse rate within 1 year of diagnosis is known to be 40%–50% (9). As bowel damage accumulates, patients are exposed to repeated surgical resections, leading to the progressive loss of intestinal function and disability (1). Intensive treatments, including the use of biologics, effectively reduce relapses in pediatric CD (10,11). Initiating intensive treatment before the occurrence of relapse could potentially prevent relapse and its associated complications; however, accurately predicting the precise time point (TP) of relapse remains a significant challenge.

Recently, several studies have been published on the prediction of CD prognosis, including relapse, based on machine learning using clinical data (12). These studies predicted the responses to specific drugs or future changes in disease activity, and these predictions were generally made at limited TPs, such as at the time of diagnosis, drug discontinuation, or surgery (13–19). Although the condition of pediatric patients with CD can change over time after diagnosis, previous studies could not investigate these multiple time windows (TWs) and points. Considering these issues, the aim of this study was to develop a time-aggregated relapse prediction model in multiple TWs and time points for pediatric CD.

METHODS

Study setting

This retrospective study included patients with CD from the division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Sinchon Severance Hospital, in South Korea. It is a tertiary teaching hospital with approximately 25 annual CD cases. Ethical approval was obtained from the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine. The requirement for informed consent was waived owing to the retrospective nature of the study (IRB number: 4-2022-1602). All authors had access to the study data and reviewed and approved the final manuscript.

Study participants

All pediatric patients diagnosed with CD between January 01, 2015, and November 30, 2022, were included in our initial study population. The patient flowchart is shown in Supplementary Figure S1, http://links.lww.com/CTG/B220. Patients who received treatment for more than 3 months after diagnosis were included in the study. Data from the first 3 months were not used.

Study outcome

In this study, clinical relapse was defined as a Pediatric Crohn's Disease Activity Index (PCDAI) (Figure 1) score of $\geq$ 30, indicating a worsening of the disease (20). PCDAI scores were obtained by an experienced pediatric gastroenterologist after the clinical examination. The PCDAI is a highly selective indicator for assessing pediatric CD relapse as it combines inflammation levels, such as erythrocyte sedimentation rate, with other factors associated with clinical presentations of CD, such as abdominal pain, stool per day, abdominal tenderness, and weight loss (21). A PCDAI score of $\geq$ 30, which indicates moderate to severe pediatric CD, has been widely used as a criterion for clinical relapse (9,21–24).

Study predictors

Patients' clinical information was extracted from the Severance Clinical Research Analysis Portal. As candidate input predictors, we used both time-adaptive variables, which were measured repeatedly, and static variables collected at the time of diagnosis. When a time-adaptive variable had multiple measurements within a specific TP, the median value were used as the predictor. Demographic data, including age and sex, were used as static variables. The results of 13 laboratory tests, including CRP level and erythrocyte sedimentation rate, were also included as time-adaptive variables. In total, 15 variables were used as study predictors. Variables used in model and their descriptions are presented in Supplementary Table S2, http://links.lww.com/CTG/B223.

Time-aggregated design

The first 3 months after diagnosis served as a wash-out period and were spent on the initial induction treatment to heal from the worsening condition at diagnosis; data from this period were not included in the analysis (20). We constructed models using data from multiple TPs (TP0-6) to determine whether relapse occurred within multiple TWs (TW3-7) (Figure 1). Seven TPs were

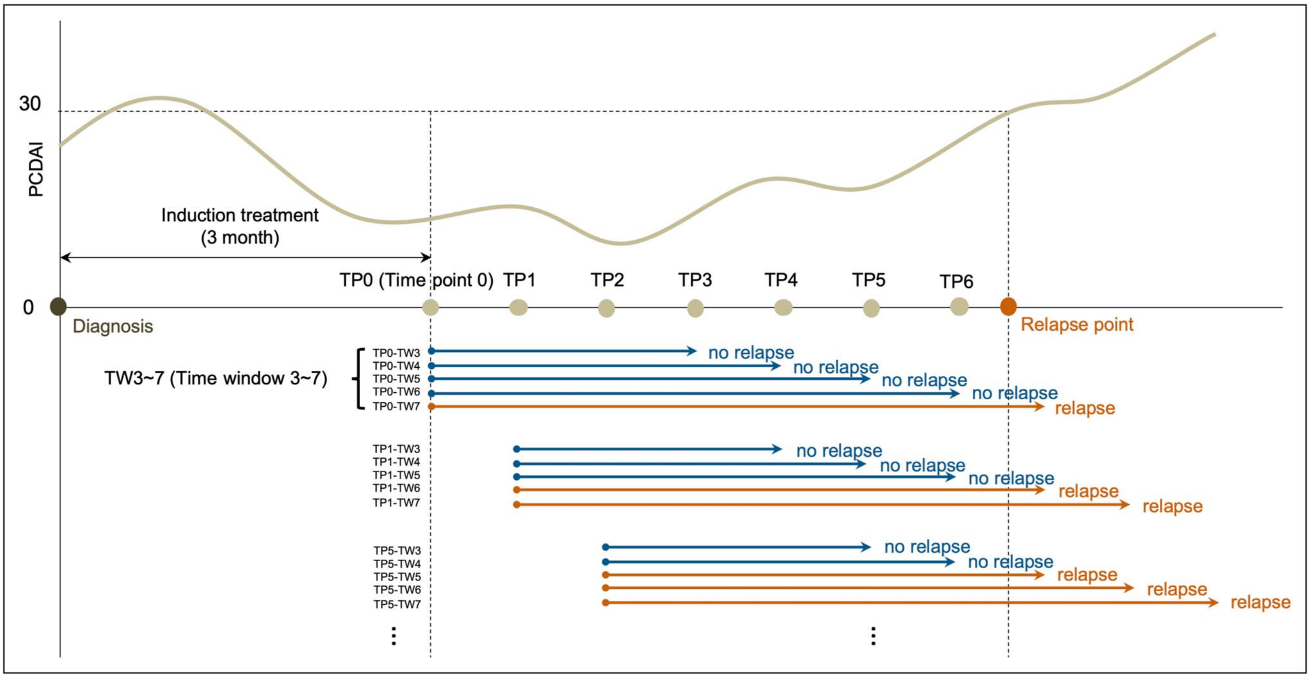

Figure 1. Overall design for time-aggregated pediatric Crohn's disease relapse prediction model. Data from the first 3 months of induction treatment after diagnosis were not included. We assigned 7 TPs with 1-month intervals from the end of induction treatment and constructed cohorts using the most recent data available at each TP. For each TP, we assigned 5 time windows, ranging from 3 to 7 months, with 1-month intervals, and independent models were constructed to assess whether there was a relapse event within each TW. Relapse of pediatric Crohn's disease in this study was defined as an increase of the PCDAI score over 30 points. PCDAI, Pediatric Crohn's Disease Activity Index; TP, time point; TW, time window.

assigned at 1-month intervals from the end of the induction treatment. The earliest TP was at the end of the induction treatment (TP0), and the latest TP was 6 months after the end of the induction treatment (TP6). At each TP, we created a data set reflecting the patient status. Using data from each TP, the models evaluate whether a relapse will occur within a specific TW. Of the 5 TWs, the shortest was 3 months (TW3), followed by 1-month intervals, and the longest was 7 months (TW7). For instance, the model for TP4-TW3 uses data collected 4 months after the end of induction treatment (TP4) to predict whether a relapse will occur within 3 months from that point (TW3). In total, 35 distinct models were developed by combining the 7 TPs and 5 TWs.

Model development

The XGBOOST model was used, and hyperparameters, including learning rate, minimum split loss for further tree partitioning, and maximum tree depth, were set using R studio (ver 4.1.0) and the XGBOOST package (ver 1.4.1) (25). We evaluated the classification performance of our model using 5-fold cross-validation. For each cross-validated fold, we randomly divided each data set into a training set (70%), a validation set (10%), and a test set (20%), stratified by relapse status.

Feature importance

To determine the variables that contributed significantly to the decisions in each model, we used the Shapley additive explanations method (26). The feature importance was computed and visualized for TW and TP.

Statistical analysis

Categorical variables are expressed as frequencies and percentages, and continuous variables as means and SDs. Comparison tests were performed using analysis of variance and χ^2 tests at a 5% significance levels. The area under the receiver operating characteristic curve (AUROC) and 95% confidence interval with 5-fold cross-validation were reported. Clinical values are presented using box plots with error bars. Features were selected based on their importance and clinical domain knowledge. Asterisks (*) indicate the statistical significance. The asterisk indicates that the *P* value is less than 0.05. Two asterisks indicate *P* value less than 0.01. Three asterisks indicate *P* value less than 0.001.

RESULTS

From January 1, 2015, to November 30, 2022, 243 pediatric patients with CD were enrolled in the Division of Gastroenterology, Hepatology, and Nutrition (Supplementary Figure S1, http://links.lww.com/CTG/B220). After excluding 62 patients who did not maintain treatment for at least 3 months following diagnosis, a final cohort of 180 patients was included in the study. Most of the patients (68.9%, n = 124) were male, and the mean age was 164.5 ± 31.2 months. Except for CRP and fecal calprotectin levels, the mean values of the laboratory tests were within the normal range. CRP and fecal calprotectin are markers that reflect inflammation of the gastrointestinal tract, and the mean values of these markers were elevated compared with the normal range. Details of the patient characteristics, including laboratory test results, medication usage, and relapse status of patients for each TP, are presented in Supplementary Table S1, http://links.lww.com/CTG/B222.

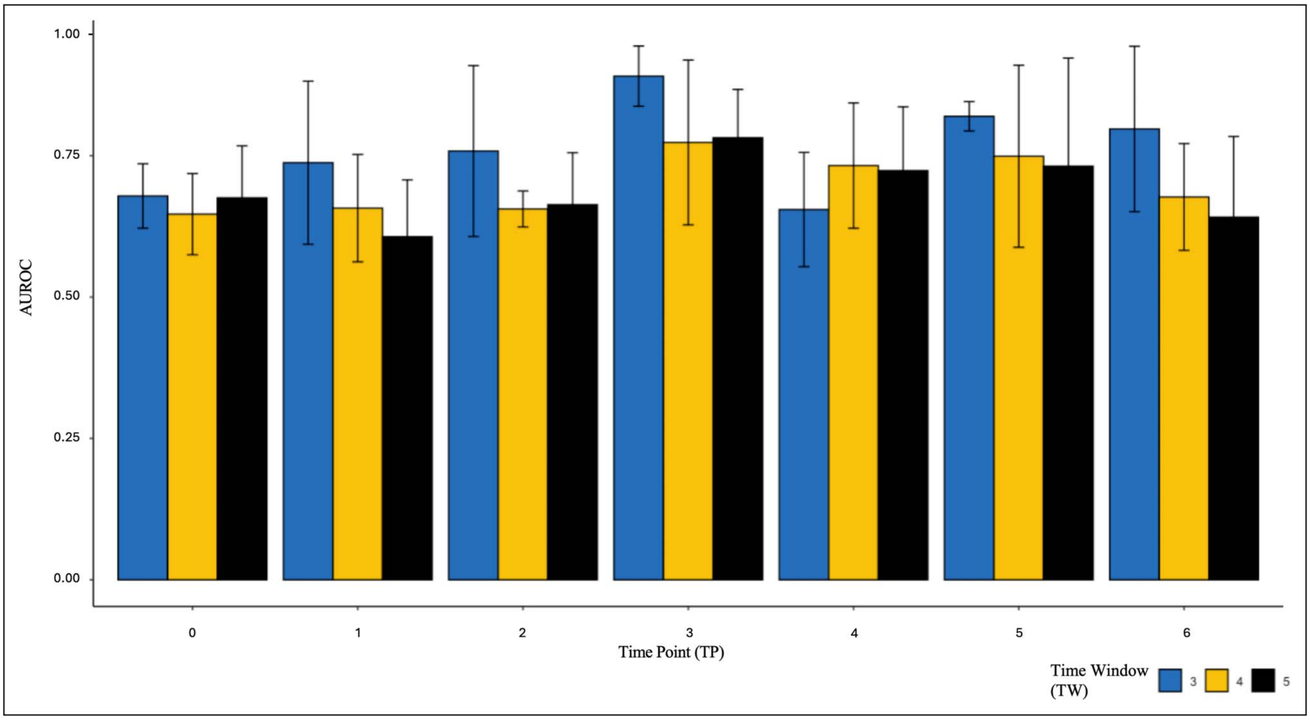

Figure 2. Performance for each TP and TW. The performance of the model at each TP is calculated with the AUROC score. Confidence interval was obtained with 5-fold cross validation. The AUROC score was highest at TP3 and TW3 (0.891). AUROC, area under the receiving operating characteristics curve; TP, time point; TW, time window.

The AUROC values obtained for each combination of TP and TW are presented in Figure 2. When comparing the performances at the same TP, TW3 generally demonstrated the highest AUROC values (TP0, TP1, TP2, TP3, TP5, and TP6). However, when comparing the performances at the same TW, TP3 mostly yielded the highest AUROC values (TW3, TW4, TW5, and TW7). The highest AUROC (0.891) was achieved with the combination of TW3 and TP3.

For TW and TP, we computed variable importance using the Shapley method and displayed them as heatmaps. Figure 3 shows the variable importance of TW3 across different TPs. The results of the variable importance in different TWs are shown in Supplementary Figure S2, http://links.lww.com/CTG/B221. As shown in Figure 3, CRP and lymphocyte fractions were identified as important variables in the TW3 models. For TW3, CRP was the most important variable at TP0, TP4, and TP5, whereas the lymphocyte fraction was the most important variable at TP2 and TP3. CRP level and lymphocyte fraction were also important variables in other TWs, as shown in Supplementary Figure S2, http://links.lww.com/CTG/B221.

The values of the lymphocyte fraction, neutrophil fraction, monocyte fraction (the 3 indicators that compose the leukocyte fraction), and CRP on TP3 were analyzed in pediatric patients with CD and compared with those who experienced relapse within 3 months (relapse group) and those who did not (nonrelapse group) (Figure 4). In the relapse group, C-reactive protein (CRP), neutrophil fraction, and monocyte fraction were significantly increased, whereas the lymphocyte fraction was significantly decreased. Specifically, on TP3, the lymphocyte fraction showed a marked difference, with a value of 31.4 (SD: 10.6) in the nonrelapse group and 18.5 (SD: 3.7) in the relapse group.

DISCUSSION

To the best of our knowledge, this is the first study to develop a time-aggregated model for predicting pediatric CD relapse in a multi-TP, multi-TW setting. We identified the optimal TP and TW that robustly predicted pediatric CD relapse, with an AUROC value of 0.891. Our model assessed the condition of patients using multiple clinical measurements and provided useful decision-making support for the follow-up of patients with CD in a clinical context. We also identified significant variables such as CRP levels and lymphocyte fractions for predicting relapse at multiple TPs. The variables were compared between the relapse and nonrelapse groups. In particular, when considering 3-month TWs (TW3) at 3 months after the end of induction treatment (TP3), the values of CRP and lymphocyte fraction showed a significant difference between the relapse and nonrelapse groups. Our study showed that relapse prediction models changed over time after pediatric CD diagnosis, and the variables contributing to relapse also changed at different TPs.

The relapse of pediatric CD must be minimized because the accumulation of progressive intestinal damage leads to the progressive loss of bowel function and various sequelae, such as the requirement for bowel resection and the prevalence of intestinal cancer (1,27). Intensive treatment, including biologics, reduces the likelihood of relapse in limited cases, such as after the diagnosis of severe CD or bowel resection for CD (10,11). To determine when to start intensive treatment, it is important to know when relapse is likely to occur. Accordingly, various studies have been conducted to predict CD prognosis. Kiyokawa et al (28) used deep learning to analyze pathological images and assess the likelihood of CD relapse after bowel resection. However, this study relied on imaging data that were only available at the time of

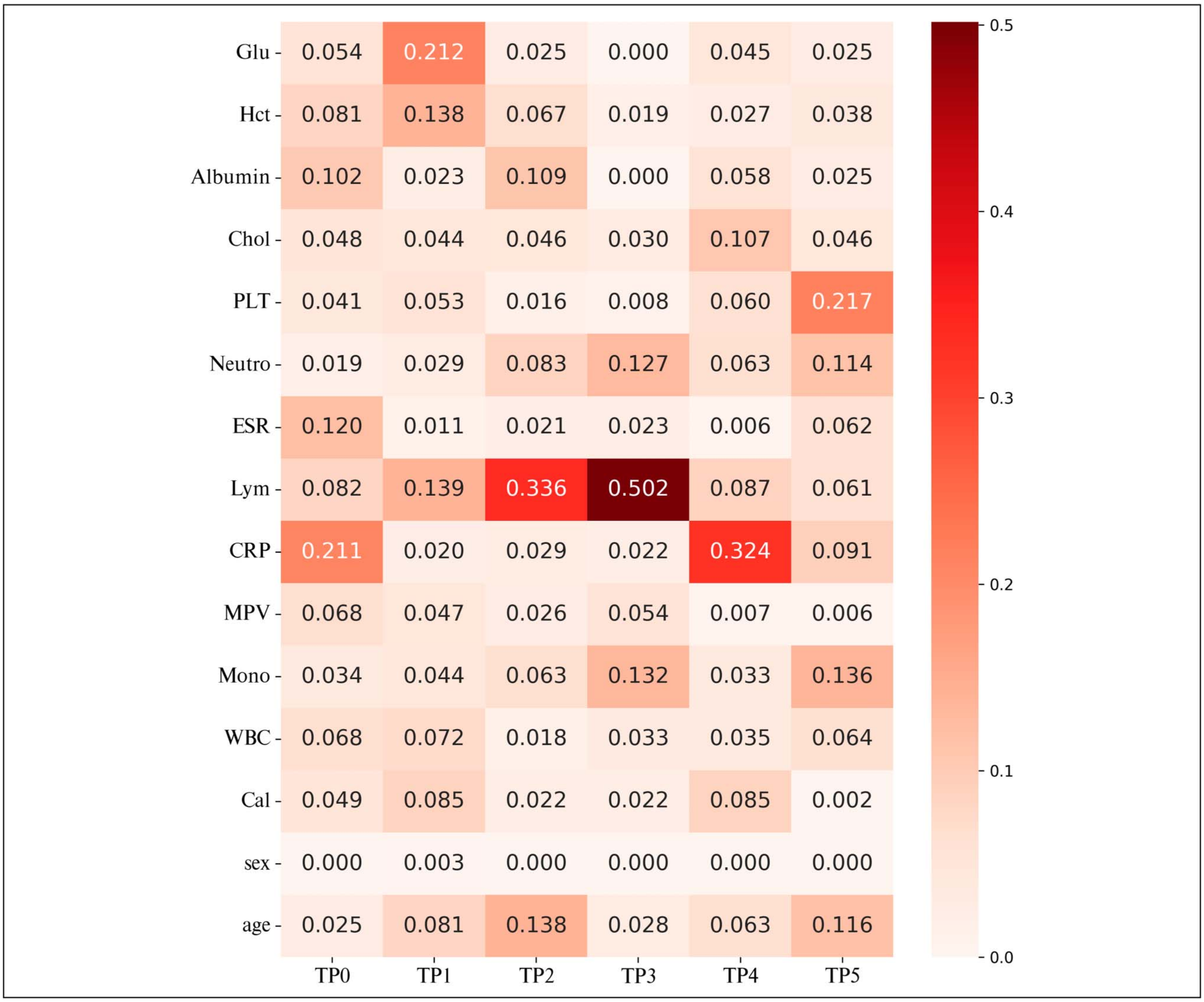

Figure 3. Heatmap for relative importance for predicting relapse within 3 months based on each time point. Shapley values were calculated for features of time-aggregated models predicting pediatric Crohn's disease relapse. The relative importance was calculated by dividing the Shapley value of each variable by the sum of the total Shapley values in each model. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hct, hematocrit; MPV, mean platelet volume; PLT, platelet; TP, time point; TW, time window; WBC, white blood cell.

initial diagnosis or surgery in pediatric patients with CD, which limits the use of time-series data to create models that predict relapse over multiple TPs. On the other hand, Gomollón et al (19) proposed a model for predicting CD relapse by analyzing text data from electronic health records using natural language processing techniques; however, its applicability in various clinical settings remains unverified due to linguistic constraints. In addition, many studies have used machine learning to predict the prognosis of CD. Waljee et al conducted a study in adult patients with CD to predict remission at 1 year after diagnosis based on test results at diagnosis and reported an AUROC of 0.78 (17). Previous CD prognostic prediction studies have mostly been conducted in adult patients or in a combined population of pediatric and adult patients with CD (13–19). Previous studies have also used single, fixed TWs to predict relapse or remission, and the timing of relapse prediction is also limited to predicting relapse after a specific event, such as diagnosis, medication discontinuation, or surgery (13–19).

To address this limitation, it is necessary to conduct studies comparing the model performance at multiple TPs and TWs in predicting pediatric CD relapse. In this study, the 3-month TWs at 3 months after the end of the induction treatment (TW3-TP3) performed best in predicting CD relapse, with an AUROC of 0.891. The models at earlier TPs (TP0 and TP1) demonstrated a lower performance in predicting CD relapse. This finding suggests that additional tests or shorter follow-up periods may be necessary to accurately assess the likelihood of relapse during the early postinduction period. While previous studies have been limited to predictions at limited TPs (e.g., the time of diagnosis, drug discontinuation, or after surgery), our results show that other TPs, such as those 3 months after the end of maintenance treatment, can also be valid for predicting relapse.

To validate our model clinically, the Shapley values of the variables were calculated. CRP and lymphocyte fraction were identified as key variables associated with relapse. A 2006 study on CD relapse prediction models showed that CRP was one of the

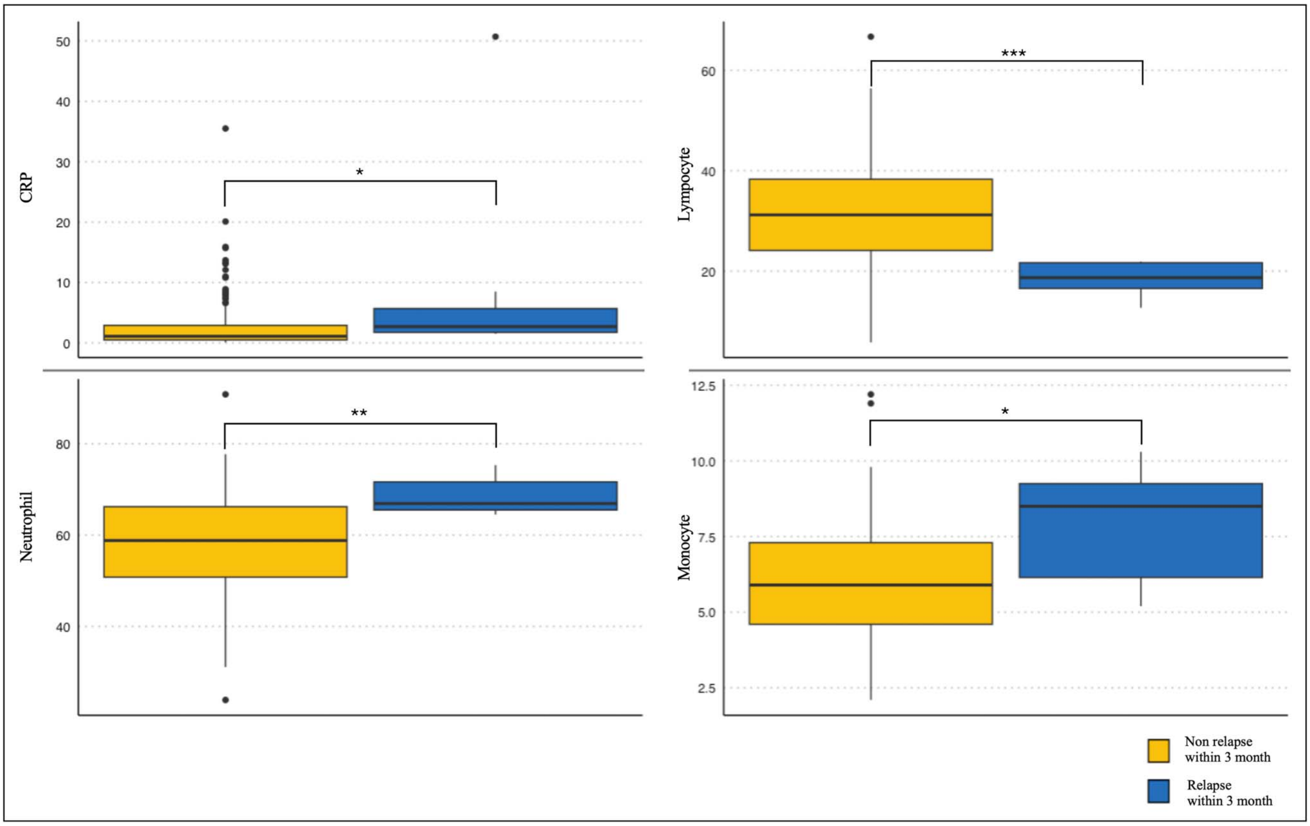

Figure 4. Comparisons of variables between relapse and nonrelapse groups at each TP. At each TP, the values of the variables were compared in the relapse and nonrelapse groups. The variables, CRP, lymphocyte fraction, neutrophil fraction, and monocyte fraction, which were identified as significant variables in Supplementary Figure S1, http://links.lww.com/CTG/B220, were compared. The mean value and confidence interval of the values were shown. The asterisk (*) represents the significance of the statistical test, wherein * means that the *P* value is < 0.05, ** means that the *P* value < 0.001, and *** means *P* value < 0.0001. CRP, C-reactive protein; TP, time point.

most important markers of CD relapse (29), which has been supported by several other studies (30,31). CRP is also highly correlated with clinical disease activity, endoscopic activity, and histological activity in inflammatory bowel disease (32). A reduction in lymphocyte counts is associated with CD relapse. Reduced lymphocytes levels in CD are linked not only to early postoperative recurrence but also to the development of granulomas and the necessity for reoperations (33–35). Lymphocyte counts are significantly decreased in patients with CD compared with control groups, and among CD subtypes, patients with fistulizing CD, which is considered a more severe clinical phenotype, exhibit even lower lymphocyte counts compared with those with nonfistulizing CD (36,37). However, unlike previous studies that only used information at a specific TP, such as the time of surgery, our study investigated the importance of the lymphocyte counts in relapse at various TPs. Notably, we found a prominent difference in the lymphocyte fraction between the relapse (18.5%) and nonrelapse (31.4%) groups at TP3-TW3, which was the most predictive TP for relapse.

The course of pediatric CD is influenced not only by the patient's genetic background and condition at diagnosis but also by a variety of external variables, such as adherence to treatment, dietary habits, and the occurrence of infections (38,39). Therefore, predicting pediatric CD relapse requires a time-aggregation study to support the continuous monitoring of multiple TPs. In various clinical settings, the real-time prediction of clinical events at multiple TPs is useful for clinical decision support (40,41). In this context, we applied real-time aggregated machine learning prediction models to predict pediatric CD relapse. Our study collected data from pediatric patients with CD at multiple TPs from the end of induction treatment to a subsequent 6-month follow-up, updated the latest data from each TP, and constructed models independently at each point. To the best of our knowledge, this is the first real-time aggregation study to predict CD prognosis.

A limitation of this study is that it was conducted at a single center, and the sample size was relatively small. Owing to the limited amount of data, the study was only analyzed up to the 6-month TP after the end of maintenance treatment, as cases of relapse dropped over time, and there were insufficient data to build a model at later TPs. Furthermore, endoscopic and imaging data were not used in this study. Despite the significance of endoscopy and imaging results in predicting prognosis in pediatric CD, these data were only collected at the time of diagnosis, and were therefore unsuitable for the purpose of this study, which aimed to assess the predictive performance of the model at multiple TPs.

In conclusion, we developed a time-aggregated model to predict relapse in pediatric patients with CD using multiple TPs and TWs. We identified significant variables for predicting relapse in pediatric patients with CD to provide evidence supporting real-time clinical decision making. Furthermore, our study confirmed that CRP level and lymphocyte fraction are robust indicators of CD relapse across various TPs and TWs.

CONFLICTS OF INTEREST

Guarantor of the article: Yu Rang Park, PhD.
Specific author contributions: S.J.: data curation: lead; conceptualization: supporting; investigation: lead; project administration: equal; writing–original draft: equal. J.Y.Y.: conceptualization: lead; formal analysis: lead, project administration: equal; methodology: lead; writing–original draft: equal; writing–review and editing: equal; S.P.: data curation: supporting; conceptualization: supporting; H.L.: data curation: supporting; conceptualization: supporting. H.K.: project administration: supporting; supervision: equal, writing–review and editing: supporting. Y.R.P.: project administration: lead, methodology: supporting; supervision: equal; writing–review and editing: equal.
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Potential competing interests: None to report.
Data availability: The data used to support the findings of this study are not publicly available because the study involved individual checkup data, but are available from the corresponding author on reasonable request.

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Study Highlights

WHAT IS KNOWN

- ✓ Pediatric Crohn's disease (CD) relapse must be minimized because the accumulation of progressive intestinal damage leads to progressive loss of bowel function and various sequelae.
- ✓ Various studies have attempted to predict the prognosis of CD; however, these predictions have been limited to fixed time points (TP), such as at the time of diagnosis, drug discontinuation, or surgery.

WHAT IS NEW HERE

- ✓ We developed a time-aggregated model to predict pediatric CD relapse at multiple TPs and time windows (TWs), and found the optimal TP and TW.
- ✓ This study identified important variables that predict relapse in pediatric patients with CD to support real-time clinical decision making. In particular, we found that CRP and lymphocyte fraction were robust indicators of pediatric CD relapse across various TPs and TWs.
- ✓ We highlighted the importance of developing independent models at different times and with different TWs to predict the event occurrence. Our model supports real-time clinical decision making with more accurate and timely recurrence prediction by considering the temporal pattern of disease progression.

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