Predicting Response to Exclusive Enteral Nutrition Induction Therapy in Children with Crohn Disease Using Clinical Data

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Background

Exclusive enteral nutrition (EEN) is recognized as a first line therapy for the induction of remission in luminal pediatric Crohn Disease (pCD) [1], achieving a remission rate of around 80% [2]. However, patients who are unresponsive to EEN often endure significant physical, mental, and financial burden and spend weeks consuming an unpalatable diet before being switched to an alternative treatment regimen. The aim of this study is to build a machine learning model capable of identifying EEN non-responders from clinical data routinely collected at the time of diagnosis to allow for more personalized treatment plans, using a robust, prospectively collected national dataset.

Methods

A prospectively-followed cohort of pediatric patients, who were prescribed EEN as their first treatment after being diagnosed with CD (n=308), was collected through the Canadian Children Inflammatory Bowel Disease Network (CIDsCaNN) inception cohort (2013-2020). For this initial analysis, patients with weighted Pediatric Crohn Disease Activity Indexes (wPCDAI) collected after at least 4 weeks on EEN were compiled into a dataset (n=108). Patients were labelled as EEN responders if their wPCDAI after EEN induction was < 12.5, indicating successful remission [non-responders n=46 (43%), responders n=62 (57%)] [3].

The dataset contained the following baseline clinical data: blood test results (Hgb, ESR, CRP, Alb, Htc, Plt), Paris Classifications, height and weight Z-scores, as well as wPCDAI, SES-CD (simple endoscopic score, CD), PGA (physician global assessment), and Mayo scores. 60% of patients were prescribed at least one other therapeutic (steroid, biologic, or immunomodulator) for part of their EEN induction. The classes of other prescribed therapeutics and the prescription duration were used as additional features in the dataset. Pediatric Ulcerative Colitis Activity Indexes (PUCAI) were calculated and included as a feature in the dataset. While not traditionally associated with CD, PUCAI scores were used as a surrogate measure for colonic CD.

Odds ratios were calculated to determine whether any features correlated with response to EEN induction therapy. A machine learning classifier for predicting response to EEN was also built. Maximum relevance minimum redundancy (MRMR) feature selection [4] and a nested cross-validation scheme were used to optimize the model (find the best subset of features and hyperparameter settings) and assess its performance, as measured by the area under its Receiver Operating Characteristic (ROC) curve. Different types of classifiers including random forests, naïve Bayes, support vector machines, and logistic regression were tested.

Through exploratory data analysis conducted as part of this study, a dashboard for viewing the outcomes of the study cohort has been constructed (**Figure 1**). The dashboard can be accessed at:

Results

PGA scores were found to be predictive of response to EEN induction. An increase in PGA score (e.g. moving from “mild disease” to “moderate disease”) correlated with an increased likelihood of EEN failure (Odds Ratio 3.1, 95% CI [1.7,5.8], p=0.0001). PUCAI scores were also predictive of response to EEN induction. Higher PUCAI scores correlated with an increased likelihood of EEN failure (Odds Ratio 1.4 for a 10-point PUCAI increase, 95% CI [1.07,1.7], p=0.009).

The best classifier for predicting EEN response was a random forest consisting of 20 decision trees, each with a maximum depth of 3, using only four features from the dataset: PGA, PUCAI and SES-CD scores, and Htc. The classifier achieved an area under the ROC curve of 0.75 ± 0.07 (**Figure 2**).

Conclusions

Higher PGA, PUCAI, and SES-CD scores show potential for predicting patients less likely to respond to EEN induction. Higher PUCAI scores may indicate distal colonic CD which is associated with more severe disease phenotypes [5]. Likewise, lower Htc levels demonstrate predictive power and have previously been identified as a marker of complicated CD behavior [6]. Overall, these findings suggest that more severe disease activity at the time of diagnosis is associated with reduced efficacy of EEN induction therapy.

This study’s findings are limited by the presence of concurrent therapies during EEN induction and a small sample size due to the limited availability of wPCDAI scores post-EEN induction. In future work, more accurate classifiers may be built by incorporating alternative measures of EEN remission to allow for a greater number of patients to be included in the dataset, as well as research data, including microbiome and host genetic data.

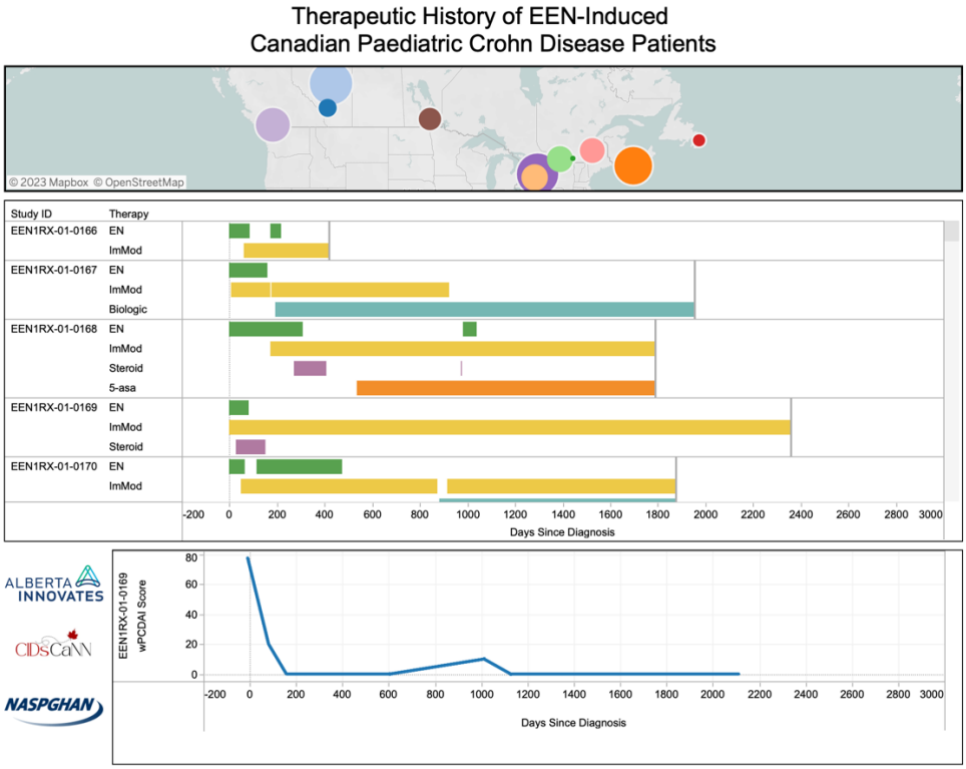

Figure 1. A dashboard for viewing the therapeutic history of Canadian pCD patients initially treated with ENN. wPCDAI is displayed to track disease activity over time.

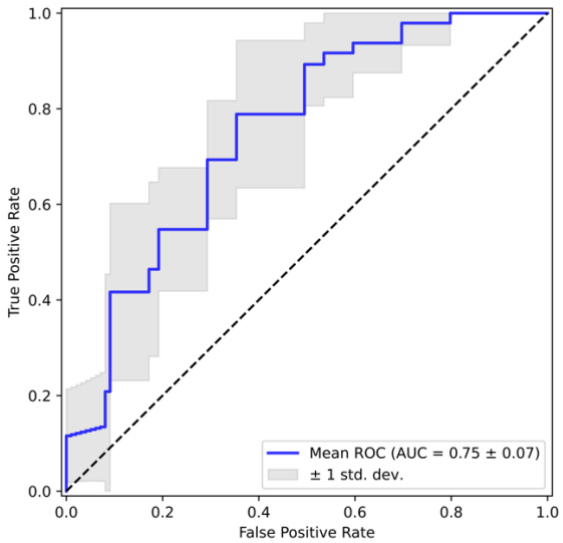

Figure 2. ROC curve showing the performance of the random forest. A positive label indicates EEN induction failure.

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