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Development and validation of multiparametric models based on computed tomography enterography to determine endoscopic activity and surgical risk in patients with Crohn's disease: A multi-center study

Ruiqing Liu [a,1], Shunli Liu [b,1], Li Yi [c], Dongsheng Wang [a], Xiaoming Zhou [b], Wang Zhiming [c], Keyu Ren [d], Jia Ke [e], Weiming Zhu [c], Yun Lu [a,*]

[a] Department of Gastrointestinal Surgery, The Affiliated Hospital of Qingdao University, 16 Jiangsu Road, Qingdao, Shandong, China
[b] Department of Radiology, The Affiliated Hospital of Qingdao University Qingdao, 16 Jiangsu Road, Qingdao, Shandong, China
[c] Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, 210002, Jiangsu Province, China
[d] Department of Gastroenterology, The Affiliated Hospital of Qingdao University, Qingdao, China
[e] Department of Colorectal Surgery, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, 510655, Guangdong, China

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ABSTRACT

Objective: To develop novel multiparametric models based on computed tomography enterography (CTE) scores to identify endoscopic activity and surgical risk in patients with Crohn's disease (CD).

Methods: We analyzed 171 patients from 3 hospitals. Correlations between CTE outcomes and endoscopic scores were assessed using Spearman's rank correlation analysis. Predictive models for moderate to severe CD were developed, and receiver operating characteristic (ROC) curves were constructed to determine the area under the ROC curve (AUC). A combined nomogram based on CTE scores and clinical variables was also developed for predicting moderate to severe CD and surgery.

Results: CTE scores were significantly correlated with endoscopy scores at the segment level. The global CTE score was an independent predictor of severe (HR = 1.231, 95% CI: 1.048–1.446, p = 0.012) and moderate-to-severe Simplified Endoscopic Scores for Crohn's Disease (SES-CD) (HR = 1.202, 95% CI: 1.090–1.325, p < 0.001). The nomogram integrating CTE and clinical data predicted moderate to severe SES-CD and severe SES-CD scores in the validation cohort with AUCs of 0.837 and 0.807, respectively. The CTE score (HR = 1.18; 95% CI: 1.103–1.262; p = 0.001) and SES-CD score (HR = 3.125, 95% CI: 1.542–6.33; p = 0.001) were independent prognostic factors for surgery-free survival. A prognostic nomogram incorporating CTE scores, SES-CD and C-reactive protein (CRP) accurately predicted the risk of surgery in patients with CD.

Conclusion: The newly developed CTE score and multiparametric models displayed high accuracy in predicting moderate to severe CD and surgical risk for CD patients.

* Corresponding author.
E-mail address: luyun@qdu.edu.cn (Y. Lu).
[1] These two authors contributed equally to this work.

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1. Introduction

Crohn's disease (CD) is a chronic idiopathic inflammatory disease that causes transmural inflammation throughout the gastrointestinal tract [1]. Accurately grading the severity of inflammation is critical to the treatment modalities of patients with CD [2]. To

Abbreviations

CD	Crohn's disease
CTE	computed tomography enterography
ROC	operating characteristic curves
AUC	area under the ROC curve
SES-CD	Simplified Endoscopic Scores for Crohn's Disease
CDEIS	Crohn's Disease Endoscopic Index of Severity
SEMA-CD	simplified endoscopic mucosal assessment for Crohn's Disease
MH	Mucosal healing
TH	transmural healing
PPV	positive predictive value
NPV	negative predictive value
SFS	surgery-free survival
MRE	magnetic resonance enterography.
CRP	C-reactive protein
WBC	white blood cell
Hb	hemoglobin
PLT	platelet count
ALB	albumin
BMI	Body Mass Index
5- ASA	5-aminosalicylic acid
Anti-TNF	anti-Tumor necrosis factor

date, endoscopy remains the reference standard for assessing the mucosal status of CD [3]. Several endoscopic severity scoring systems, including the Crohn's Disease Endoscopic Index of Severity (CDEIS), have been applied in daily practice and accurately correlated with biochemical and clinical disease markers [4,5]. In addition, several new endoscopic scores have been developed, such as the Simple Endoscopic Score for Crohn's Disease (SES-CD), which is associated with the standard CDEIS and enables retrospective collection of information on mucosal status [6,7].

However, there are several important limitations to endoscopy. Since more than 30% of patients may present with more proximal lesions that are not confined to the terminal ileum, endoscopic evaluation has a restricted role in detecting such lesions [8]. In addition, ileocolonoscopy is an invasive procedure that may increase the risks of complications, especially in cases of a severe flare. Ileocolonoscopy induces discomfort, and repeated colonoscopies are not well tolerated, which also limits its application in the long-term follow-up of patients with CD [9]. Furthermore, endoscopic evaluation with various scoring systems is considered complicated and time-consuming in daily practice [6,7]. All these limitations require an alternative approach to assess mucosal activity in patients with CD.

Computed tomography enterography (CTE), utilizing thin-section scanning and multiplane reconstruction, has recently evolved as a useful diagnostic modality for imaging of the CD lesions [10]. In previous studies, the correlation between radiological signs and inflammatory activity has been reported, indicating the potential of CTE in disease monitoring [11,12]. However, most studies focused on mural findings rather than on mesenteric alterations and transmural damage. Mucosal healing (MH), defined by a SES-CD of 0–2, is recommended as a therapeutic target in clinical practice [13]. However, due to its transmural nature, CD can lead to cumulative digestive tract damage and complications, including strictures, fistulas, and abscesses. Over time, more than 50% of patients develop such complications and therefore require intestinal surgery [14]. For this reason, clinical symptoms and MH targeting have proven to be insufficient to predict the long-term prognosis of patients with CD, such as the need for surgery [15]. Transmural healing (TH) has thus emerged as a better predictor of better outcome [16]. CTE cross-sectional imaging is considered a promising tool for identifying TH with specific transmural and extramural features. In our previous study, a CTE-based scoring system was demonstrated to be accurate in predicting postoperative complications of CD [17]. However, the utility of the CTE index based multiparametric models in grading bowel injury and surgical risk is unclear.

A better correlation between CTE performance and endoscopic scores in patients with CD may contribute to the development of a practical CTE scoring system that can provide objective measures to guide the severity determination and predict long-term prognosis of CD. Thus, the purpose of this study was to evaluate the diagnostic accuracy of a scoring system based on CTE results in detecting endoscopic disease activity and to develop multiparametric models to predict severe endoscopic activity and surgical risk in patients with CD.

2. Patient and method

2.1. Patients

This is a retrospective study. Patients who received CTE in center 1 (Jinling Hospital), center 2 (Affiliated Hospital of Qingdao University) and center 3 (Sixth affiliated hospital of Sun Yat-sen University) from April 2017 to June 2019 were recruited for this study (Fig. 1). Inclusion criteria: (a) CD diagnosis (proven by endoscopy and histological analysis); (b) adequate CTE image quality with good intestinal dilatation; (c) underwent colonoscopy within 3 weeks of CTE; and (d) complete colonoscopy imaging data. Exclusion criteria: (a) history of bowel resection; (b) the interval between endoscopy and CTE examination exceeded 3 weeks; (c) missing clinical data; and (d) recent history of severe or eventual infections. A total of 171 patients met the inclusion criteria, and 256 bowel segments were finally analyzed (Fig. 1). Patients were divided into two cohorts: the training cohort (n = 121 for centers 1 and 2) and the validation cohort (n = 50 for center 3). Baseline clinical characteristics, including age, sex, disease duration, Montreal classification and concomitant medications, were well balanced between the training and validation cohorts (Table 1). The study protocol was approved by the Clinical Research Ethics Committee of the three centers (QYFY-WZLL26446).

2.2. CTE image acquisition

Patients underwent CTE following oral administration of polyethylene glycol solution. In all cases, patients were required to eat a low-residue diet and fast overnight the day before the examination. Patients received 1.0–1.2 l of isotonic polyethylene glycol (PEG) solution orally 60–120 min before CT scanning to obtain adequate bowel distension. All patients were placed in the supine position, and the scan covered the entire abdomen. The patients were trained to hold their breath during the scanning. CTE image acquisition was obtained in the enteric and venous phases of enhancement at 50 and 70 s after intravenous administration of iodinated contrast media, respectively (Omnipaque 350; GE Healthcare, Milwaukee, WI, USA). The scanning parameters of the CTE examination are listed in the Supplementary materials.

2.3. CTE index evaluation

CTE images were evaluated by two radiologists (LSL and ZXM, with 7 and 15 years of abdominal imaging diagnosis experience, respectively) unaware of endoscopic scores according to the criteria described in Fig. 2A–G. Based on a literature review and our previous work, eight parameters were selected and calculated, including mural hyperenhancement, mural stratification (target sign), mesenteric hypervascularity (comb sign), mesenteric fibrofatty proliferation, mesenteric fat density, intestinal fistula, bowel stricture and lesion length [17]. The length of intestinal lesions was measured in longitudinal and transverse sections between the interfaces of the inflamed and normal lumen. Mesenteric fibrofatty proliferation was classified by measuring the mesenteric fat area, and mesenteric fat density was determined by CTE values of a surrounding mesenteric area. These parameters were evaluated in each visual segment. The sum of all segments was also considered. Evaluation of interrater agreement was performed using the agreement-kappa test for the CTE variables (Supplementary Table S1).

2.4. Evaluation of endoscopic findings

The endoscopic activity was evaluated by colonoscopy according to the SES-CD. The overall SES-CD for each patient was the sum of the scores of the terminal ileum and the four colonic segments. Mucosal healing (MH) was defined by the absolute SES-CD endoscopic subscale of 0 or 2. The SES-CD classified patients with CD as inactive (0–2), mild (3–6), or moderate-severe (≥7) by SES-CD (see Supplementary Table 2). Binary global endoscopic severity categories were established based on SES-CD scores. Mucosal healing (MH) was defined as SES-CD ≤ 2; severe SES-CD was defined as SES-CD ≥16; and moderate to severe SES-CD was defined as SES-CD ≥7. In

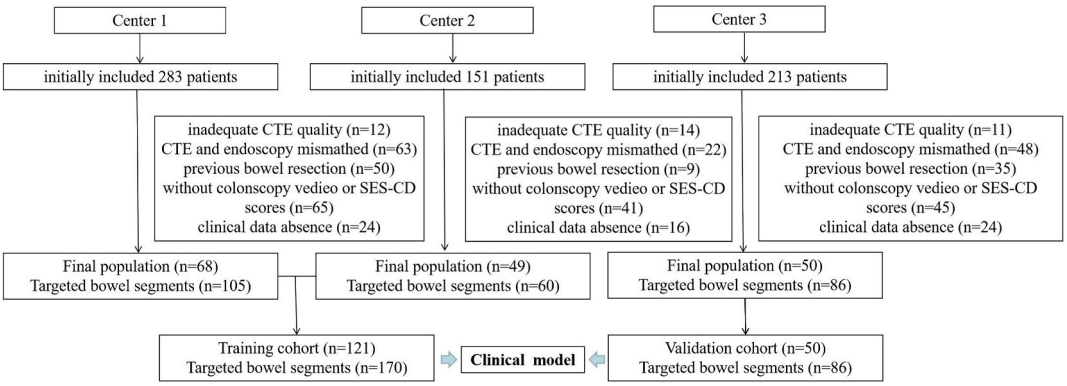

Fig. 1. Process diagram of data collection and model construction.

Table 1
Baseline Clinical characteristics of patients included in this study.

	All (n = 171)	Training (n = 121)	Validation (n = 50)	*p* value
Male, n (%)	109 (63.74)	73 (60.33)	36 (72.0)	0.29
Age at diagnosis, median (SD)	32.63 (10.54)	33.52 (10.06)	30.48 (11.44)	0.08
Disease duration (months), median (SD)	65.11 (10.42)	65.11 (8.60)	65.12 (11.12)	0.99
BMI>18.5, n (%)	83 (48.5)	57 (46.7)	26 (52.0)	0.62
Disease location				
Terminal leal, n (%)	23 (13.45)	16 (13.22)	7 (14.0)	0.89
Ileocolonic, n (%)	91 (53.22)	67 (55.37)	24 (48.0)	0.40
Colonic, n (%)	57 (33.33)	38 (31.40)	19 (38.0)	0.48
Upper GI, n (%)	22 (12.87)	10 (8.26)	4 (8.0)	0.95
Perianal involvement, n (%)	25 (14.62)	18 (14.88)	7 (14.0)	0.88
Disease behavior				
Non-stricturing & Non-Penetrating	23 (13.45)	19 (15.7)	4 (8.0)	0.22
Stricturing disease	69 (40.35)	52 (42.98)	17 (34.0)	0.31
Penetrating disease	79 (46.2)	50 (41.32)	29 (58.0)	0.06
Concomitant treatments				
5-ASA, n (%)	53 (30.99)	39 (32.23)	14 (28.0)	0.72
Steroids, n (%)	19 (11.11)	14 (11.57)	5 (10.0)	0.77
Immunosuppressants, n (%)	24 (14.04)	15 (12.4)	7 (14.0)	0.80
Anti-TNF antibodies, n (%)	41 (24.0)	24 (19.8)	17 (34.0)	0.08
CRP (mg/l), median (SD)	17.59 (36.71)	22.19 (23.58)	26.67 (17.008)	0.09
WBC (10^9/l), median (SD)	8.033 (6.187)	8.643 (21.53)	6.555 (75.23)	0.05
Hb (g/l), median (SD)	117.9 (21.5)	121.3 (7.178)	119.7 (55.37)	0.06
PLT (10^9/l), median (SD)	278.7 (121.6)	265.6 (116)	310.6 (130.1)	0.03
ALB (g/l), median (SD)	36.06 (6.65)	36.22 (130.1)	35.68 (5.2)	0.63
Failed ileocecal valve intubation, n (%)	28 (16.38)	20 (16.53)	8 (16.0)	0.93
with colonic strcture, n (%)	22 (12.87)	16 (13.22)	6 (12.0)	0.83
without colonic strcture but failed to pass ileocecal valve, n (%)	6 (3.51)	4 (3.31)	2 (4.0)	0.82
Bowel segments with SES-CD scores available				
Terminal ileum	118 (69.1)	86 (71.07)	32 (64.0)	0.37
Right colon	76 (44.44)	49 (40.50)	27 (54.0)	0.13
Transverse colon	30 (17.54)	18 (14.88)	12 (24.0)	0.19
Left colon and rectum	32 (18.71)	21 (17.36)	11 (22.0)	0.52

Note: CRP C-reactive protein, WBC white blood cell, Hb hemoglobin, PLT platelet count, ALB albumin, BMI Body Mass Index, GI gastrointestinal, 5-ASA 5-aminosalicylic acid, Anti-TNF anti-Tumor necrosis factor.

this study, 28 (16.38%) of 171 patients failed to successfully insert the cecum, and 22 (12.87%) failed to complete cecum insertion due to colonic stricture. Segmental SES-CD scores were available in 118 (69.1%) patients with terminal ileum, 76 patients (44.44%) with right-sided colon, 30 patients (17.54%) with transverse colon, and 32 patients (18.71%) with left-sided colon and rectum (Table 1). For incomplete colonoscopy, endoscopic scores were calculated based on the segment explored.

2.5. Clinical data collection

Data were collected from a prospectively maintained database including patient demographics, medications used, preoperative laboratory examinations (including CRP (C-reactive protein), WBC (white blood cell), Hb (hemoglobin), PLT (platelet count), ALB (albumin)), therapeutic procedures, and Montreal classifications. Furthermore, CTE images and endoscopy were obtained from the medical imaging department within three weeks.

2.6. Patient follow-up and endpoints

Follow-up information was collected from outpatient electronic records and telephone interviews. Patients were assessed every 3–6 months until 4 years. The evaluation included routine laboratory examinations, endoscopy or computed tomography. The endpoint of this study was surgery-free survival (SFS), defined as the time from diagnosis to surgery for CD or the final follow-up time.

2.7. Statistical analysis

All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL) and R software version 4.0.1 (Vanderbilt University, Nashville, TN). Continuous variables are expressed as the mean ± standard deviation. The Spearman correlation test or linear regression analysis (depending on the dependent variable type) was used to assess the correlation between specific imaging findings and endoscopic scores. We integrated the CTE scores with other clinical variables in the multivariate logistic regression model to identify moderate to severe endoscopic activity. A prognostic model for individualized SFS predictions in the multivariate Cox regression model was established and graphically represented as a nomogram using the "rms" package of R software. Survival curves were estimated and compared between the high CTE and low CTE groups by the Kaplan-Meier method and log-rank test.

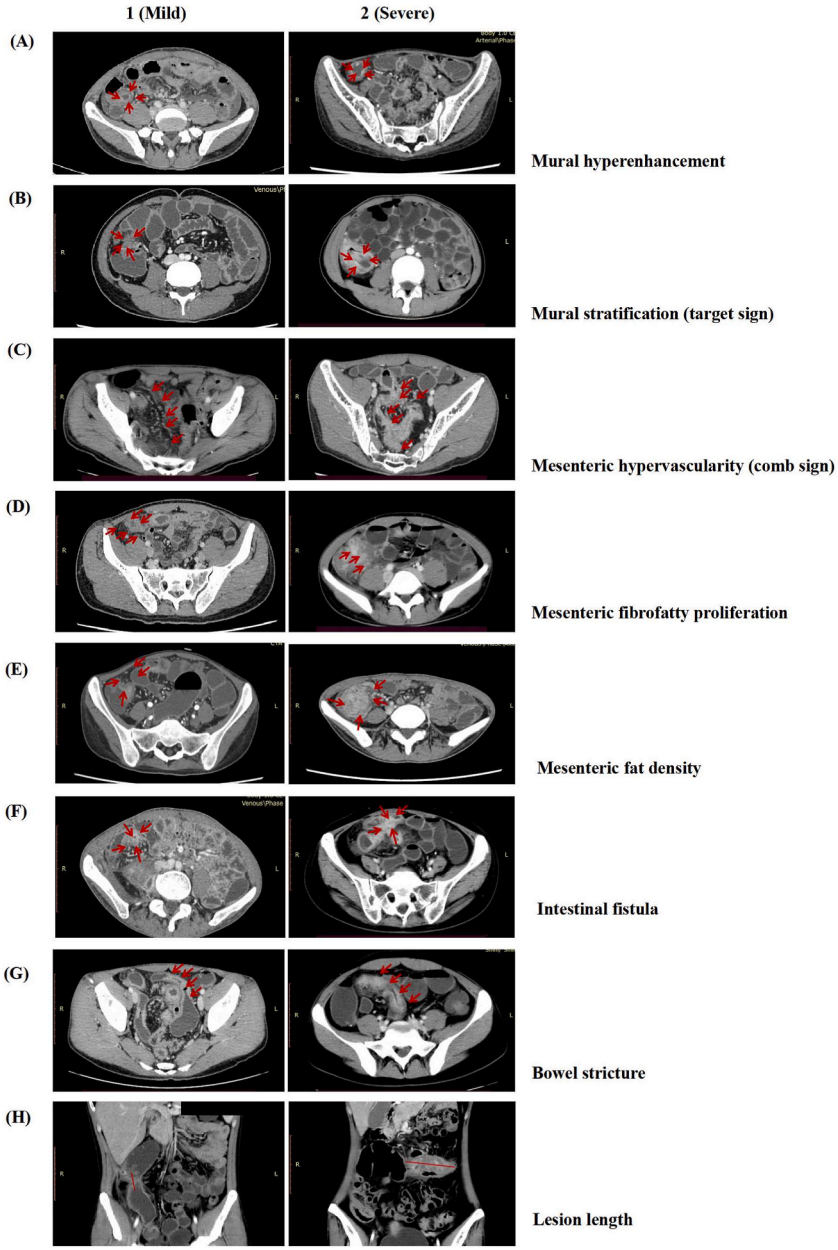

Fig. 2. Computed tomography enterography (CTE) parameters: (A) Mural stratification (target sign), (B) mesenteric hypervascularity (comb sign), (C) mural hyperenhancement, (D) mesenteric fibrofatty proliferation, (E) mesenteric fat density, (F) intestinal fistula (any), (F) intestinal fistula (any), and (G) lesion length. In each figure, red arrows indicate the findings.

3. Result

3.1. Correlations between CTE scores and endoscopic values

The prevalence of qualitative findings in CTE images and endoscopic reports was comparable in the two cohorts ($p > 0.05$, Table S3). At the segmental level, ulcer size (endoscopic index) was significantly or moderately correlated with ulcer surface, affected surface, and lesion length (CTE index) (Fig. 3 A- B, Tables S4–5, $r > 0.5$, $p < 0.001$). Mesenteric fibrofatty proliferation was found to be moderately correlated with the four SES-CD indices in both cohorts as measured by CTE outcomes in the mesentery ($r > 0.45$, $p < 0.001$). In both the training and validation cohorts, segmental CTE scores showed a good correlation with SES-CD scores ($r > 0.6$, $p < 0.001$) (Fig. 3C and D). At the individual level, global CTE scores exhibited a moderate correlation with SES-CD scores ($r = 0.416$; $p < 0.001$) in the training cohort and a weak correlation in the validation cohort ($r = 0.213$; $p < 0.001$) (Fig. S1).

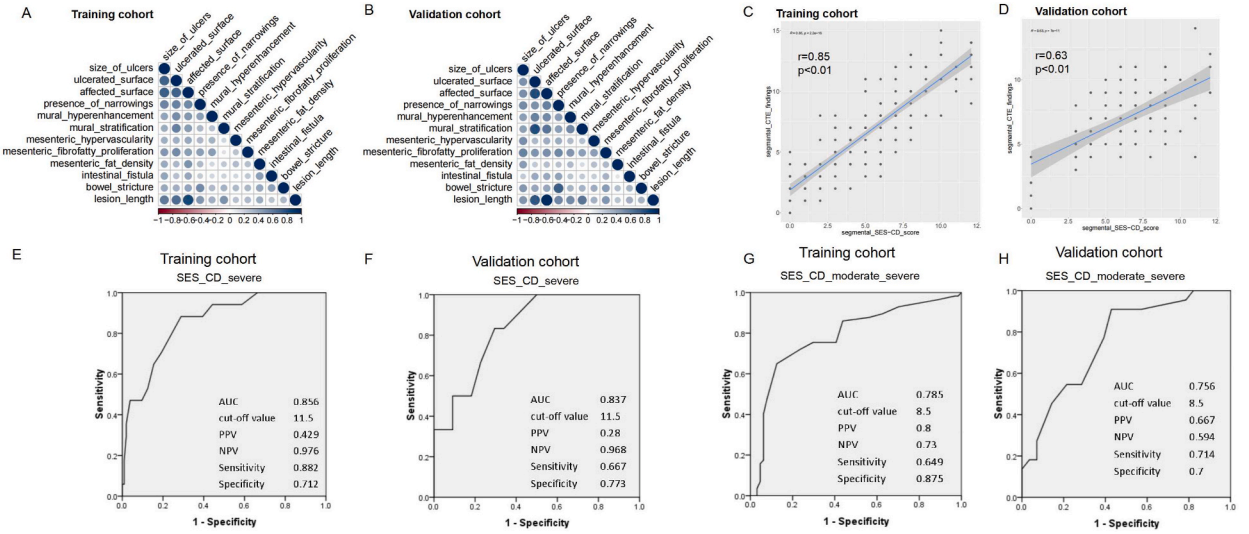

Fig. 3. The correlation between segmental CTE indices and endoscopic presentations. (A) A correlation matrix with correlation coefficients from −1 (negative correlation; red) to 1 (positive correlation; blue) in the training cohort. (B) A correlation matrix with correlation coefficients from −1 (negative correlation; red) to 1 (positive correlation; blue) in the validation cohort. (C) The correlation between segmental CTE score and SES-CD score in training cohorts. (D) The correlation between segmental CTE score and SES-CD score in validation cohorts. (E–F) ROC curve for the prediction of severe SES-CD scores in the training and validation cohorts. (G–H) ROC curve for the prediction of moderate to severe SES-CD scores in the validation cohort. AUC, the area under the ROC curve; PPV, positive predictive value (PPV); NPV, negative predictive value.

3.2. *The predictive capability of global CTE scores for individual endoscopic activity*

The proportions of patients with severe and moderate-to-severe SES-CD scores in the training cohort were 14.0% and 47.1%, respectively, compared with the corresponding proportions in the validation cohort (12.0% and 44%, $p > 0.05$, Table 2). We selected severe and moderate-to-severe SES-CD scores as final test variables. As illustrated in Fig. 3 E and F, ROC curve analysis showed that the presence of severe SES-CD scores could be predicted in the training and validation cohorts, with AUCs of 0.856 and 0.837, respectively, and cutoffs of 11.5 for both cohorts. For the detection of moderate-to-severe SES-CD, the overall CTE score performed the best with a cutoff value of 8.5 (Fig. 3G and H).

3.3. *Multiparametric predictive model for severe and moderate-to-severe SES-CD*

Univariate and multivariate analyses for severe and moderate-to-severe SES-CD were performed (Table 3 and Fig. S2). To further visualize the logistic regression results and develop a practical tool, the coefficients derived from the multivariate analysis were used as weights to elaborate a nomogram, which facilitated the practical application of the model to identify severe and moderate-to-severe patients (Fig. 4A and B). A novel nomogram using four parameters, including CTE scores, ileum and colon involvement, CRP and WBC, revealed the excellent ability to predict the risk of severe SES-CD scores with a ROC curve of 0.947 for the training cohort and 0.807 for the validation cohort (Fig. 4C and D). Similarly, a nomogram for moderate-to-severe SES-CD, derived by summing CTE scores, perianal disease and ALB, revealed improved accuracy with a ROC curve of 0.802 for the training cohort and 0.837 for the validation cohort (Fig. 4E and F). Calibration plots and decision curves for all models and predictors of SES-CD are presented in Figs. S3–4.

Table 2
Patients stratification based on the SES-CD score.

	All (n = 171)	Training (n = 121)	Validation (n = 50)	*p* value
Severe SES-CD, n (%)				
≥16	33 (19.3)	17 (14.0)	6 (12.0)	0.81
< 16	138 (80.7)	104 (86.0)	44 (88.0)	
Moderate to severe SES-CD, n (%)				
≥7	95 (55.6)	57 (47.1)	22 (44.0)	0.74
< 7	76 (44.4)	64 (52.9)	28 (56.0)	
MH, n (%)				
≤2	6 (3.5)	5 (4.1)	1 (2.0)	0.67
> 2	165 (96.5)	116 (95.9)	49 (98.0)	

Note: The severe SES-CD was defined as SES-CD score ≥16; the moderate to severe SES-CD was defined as SES-CD ≥7; the MH was defined as SES-CD ≤ 2.

Table 3
Clinical and CTE parameters in the training cohort for two SES-CD sub-classifications.

	severe SES-CD score			moderate to severe SES-CD score		
	≥16 (n = 17)	< 16 (n = 104)	*p* value	≥7 (n = 57)	< 7 (n = 64)	*p* value
male, n (%)	10 (58.82)	63 (60.58)	0.89	37 (64.91)	36 (56.25)	0.36
Age at diagnosis, >40 years old, n (%)	4 (23.52)	10 (9.62)	0.11	9 (15.79)	5 (7.81)	0.26
Disease duration, >5 years, n (%)	8 (47.06)	73 (70.19)	0.09	39 (68.42)	42 (65.63)	0.85
BMI, >18.5, n (%)	9 (52.94)	48 (46.15)	0.61	30 (52.63)	27 (42.19)	0.28
Disease location						
Upper GI, n (%)	0 (0)	10 (9.62)	0.35	5 (8.77)	5 (7.81)	1
Ileal, n (%)	2 (11.76)	31 (29.81)	0.15	15 (26.32)	18 (28.13)	0.84
Ileocolonic, n (%)	14 (82.35)	58 (55.77)	0.06	34 (59.65)	38 (59.38)	1
Colonic, n (%)	1 (5.88)	12 (11.54)	0.69	6 (10.53)	7 (10.94)	0.94
Perianal involvement, n (%)	4 (23.53)	14 (13.46)	0.28	15 (26.32)	3 (4.69)	0.001
CRP (mg/l), median (SD)	31.18 (22.93)	9.089 (22.29)	<0.001	13.82 (19.26)	10.74 (26.92)	0.48
WBC (10^9/l), median (SD)	14.56 (12)	7.676 (5.30)	<0.001	9.32 (8.06)	8.04 (5.92)	0.32
Hb (g/l), median (SD)	123.2 (19.41)	121 (21.93)	0.7	118.9 (19.16)	123.4 (23.39)	0.26
PLT (10^9/l), median SD)	211.6 (62.58)	227.1 (104)	0.43	227.6 (77.59)	222.5 (73.6)	0.71
ALB (g/l), median (SD)	33.4 (5.82)	36.69 (7.30)	0.08	34.62 (6.38)	37.65 (7.59)	0.02
CTE scores, median (SD)	16.18 (5.10)	9.00 (4.58)	<0.001	12.39 (4.78)	7.859 (4.77)	<0.001

Note: CRP C-reactive protein, WBC white blood cell, Hb hemoglobin, PLT platelet count, ALB albumin, BMI Body Mass Index, GI gastrointestinal, 5-ASA 5-aminosalicylic acid, Anti-TNF anti-Tumor necrosis factor.

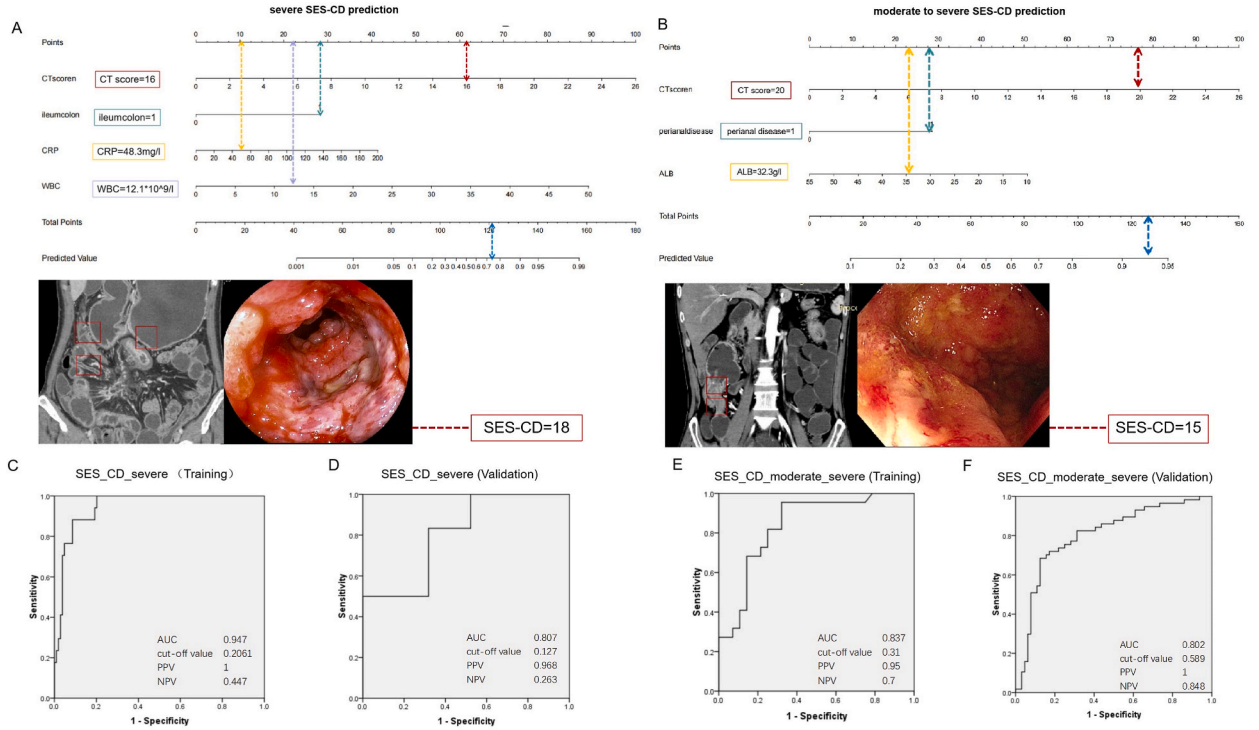

Fig. 4. Development and validation of the multivariable model. (A) The nomogram image displays a case with a CTE score of 16, ileum and colon involvement, a CRP level of 48.3 mg/l and a WBC count of 12.1*10^9/l, with a total score of 121.5. The probability of a severe SES-CD predicted by the multivariable model was 0.74. The image on the lower left shows three diseased bowel segments in the CTE image of the patients with a total SES-CD score of 18, indicating severe endoscopic activity. (B) The nomogram image shows a case with a CTE score of 20, perianal disease and an ALB of 32.3 g/l, with a total score of 124.8. The model predicts that the probability of the patient having a moderate to severe SES-CD score is 0.93. The image on the lower right shows two diseased bowel segments in the CTE image of the patient with a total SES-CD score of 15, indicating moderate endoscopic activity. (C–D) Predictive accuracy of the constructed models for individualized severe SES-CD presentations in the training and validation cohorts. (E–F) Predictive accuracy of constructed models for the individualized mild-to-severe SES-CD presentations in the training and validation cohorts.

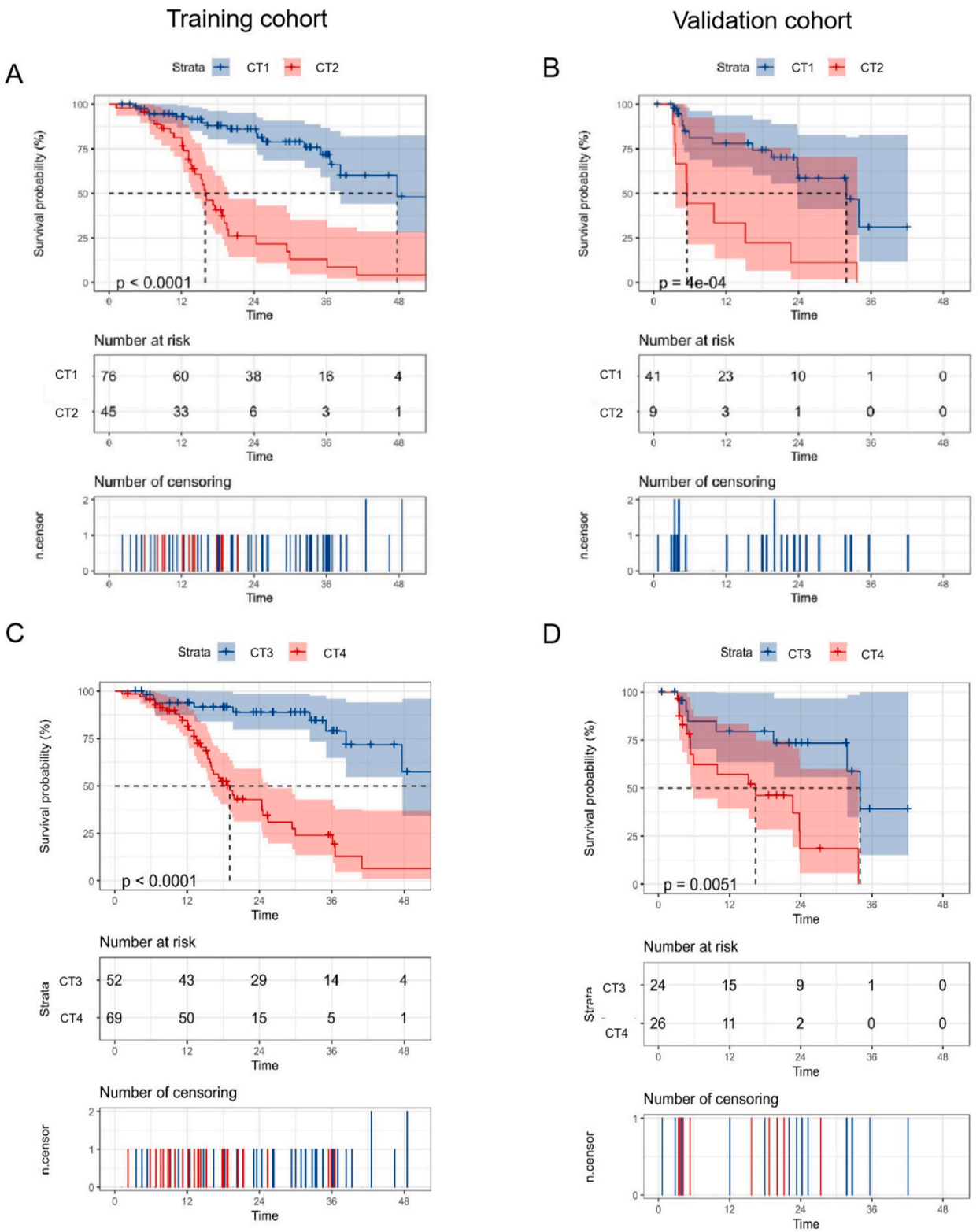

Fig. 5. The cumulative surgery rates predicted by the CT score for the different risk stratifications. (A–B) Surgery-free survival curves for non-severe CTE scores (CT1, <11.5) and severe CT scores (CT2, ≥11.5) in the training and validation cohorts. (C–D) Surgery-free survival curves for non-moderate-to-severe CTE scores (CT3, <8.5) and moderate-to-severe CT scores (CT4, ≥8.5) in the training and validation cohorts. P values were calculated by log-rank test.

3.4. Surgery-free survival (SFS) rates based on CTE scores

As CTE scores of 11.5 and 8.5 had high diagnostic accuracy for severe and moderate-to-severe SES-CD (Fig. 4), we stratified the patients into 2 grades: severe (with a cutoff value of 11.5) and moderate-to-severe (with a cutoff value of 8.5) (Table S6). Cumulative SFS rates were significantly different between the groups stratified based on CTE scores in the training and validation cohorts (Fig. 5A–D, all $p < 0.001$, log-rank test). The Kaplan−Meier curves for the 4-year SFS rate decreased in the severe and moderate-to-severe CTE groups compared to the non-severe (Fig. 5A and B) and non-moderate-severe CTE groups (all $p < 0.001$, log-rank test) (Fig. 5C and D). In a multivariable Cox regression analysis, including the clinical and endoscopic factors, the CTE score (HR = 1.18; 95% CI: 1.103–1.262; $p = 0.001$) and SES-CD score (HR = 3.125, 95% CI: 1.542–6.33; $p = 0.001$) were independent prognostic factors for SFS (Table S7). A prognostic nomogram yields quantitative probabilities of survival at certain time points, with higher total scores indicating worse clinical outcomes. Fig. 6A illustrates the prognostic nomogram built for 2- and 4-year SFS based on the 3 prognostic factors (CTE score, SES-CD and CRP>20 mg/l) identified in the training set. The time-dependent ROC curves of the multiparametric prediction model are displayed in Fig. 6B. Across a range of threshold probabilities, the multiparametric prediction model yielded clinical benefits for the 2-year time-based decision curve analysis for both cohorts (Fig. 6C–E).

4. Discussion

In this study, we conclusively demonstrated the high accuracy of CTE-based models to predict the severity of CD endoscopy. In addition, a significant link between CTE scores and the risk of surgical intervention was disclosed.

Defining CD activity only by endoscopy is insufficient for clinicians [18,19]. The primary drawback of endoscopy is the inability to routinely evaluate the whole gastrointestinal tract, submucosal and mesenteric lesions, and some of the main CD complications [10,20,21]. These facts prompted researchers to investigate alternative methods, such as CTE, to measure the extent and severity of CD disease [22,23]. In this study, we first evaluated the correlations between parameters obtained from CTE images and endoscopic observations in corresponding bowel segments. Our data indicated that the ulcerated surface, an endoscopic index, was associated with the following CTE findings: mural hyperenhancement, mural stratification, mesenteric fibrofatty proliferation and lesion length. Comparable results were also obtained from MRE-based studies [24–27]. Our data also suggested that mesenteric inflammatory changes detected by the CTE technique, particularly mesenteric fibrofatty proliferation, correlated with the SES-CD index, consistent with previous findings [28,29]. Mesenteric fat, also known as creeping fat, is a typical sign of CD and may function as an "outside-in" regulator of intestinal inflammation [30,31]. It would be highly significant to include mesenteric signs in the CTE evaluation list.

There are no universally accepted CTE scoring systems to define the endoscopic index of severity. Therefore, we explored the link between integrated CTE scores and endoscopic scores at both segmental and global scales [32]. In the present study, a good correlation between segmental endoscopic score and CTE score was observed. However, the relationship between global CTE scores and SES-CD

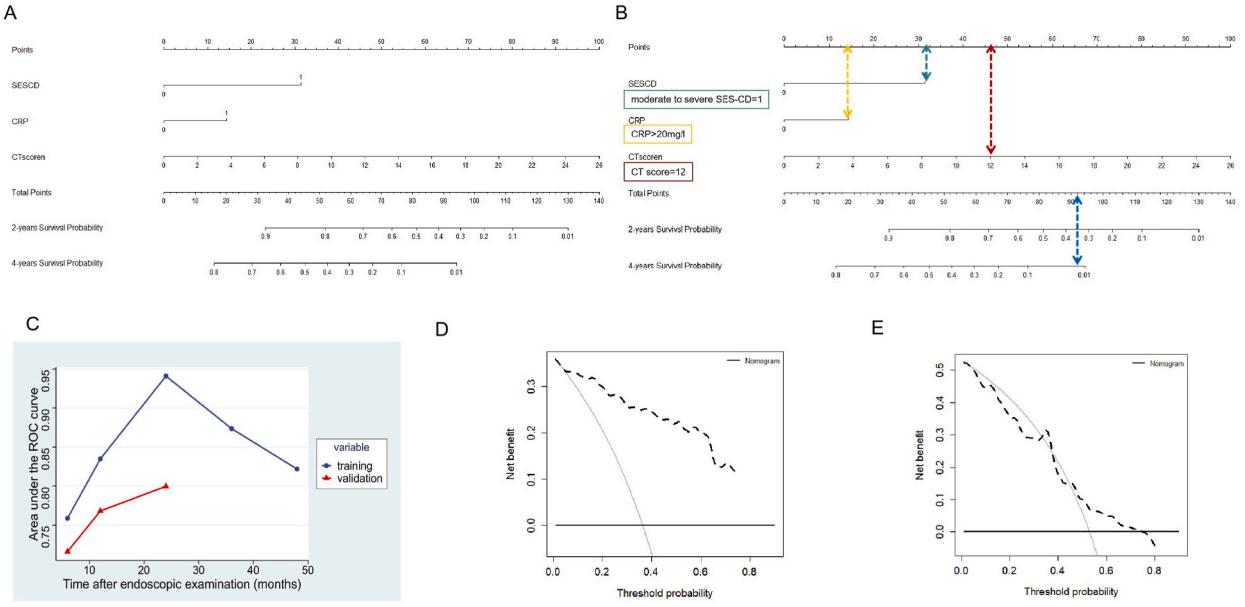

Fig. 6. Construction of clinical nomogram incorporating CTE scores, SES-CD scores and clinical information. (A) A clinical nomogram to predict surgical risk in CD based on the multivariate analysis of CTE score, SES-CD (moderate-to-severe) and CRP (>20 mg/l). (B) A case with moderate-to-severe CD, CRP (>20 mg/l) and CTE score (=12) was identified with a nomogram score of 12, a 2-year SFS survival probability of 0.35 and a 4-year SFS survival probability of 0.02. (C) Training and validation of the discriminatory performance of clinical nomogram in the cohort. (D–E) Decision curve analysis for the clinical nomogram in the training and validation cohorts.

was relatively poor at the individual scale. This could be explained by the possible mismatch between CTE and colonoscopy assessments. Of note, ileum intubation failure poses a significant challenge when using the SES-CD as the primary outcome. In our study, 28 (16.38%) of 171 patients had failed cecal insertion and 22 (12.87%) failed to complete cecal insertion due to colonic stricture (Table 1). Numerous patients with moderate-to-severe CD partially lacked endoscopic scoring information due to colonic strictures. Some of them were underestimated as low SES-CD scores. From this perspective, CTE pictures suggested the possibility of re-evaluating the missing severe SES-CD subscore, which improved the accuracy of assessing disease activity when the colonoscopy was insufficient.

Accurate identification of moderate to severe CD is essential for decision-making in CD management because these patients are at high risk for disease-related complications and abdominal surgery [33]. Therefore, we focused on moderate to severe CD identification. Surprisingly, the CTE score in the current study revealed substantial performance in discriminating moderate to severe SES-CD from mild SES-CD activity (Fig. 3). Thus, CTE is a technique that can be used simultaneously to detect more severe CD. The assessment of CD activity is based on a combination of symptoms, clinical findings, and endoscopy [34,35]. We hypothesized that clinical traits and laboratory data in CD might be correlated with endoscopic findings, especially in severe lesions. The results indicated that CTE scores, ileum and colon involvement, CRP and WBC were independent indicators for severe SES-CD; CTE scores were an independent indicator for moderate-to-severe SES-CD scores (Fig. S2). The characterization of various predictive parameters in the multivariate analysis allowed us to develop, for the first time, a combined predictive model that provided improved accuracy in identifying patients with moderate to severe SES-CD scores (Fig. 4).

CD is a disease that progresses from an inflammatory phenotype to a structuring and penetrating illness over time, frequently necessitating further surgery.[39] The concept of TH has recently evolved as an essential therapeutic target and predictor of surgery [36,37]. Accumulating evidence has suggested that CTE is a practical tool to recognize TH [38,39]. Here, we identified the risk factors for CD-related surgery and found that CTE score, SES-CD and CRP were significant predictors for surgical-free survival in patients with CD. We also attempted to stratify the surgical risks according to CTE scores. With a cutoff value of 11.5, the severe CTE score group ($\geq$11.5) had a significantly lower surgery-free survival rate than the non-severe CTE score group. Additionally, we used a cutoff value of 8.5 to define moderate-to-severe CTE scores and found that those with lower CTE scores had a higher probability of surgery-free survival. Based on clinical characteristics and CTE scores, we subsequently developed a predictive nomogram with good accuracy and specificity. Our model demonstrated strong discriminating performance in the training and validation cohorts of time-dependent ROC analysis, probably due to the inclusion of these additional independent risk factors that provided a more comprehensive description of the potential severity of bowel injury. The multivariable model developed in our study can be regarded as a risk stratification index, which was proposed based on the disease burden (CRP), endoscopic activity (SES-CD) and transmural damage (CTE score). Top-down therapy methods, which include anti-TNF and immunosuppressants, may be suggested first for patients with high surgical risk identified by this model.

Our study has several limitations. First, the sample sizes in the training and validation cohorts were restricted. This is generally a feature of studies using endoscopic scores and surgery-free survival as endpoints. Future expansion of the sample size would be desirable. Second, the application of the proposed multivariate model in clinical practice appears to be complex compared with a single SES-CD score or CTE score. Therefore, future work should focus on simplifying the developed models to build a practical and multifunctional decision-making assistance tool. Finally, due to its radiological nature, CTE is usually limited in the routine follow-up of CD patients, but our data suggested that it is more useful when considering disease progression with surgery risk [40].

In conclusion, this study highlighted the value of the newly developed CTE score in the detection of moderate to severe lesions in patients with CD. By incorporating clinical variables and CTE scores, we established multivariable models to improve the accuracy of diagnosis of endoscopic activity and the prediction of surgical risk.

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Author contribution statement

Ruiqing Liu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Shunli Liu: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Li Yi: Wang Zhiming: Analyzed and interpreted the data.

Dongsheng Wang: Xiaoming Zhou: Contributed reagents, materials, analysis tools or data.

Keyu Ren: Jia Ke: Performed the experiments.

Weiming Zhu: Conceived and designed the experiments.

Yun Lu: Conceived and designed the experiments; Wrote the paper.

Data availability statement

Data will be made available on request.

Ethics statement

The present clinical study was carried out at the Jinling Hospital, Affiliated Hospital of Qingdao University and Sixth affiliated hospital of Sun Yat-sen University, in full compliance with ethical principles, including the World Medical Association Declaration of Helsinki and the additional requirements of Chinese law. The ethics committees of Jinling Hospital, Affiliated Hospital of Qingdao University and Sixth affiliated hospital of Sun Yat-sen University, responsible for the evaluation of studies involving patients classified the study as exempt from ethical review, as all procedures performed were routine, and involve the use of existing data that contain only non-identifiable data about human beings (Number: QYFY-WZLL26446).

Informed consent statement

All selected participants were informed about the conditions and the type of study that would be carried out, and they completed and signed the informed consent according to the agreement of the Declaration of Helsinki of 1994.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19942.

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