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Intestinal tuberculosis or Crohn's disease: a review of the diagnostic models designed to differentiate between these two gastrointestinal diseases

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Differentiating Crohn's disease (CD) from intestinal tuberculosis (ITB) is a diagnostic dilemma, particularly in regions where ITB is prevalent and CD incidence is increasing, because both diseases can present quite similarly, and diagnostic tests to identify *Mycobacterium tuberculosis* in tissue samples have rather poor sensitivity. Studies that were conducted to determine the factors that differentiate CD from ITB identified some significant characteristics, but none of those characteristics are exclusive to either ITB or CD. Many diagnostic models or scoring systems that use one to several diagnostic parameters have been proposed to help distinguish these two intestinal diseases. Early models consisted of parameters common to routine clinical practice, such as clinical features, and endoscopic and pathologic findings. The later models also include more advanced diagnostic parameters like high-resolution imaging and serological testing. However, the number and types of parameters differ among diagnostic models, and the systems used to calculate scoring also vary from model to model. Enhanced awareness and understanding of the currently available diagnostic models will help physicians determine which model(s) is/are most suitable for differentiating CD from ITB in their clinical practice. **(Intest Res 2021;19:21-32)**

Key Words: Intestinal tuberculosis; Crohn disease; Diagnosis

INTRODUCTION

Differentiating intestinal tuberculosis (ITB) from Crohn's disease (CD) is important, particularly in regions where ITB and CD are not only rarely observed. A definite diagnosis of ITB depends on methods that have unsatisfactorily low sensitivities, including 5.3% to 37.5% for acid-fast bacilli tissue staining,[1-3] 23% to 46% for mycobacterial culture,[4,5] and 36.4% to 67.9% for polymerase chain reaction.[3,4,6-8] As a result, ITB cannot be confidently excluded–even when all of the above results are negative. In response to this diagnostic dilemma, the current Asia-Pacific guidelines recommend 8–12 weeks of empirical antituberculosis treatment (ATT) for patients with diagnostic uncertainty due to the possible onset of potentially fatal complications if immunosuppressive agents are inappropriately prescribed to ITB patients.[9] However, 8–12 weeks of empiric ATT can delay appropriate CD treatment, and this can lead to exacerbation of disease and disease-related complications.[10] Additionally, ATT can cause many side effects, and may facilitate the development of *Mycobacterium tuberculosis* drug resistance. As a consequence of the difficulty distinguishing between these two conditions, many studies have been conducted that aimed to identify factors that could improve our ability to reliably diagnose these 2 gastrointestinal diseases. Those studies did identify some significant characteristics, but none of those characteristics are exclusive to either ITB or CD. Alternatively, those research teams integrated the factors that they identified with established and more recently developed diagnostic parameters to create diagnostic

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models that could increase the accuracy of diagnosis. However, the number and types of parameters differ among diagnostic models, and the systems used to calculate scoring also vary from model to model. The early models included diagnostic parameters routinely available and used in clinical practice, such as clinical features, endoscopic findings, and pathologic findings. The diagnostic models developed later included more advanced diagnostic parameters, such as high-resolution imaging and serological testing. In this review, we set forth to summarize all of the models designed to differentiate ITB from CD that have been published to date. The search strategy was performed in PubMed database with the search term of ("intestinal" AND "tuberculosis") AND ("Crohn" OR "Crohn's disease"). Only articles reporting a model or a systematic score for differentiating between CD and ITB were included. Fifteen models or scoring systems were identified. The models are classified into the 5 following groups: (1) models that integrate clinical and endoscopy; (2) models that integrate clinical, endoscopy, and pathology; (3) models that integrate clinical, endoscopy, pathology, and imaging; (4) models that integrate clinical, endoscopy, pathology, imaging, and laboratory; and (5) a model that includes adjustable integrated variables. Improved awareness and understanding of the currently available diagnostic models for differentiating CD and ITB may improve diagnosis, treatment, and outcomes.

MODELS INTEGRATING CLINICAL AND ENDOSCOPY

In 1972, Tandon and Prakash[11] reported the pathology of ITB and its distinction from CD based on 169 cases (10 CD and 159 ITB) who presented with intestinal obstruction and who underwent intestinal resection. They observed that ITB rarely involved the anus, the length of strictures was generally less than 3 cm, and the ulcers were usually circumferential and generally traveled in transverse axis. In contrast, CD commonly involved the anus, had long segmental stricture, and the ulcers were more prominent along mesenteric attachment and traveled in longitudinal axis. After endoscopy was introduced into routine clinical practice, similar characteristics were reported in endoscopic findings.[12,13]

In 2006, Lee et al.[14] proposed the first scoring system based on colonoscopic findings (Table 1).[6,14-17] This system was developed based on data from 44 CD and 44 ITB patients. Lee's system includes 8 endoscopic findings, four of which favor CD, including longitudinal ulcers, aphthous ulcers, cobblestone appearance, and anorectal involvement. The other 4 favor ITB, including transverse ulcers, scars or pseudopolyps, a patulous ileocecal valve, and involvement of less than 4 of 6 segments of the colon, including the ileocecum, ascending colon, transverse colon, descending colon, sigmoid colon, and anorectum. Each finding favoring CD is given a score of +1, and each finding favoring ITB is given a score of –1. The final score represents the summation of all findings. A diagnosis of CD will be made if the final score is a positive value, whereas ITB will be diagnosed if the final score is negative. If the final score is zero, the diagnosis is indeterminate. This scoring system was used to evaluate their 88 patients, and they were able to achieve a correct diagnosis in 77 patients (87.5%). Regarding the remaining patients, 7 (8%) were misdiagnosed, and 4 (4.5%) had a score of zero (indeterminate diagnosis). There was no validation cohort in that study. A 2015 study by Mao et al.[18] reported the accuracy of this endoscopic model to be 66.7%.

Some clinical manifestations were also observed to be different between CD and ITB.[1,4,19,20] Two diagnostic models based on the integration of clinical and endoscopic findings were developed, both used logistic regression to identify significant parameters, and both constructed their models using a logistic regression equation. Those two models are described as follows.

In 2011, Li et al.[15] conducted a retrospective study in 130 CD and 122 ITB patients. Multivariate analysis revealed 6 significant clinical parameters, and 6 significant endoscopic parameters as shown in Table 1. They then constructed 2 logistic regression models–one based on clinical parameters, and the other based on endoscopic parameters. The mathematical equation for the clinical model is $P = 1/(1+e^{-[0.708+1.409*\text{hematochezia}+2.798*\text{surgery history}+2.713*\text{perianal disease}-4.728*\text{pulmonary tuberculosis}-2.066*\text{ascites}-2.414*\text{PPD skin test}]})$, and the one for the endoscopic model is $P = 1/(1+e^{-[0.283+1.499*\text{rectal involved}+1.753*\text{longitudinal ulcers}+2.787*\text{cobblestone sign}-1.432*\text{ileocecal valve involved}-2.379*\text{transverse ulcers}-3.343*\text{rodent-like ulcers}]})$. For the clinical model, a diagnosis cutoff of 0.327 was obtained with a sensitivity, specificity, and accuracy of 90.3%, 76.8%, and 83.8%, respectively. For the endoscopic model, a diagnosis cutoff of 0.534 was obtained with a sensitivity, specificity, and accuracy of 82.9%, 82.0%, and 82.5%, respectively. There was no validation cohort in that study.

In 2017, Jung et al.[17] performed a retrospective study in 158 CD and 98 ITB patients. They divided their patients equally into development and validation sets. For model development, clinical, endoscopic, and pathologic parameters were

Table 1. Models That Integrate Only Endoscopic Findings or Combination of Clinical, Endoscopic, and Pathologic Findings

Author (year)	Country	Study design	Model type	Parameters	Model detail	Performance
Lee et al. (2006)[14]	Korea	Prospective, CD 44, ITB 44	Scoring system	8 Endoscopic findings	Favor CD (+1/each): longitudinal ulcer, aphthous ulcer, cobblestone appearance, anorectal involvement Favor ITB (-1/each): transverse ulcer, scars or pseudopolyps, patulous ileocecal valve, involvement < 4 segments Final score: 1–4: CD 0: indeterminate −1 to -4: ITB	Correct diagnosis: 87.5% Incorrect diagnosis: 8% Indeterminate: 4.5%
Makharia et al. (2010)[6]	India	Prospective, CD 53, ITB 53 for training; CD 20, ITB 20 for validation	LR model	4 Findings (2 clinical, 1 endoscopic, and 1 pathologic)	+2.3 × weight loss −2.1 × blood in stool −2.5 × sigmoid colon involvement −2.1 × focally-enhanced colitis +7	AUROC Training: 0.906 Validation: 0.893
Li et al. (2011)[15]	China	Retrospective, CD 130, ITB 122	LR model	6 Clinical and 6 endoscopic findings	Clinical score: Hematochezia History of surgery Perianal disease Pulmonary TB Ascites PPD skin test Endoscopy score: Rectum Longitudinal ulcer Cobblestone appearance IC valve involve Transverse ulcer Rodent-like ulcer	Clinical: Sen. 90% Spec. 77% Acc. 84% Endoscopy: Sen. 83% Spec. 82% Acc. 83%
Yu et al. (2012)[16]	China	Retrospective, CD 53, ITB 43	LR model	3 Findings (1 clinical, 1 endoscopic, and 1 pathologic)	−2.0 × night sweat +3.6 × longitudinal ulcer −3.8 × granuloma	AUROC: 0.864
Jung et al. (2016)[17]	Korea	Retrospective, CD 79, ITB 49 for training; CD 79, ITB 49 for validation	LR model	7 Findings (4 clinical and 3 endoscopic)	Age Female sex Diarrhea Ring-shaped ulcer Longitudinal ulcer Sigmoid colon involvement Suspected pulmonary TB	AUROC Training: 0.979 Validation: 0.978

CD, Crohn's disease; ITB, intestinal tuberculosis; LR, logistic regression; AUROC, area under receiver operating characteristic curve; TB, tuberculosis; PPD, purified protein derivative; IC, ileocecal; Sen., sensitivity; Spec., specificity; Acc., accuracy.

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included in univariate analysis, and a receiver operating characteristic (ROC) curve was calculated for each parameter. The factors with an area under the ROC curve (AUROC) of at least 0.7 were selected for inclusion in their model. Five parameters including age, diarrhea, ring-shaped ulcer, longitudinal ulcer, and sigmoid involvement, were identified and included. Two factors with an AUROC curve close to 0.7 (suspicious radiological pulmonary tuberculosis and gender) were also included, because comparative analysis revealed that the 7-factor model yielded greater diagnostic accuracy than the 5-factor model. The formula for that model is shown, as follows:

$1/(1+e^{-[-4.423+0.037*age+2.226*sex-2.203*diarrhea+2.345*tran\_ring-1.911*longitudinal-2.123*sigmoid+5.606*pul\_tbc]})$.

In the validation set, the sensitivity, specificity, positive predictive value, and negative predictive value at a cutoff level of 0.35 was reported to be 98.0%, 92.4%, 88.9%, and 98.6%, respectively.

The models integrating clinical and endoscopy are summarized in Table 1.

MODELS INTEGRATING CLINICAL, ENDOSCOPY, AND PATHOLOGY

Pulimood et al.[21] reported significant pathologic findings that could differentiate ITB from CD, including microgranuloma and focally-enhanced colitis, which favored a diagnosis of CD, whereas multiple large and confluent granuloma, ulcers lined by conglomerate epithelioid histiocytes, and disproportionate submucosal inflammation favored ITB.

In 2010, Makharia et al.[6] conducted a prospective study in 53 CD and 53 ITB patients. Clinical manifestations, endoscopic findings, and pathologic findings were included in univariate analysis. Of the parameters in included in subsequent multivariate analysis, 4 significant parameters were identified. Of those, blood in stool, sigmoid colon involvement, and focally-enhanced colitis favored CD, and weight loss favored a diagnosis of ITB. The formula for that model is shown, as follows:

score = 2.3*weight loss–2.1*blood in stool–2.5*involvement of sigmoid colon–2.1*focally enhanced colitis+7

A higher score predicted a greater likelihood of ITB. The AUROC value was 0.906 for differentiating CD from ITB in the training cohort. They validated their system in another 20 CD and 20 ITB patients and obtained an AUROC value of 0.893. At a cutoff value of 5.1, the sensitivity and specificity in the validation model was 90% and 60%, respectively.

A 2012 retrospective study by Yu et al.[16] included 53 CD and 43 ITB patients. Multivariable logistic regression analysis revealed night sweats (odds ratio [OR], 0.1; 95% confidence interval [CI], 0.02–0.1), longitudinal ulcers (OR, 35.5; 95% CI, 1.8–683.2), and granulomas (OR, 0.02; 95% CI, 0.002–0.2) to be significant predictors for differentiating CD from ITB. The model integrating these 3 factors had an AUROC value of 0.8642 (95% CI, 0.79–0.94), and the formula for that model is shown, as follows:

score = –2.0*night sweat+3.6*longitudinal ulcers–3.8*granuloma

A higher score predicts a greater likelihood of CD. At a cutoff value of –3.30, the sensitivity, specificity, and the ability to identify the two diseases correctly was 67.4%, 92.5%, and 79.9%, respectively. There was no validation cohort in that study.

The models integrating clinical, endoscopy, and pathology are summarized in Table 1.

MODELS INTEGRATING CLINICAL, ENDOSCOPY, PATHOLOGY, AND CTE

Cross-sectional imaging is being increasingly used as a diagnostic tool. In 1998, Makanjuola[22] was the first to report findings that differentiate ITB from CD on conventional CT of the abdomen in 9 CD and 18 ITB. Regarding bowel wall changes, concentric bowel wall thickening of equal to or greater than 6 mm and mural stratification were found in CD, while concentric bowel wall thickening less than 6 mm and asymmetrical bowel wall thickening were more often observed in ITB. Mesenteric fibrofatty change and the comb sign were found only in CD, whereas lymphadenopathy larger than 1 cm and lymph node (LN) with central necrosis were identified only in ITB. Parietal thickening and ascites were found only in ITB.

More recently, a computed tomography enterography (CTE) technique was introduced to better examine bowel wall changes. In 2013, Park and Lim[23] reported the findings of CTE in 64 CD and 17 ITB. They found that segmental involvement (6–40 cm), moderate wall thickening (5–9 mm), asymmetrical distribution, fibrofatty change, and comb sign were significantly more often observed in CD. Among those findings, comb sign had the best performance with a sensitivity, specificity, and accuracy in diagnosis of CD of 74.1%, 90.9%, and 76.9%, respectively.

In 2014, Zhao et al.[24] performed a retrospective study in 141 CD and 47 ITB using logistic regression method to establish 2 models based on the integration of clinical manifestations and

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CTE. The clinical model included hematochezia, perianal disease, positive purified protein derivative (PPD) test, ascites, pulmonary tuberculosis, and night sweats. The mathematical equation for that model is $P = 1/(1+e^{-[1.738+1.401*\text{hematochezia}+3.746*\text{perianal disease}-4.746*\text{positive PPD test}-2.022*\text{ascites}-1.867*\text{pulmonary TB}-3.204*\text{night sweat}]})$. The AUROC value for this model was 0.916. At a diagnostic threshold of 0.806, the sensitivity, specificity, and accuracy was 94.3%, 80.4%, and 91%, respectively.

The CTE model included left colon involvement, asymmetrical pattern of involvement, abscess, comb sign, LN distribution along the right colic artery, contracture of ileocecal valve, fixed patulous ileocecal valve, and LN with central necrosis. The mathematical equation for that model is $P = 1/(1+e^{-[-1.525+2.901*\text{left colon involvement}+3.925*\text{asymmetrical pattern of involvement}+3.441*\text{abscess}+4.539*\text{comb sign}-2.825*\text{LN distribution along right colic artery}-5.367*\text{contracture of ileocecal valve}-4.264*\text{fixed patulous ileocecal valve}-5.059*\text{LN with central necrosis}]})$. The AUROC value for this model was 0.986. At a diagnostic threshold of 0.682, the sensitivity, specificity, and accuracy was 96.5%, 93.6%, and 95.7%, respectively. There was no validation cohort in that study.

In 2015, Mao et al.[18] conducted a prospective study in 105 consecutive patients (67 CD and 38 ITB) who underwent CTE and colonoscopy. Multivariate analysis showed segmental small bowel involvement (OR, 0.104; 95% CI, 0.022–0.50) and comb sign (OR, 0.02; 95% CI, 0.003–0.26) to be independent predictors of CD. No significant findings favoring ITB were identified in multivariate analysis. They then added segmental small bowel involvement and comb sign to the endoscopic model by Lee et al.[14] When the endoscopic score of the Lee et al. model is a positive value, a diagnosis of CD will be made regardless of CTE findings. However, when the endoscopic score is zero or less, the CTE findings will be included and evaluated. If there is presence of either segmental small bowel involvement or the comb sign, the diagnosis will be changed to CD. Using this algorithm, the accuracy of diagnosis significantly increased from 66.7% (70/105) to 95.2% (100/105) in the development cohort. They then validated their algorithm in 60 new patients (40 CD and 20 ITB), which showed that the additional CTE findings improved the accuracy of diagnosis from 71.6% when based on the endoscopic score alone to 88.3% when incorporating CTE findings ($P<0.001$). Although these results look promising, the limitation of this algorithm is its low specificity. The reported specificity in the validation cohort was only 80%, which means that a significant number of patients with ITB would have been misdiagnosed as CD, and that they would have inappropriately been prescribed immunosuppressive agents.

In 2015, Zhang et al.[25] performed a prospective study in 92 CD and 31 ITB patients. The model used logistic regression equation based on 6 parameters which were statistically significant in multivariate analysis. The mathematical equation for the model is $P = 1/(1+ e^{-[-1.279+4.814*\text{perianal disease}-5.151*\text{transverse colon}-3.662*\text{rodent-like ulcer}+5.399*\text{skip lesion}-3.897*\text{fixed patulous IC valve}+4.477*\text{comb sign}]})$. The AUROC value for this model was 0.994. At a diagnostic threshold of 0.508, the sensitivity, specificity, and accuracy was 97.8%, 96.8%, and 97.6%, respectively. There was no validation cohort in this study.

In 2015, Kedia et al.[26] performed a retrospective study in 44 CD and 50 ITB patients who underwent CT enteroclysis/CTE/CT abdomen before starting treatment. Multivariate analysis revealed ileocecal involvement, long segment involvement, and presence of LN ≥1 cm to be statistically significant factors. The score created based on these findings was calculated using the following formula:

Risk score = long-segment involvement+(1–ileocecal region involvement)+(1–lymph nodes ≥1 cm)

Scoring for this system ranges from 0 to 3, and a higher score predicted a greater likelihood of CD. When the score was extremely high or low, its specificity was good. More specifically, if the score was 3, the specificity for diagnosis of CD was 90%, and if the score was 0, the specificity for diagnosis of ITB was 100%. However, the sensitivity was poor, as evidenced by the 37% sensitivity for diagnosis of CD when the score was 3, and the 14% sensitivity for diagnosis of ITB when the score was 0. Furthermore, the performance of score values of 1 or 2 was found to be unsatisfactory. The sensitivity and specificity for diagnosis of CD when the score was 2 was only 32% and 50%, respectively. The corresponding values for diagnosis of ITB when the score was 1 was 44% and 87%, respectively. Although the results of this model demonstrate limitations, the results supported that CTE should play some role in differentiating ITB from CD.

The same research group then conducted another study in CTE findings in 2017. That study found visceral fat (VF) quantification to be a significant surrogate marker for differentiating CD from ITB.[27] They observed that the VF area and the VF/subcutaneous fat (SC) ratio were both significantly higher in CD patients than in ITB patients. A cutoff of 0.63 for the VF/SC ratio had a high sensitivity (81%) and specificity (78%) for differentiating CD from ITB in the validation cohort. In 2018, that group proposed a new risk score based on CTE findings of VF/SC ratio >0.63 and long segment involvement ≥3 cm.[27]

The risk score is defined as follows: VF/SC ratio >0.63+long segment involvement (≥3 cm), where VF/SC ratio >0.63 = 1 and presence of long segment involvement is = 1. In their algorithm, patients with necrotic lymph node was diagnosed as ITB regardless of their risk score results. The risk score then was applied to the remaining patients. Among the remaining patients with a score of 2, a diagnosis of CD was made correctly with 50% sensitivity and 100% specificity in the validation cohort. Using this algorithm, 43% of patients (55/128) could obtain a correct diagnosis based on CT alone.

The models integrating clinical, endoscopy, pathology, and CTE are summarized in Table 2.[18,24-26,28]

MODELS INTEGRATING CLINICAL, ENDOSCOPY, PATHOLOGY, IMAGING, AND LABORATORY

The anti-*Saccharomyces cerevisiae* antibody (ASCA) has been recognized as a specific serologic marker of CD. ASCA was reported to be positive in about 50% of CD patients.[29] However, the results of studies using ASCA for differentiating ITB from CD are conflicting.[30-32] More recently, interferon-gamma release assay (IGRA), which has been available for several years for the diagnosis of latent tuberculosis, has been increasingly used for differentiating ITB from CD. IGRA detects a cell-mediated immune response by measuring *in vitro* interferon-γ production in response to stimulation by antigens derived from *M. tuberculosis*. Many studies have reported its utility in differentiating ITB from CD in Asians, including a meta-analysis that was conducted in 2014.[33]

In 2015, Huang et al.[34] performed a prospective study in 25 CD and 40 ITB patients. They found 16 parameters that were significantly different between CD and ITB in univariate analysis. Of those, 12 parameters with a high specificity (7 favored CD, 5 favored ITB) were selected for the development of a scoring system. Each parameter that favors CD is given a score of +1, including longitudinal ulcers, nodular hyperplasia, cobblestone appearance, intestinal diseases, intestinal fistulas, target sign, and comb sign. Each parameter that favors ITB is given a score of –1, including night sweats, positive PPD tests, positive T-SPORT.TB (a type of ELISpot assay that is used for tuberculosis diagnosis that belongs to the group of IGRA), ring ulcers, and ulcer scars. The final score represents the summation of all findings. The obtained AUROC value was 0.997, and at a cutoff of –0.5, the diagnostic sensitivity, specificity, and accuracy was 100%, 95%, and 97%, respectively. Although the score performed very well, the sample size was small and there was no validation cohort in that study.

In 2017, Bae et al.[35] conducted a prospective study that integrated imaging findings and serology into the previous endoscopic scoring system by Lee et al. There were 40 CD and 40 ITB patients in the development cohort. In addition to colonoscopy, all patients underwent the following investigations: ESR, ASCA IgA and IgG, QuantiFERON-TB Gold In-Tube Test (QFT-G; QIAGEN, Hilden, Germany), chest X-ray, and small bowel follow through. All evaluated parameters were compared between CD and ITB patients. Multivariate analysis revealed positive ASCA IgA and/or IgG and proximal intestine involvement (small intestine at least 20 cm proximal to ileocecal valve) to be independent predictors of CD, and positive QFT-G and typical pulmonary tuberculosis findings to be factors independently associated with ITB. They then integrated these significant parameters into their new model, as shown in Table 3.[34-38] When the cutoff score was set at 0 or above, the accuracy of the score for diagnosis of CD was 96.3%, with a sensitivity of 95% and a specificity of 97.5%. The performance of their new model reflected improvement over the model that included only endoscopy. They then validated the model in an additional 37 patients (14 CD and 23 ITB). The AUROC value when the model was applied in the validation group was 0.981.

In 2018, Wu et al.[36] performed a prospective study in 239 patients (153 CD and 86 ITB). They randomly divided their study patients into the training set (70%) and the validation set (30%). Five parameters were significant in multivariable analysis, including perianal disease, pulmonary involvement, longitudinal ulcer, left colon involvement, and the TB-specific Ag (TBAg)/phytohaemagglutinin (PHA) ratio in T-SPOT.TB. Those 5 parameters were then included in their predictive model that was developed based on logistic regression analysis. The mathematical equation for that model is shown, as follows:

$$P = 1/(1+e^{-[-1.950-2.372*\text{perianal disease}+2.746*\text{pulmonary involvement}-3.284*\text{longitudinal ulcer}-1.738*\text{left colon}+7.477*\text{TBAg/PHA ratio}]})$$

When that model was applied to the validation cohort, the AUROC value was 0.95. At a cutoff value of 0.29, the sensitivity, specificity, and accuracy was 88.5%, 93.5%, and 91.7%, respectively.

A 2019 prospective study by He et al.[37] included 310 consecutive patients (219 CD and 91 ITB). Of those, 212 patients (143 CD and 69 ITB) were included in the derivation cohort. A prediction model was then developed using a 2-step approach. In the first step, potentially informative variables were identified and ranked based on random forest analysis. The

Table 2. Models that Use Only CTE or Integrate CTE to Clinical and Endoscopic Findings

Author (year)	Country	Study design	Model type	Parameters	Model detail	Performance
Zhao et al. (2014)[24]	China	Retrospective, CD 141, ITB 47	LR model	6 Clinical and 8 CTE findings	Clinical model: Hematochezia Perianal disease PPD test Ascites Pulmonary TB Night sweats CTE model: Left colon Asymmetrical wall Abscess Comb sign LN along right colic artery Contracted IC Fixed patulous IC LN with necrosis	AUROC Clinical model: 0.916 CTE model: 0.986
Mao et al. (2015)[18]	China	Prospective, consecutive 67 CD, 38 ITB for training; 40 CD, 20 ITB for validation	Algorithm (combined with Lee's endoscopic score)	2 CTE findings and 8 endoscopic findings	Presence of comb sign and/or segmental small bowel lesion	Increased accuracy of endoscopic score alone 71.6% to 88.3%
Zhang et al. (2015)[25]	China	Prospective, CD 92, ITB 31	LR model	1 Clinical, 2 endoscopic, and 3 CTE findings	Perianal disease Transverse ulcer Rodent-like ulcer Skip lesion (CTE) Fixed patulous IC (CTE) Comb sign (CTE)	AUROC 0.994
Kedia et al. (2015)[26]	India	Retrospective, CD 54, ITB 50	Scoring system	3 CT/CTE findings	Long segment involvement + (1–ileocecal region involvement) + (1–LN ≥ 1 cm)	Risk score for CD 3: Sen. 37%, Spec. 90% Risk score for ITB 0: Sen. 14%, Spec. 100%
Kedia et al. (2018)[28]	India	Retrospective, 32 CD, 27 ITB for training; 38 CD, 31 ITB for validation	Scoring system	2 CT/CTE findings	VF/SC ratio >0.63 + long segment involvement	Validation set: Risk score for CD 2: Sen. 50%, Spec. 97% Risk score for ITB 0: Sen. 61%, Spec. 84%

CTE, computed tomography enterography; CD, Crohn's disease; ITB, intestinal tuberculosis; LR, logistic regression; PPD, purified protein derivative; TB, tuberculosis; LN, lymph node; IC, ileocecal valve; AUROC, area under receiver operating characteristic curve; Sen., sensitivity; Spec., specificity; VF/SC ratio, visceral fat to subcutaneous fat ratio.

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Table 3. Models That Integrate Clinical, Endoscopic, Pathologic, Imaging, and Laboratory Findings

Author (year)	Country	Study design	Model type	Parameters	Model detail		Performance
Huang et al. (2015)[34]	China	Prospective, CD 25, ITB 40	Scoring system	12 Findings (2 clinical, 5 endoscopic, 4 CTE, and 1 IGRA)	Favor CD (+1) Longitudinal ulcer Nodular hyperplasia Cobblestone appearance Intestinal diseases Intestinal fistulas Target sign Comb sign	Favor ITB (−1) Night sweats Positive PPD test Positive T-SPOT.TB Ring-shaped ulcer Ulcer scars	AUROC: 0.997
Bae et al. (2017)[35]	Korea	Prospective, CD 40, ITB 40 for training; CD 14, ITB 23 for validation	Scoring system	8 Endoscopic findings, 2 Images (CXR, SBFT), and 2 laboratory tests (ASCA, IGRA)	Endoscopic score (8 findings) (+)→1, 0→0, (−)→(−1)	Lab-Radio score Favor CD (+1) Proximal SB (SBFT) ASCA Favor ITB (−1) Pulmonary TB (CXR) IGRA (+)→1, 0→0, (−)→(−1)	AUROC Training: 0.990 Validation: 0.981
					Summation: (−2, −1)→ITB, (0, 1, 2)→CD		
Wu et al. (2018)[36]	China	Prospective, CD 107, ITB 60 for training; CD 46, ITB 26 for validation	LR model	5 Findings (2 clinical, 2 endoscopic, and 1 IGRA)	Perianal disease Longitudinal ulcer Left colon Pulmonary TB TB-specific Ag to phytohaemagglutinin		AUROC Training: 0.975 Validation: 0.950
He et al. (2019)[37]	China	Prospective, CD 143, ITB 69 for training; CD 76, ITB 22 for validation	Step1: select variable from a random forest regression model Step 2: LR model	2 Models 8 Findings (1 clinical, 2 endoscopic, 3 CTE, and 2 IGRA/PPD)	Model 1 Age Rectal involvement Transverse ulcer Skip involvement of small bowel Comb sign IGRA Model 2 Age Rectal involvement Transverse ulcer Skip involvement of small bowel Target sign PPD		AUROC Training: 0.977 Validation (cutoff $P=0.5$) Sen. 86.8% Spec. 90.9% Acc. 87.8% AUROC Training: 0.930 Validation (cutoff $P=0.5$) Sen. 84.2% Spec. 100% Acc. 87.8%
Limsrivilai et al. (2017)[38]		Meta-analysis Validation cohort 29 CD, 22 ITB	Step 1: select significant variables with low heterogeneity based on meta-analytic results Step 2: integrate the variables into Bayesian model	9 Clinical, 8 endoscopic, 5 pathologic, 5 CTE, and 1 IGRA (can select only available parameters)	bit.ly/ITBvsCD		AUROC Clinical+endoscopy: 0.920 Clinical+endoscopy+ pathological findings: 0.943

CD, Crohn's disease; ITB, intestinal tuberculosis; CTE, computed tomography enterography; IGRA, interferon-gamma release assay; PPD, purified protein derivative; T-SPOT.TB, a type of ELISpot assay that is used for tuberculosis diagnosis that belongs to the group of IGRAs; AUROC, area under receiver operating characteristic curve; CXR, chest X-ray; SB, small bowel; SBFT, small bowel follow through; ASCA, anti-*Saccharomyces cerevisiae* antibody; LR, logistic regression; TB, tuberculosis; Sen., sensitivity; Spec., specificity; Acc., accuracy.

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most informative variables were then selected to build the model. Eight variables, including age, rectal involvement, transverse ulcer, skip involvement of the small bowel, target sign on CTE, comb sign on CTE, IGRAs, and PPD test, were selected. For the second step, the selected variables were incorporated into the model using a logistic regression equation. Two models were built. Each shared the same 4 parameters, including age, rectal involvement, transverse ulcer, and skip involvement of the small bowel. The other two variables in model 1 were comb sign and IGRA, and the other two variables in model 2 were target sign and PPD. Nomograms calculating CD probability based on the results of logistic regression were constructed for ease of use. Both models were validated in the other 98 consecutive patients (76 CD and 22 ITB). At a cutoff point of $P=0.5$, the sensitivity, specificity, and accuracy of model 1 was 86.8%, 90.9%, and 87.8%, respectively; and the corresponding values for model 2 were 84.2%, 100%, and 87.8%, respectively.

The models integrating clinical, endoscopy, pathology, imaging, and laboratory tests are summarized in Table 3.

MODEL WITH ADJUSTABLE INTEGRATED VARIABLES

In 2017, Limsrivilai et al.[38] developed a model based on the results of a meta-analysis. Studies that were conducted to differentiate CD from ITB from inception to September 2015 were included. Fifty-five variables that were mentioned in at least 3 studies were selected for meta-analysis. Random effects model was used to determine the significance of each variable. Significant dichotomous variables with low-to-moderate heterogeneity defined by an I^2 value less than 50% were selected for development of the model. The model calculated the probability of ITB based on the relative prevalence of ITB versus CD (the pretest probability of ITB, P_0) and the likelihood ratio (LR) for ITB of each predictor variable in the model. The formula that was developed is shown, as follows: $P' = (P_0 * LR)/([1 - P_0] + [P_0 * LR])$. Using this model, ITB probability can be calculated using only available variables. For any parameters with no available results, the model defaults to an LR of 1 for that parameter, which results in that parameter having no effect on the calculated ITB probability. For example, users can calculate ITB probability with only clinical variables, only endoscopic variables, or a combination of clinical and endoscopic variables. The model was validated in 49 patients (27 CD and 22 ITB). The AUROC value for this model, including clinical and endoscopic variables, was 0.920, and the AUROC value increased to 0.943 when pathologic data was added. However, this model has some limitations. First, it does not include continuous variables. So, potential variables like age and duration of symptoms cannot be included. Second, the relative prevalence of ITB and CD needs to be input into the model. Third, some parts of the model, such as CTE variables, were based on the results of a small number of studies. Fourth and last, since the model included only studies published before September 2015, new variables, such as VF/SC ratio, were not included.

A summary of this model is shown in Table 3.

Which model should be used? Model selection should be made after considering the following factors: (1) model performance and validation; (2) availability of data to satisfy the parameters included in the model; or (3) ease of use and thorough understanding of the model.

Surprisingly, no studies have yet been conducted to externally validate any of the models, and there have been no studies that have compared the different models in the same study cohort. All models were reported to have an AUROC value greater than 0.85. However, only the models by Makharia et al.,[6] Jung et al.,[17] Mao et al.,[18] Kedia et al.,[28] Bae et al.,[35] Wu et al.,[36] He et al.,[37] and Limsrivilai et al.[38] were tested in validation cohorts in their original studies. Among those models, the models by Makharia et al.,[6] Mao et al.,[18] Bae et al.,[35] Wu et al.,[36] and He et al.[37] were developed and validated based on prospective data.

Model-specific data availability is important. The models that include only clinical and endoscopic findings are the most feasible for use in limited-resource settings, and all gastroenterologists can use these models. This group includes the endoscopic model by Lee et al.,[14] and the models by Li et al.,[15] Jung et al.,[17] and Limsrivilai et al.[38] Even pathologic findings, which are normally routinely obtained, may not be available in all settings due to the lack of GI pathologists in many areas. CTE and serological tests are somewhat beneficial, but one or both are not available in many regions, and these investigations can increase cost of diagnosis. Therefore, in settings where patients have unequal access to diagnostic investigations, the adjustable model developed by Limsrivilai et al. may be most suitable.

Ease of use is an essential characteristic of any model that needs to be used in routine clinical practice. Many research groups developed and proposed models based on logistic regression calculation.[6,15-17,24,37] Even though the formula can be created and calculated using Microsoft Excel (Microsoft Corp.,

Redmond, WA, USA), they are still potentially and prohibitively complicated, particularly for general physicians who do not perform research and who are unfamiliar with logistic regression. Models based on simple calculations are easier to use than those that use logistic regression analysis.[14,27,29] The models by Mao et al.[18] and Bae et al.[35] give a simple score for each finding and integrate the parameters in a diagnostic algorithm. Although they use complicated formulas and they include many variables, the models by He et al.[37] and Limsrivilai et al.[38] were designed for easy use by clinicians. He et al. designed nomograms to calculate the probability of CD, and Limsrivilai et al. designed a website that physicians can use to input data by dropdown menu for each parameter to calculate the probability of ITB. That website can be accessed at bit.ly/ITBvsCD.

CONCLUSION

Many models have been proposed to differentiate ITB from CD to help decrease the rate of incorrect empirical therapy. The currently available diagnostic models increase the probability of correct diagnosis, appropriate treatment, and improved patient outcomes. Physicians can choose the model that is most appropriate for their use while taking into consideration model performance, availability of parameter data, and ease of use. However–although improvement has been made, none of the currently available models is able to reliably and conclusively able to differentiate CD from ITB. Continued research is, therefore, required. Furthermore and interestingly, none of the models have been validated externally and compared with the other models. External validation and comparison of performance among models in the same cohort is, therefore, warranted.

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