

Development and Validation of a New Algorithm Model for Differential Diagnosis Between Crohn's Disease and Intestinal Tuberculosis: A Combination of Laboratory, Imaging and Endoscopic Characteristics

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TITLE PAGE

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Short running head

Development and Validation of a New Model for CD and ITB

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Abstract

Background: Sometimes in clinical practice, it was a great challenge to distinguish Crohn's disease (CD) and intestinal tuberculosis (ITB), we conducted this study was to identify simple and useful algorithm for distinguishing them.

Methods: We retrospectively reviewed the medical history of the patients who were diagnosed as ITB or CD. We firstly identified ITB patients, and then the patients diagnosed with CD were matched by age, sex, and admission time in a 1:1 ratio. Patients who admitted between May 1, 2013 and April 30, 2019 were regarded as training cohort, and patients admitted between May 1, 2019 and May 1, 2020 were regarded as validation cohort. We used multivariate analysis to identify the potential variables, and then we used R package rpart to build the classification and regression tree (CART), and validated the newly developed model.

Results: In total, the training cohort included 84 ITB and 84 CD patients, the validation cohort included 22 ITB and 22 CD patients. Multivariate analysis showed that, positive T-SPOT, ≥ 4 segments involved, longitudinal ulcer, circular ulcer, and aphthous ulcer were confirmed as independent discriminating factors. Using these parameters to build the CART model made an overall accuracy rate was 88.64%, with sensitivity, specificity, NPV, and PPV being 90.91%, 86.36%, 90.48% and 86.96%, respectively.

Conclusion: We developed a simple and novel algorithm model covering laboratory, imaging, and endoscopy parameters with CART to differentiate ITB and CD with good accuracy.

Key words

Crohn's disease; intestinal tuberculosis; diagnosis; algorithm; CART

Introduction

Crohn's disease (CD) and intestinal tuberculosis (ITB) are two intestinal diseases with different etiology, pathogenesis, and treatment. Sometimes in clinical practice, it was a great challenge to distinguish the two diseases. It was reported that the misdiagnosis rate between the two diseases could reach 50%-70% [1]. The diagnosis of ITB can be made when acid fast bacilli (AFB) and granulomas with caseous necrosis are found in histopathology, but the positive rates are low [2, 3]. If ITB could not be excluded, 8-12 weeks of empirical antituberculosis treatment (ATT) is recommended, avoiding the severe adverse events if immunosuppressive drugs are prescribed to ITB patients by mistake [4, 5]. Nevertheless, the ATT can delay CD treatment, and ATT has many side effects [5, 6]. Hence, models that can be used at the bedside for easy and accurate differential diagnosis would be extremely useful in clinical practice. As a result, many researchers have tried to identify parameters and models that could improve the accuracy rate [7-9]. However, there are various kinds of parameters, and the scoring systems also vary from each other, and some models are complex to use. Therefore, we conducted this study to investigate the laboratory, imaging and endoscopic characteristics of CD and ITB, and to identify simple and useful algorithm for distinguishing the two diseases.

Mehtods

Patients

We retrospectively reviewed the medical history of the patients who were diagnosed as ITB or CD between May 1, 2013 and May 1, 2020. The inclusion criteria were: (1) had results of T-SPOT; (2) had undergone colonoscopy or trans-anal enteroscopy in our hospital so as to obtain the endoscopic characteristics; (3) had the results of computed tomography enterography (CTE) or magnetic resonance enterography (MRE) so as to obtain imaging characteristics; (4) the diagnosis was not confirmed when the patients visited our hospital; (5) the patients had not received any treatment or had received ATT or glucocorticoids or immunosuppressive agents for no more than 1 week; (6) the diagnosis of either ITB or CD could be confirmed. The exclusion criteria were: (1) the result of T-SPOT or endoscopic characters or CTE/MRE was not complete; (2) had received treatments for more than 1 week; (3) final diagnosis could not be confirmed; (4) ITB and CD both existed; (5) had colectomy before this hospitalization.

Diagnostic criteria

The confirmed diagnosis for ITB required one of the following: (a) caseating granulomas detected in endoscopy biopsy, surgical specimen, or mesenteric lymph nodes; (b) demonstration of AFB on smears or histological sections or positive culture for AFB; (c) strong suspicion of ITB with a good response to ATT without recurrence; a good response to ATT was determined by relief of symptoms and disappearance of ulcerations on endoscopic examination [7, 8, 10].

The confirmed diagnosis for CD was made based on the management consensus of inflammatory bowel disease for the Asia-Pacific region [11], which included clinical, endoscopic, histological, and radiological characteristics and/or biochemical evaluation.

Study design

Firstly, we identified the patients diagnosed with ITB who met all the inclusion criteria, and classified them as group 1. Then the patients diagnosed with CD were matched by age, sex, and admission time in a 1:1 ratio, and they were classified as group 2. We reviewed the medical history of the patients including age, sex, weight, height, symptoms, present and past history, laboratory results [blood routine, erythrocyte sedimentation rate (ESR), albumin, hsCRP, stool routine, T-SPOT and PPD skin test], endoscopy results (location of lesions, shape of ulcers, cobblestone appearance, pseudopolyp, scar, and stricture), imaging results (enlargement of celiac lymph nodes, peritoneal abscess, bowel wall thickening, stricture, comb sign, target sign, adipose creeping sign, ≥ 4 segments involved, intestinal fistula, perianal diseases and chest X-ray/CT), pathology results (acid fast bacilli staining, granulomas, caseous necrosis or non-caseous necrosis), diagnosis, treatment and follow-up results. Patients who admitted between May 1, 2013 and April 30, 2019 were regarded as training cohort, the information of which was used to develop the algorithm; and patients admitted between May 1, 2019 and May 1, 2020 were regarded as validation cohort, the information of which was used to validate the algorithm. The study was approved by the ethics committee in our hospital.

Statistical Analysis

IBM SPSS Statistic Version 24.0.0.0 was used to compare the differences between the two groups. Continuous variables without normal distribution were presented with median (lower and upper interquartile range), and tested by nonparametric Wilcoxon rank-sum test. Categorical variables were presented with number (percentage), and were tested by χ^2 test. Statistical significance was defined as $P < 0.05$ (two-tailed). After the comparison, we identified some parameters which had statistical differences between the two groups, and selected them as potential variables to build the

algorithm.

The study end point was to develop an algorithm to differentiate ITB and CD, and to validate it.

One hundred and sixty-eight and forty-four cases were allocated to the training cohort and validation cohort, respectively. Parameters with statistical significance were enrolled into logistic regression for multivariate analysis. Independent discriminating factors selected by the logistic model were then used to build a decision tree based on the R package rpart (<https://CRAN.R-project.org/package=rpart>). Briefly, this is a nonparametric regression method based on binary recursive partitioning of data in the training set to build a model like a tree structure, which is also called classification and regression tree (CART). It incrementally divides the data into smaller subclasses according to the amount of information gained by each partition into a subclass until no additional information could be gained by a split [12]. It generated a tree structure flow chart to differentiate ITB and CD that is easy to interpret. The overall sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and predictive accuracy of the CART were evaluated using data of the validation cohort. $P < 0.05$ was regarded as statistical significance. R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org>) was used to perform the statistical analysis.

Results

Baseline and laboratory characteristics of the training cohort

In total, the training cohort included 84 ITB and 84 CD patients, the validation cohort included 22 ITB and 22 CD patients. In the training cohort, the ratio of patients with diarrhea, symptoms of perianal diseases (perianal pain, perianal discomfort, perianal pus or fluids), anemia, $PLT >$

$300 \times 10^9/L$, $hsCRP > 3mg/L$, and positive occult blood test was statistically higher in group 2 than that in group 1; the ratio of positive PPD skin test and positive T-SPOT was higher in group 1 (The details are shown in Table 1).

Imaging characteristics of the training cohort

The CTE/MRE results analysis showed that, the ratio of patients with comb sign, target sign, adipose creeping sign and ≥ 4 segments involved was significantly higher in group 2 (CD) than that in group 1 (ITB). Anal magnetic resonance image (MRI) results showed that more patients in group 2 have anal fistula or perianal abscess. Chest X-ray/CT results showed that more patients in group 1 had pulmonary TB and calcification (The imaging characteristics of the training cohort are shown in Table 2).

Endoscopy and pathology characteristics of the training cohort

The endoscopy results showed that, the ratio of patients with longitudinal ulcer, aphthous ulcer (the endoscopy images are shown in Figure 1), rectum involvement, sigmoid colon involvement was significantly higher in group 2 than that in group 1. More patients in group 1 had circular ulcer, and the pathology result showed that, the ratio of caseous necrosis was also higher in group 1 (The endoscopy and pathology characteristics of the training cohort are shown in Table 3).

Multivariate analysis and diagnostic values of the factors

When these parameters were entered into a multivariate analysis, positive T-SPOT, ≥ 4 segments involved, longitudinal ulcer, circular ulcer, and aphthous ulcer were confirmed as independent discriminating factors (Table 4 shows the multivariate analysis results). Further analysis of the diagnostic values of these factors is shown in Table 5. The most sensitive and specific parameters for differentiating ITB and CD when used in isolation were circular ulcer (sensitivity 100%) and

longitudinal ulcer (specificity 100%). However, circular ulcer was not specific for ITB, because 50% of CD patients had a circular ulcer. Similarly, longitudinal ulcer was specific to CD, but the true positive rate was only 40.91% in CD patients.

The CART analysis of training and validation cohorts

The first factor that split the training population was T-SPOT. 86.36% of the patients with positive T-SPOT were diagnosed as ITB, while 90% of the patients with negative T-SPOT were diagnosed as CD. The CART analysis result is shown in Figure 2. From the figure, we could find that, patients with positive T-SPOT and circular ulcer but without aphthous ulcer have high reliability in the diagnosis of ITB; patients with negative T-SPOT and with ≥ 4 segments involved/longitudinal ulcer have high reliability in the diagnosis of CD.

When we tested this algorithm using the data in the validation cohort, the overall accuracy rate was 88.64% (39 in 44 patients). The sensitivity, specificity, NPV, and PPV of differential diagnosis of ITB from CD was 90.91%, 86.36%, 90.48% and 86.96%, respectively (Table 6).

Discussion

Differentiating ITB from CD is sometimes very difficult in some patients, especially in the areas where both ITB and CD are prevalent, as there are many similarities between ITB and CD in clinical manifestations, laboratory results, imaging, endoscopic and even histological characteristics. On the other hand, the misdiagnosis or delayed diagnosis can result in tubercle bacillus diffusion, drug adverse events and medical expenditure increase [13]. Hence, there is an urgent need for developing accurate and easy diagnostic tools to differentiate ITB and CD. Many previous studies have been conducted to construct models that could improve the accuracy [7-9,

14, 15], but they used different diagnostic models and scoring systems, and some of them were not easy to use, as they may need a calculator or a computer. In this study, we finally selected five parameters (positive T-SPOT, ≥ 4 segments involved, longitudinal ulcer, circular ulcer, and aphthous ulcer) covering laboratory, imaging and endoscopic characteristics, and constructed the CART algorithm, which could be used at the bedside for easy and accurate differential. To our knowledge, this is the first study to use CART to differentiate ITB and CD.

In this study, we firstly compared the clinical, imaging, endoscopic and pathologic characteristics between ITB and CD in the training cohort. For clinical characteristics in the training cohort, patients with CD were more likely to have diarrhea, and symptoms of perianal diseases, this was in accordance with previous studies [7, 14]. For laboratory characteristics, patients with CD were more likely to have anemia, $PLT > 300 \times 10^9/L$, $hsCRP > 3mg/L$, and positive occult blood test than ITB, the results were close to some of the previous studies, but some were not in consistency [7, 9, 14]. Patients with ITB had much higher rate of positive T-SPOT, which was a very important parameter in the CART, as it split the patients in the first step. A meta-analysis showed that, the pooled sensitivity and specificity of interferon- γ release assays (IGRAs, including T-SPOT and QuantiFERON-TB Gold) for the differential diagnosis of ITB from CD were 82.8% and 86.7%, respectively [16], indicating that it was a good independent discriminating factors. In this study and in clinical, some patients had a positive TB test but the final diagnosis was CD, the algorithm helped us to differentiate this as follows: if they also had aphthous ulcer, then the probability of CD was about 83.33%; if they did not have aphthous ulcer no circular ulcer, but have ≥ 4 segments involved and longitudinal ulcer, then probability of CD was very high, otherwise, the diagnosis would incline to ITB.

For imaging characteristics, especially CTE/MRE, patients with CD were more likely to show comb sign, target sign, adipose creeping sign and ≥ 4 segments involved. Kedia et al. showed that comb sign was more common in CD [17], and no studies had compared target sign or adipose creeping sign in ITB and CD, but some studies have used them to build the differential models [8, 18]. In our study, these three factors were probably easy to get influenced by other factors, and they failed to be selected as potential parameters in CART. Except for these signs in CTE, Kedia et al. also evaluated other characteristics in CTE, and they found that, necrotic lymph nodes were specific for ITB, while the combination of long segment lesion and visceral to subcutaneous fat ratio (VF/SC) ratio > 0.63 was specific for CD, using these characters could make an accuracy rate of 43% [17].

For endoscopic characteristics, rectum or sigmoid colon involvement and longitudinal ulcers, aphthous ulcers were more common in CD, whereas transverse ulcers were more common in ITB, our results is the same as the previous published ones [9, 14, 19]. Lee et al. selected eight endoscopic characteristics along to build the models: transverse ulcers, less than 4 segment lesions, patulous ileocecal valve, and pseudopolyp (favored ITB); anorectal lesions, aphthous ulcers, longitudinal ulcers, and cobblestone appearance (favored CD), and they hypothesized that if there were more parameters favored of ITB than CD, then a diagnosis of ITB could be made, and vice versa. This endoscopic model could make an accuracy rate of 87.5% and the PPV for CD and ITB was 95% and, respectively, indicating that a systematic analysis of endoscopic findings is very useful in differentiating ITB and CD [20]. In our study, we found that the shapes of the ulcers were very important parameters in differentiating ITB and CD, and transverse ulcers, longitudinal ulcers, and aphthous ulcers were all selected in our CART model. Regarding the importance of the

shapes of the ulcers, we suppose that it may be possible to use the artificial intelligence (AI) technique, which is now very popular, to help in differentiating ITB and CD. As it can be taught to identify the characteristics of the ulcers (such as the shapes), and if we further enter some other parameters, after calculation and combination, the AI might give us a satisfied answer.

For pathologic characteristics, granulomas and non-caseous necrosis could be seen in both groups, while caseous necrosis and positive AFB staining was exclusive to ITB, but the sensitivity was low. Qian et al. compared granulomatous lymphangitis and granulomas in CD and ITB, and they concluded that, neither granulomatous lymphangitis nor granulomas was specific for CD, but their morphology and distribution could help in the differential diagnosis [21]. In our study, the pathologic characteristics were not selected as parameters to build the CART model, but we suppose that, if we study the morphology and distribution of granulomas next time, we may find some meaningful parameters.

Using a single parameter to distinguishing ITB and CD has very limited use in clinical practice, as its sensitivity or specificity is usually low. Hence, an integration of various categories of valuable parameters to establish a model could possibly help to deal with this question. Mao et al. selected 2 CTE findings and 8 endoscopic findings to build the model, and they found that the accuracy rate increased from 71.6% to 88.3%, compared with using endoscopic findings alone [22]. Bae et al. also developed a scoring system using 8 endoscopic findings, chest ray, small bowel follow through, and 2 laboratory tests [anti-*Saccharomyces cerevisiae* antibodies (ASCA) and IGRAs], which showed very good results, with an accuracy rate of 96.3% [9]. But there is limitation in their model, as in our hospital and many other hospitals in China, ASCA is not routine tested, we may fail in using this model. Some studies used likelihood ratio models to differentiate these two

diseases [7, 23], and their accuracy rate could reach 95.7%. But these models usually contained a very complex formula, and need a calculator, so they are difficult to be applied at the bedside. In our CART model, the parameters are easy to obtain, and does not need any calculation, we think it will be more convenient to use.

There are some limitations in this study. Firstly, this is a single-centered, retrospective study, and the sample size is limited, prospective, larger sample-sized, and multi-centered study is still needed to make it more convincing and can be applied to other centers. Secondly, CART itself also has disadvantages, for example, in some branches, the accuracy rate was not that satisfied, and that as CART is not based upon a probabilistic model, so the CART tree cannot provide the probability level or confidence interval of the predictions [24, 25].

In conclusion, we developed a simple and novel algorithm model covering laboratory, imaging, and endoscopy parameters with CART to differentiate ITB and CD with good accuracy, but external validation is warranted. Except for our model, many models have been proposed in the previous published studies, and we can select the model that is most appropriate and easy to apply.

Abbreviations

CD: Crohn's disease; ITB: Intestinal tuberculosis; CART: Classification and regression tree; AFB:

Acid fast bacilli; ATT: Antituberculosis treatment; CTE: Computed tomography enterography;

MRE: Magnetic resonance enterography; ESR: Erythrocyte sedimentation rate; NPV: Negative

predictive value; PPV: Positive predictive value; AI: Artificial intelligence; ASCA:

Anti-Saccharomyces cerevisiae antibody.

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Author's Contribution

LY collected the data, performed the statistical analysis and wrote the manuscript draft. CYH collected the data, performed the statistical analysis. PX, YJY and ZWJ collected the data. ZM and LCJ designed the study and revised the manuscript.

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Availability of data and materials

The datasets used are available from the corresponding author on reasonable request

Ethics approval

This study was approved by the ethical principles of the Declaration of Helsinki 1964 and the ethics committee of the Sixth Affiliated Hospital, Sun Yat-sen University, and the informed consent was waived

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

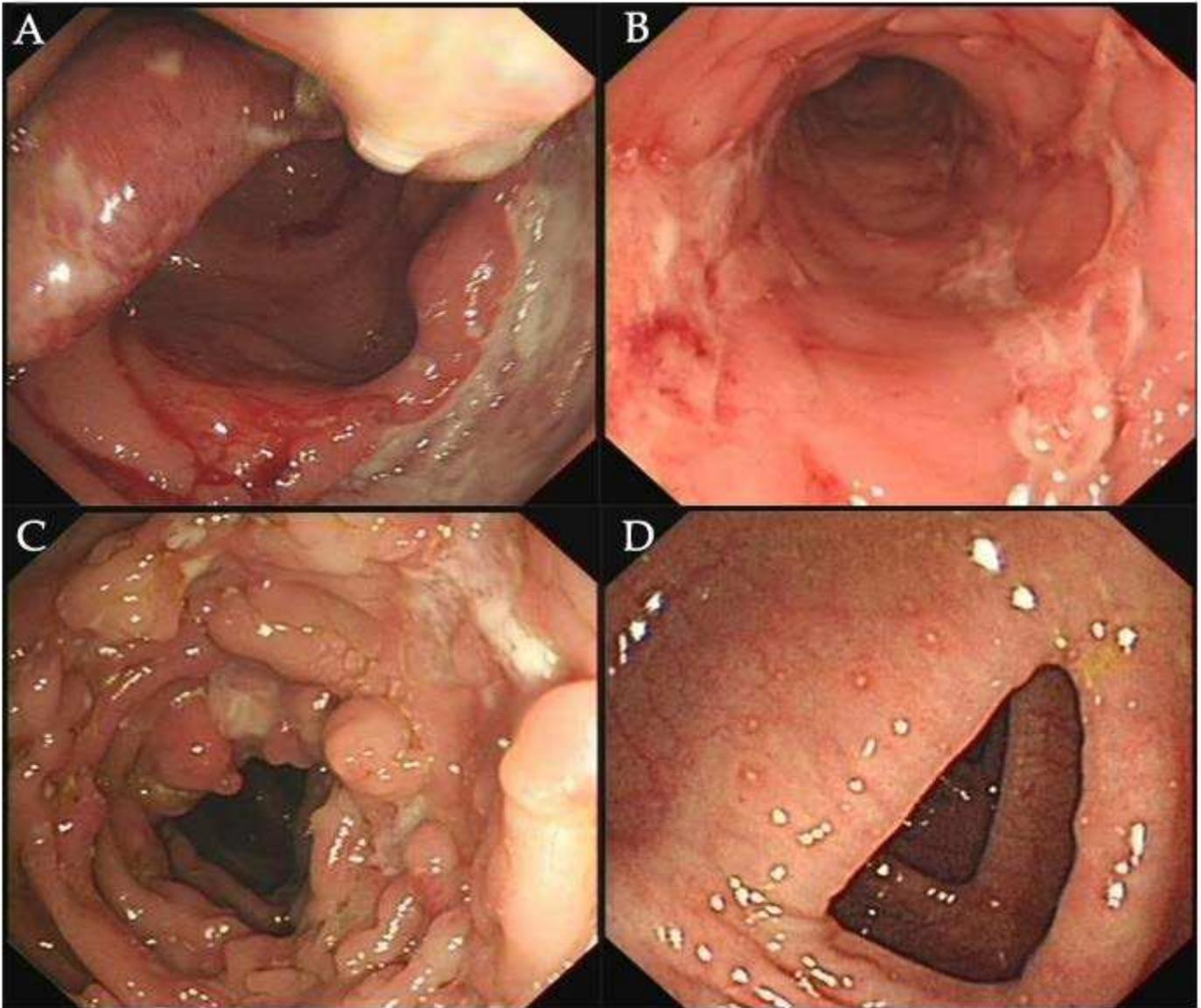


Figure 1

Endoscopy images of A. circular ulcer; B. longitudinal ulcer; C. cobblestone appearance; D. aphthous ulcer.

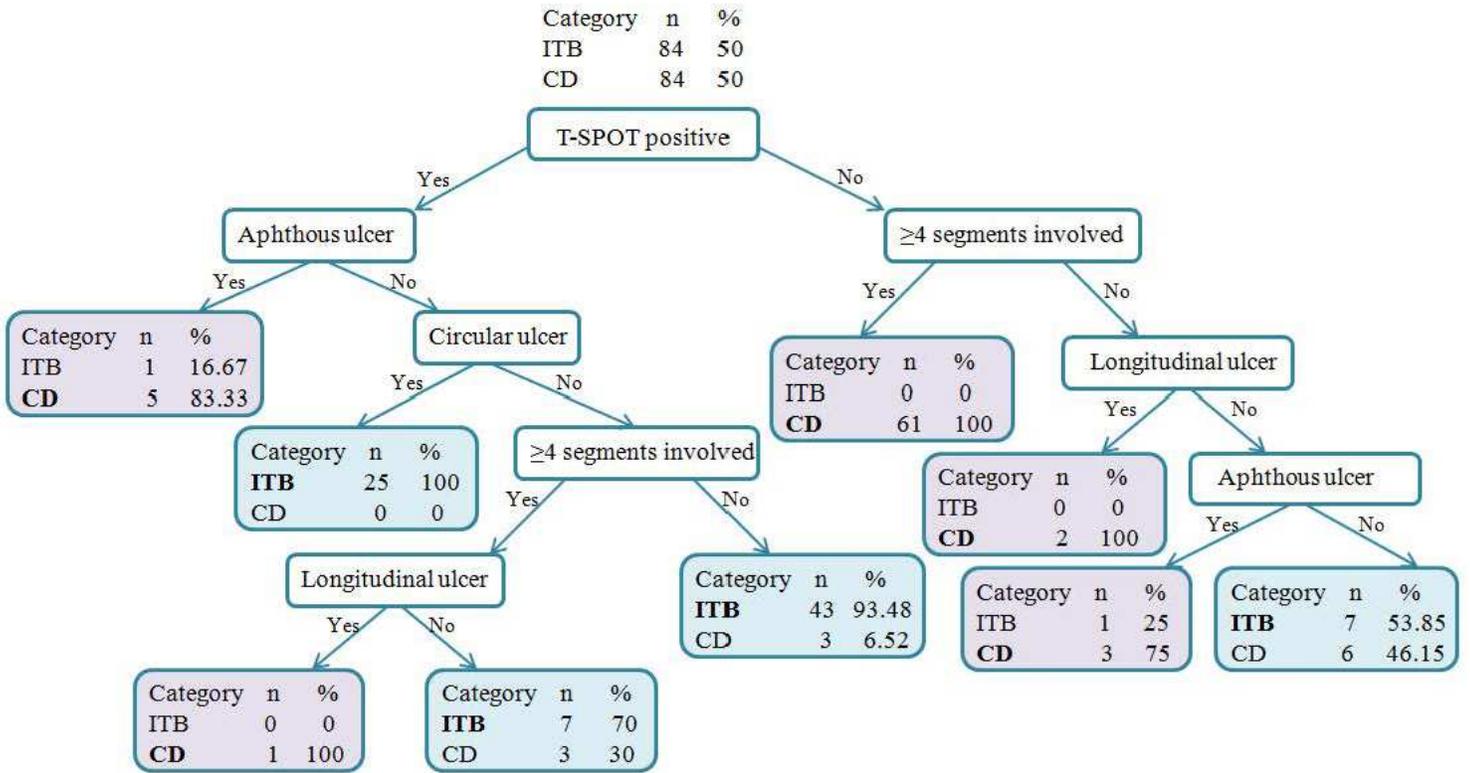


Figure 2

The classification and regression tree (CART) analysis in the training cohort (the purple background stands for diagnosis of CD, and green background stands for diagnosis of ITB). ITB, intestinal tuberculosis; CD, Crohn's disease.