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Analysis of Using the Total White Blood Cell Count to Define Severe New-onset Ulcerative Colitis in Children

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Abstract

Objectives: The aim of this study was to assess common laboratory tests in identifying severe ulcerative colitis in children at diagnosis.

Methods: A cohort of 427 children 4 to 17 years of age newly diagnosed with ulcerative colitis (UC) was prospectively enrolled. Boosted classification trees were used to characterize predictive ability of disease attributes based on clinical disease severity using Pediatric Ulcerative Colitis Activity Index (PUCAI), severe (65+) versus not severe (<65) and total Mayo score, severe (10–12) versus not severe (<10); mucosal disease by Mayo endoscopic subscore, severe (3) versus not severe (<3); and extensive disease versus not extensive (left-sided and proctosigmoiditis).

Results: Mean age was 12.7 years; 49.6% (n = 212) were girls, and 83% (n = 351) were Caucasian. Severe total Mayo score was present in 28% (n = 120), mean PUCAI score was 49.8 ± 20.1, and 33% (n = 142) had severe mucosal disease with extensive involvement in 82% (n = 353). Classification and regression trees identified white blood cell count, erythrocyte sedimentation rate, and platelet count (PLT) as the set of 3 best blood laboratory tests to predict disease extent and severity. For mucosal severity, albumin (Alb) replaced PLT. Classification models for PUCAI and total Mayo provided sensitivity of at least 0.65 using standard clinical cut-points with misclassification rates of approximately 30%.

Conclusions: A combination of the white blood cell count, erythrocyte sedimentation rate, and either PLT or albumin is the best predictive subset of standard laboratory tests to identify severe from nonsevere clinical or mucosal disease at diagnosis in relation to objective clinical scores.

Keywords

classification tree analysis; inflammatory bowel disease; laboratory values

At the time of diagnosis of ulcerative colitis (UC) signs and symptoms are variable and subjective (1) and various measures are used to define clinical disease severity for decisions on initial therapy. Laboratory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), platelet count (PLT), albumin (Alb), and fecal calprotectin (fCal) are nonspecific objective measures but in a remarkable number of children one or several tests can be normal (2–4). As part of a large prospective multicenter trial in newly diagnosed childhood UC (PROTECT, NCT01536535), laboratory tests concomitantly with careful phenotypic classification of clinical disease severity, extent of colonic disease, and degrees of mucosal inflammation were systematically collected. Our goal was to evaluate the utility of these laboratory tests in predicting severe clinical and mucosal disease as categorized by current tools that use patient symptoms and mucosal inspection on colonoscopy.

METHODS

Patient Population

Eligibility, exclusionary, and diagnostic criteria for study patients between the ages of 4 and 17 years recruited from 29 participating centers between July 2012 and April 2015 in the PROTECT study have been previously described (4–6).

Disease Extent

Disease extent was classified as proctosigmoiditis, left-sided (active mucosal inflammation from rectum to the splenic flexure), or extensive disease (extending anywhere from splenic flexure to the cecum) based on inflamed mucosa visualized by colonoscopy. There were hospitalized patients (n=30; 7% of cohort) who had severe/fulminant clinical disease that received only a flexible sigmoidoscopy because of safety concerns that were assigned to the extensive colitis group.

Disease Activity

Clinical disease activity was determined using the Pediatric Ulcerative Colitis Activity Index (PUCAI) (7) total score classified as mild (PUCAI = 10–34), moderate (PUCAI = 35–64), and severe (PUCAI ≥65) and the total Mayo score (8) based on its 4 parameters (stool frequency, rectal bleeding, endoscopic subscore, and Physician Global Assessment) with each parameter of the score ranging from 0 to 3 and total score (range 0–12) classified as with severe activity ≥10. Endoscopic findings of the rectosigmoid region were used as visual evidence of mucosal disease severity and recorded as the Mayo endoscopic subscore according to a referenced 4-point pictorial scale system (0 inactive, 1 mild, 2 moderate, 3 severe).

Laboratory Assessment

At baseline, blood work was collected within 2 weeks before the colonoscopy or in a 2-week period of time from endoscopy to initial UC treatment and not more than 2 days after initiating treatment. Tests included Hb, PLT, white blood cell count (WBC), Alb, ESR, and CRP as described (5,6). Observed values of all laboratory studies are reported with the exception of CRP and Hb. CRP is reported with respect to the upper limit of normal (ULN) for the local laboratory. Hb is reported as below the lower limit of normal (LLN) and 2 g/L below the LLN. Normal Hb values are based on age and sex (3). Assay for fCal (9) was performed centrally by BÜHLMANN fCAL ELISA kit (Buhlmann Laboratories AG, Schönenbuch, Switzerland) from stool samples collected before colonoscopy cleanout or ≥2 days after colonoscopy but not >3 days after initial UC treatment. The extended range procedure was used for samples (working range 30–1800 μg/g feces with additional 1:50 dilution for values >1800 μg/g feces).

Statistical analysis (see Supplemental Digital Content 1, http://links.lww.com/MPG/B854, Statistical analysis plan). Data collection and reporting followed the STROBE guidelines for observational studies (10). In brief, associations were measured using chi-squared test for categorical variables, a mean-score chi-squared test for ordinal variables, and analysis of variance for continuous variables.

Boosted classification trees (11,12) were used to characterize the biomarkers' predictive ability to classify disease extent or clinical activity discretized as severe versus not severe. The maximum depth for each tree was set to 3 nodes. Participants were included in the modeling if they had at least 1 nonmissing laboratory value. In building the classification models, the classification tree function rpart (12) defaults were used to obtain models based on all available data. Because of higher rates of missing data for fCal, secondary

classification models for clinical disease activity using the PUCAI and total Mayo were, however, fit without fCal as a candidate predictor. For each classification model, we present the relative importance of the predictors; partial dependence plots; and the crossvalidated misclassification error. Partial dependence plots qualitatively show the relationship between realizing the more severe outcome and values of a predictor, accounting for average effects of the other variables (13).

To maximize clinical usefulness, classification trees were developed by adjusting the node cut points to generally accepted abnormal values. Thus, the cut point for ESR was changed to be ≤20 mm/h, Alb was ≤3.5 g/L, WBC was ≥12 × 10^9/L, CRP was >ULN for individual study site laboratory; Hb was <LLN based on sex and age (3); and PLT was ≥500 × 10^9/L. For fCal, ≥1800 μg/g feces (maximum ELISA kit extended range). For each outcome observed classification error, specificity, and sensitivity, and sample size are presented. Descriptive statistics were generated using SAS software. Graphics and analyses used R 3.4.0 (14). Graphics used the grid, gridExtra (15), ggplot2 (16), pdp (17), and rpart.plot (18) packages.

Ethical Standards

Informed consent/assent was obtained in all cases. Local investigational review boards at all investigative sites approved the study. This study was registered with clinicaltrials.gov (NCT01536535).

RESULTS

Study Population

In the PROTECT Study, 467 participants were enrolled at 29 participating sites with data available for analysis on 427 (See Table, Supplemental Digital Content 2, http://links.lww.com/MPG/B854, Patient demographics at diagnosis). Forty patients were excluded because of change in diagnosis to Crohn disease, incomplete data, or study withdrawal (5,6). Treatments and outcomes have been previously published (6). Mean age ± standard deviation was 12.7 ± 3.3 years, 49.6% (212/427) girls, 83% (351/419) Caucasian, and 82% (353/427) had extensive disease.

The occurrence of missing data was low for baseline blood tests (see Table, Supplemental Digital Content 3, http://links.lww.com/MPG/B854, Laboratory tests with PUCAI clinical disease severity) and ranged from 1% (2/427) for Alb to 9% (39/427) for ESR. The exception was CRP with 26% (110/427) of subjects having missing values. Baseline assessments for fCal were available for 56% (240/427). All participants had complete data on disease extent, baseline PUCAI, total Mayo score, and endoscopy assessments of the rectosigmoid region for Mayo endoscopic subscore.

Individual Laboratory Tests

The percentage of patients with UC with low Hb values differed across levels of disease extent assessed by length of bowel involved, clinical disease severity assessed by PUCAI, and mucosal inflammation assessed by Mayo endoscopic subscore (Spearman correlations

ranged from −0.18 to −0.21). About one-third of patients with extensive disease, clinically severe disease, or that appeared severe at colonoscopy had a below-normal Hb value (Fig. 1A).

A correlation existed between elevated WBC and colonic disease extent, clinical disease severity, and mucosal appearance, based on either the continuous WBC (Spearman correlations 0.25–0.36) or the proportion of patients with WBC >12 × 10^9/L (Fig. 1B; see also Table, Supplemental Digital Content 3, http://links.lww.com/MPG/B854, Laboratory tests with PUCAI disease severity). Similarly, elevated PLT showed a trend for worse disease (Spearman correlation 0.21–0.28, Fig. 1C; see also Table, Supplemental Digital Content 3, http://links.lww.com/MPG/B854, Laboratory tests with PUCAI clinical disease severity). In contrast, Alb values were more likely to be lower for those with extensive disease than nonextensive disease and for those with greater severity of clinical disease (Spearman correlations −0.25 to −0.32, Fig. 1D). Lower mean and median Alb values and percentage with low Alb <3.5 g/L all correlated with increasing clinical disease severity (see Table, Supplemental Digital Content 3, http://links.lww.com/MPG/B854, laboratory tests with PUCAI disease severity).

Many participants had ESR <20mm/h (Fig. 1E); however, fewer had a normal ESR of <20mm/h with increasing PUCAI clinical disease severity (see Table, Supplemental Digital Content 3, http://links.lww.com/MPG/B854, laboratory tests with PUCAI disease severity). Overall, the mean ESR was greater for worse clinical severity of disease based on PUCAI determinations (see Table, Supplemental Digital Content 3, http://links.lww.com/MPG/B854, laboratory tests with PUCAI disease severity). Correlations of ESR with disease extent and severity assessments ranged from 0.28 to 0.37. Similarly, although many patients did not have a CRP >ULN (Fig. 1F) a greater proportion of patients with CRP >ULN or 2 times >ULN had clinically worse disease based on PUCAI and Mayo endoscopy subscore (Spearman correlations 0.25–0.33, Fig. 1F; see also Table, Supplemental Digital Content 3, http://links.lww.com/MPG/B854, laboratory tests with PUCAI disease severity). A weaker association was found with disease extent, although the numbers were very small for some categories.

fCal determinations showed no differences between patients when comparing assessment on length of the colon involved or mucosal disease activity based on Mayo endoscopic subscore but median values were different for clinical disease severity based on PUCAI with large ranges (Spearman correlation 0.24, Fig. 1G; see also Table, Supplemental Digital Content 3, http://links.lww.com/MPG/B854, laboratory tests with PUCAI disease severity). The percentages of patients with mild, moderate, or severe UC with a fCal level >250 μg/g feces did not differ.

Classification and Regression Tree Analysis

Classification and regression tree analysis was used to determine the relative importance of the laboratory tests for classifying clinical disease severity, severity of mucosal inflammation, and extent of colon involved (Fig. 2). Although fCal was the second most important variable for clinical disease severity as assessed by PUCAI and total Mayo score, it had the least influence of the 5 variables for extent of colon involved or severity of

mucosal disease at colonoscopy. As fCal was not available for all physicians and patients due to cost and other factors, classification models were fit including fCal and also without including fCal. WBC ranked as the most important predictor for all the measures of disease severity whether they were clinical (ie, PUCAI, total Mayo score) or mucosal endoscopic severity. For extent of disease, WBC ranked as the third most important predictor with ESR and Alb as first and second variable of importance, respectively.

The best-fit classification tree for clinical disease severity as measured by PUCAI identified ESR, WBC, and PLT as the set of predictors. The model using clinically relevant laboratory cut-offs identified that patients with a combination of normal ESR and normal WBC (36% of patients) had a probability of 0.12 of being clinically severe. If ESR was, however, >20mm/h (59% of patients) then patients had a probability of about 0.4 of being classified as clinically severe regardless of WBC (Fig. 3A). The classification tree has a misclassification rate of 0.35 and a sensitivity of 0.65 with 46 participants of 427 that could not be classified due to missing values for the laboratory tests. Similarly, for disease severity assessed by total Mayo score, the classification tree also identified ESR, WBC, and PLT as predictors and the model based on clinically relevant cut-points also identified the same combination of normal ESR and normal WBC (36% of patients) with probability of 0.12 of being severe. In addition, elevated WBC with normal ESR (6% of patients) or elevated WBC with both elevated ESR and elevated PLT (9% of patients) had a probability of >0.50 of being clinically severe (Fig. 3B). In this latter classification tree, there was a misclassification rate of 0.27, a sensitivity of 0.74, a specificity of 0.63, and 46 participants of 427 that could not be classified.

Classification trees which included fCal determinations <1800 μg/g feces added moderate improvements in sensitivity and specificity for PUCAI (0.70 and 0.61, respectively), but minimal change in fit for total Mayo score (Fig. 3C and D) with 207 participants of 427 that could not be classified. The best fit classification trees which included fCal (Figure, Supplemental Digital Content 4, http://links.lww.com/MPG/B854, classification tree with best fit, A and B) and allowed nodes to be defined by any laboratory value rather than forcing clinically relevant cut points had improved sensitivity and reduced specificity compared to the models based on clinically relevant cut-points (PUCAI: sensitivity=0.91, specificity=0.38; total Mayo: sensitivity 0.93, specificity 0.34). The nodes for severity were at ESR <36, fCal <2836, several cut-points of WBC including <13 and <7.3, and PLT ≥452.

The best-fit classification tree for severe mucosal appearance based on the Mayo endoscopic subscore identified ESR, WBC, and Alb as predictors. Using a model with clinically relevant cut-off values for laboratory tests, a normal ESR with a normal Alb (35% of patients) had a probability of 0.19 of being severe, whereas an elevated ESR with elevated WBC (19% of patients) had a probability of 0.58 of having severe mucosal disease (Fig. 4A). This had a sensitivity of 0.70, a specificity of 0.58, and a misclassification rate of 0.32 and 46 of 427 participants were not classified. When fCal was included in the tree model building, it was not selected as a parameter, The best fit classification tree which allowed nodes to be defined by any laboratory value rather than forcing clinically relevant cut points had improved sensitivity and reduced specificity (sensitivity=0.94, specificity=0.20) (see Figure, Supplemental Digital Content 4, http://links.lww.com/MPG/B854, classification tree

with best fit, C). The nodes defining mucosal severity were at ESR <24, WBC <16, and Alb ≥3.

The best-fit classification tree for extensive disease/pancolitis identified ESR, WBC, and PLT as predictors. Because 83% of the patients have extensive disease, the model based on clinically relevant cut-points identified all branches as extensive with probability >0.50. As shown in Figure 4B, those least likely to have extensive disease with 0.64 probability are those with normal ESR, normal PLT, and normal WBC (34% of patients). This analysis had specificity of 0.84 and a misclassification rate of 0.16 with 46 of 427 participants not classified. When fCal was included, it was not determined to be among the top 3 variables to define extensive disease. A best-fit classification tree for extensive colon involvement (Figure, Supplemental Digital Content 4, http://links.lww.com/MPG/B854, classification tree with best fit, D) without using clinically relevant cut-offs had improved sensitivity (0.32) and specificity (0.96), and classified the lowest probability of extensive disease (0.27 probability, in 10% of patients) as ESR <14, PLT <276, and WBC ≥5.3.

CONCLUSIONS

The multicenter PROTECT study allowed for analysis of baseline laboratory parameters and clinical measures of clinical and mucosal disease severity at diagnosis. Among the laboratory parameters studied, WBC was the variable of most statistical importance for differentiating severe clinical and endoscopic mucosal disease for all parameters. The exception was defining the extent of colonic involvement in which it trailed the relative importance of ESR and Alb (Fig. 2). When excluding fCal, an ESR, WBC, and PLT formed the best-fit 3-node classification and regression tree model to predict clinical disease severity based on PUCAI and total Mayo score and disease extent. For endoscopic mucosal severity, Alb was identified in place of ESR in the best-fit model. Although generally not considered to be an important parameter for determination of clinical disease severity, the importance of WBCs in UC has been noted previously in a retrospective single-center cohort study, an elevated WBC at diagnosis was found to be associated with colectomy at 3 years (19).

Hb was not found to be 1 of the 5 top parameters influencing the identification of either severe clinical or mucosal disease at diagnosis. This may be due to the many potential mechanisms for the development of anemia in UC (20) including serious rapid blood loss in very severe and active UC or to slower causes. Anemia related to the slower causes may include indolent development of anemia of chronic disease and/or development of iron-deficiency anemia in those patients with UC with nonvisible, microscopic blood loss occurring covertly.

In contrast, median fCal values were found to separate clinical disease severity at diagnosis but only at values well beyond what is available through clinical laboratories. Thus, its practical usage to define clinical disease severity is limited. Although the use of fCal in children to use as screening tool for defining patients with IBD has been evaluated (2,21), with sensitivity being similar to adults at a cut-off of 50 μg/g feces, specificity is lower than in adults with a range of 44% to 93% in a systematic review (21). The addition of fCal to other blood markers in children with IBD symptoms reported the proportion

of patients with IBD correctly classified as low risk increased from 33% to 91% and those with IBD incorrectly classified as low risk decreased from 16% to 9% (2). Areas of uncertainty in using fCal as a screening tool include borderline results (50–150 μg/g feces) as most within this range do not have IBD, availability and reporting parameters of actual numbers following dilutions versus thresholds (21). For patients with established IBD, serial determinations can, however, aid in determining reactivation of disease (22).

The total WBC plus ESR, and usually PLT are the top 3 tests studied with highest relative importance for defining severe from nonsevere clinical and mucosal disease using classification tree analyses. Although WBC has the largest numerical relative importance, there is no statistical test showing it is statistically superior to the others. On the contrary, WBC and ESR always come into all of the classification trees and PLT come into 3 out of 4. Specifically, WBC, ESR, and PLT were the strongest predictors of severe clinical disease as measured by PUCAI, total Mayo score, and disease extent. As detailed in the methods section, extensive disease included patients with disease to hepatic flexure to those with disease beyond this region of the colon and so whether there was a relationship between the variables and this distinction cannot be determined with our data. For PUCAI and total Mayo score, the classification tree using standard clinical cut-points for these parameters predicted disease severity with sensitivity of 0.65 or greater, and using the best-fit cut-points, sensitivity was >0.90.

In summary, no one combination of tests identified all the different measures of severe UC. Our data suggest that WBC, ESR, and PLT are the best subset of 3 common laboratory blood tests to identify severe clinical and mucosal UC disease in children at diagnosis. Future studies should determine whether choice of initial treatment based on the WBC, ESR, and PLT improves disease responsiveness and outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What Is Known

- Among common blood tests, up to 40% are normal in severe clinical ulcerative colitis.
- An abnormal fecal calprotectin in patients with blood markers and symptoms suggestive of ulcerative colitis improves the ability for diagnosis.
- Elevated total white blood cell counts have been associated with greater colectomy rates.

What Is New

- Total white blood cell count ranked as the most important predictor for clinical or mucosal measures of severe ulcerative colitis.
- The total white blood cell count plus erythrocyte sedimentation rate, and usually platelets had the highest relative importance associated with severe clinical and mucosal disease.
- No one combination of tests could identify all the different clinical measures of severe disease.

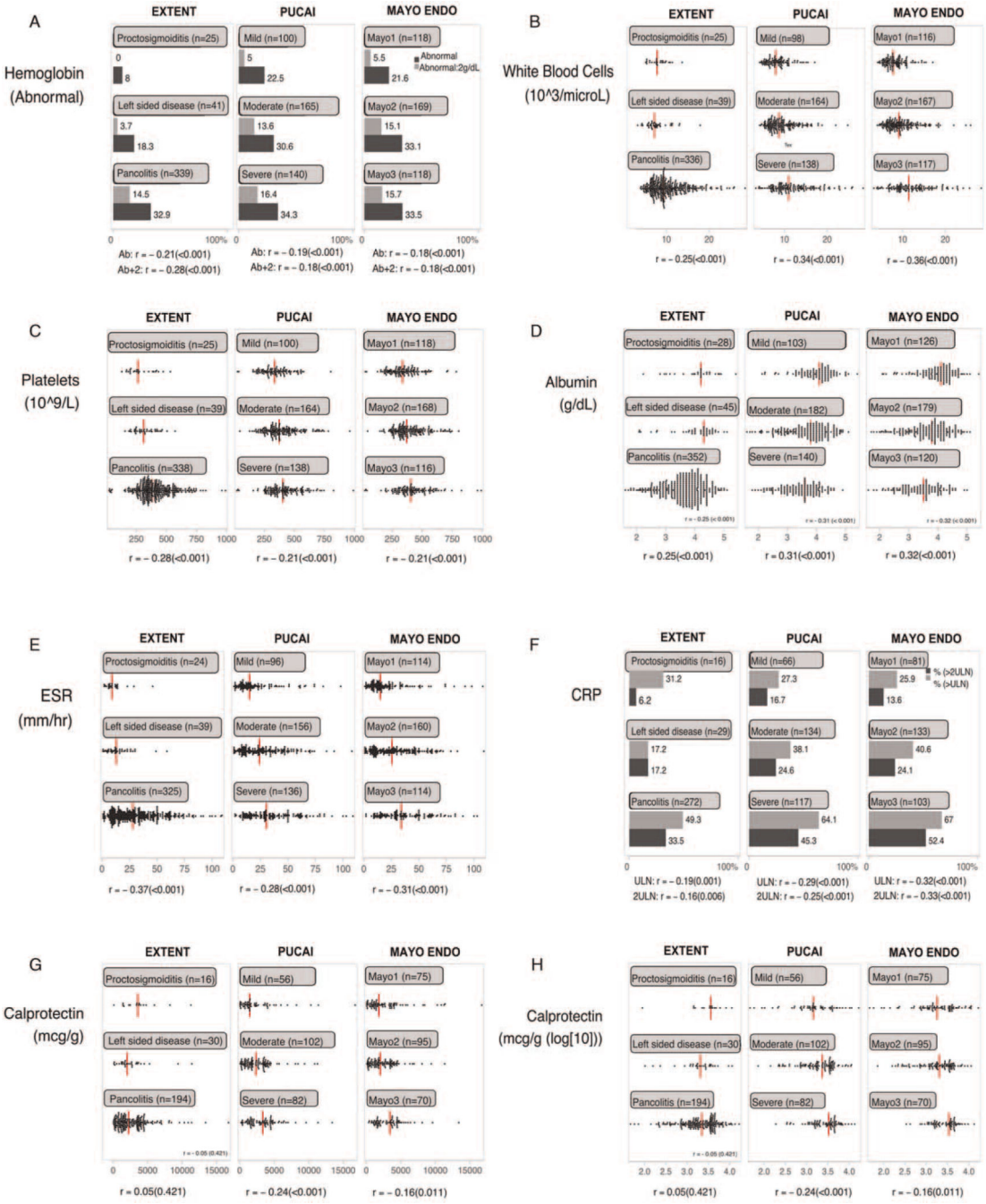

FIGURE 1.

Association of laboratory values with disease extent and clinical disease activity. In each panel, the distribution of laboratory values is shown by extent of disease (left subpanels), and clinical disease severity using PUCAI determinations (middle subpanels) and mucosal disease severity by Mayo endoscopic subscores with Mayo 1 (mild), 2 (moderate), and 3 (severe) (right subpanels). The vertical red lines are median values. A) Patients (5) with low hemoglobin based on patient sex and age (black bars) and patients (%) with normal hemoglobin 2 g/L below normal (grey bars). B) Total White blood cell count. C)

Platelet counts. D) Serum albumin. E) Erythrocyte Sedimentation Rate. F) Patients (%) with C-reactive protein (CRP) above the upper limit of normal (grey bar) and >2 times the upper limit of normal (black bars). G) Fecal calprotectin levels. H) log 10 transformation of fecal calprotectin levels. PUCAI = Pediatric Ulcerative Colitis Activity Index.

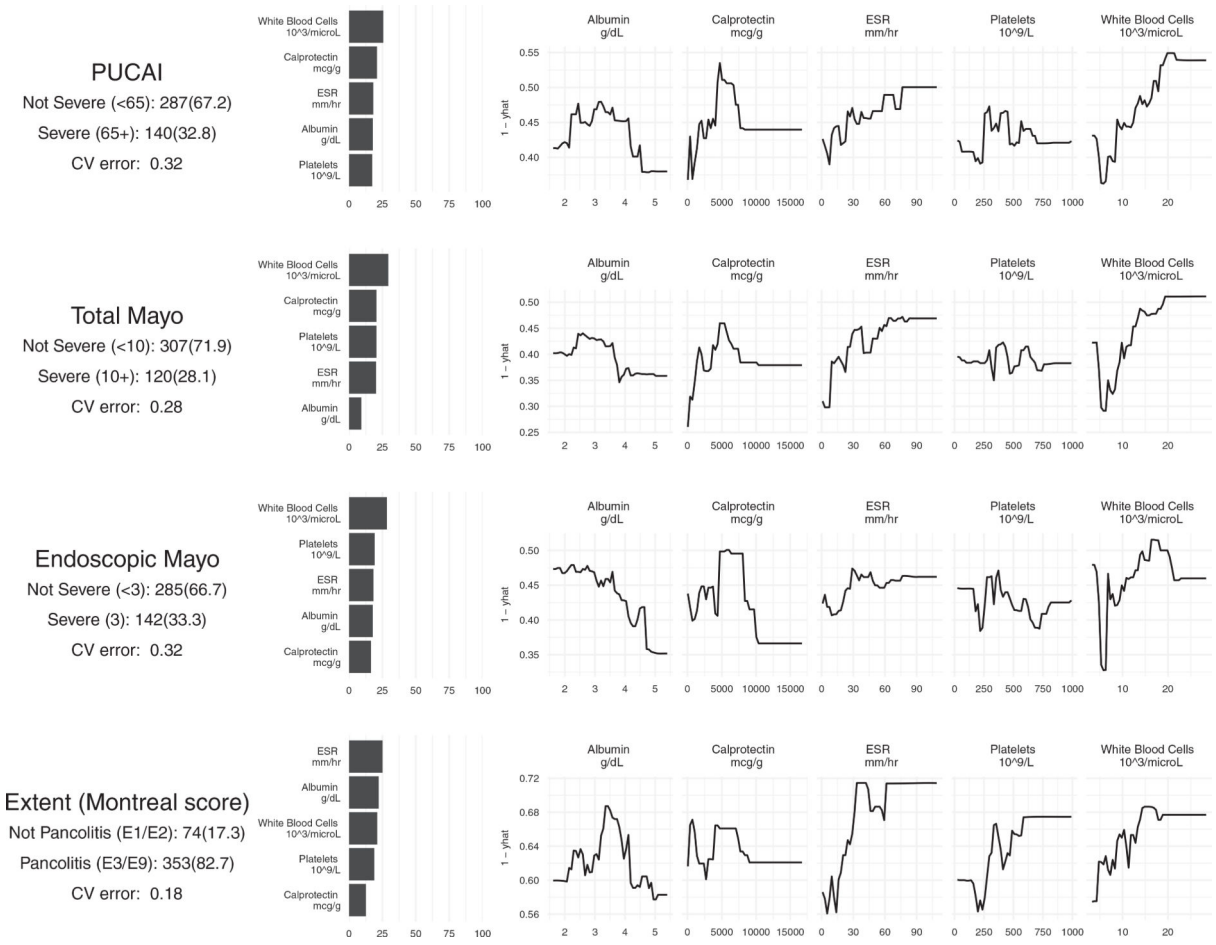

FIGURE 2.

Variable importance and partial dependence plots per outcome. Variable importance (bar charts) and partial dependence (line plots) were computed from the classification and regression tree models. Variable importance measures a covariate's relative contribution to prediction. A higher value means a covariate is more important to predicting the outcome. Partial dependence plots show how the value of each covariate affects model predictions averaged overall other covariates. For a higher value of that, the model is more likely to predict a subject has more severe disease. For example, higher values of white blood cell count (WBC) are predictive of more severe disease in each outcome. Crossvalidation (CV) error is included. CV = crossvalidation; ESR = erythrocyte sedimentation rate; PUCAI = Pediatric Ulcerative Colitis Activity Index.

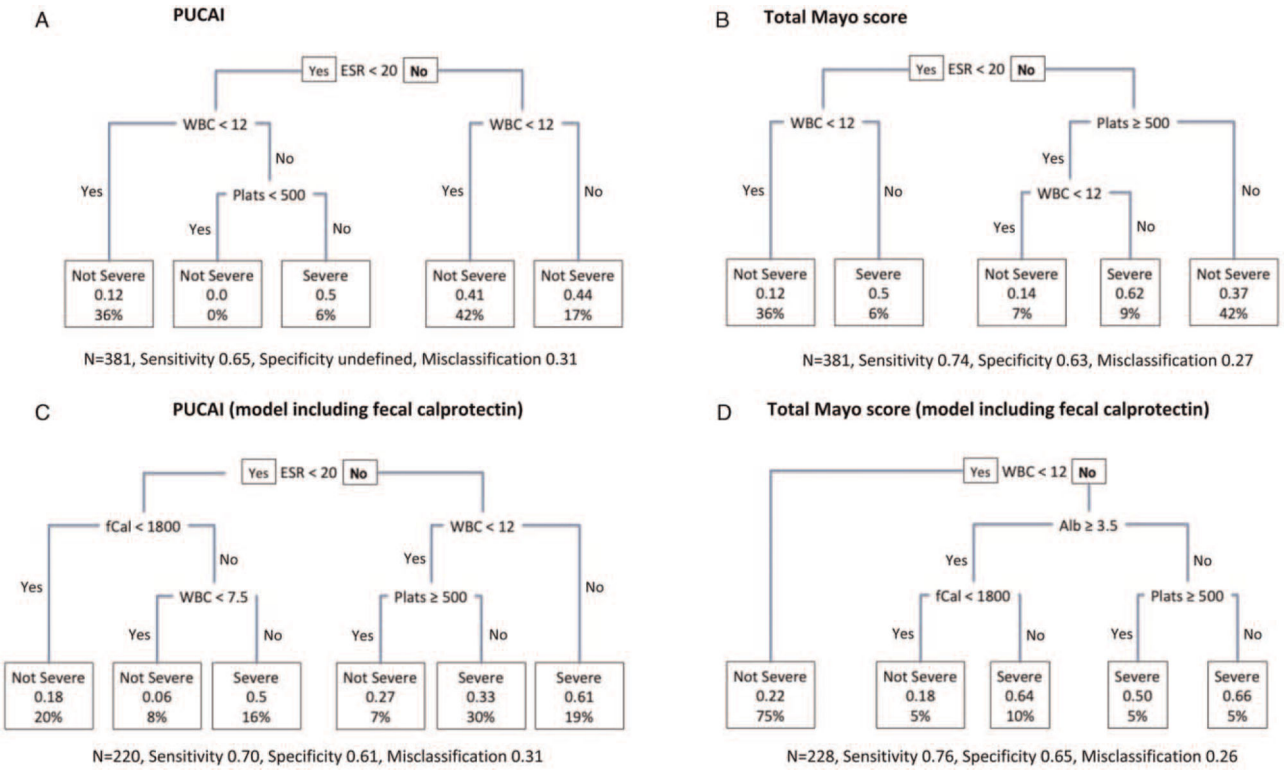

FIGURE 3.

Classification and regression tree model for clinical disease severity. Analysis for severe disease (Pediatric Ulcerative Colitis Activity Index [PUCAI] ≥65) versus not severe disease with (C) and without (A) fecal calprotectin (fCal) analyzed. There were 46 of 427 not classified with fCal removed from analysis and 207 subjects not classified with fCal included. Severe clinical disease defined by total Mayo score of ≥10 versus not severe disease are shown in (B) (no fCal in analysis; 46 not classified) and (D) (inclusive of fCal; 199 not classified). Each box shows predicted outcome (defined as severe if the probability is 50% or greater), the probability being classified as severe, and percentage of the sample. ESR = erythrocyte sedimentation rate; PUCAI = Pediatric Ulcerative Colitis Activity Index.

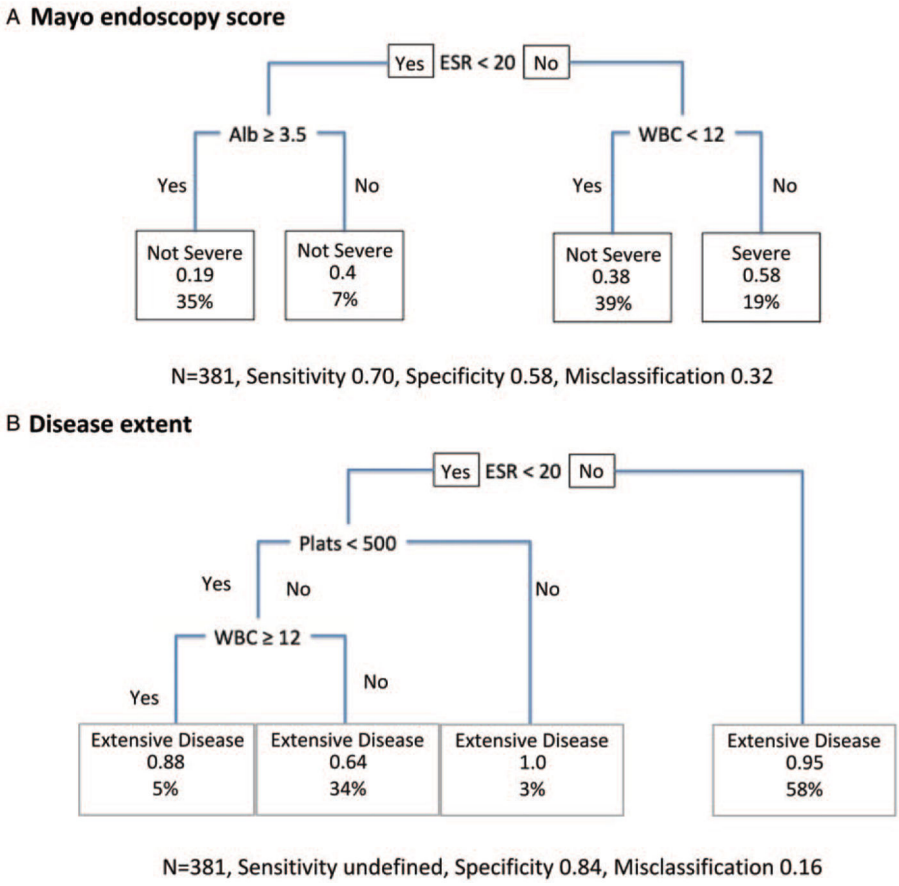

FIGURE 4.

Classification tree model for severe mucosal disease and extensive colonic involvement. A, Mayo endoscopic subscore of 3 for severe mucosal disease versus not severe mucosal disease with a Mayo endoscopic subscore of 1 or 2. B, Extensive disease (proximal to the splenic flexure) versus nonextensive disease (rectum to splenic flexure). Of 427 participants, 46 were not classified in each analysis. The 3 values in each box (leaf) correspond to the predicted outcome of the leaf (defined as severe if the probability of severe is ≥50%, otherwise defined as nonsevere), the probability being classified as severe, and the percentage of the sample in the leaf. ESR = erythrocyte sedimentation rate.