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Original Article

ORIGINAL ARTICLE

Visceral adipose volume is correlated with surgical tissue fibrosis in Crohn's disease of the small bowel

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Abstract

Background This study explored the diagnostic performance of visceral adiposity to predict the degree of intestinal inflammation and fibrosis.

Methods The patients with Crohn's disease (CD) who underwent surgical small bowel resection at the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between January 2007 and December 2017 were enrolled. We evaluated the intestinal imaging features of computed tomography enterography (CTE), including mesenteric inflammatory fat stranding, the target sign, mesenteric hypervascularity, bowel wall thickening, lymphadenopathy, stricture diameter, and maximal upstream diameter. We used A.K. software (Artificial Intelligence Kit, version 1.1) to calculate the visceral fat (VF) and subcutaneous fat (SF) volumes at the third lumbar vertebra level. Pathological tissue information was recorded. Diagnostic models were established based on the multivariate regression analysis results, and their effectiveness was evaluated by area under the curve (AUC) and decision curve analyses.

Results Overall, 48 patients with CD were included in this study. The abdominal VF/SF volume ratio (odds ratio, 1.20; 95% confidence interval, 1.05–1.38; $P = 0.009$) and the stenosis diameter/upstream intestinal dilatation diameter (ND) ratio (odds ratio, 0.90; 95% confidence interval, 0.82–0.99; $P = 0.034$) were independent risk factors for the severe fibrosis of the small intestine. The AUC values of the VF/SF ratio, the ND ratio, and their combination were 0.760, 0.673, and 0.804, respectively. The combination of the VS/SF volume ratio and ND ratio achieved the highest net benefit on the decision curve.

Conclusion The VF volume on CTE can reflect intestinal fibrosis. The combination of the VF/SF volume ratio and ND ratio of CD patients assessed using CTE can help predict severe fibrosis stenosis of the small intestine.

Key words: Crohn's disease; intestinal fibrosis; visceral fat; computed tomography enterography

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Introduction

Crohn's disease (CD) is a chronic gastrointestinal transmural inflammatory disease that often progresses to fibrosis with intestinal strictures and obstruction [1]. Despite the increasing use of immunosuppressive and biological therapies, the rate of surgery for CD treatment remains high [2, 3]. CD-associated fibrosis frequently leads to intestinal strictures and obstructions that require surgical intervention. Histopathologic assessments have shown that inflammation and fibrosis coexist to varying degrees in intestinal strictures [4, 5]. Accurate characterization of intestinal strictures is critical in the management of CD because inflammatory strictures are typically treated medically, whereas fibromuscular strictures are drug-refractory and require surgical intervention. Therefore, the complexity of CD management decisions is related to the difficulty in accurately assessing the existence and development of the fibrosis in the strictures [6].

Recently, magnetic resonance imaging (MRI) [7–9], positron emission tomography combined with diffusion-weighted MRI [10], photoacoustic tomography [11], and shear-wave elastography (SWE) [12] have been used to distinguish fibrotic strictures from inflammatory strictures. However, MRI is relatively expensive, and SWE is operator-dependent and observer-dependent, thereby restricting their general applicability. Moreover, the diagnostic performances of these new examinations have not been validated. Hence, there is no generally accepted method of assessing and differentiating the characters of intestinal stricture.

A previous study showed that the accumulation of mesenteric fat (part of the visceral fat [VF]) with fat wrapping is common in CD and is known to occur from the early onset of the disease [13]. However, it is difficult to quantitatively analyse mesenteric fat. A previous study suggested that a high ratio of visceral fat area (VFA) to subcutaneous fat area (SFA) is a marker of aggressive CD [14] and that visceral adiposity predicts postoperative CD recurrence [15]. Although there are multiple approaches to detecting VFA, the evaluation process is complicated and subjective [14, 16]. Currently, high-precision quantitative evaluation of the target area has been made possible by advanced artificial intelligence (AI) imaging technology. Compared with the traditional area evaluation, the region of interest volume has resulted in better effects and high efficiency performing calculations and evaluation [17, 18]. Whether VF volume measurements can distinguish inflamed from fibrotic bowel segments requires further investigation.

Currently, computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are the first-line methods for assessing CD activity and complications. Compared with MRE, CTE has the advantages of better availability, shorter examination time with high efficiency and low cost [19]. CTE can assess VF by measuring the VFA and SFA in the same section [20]. In this study, we hypothesized that using both AI imaging software and CTE imaging to observe, the volume of VF can help predict the type of intestinal strictures conveniently and objectively.

Materials and methods

Patients

The patients with CD who underwent surgical small bowel resection at the First Affiliated Hospital of Sun Yat-sen University (Guangzhou, China) between January 2007 and December 2017 were enrolled in this study. The inclusion criteria were as follows: (i) age $\geq$14 years with a diagnosis of CD based on clinical, imaging, endoscopic, and histological criteria; (ii) CTE performed within 1 month before surgery; (iii) available transmural histological assessment of the intestinal fibrosis; and (iv) no use of corticosteroids or antitumor necrosis factor (anti-TNF) agents for >3 months before surgery because these drugs can affect changes in the redistribution of VF [21]. Conversely, the exclusion criteria were as follows: (i) unavailable preoperative CT data; (ii) history of abdominal surgery; and (iii) presence of malignancy. All clinical data were collected at the time of admission. The study protocol was approved by the institutional Review Board of the First Affiliated Hospital of Sun Yat-sen University (No. 2018[280]).

Computed tomography enterography and visceral adipose tissue volume measurement

The CTE evaluation was performed according to a standardized protocol [22], as described in the Supplementary Material CTE protocol. We reviewed the operative notes thoroughly to identify the exact resected intestinal segment and used CTE examinations results as a reference. The following findings were recorded by a senior radiologist with >20 years of experience with abdominal radiology: (i) mesenteric inflammatory fat stranding, which involves abnormally increased fat attenuation; (ii) target sign, defined as an involved bowel wall with three concentric rings of high, low, and high density; (iii) mesenteric hypervascularity (comb sign). Bowel wall thickening was measured using the binary classification ($\leq$7, >7 mm). Additional features, such as the narrowest luminal diameter of the stricture and the diameter of the maximal upstream small bowel dilation, were measured manually [14]. The stenosis diameter to upstream intestinal dilatation diameter ratio (ND ratio), which was used to characterize the upstream dilation ratio in the study, was calculated using the following equation: 100 $\times$ narrowed diameter/upstream dilatation diameter. The venous phase scans were assessed using A.K. software (Analysis-Kit, version 1.1; GE Healthcare, Shanghai, China). Using previously reported methods, adipose tissue volumes were measured in transverse 10-mm-thick slices centered on the level of the third lumbar vertebrae (L3). The A.K. software traced the adipose tissue according to a fixed attenuation range from −190 to −30 Hounsfield units [20] and the volumes of the VFA and SFA were obtained automatically (Figure 1). A researcher blinded to the pathological information manually separated the VFA and SFA; subsequently, the volumes of these two parts were calculated automatically.

Histopathologic evaluation

A histopathologic evaluation of resected specimens was performed by a senior pathologist with >20 years of experience. One slice was stained with hematoxylin and eosin to obtain the histologic inflammation score. The most stenotic area was chosen for analysis. The inflammation and fibrosis scores were adapted from previously published histologic scores of small bowel CD and the most severe areas were documented [23]. The semi-quantitative scoring criteria are shown in Supplementary Table 1.

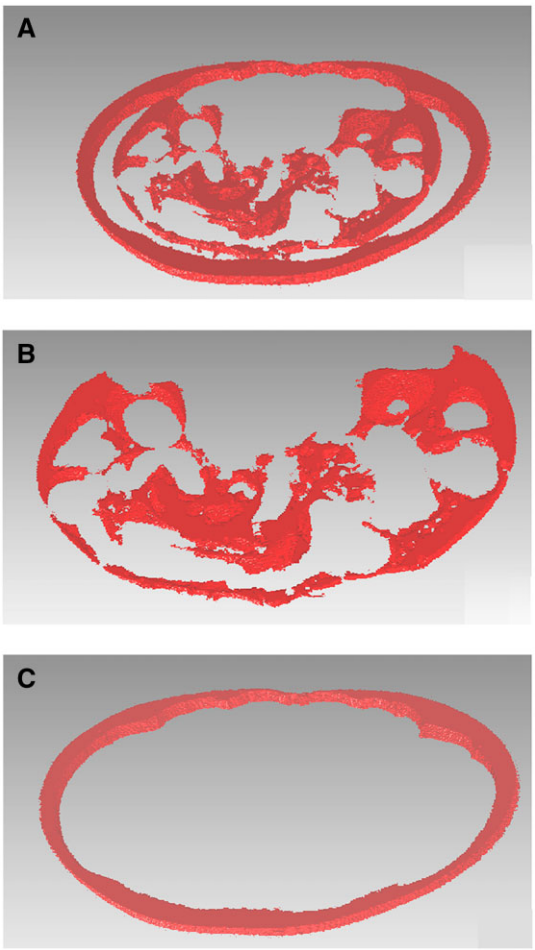

Figure 1. The 3D imaging of both visceral fat and subcutaneous fat (A), visceral fat (B), and subcutaneous fat (C) on the A.K software

Statistical analysis

Quantitative data are expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]). Qualitative data are presented as frequencies and percentages. Comparisons between groups were performed using an analysis of variance or the Kruskal–Wallis test for quantitative data; Fisher's exact test was performed to compare qualitative data. The Bonferroni test was used for pairwise comparisons. The correlation between rank variables was analysed using the Kendall tau-b correlation coefficient. Logistic regression models were used to predict the risk of high fibrosis or inflammatory scores (Grade 4). The low-score groups were combined. Variables with $P < 0.2$ according to univariate logistic regression with backward selection with a criterion of $P < 0.1$ were included in the multivariate logistic regression model. Additionally, the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Furthermore, the area under the receiver-operating characteristic curve (AUC), sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The best cut-off value was determined based on the maximum Youden index. Clinical usefulness and net benefit were estimated using a decision curve analysis and the optimal model was determined [24]. Statistical analysis was performed using two-sided comparisons; significance was defined as $P < 0.05$ using R software (version 3.6.1.; R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographic and clinical data

A total of 173 potentially eligible patients and 125 cases were excluded according to the exclusion criteria. The collection flowchart is shown in Figure 2. A total of 48 patients were included in the final cohort. The demographic and clinical data of the patients are shown in Table 1. Of these 48 patients, 27 underwent resection because of a small bowel obstruction (1 patient with complication of fistulizing disease), 15 patients underwent resection because of a small bowel stricture (6 patients with penetrating disease), 2 patients underwent resection because of a fistulizing disease complicated with abscess, 2 patients underwent resection because of abscess, and 2 patients underwent resection because of penetrating disease. Multiple strictures were observed in 10 patients with CD. According to the Montreal classification, most patients had A2 (79%), L1 (71%), and B2 (73%) subtypes. Nearly half (47.9%) of the patients had received at least one drug treatment before surgery, including 5-aminosalicylic acid (5-ASA), immunosuppressants, steroid, immunomodulator, biological agent, and herbs. Ten patients received two or three combination drug therapies. The specific treatments received before surgery are shown in Supplementary Table 2.

Bowel wall histologic evaluation

As shown in Table 2 and Supplementary Table 3, according to the histology analysis results, 9 bowel segments were classified as having an inflammation score of 2, 8 had a score of 3, and 31 had a score of 4. The fibrosis scores were 2 ($n = 15$), 3 ($n = 20$), and 4 ($n = 13$). There was no significant correlation between the inflammation and fibrosis scores (tau = −0.01, $P = 0.458$).

Parameters for the assessment of bowel fibrosis and inflammation

We analysed parameters that differed among the groups with different degrees of inflammation and fibrosis (Table 2). All 48 patients had mucosal enhancement on CTE. None of the VF/SF volume ratios, CTE imaging features, and clinical parameters had significantly different inflammation classification. We also found that only the VF/SF volume ratio ($P = 0.004$) differed among groups with different degrees of fibrosis; however, we did not observe any specific CTE imaging signs associated with pathological inflammation (all $P > 0.05$).

Using inflammation and fibrosis scores as subgroups, we tried to separate patients into two groups (Grade 2/3 group and Grade 4 group) based on severity. The baseline characteristics are shown in Supplementary Table 4. The results of the univariate binomial logistic regression of inflammation and fibrosis scores showed that only the VF/SF volume ratio was significantly associated with fibrosis (OR, 4.22; 95% CI, 1.33–13.44, $P = 0.015$) (Supplementary Tables 5 and 6). After including all variables found to be associated with the predictive factors in the univariate analysis with $P < 0.2$, a multivariate analysis demonstrated that the VF/SF volume ratio (OR, 1.20; 95% CI, 1.05–1.38, $P = 0.009$) and ND ratio (OR, 0.90; 95% CI, 0.82–0.99, $P = 0.034$) were significant predictors of severe fibrosis; however, none of the features differed significantly in their prediction of inflammation (Table 3). Using A.K. software, typical cases of severe fibrotic stenosis (Figure 3) and inflammatory stenosis (Figure 4) were observed with the corresponding images of histological pathology and CTE and 3D images of fat signaling. We further explored the association

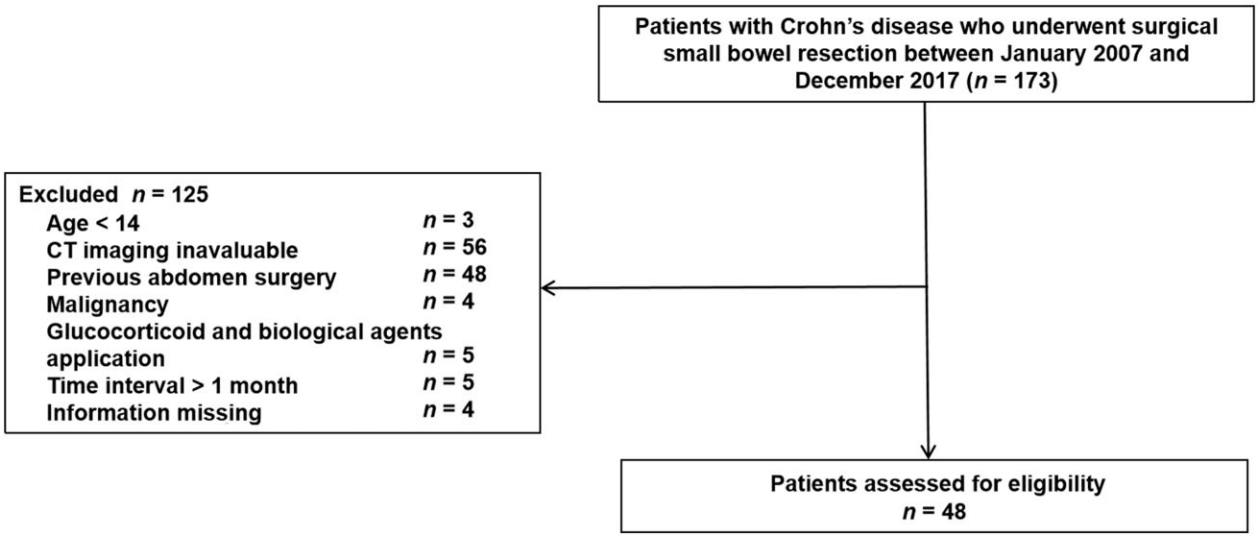

Figure 2. The flowchart of the study

Table 1. Demographic and clinical characteristics of 48 patients with small intestinal Crohn's disease

Characteristic	Value ($n = 48$)
Male, *n* (%)	37 (77.1)
Age, years, mean ± SD	31.8 ± 11.5
Disease duration, months, median (IQR)	36.0 (12.0, 60.0)
Time interval between CTE and surgery, days, mean ± SD	22.5 ± 18.9
Smoking, *n* (%)	8 (16.7)
BMI, kg/m^2, mean ± SD	17.23 ± 2.47
Montreal classification, *n*	
A1/A2/A3	2/38/8
L1/L2/L3/L4	34/6/8/0
B1/B2/B3	0/35/13
Surgery type, *n* (%)	
Ileocolonic resection	30 (62.5)
Partial small bowel resection	18 (37.5)
Most severe disease location, *n* (%)	
Ileocecum	13 (27.1)
Terminal ileum	11 (22.9)
Ileum + jejunum	24 (50.0)
Treatment before surgery[a], *n* (%)	23 (47.9)
Crohn disease activity index, mean ± SD	210.0 ± 88.6
C-reactive protein, mg/L, mean ± SD	33.9 ± 40.3
Erythrocyte sedimentation rate, mm/h, mean ± SD	39.0 ± 25.4

SD, standard deviation; IQR, interquartile range; BMI, body mass index; CTE, computed tomography enterography.
[a]The specific treatments are shown in the Supplementary material.

of the ND ratio and VF/SF volume ratio with different fibrosis scores of intestinal strictures. Differences in the VF/SF volume ratio existed for each fibrosis grade; however, the ND ratio could only predict severe fibrosis (Grade 2 vs Grade 4, $P = 0.034$; Grade 3 vs Grade 4, $P = 0.029$) (Figure 5). We also performed the univariate order logistic regression and adjusted order logistic regression of inflammation and fibrosis scores (Supplementary Tables 7–9). The results showed that the VF/SF volume ratio and ND ratio were significantly associated with the fibrosis score ($P < 0.05$).

Predictive model for severe fibrosis

As the accurate diagnosis of severe inflammation and fibrosis (score 4) with intestinal strictures is important for clinical treatment decisions, we adopted a binomial logistic regression model for further analyses. Figure 6 shows the receiver operating characteristic curve (ROC curve) of the VF/SF volume ratio, ND ratio, and the combined model for severe fibrosis degree. The VF/SF volume ratio had a high AUC value (0.760; 95% CI, 0.619–0.902) for distinguishing moderately fibrotic bowel walls (fibrotic Grades 2 and 3) from severely fibrotic bowel walls (fibrotic Grade 4) (Figure 6a). The sensitivity and specificity of using the VF/SF volume ratio with a cut-off value of 0.880 for distinguishing severe from moderate fibrosis were 76.9% and 68.6%, respectively. Moreover, the sensitivity and specificity of using an ND ratio of 0.129 as the cut-off value for distinguishing severely fibrotic from moderately fibrotic bowel walls were 76.9% and 68.6%, respectively. We built a logistic regression model to predict the probability of fibrotic stricture based on the combination of these two features. The function is as follows:

$$predict\ probability = \frac{1}{1 + e^{g(x)}}$$

$$g(x) = 1.52145 - 1.823955 \times \frac{VF}{SF} + 10.48312 \times ND\ ratio$$

The combination of the VF/SF volume ratio and ND ratio could improve the diagnostic performance and achieve the best AUC value to identify the existence of fibrosis. Under the cut-off value of 0.436, the sensitivity and specificity were 61.5% and 91.4%, respectively (Table 4 and Figure 6a). To facilitate comparisons of the different prediction models, a decision curve analysis was performed; the results showed that the combined prediction model provided a larger net benefit across the range of severe fibrosis of the bowel compared with the ND ratio alone and the VF/SF volume ratio alone (Figure 6b).

Discussion

In this study, the volume of VF and the volume of SF in patients with CD were measured using CTE. The relationship between

Table 2. CTE findings, fat parameter findings, and clinical features in different grades of intestinal inflammation and fibrosis

Factor	Inflammation			P-value	Fibrosis			P-value
	Grade 2 ($n=9$)	Grade 3 ($n=8$)	Grade 4 ($n=31$)		Grade 2 ($n=15$)	Grade 3 ($n=20$)	Grade 4 ($n=13$)	
VF/SF ratio	1.3 ± 0.7	0.8 ± 0.6	0.9 ± 0.5	0.131	0.6 ± 0.3	1.0 ± 0.6	1.4 ± 0.6	0.004
Wall thickness, *n* (%)				0.567				0.466
>7 mm	9 (100.0)	7 (87.5)	29 (93.5)		15 (100.0)	18 (90.0)	12 (92.3)	
≤7 mm	0 (0.0)	1 (12.5)	2 (6.5)		0 (0.0)	2 (10.0)	1 (7.7)	
Narrowed diameter[a], mm, median (IQR)	5.0 (4.0, 7.0)	4.0 (3.5, 5.5)	4.0 (2.0, 5.0)	0.382	5.0 (2.0, 6.0)	5.0 (3.0, 6.5)	4.0 (3.0, 5.0)	0.453
Upstream dilatation diameter[a], mm, median (IQR)	30.0 (17.0, 32.0)	33.0 (27.5, 43.5)	35.0 (23.0, 47.0)	0.333	33.0 (17.0, 50.0)	30.5 (23.5, 40.5)	32.0 (24.0, 42.0)	0.969
ND ratio	20.3 ± 6.7	13.5 ± 5.0	15.9 ± 12.0	0.378	18.3 ± 11.7	17.8 ± 11.4	11.6 ± 4.7	0.163
Hypervascularity, *n* (%)	9 (100.0)	7 (87.5)	30 (96.8)	0.396	15 (100.0)	18 (90.0)	13 (100.0)	0.232
Fat stranding, *n* (%)	8 (88.9)	7 (87.5)	31 (100.0)	0.148	15 (100.0)	18 (90.0)	13 (100.0)	0.232
Target sign, *n* (%)	8 (88.9)	8 (100.0)	30 (96.8)	0.472	14 (93.3)	19 (95.0)	13 (100.0)	0.659
Lymphadenopathy, mm	7.0 ± 2.3	6.0 ± 2.4	7.2 ± 4.0	0.698	7.3 ± 3.0	6.8 ± 4.2	6.8 ± 2.9	0.741
Male, *n* (%)	6 (66.7)	5 (62.5)	26 (83.9)	0.313	12 (80.0)	14 (70.0)	11 (84.6)	0.589
Age[a], years, median (IQR)	26.0 (23.0, 33.0)	35.0 (30.5, 45.0)	29.0 (24.0, 34.0)	0.105	28.0 (24.0, 34.0)	32.5 (24.5, 37.5)	31.0 (25.0, 35.0)	0.625
BMI[a], kg/m^2, median (IQR)	18.6 (17.3, 19.5)	15.8 (14.4, 18.3)	17.0 (15.0, 18.3)	0.167	17.1 (14.9, 18.7)	17.4 (16.2, 18.9)	15.1 (14.9, 17.3)	0.216
CDAI	159.7 ± 82.8	211.4 ± 41.7	224.2 ± 95.4	0.158	208.6 ± 84.6	211.6 ± 80.5	209.0 ± 108.5	0.994
ESR[a], mm/h, median (IQR)	19.0 (6.0, 51.0)	34.5 (29.5, 52.5)	37.0 (24.0, 51.0)	0.185	37.0 (17.0, 45.0)	37.0 (14.0, 51.0)	37.0 (29.0, 54.0)	0.550
CRP[a], mg/L, median (IQR)	33.0 (13.5, 65.9)	14.7 (2.5, 34.5)	13.7 (10.1, 44.1)	0.737	13.5 (7.3, 27.0)	13.7 (7.0, 83.4)	22.7 (13.5, 42.9)	0.769
PLT, 10^9/L	333.8 ± 163.6	329.9 ± 93.8	317.9 ± 90.4	0.908	345.1 ± 70.9	298.8 ± 109.3	344.3 ± 130.7	0.404
HCT, %	34.5 ± 8.1	33.9 ± 4.9	33.6 ± 6.1	0.928	35.7 ± 5.4	32.5 ± 6.7	33.6 ± 6.2	0.329
Disease duration[a], month, median (IQR)	36.0 (10.0, 54.0)	18.0 (3.5, 30.0)	36.0 (12.0, 72.0)	0.132	48.0 (10.0, 60.0)	30.0 (11.0, 63.0)	24.0 (12.0, 60.0)	0.903
Anemia, *n* (%)	4 (44.4)	3 (37.5)	19 (61.3)	0.392	7 (46.7)	10 (50.0)	9 (69.2)	0.434

BMI, body mass index; CDAI, clinical disease activity index; CRP, C-reactive protein; CTE, computed tomography enterography; ESR, erythrocyte sedimentation rate; HCT, red blood cell specific volume; IQR, interquartile range; ND ratio = 100 × narrowed diameter/upstream dilatation diameter; PLT, platelet; VF/SF ratio, the volume ratio of abdominal visceral fat to subcutaneous fat.

[a]The data do not follow the normal distribution.

the VF/SF volume ratio and the degree of fibrosis in the part with the most serious intestinal lesions was calculated and analysed. We found that the VF/SF volume ratio was positively correlated with the fibrosis severity of patients with CD. Furthermore, the VF/SF volume ratio showed good accuracy for distinguishing between moderate and severe fibrosis. This is the first study to adopt CTE to predict the degree of fibrosis in CD patients.

Accurate evaluations of the degree of intestinal fibrosis in patients with CD are imperative to anti-fibrosis treatment. However, methods of assessing the degree of intestinal fibrosis are limited. Recent studies have used the magnetization transfer ratio and T2* with MRI to evaluate the degree of fibrosis of local lesions based on the observer's judgment [8, 9]. These require high technology and have certain subjectivity, thus precluding objective and accurate reflections of fibrosis severity.

Table 3. Multi-variant binomial logistic regression analysis for predicting severe fibrosis and inflammatory

Feature	Odds ratio (95% CI)	P-value
Fibrosis score (2/3 vs 4)		
VF/SF volume ratio[a], increase by one unit	1.20 (1.05–1.38)	0.009
ND ratio, increase by one unit	0.90 (0.82–0.99)	0.034
Inflammatory score (2/3 vs 4)		
Gender (female vs male)	0.24 (0.05–1.12)	0.070
Anemia (yes vs no)	3.18 (0.83–12.20)	0.092

CI, confidence interval; VF/SF volume ratio, the volume ratio of abdominal visceral fat to subcutaneous fat; ND ratio = 100 × narrowed diameter/upstream dilatation diameter.

[a]The value of VF/SF volume ratio × 10; considering that the VS/VF value is low to make the OR value vary widely by one unit in the multivariate analysis, all values of the VF/SF volume ratio here are multiplied by 10.

Therefore, it is of great importance to find a better method of formulating clinical treatment strategies against fibrosis with CD.

An increase in VF, mainly mesenteric fat, is a common pathological manifestation of CD [13]. Previous studies have confirmed that the VF/SF area ratio is significantly higher for patients with CD than for those without CD [13]. Increased VF is a characteristic manifestation of complex CD [14]. Patients with stenosis and fistulas have more VF than those without stenosis and fistulas. Additionally, increased VF is an independent risk factor for recurrence after surgery [15]. It is worth noting that abnormal collagen deposition and stenosis are often accompanied by fat wrapping around the bowel. A previous study revealed a correlation between mesenteric adipose hyperplasia and intestinal fibrosis in CD patients [25]. The existence of "creeping fat" as part of the mesenteric fat wrapping around the inflamed gut was also found to have a strong correlation with transmural inflammation, fibrosis histopathology, and clinical relevance [26]. The VF/SF area ratio is commonly used to reflect the degree of VF hyperplasia [14, 21]. During the present study, we measured the volumes of VF and SF using CTE and found that the VF/SF volume ratio can accurately assess the degree of fibrosis of the intestinal lesions, with an AUC of 0.760; moreover, when further combined with the ND ratio, the AUC exceeded 0.8. Previously, VF/SF area ratios have been proven to be able to predict CD prognosis and CD recurrence; interestingly, we found that the high accuracy of this index had a theoretical basis. Moreover, previous studies have shown that the proportion of M2 macrophages in proliferated mesenteric adipose tissue is significantly increased [27] and that M2 macrophages participate in tissue repair and collagen deposition [28]. Proliferative mesenteric adipocytes can transform into macrophages, thus blocking the migration of the intestinal flora, and playing a role in resisting intestinal microorganisms, and

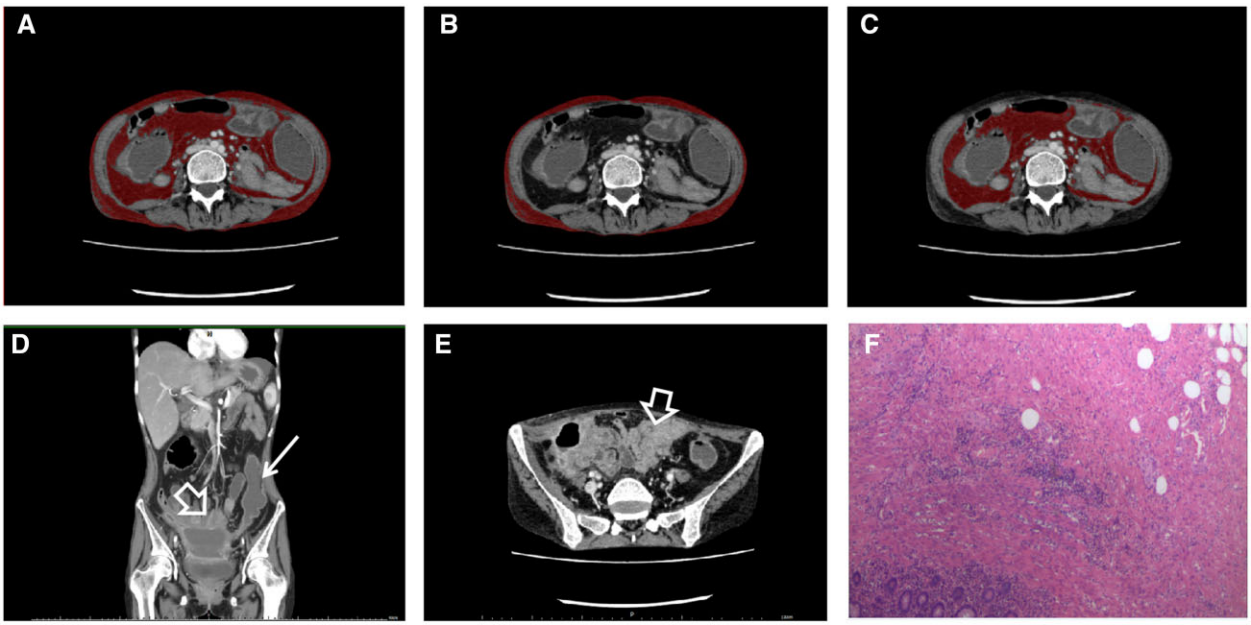

Figure 3. Clinical data of a typical case with severe fibrotic stenosis. The 44-year-old female patient suffered from Crohn's disease for >12 years with fecal incontinence and abdominal pain. Computed tomography enterography (CTE) before surgery showed that there was intestinal fistula and perianal abscess. The inflammatory score is Grade 2 and fibrosis score is Grade 4 based on histological pathology. (A) The red area shows quantitative 3D image fat signaling with A.K. software. (B) and (C) show the subcutaneous and visceral fat signaling on A.K. software, respectively. (D) and (E) show the intestinal stricture on axial CT and cross-sectional CT. The white hollow arrow shows the stricture and the white solid arrow shows the prestenotic dilation. (F) Histological specimen (corresponding area of the stricture) by hematoxylin and eosin (H&E) staining shows massive fibrosis in the intestinal wall.

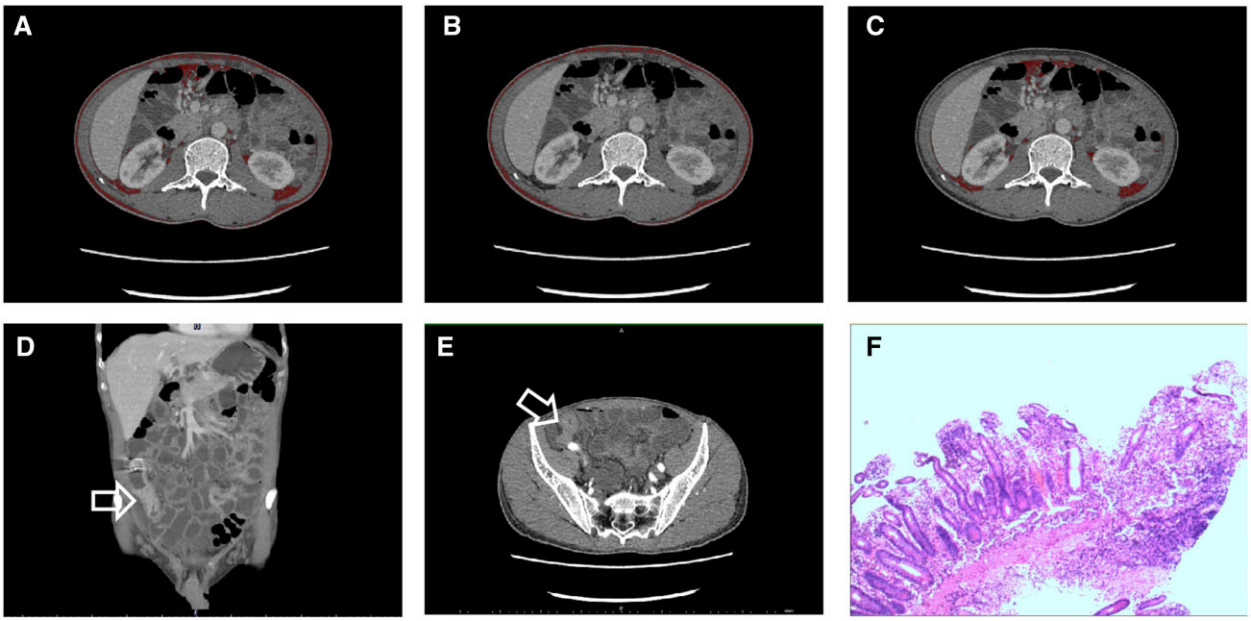

Figure 4. Clinical data of a typical case with severe inflammatory stenosis. A 53-year-old man suffered from Crohn's disease for >4 years with fever and abdominal pain. CTE showed that there was terminal ileum stenosis and bowel wall thickening. The inflammatory score is Grade 4 and fibrosis score is Grade 2 based on histological pathology. (A) The red area shows quantitative 3D image fat signaling with A.K. software. (B) and (C) show the subcutaneous and visceral fat signaling on A.K. software, respectively. (D) and (E) show the intestinal stricture on coronal CT and cross-sectional CT. The white hollow arrow shows the stricture. (F) Histological specimen (corresponding area of the stricture) by hematoxylin and eosin (H&E) staining shows inflammatory cells infiltrate the mucosa and submucosa (A color version of this figure appears in the online version of this article).

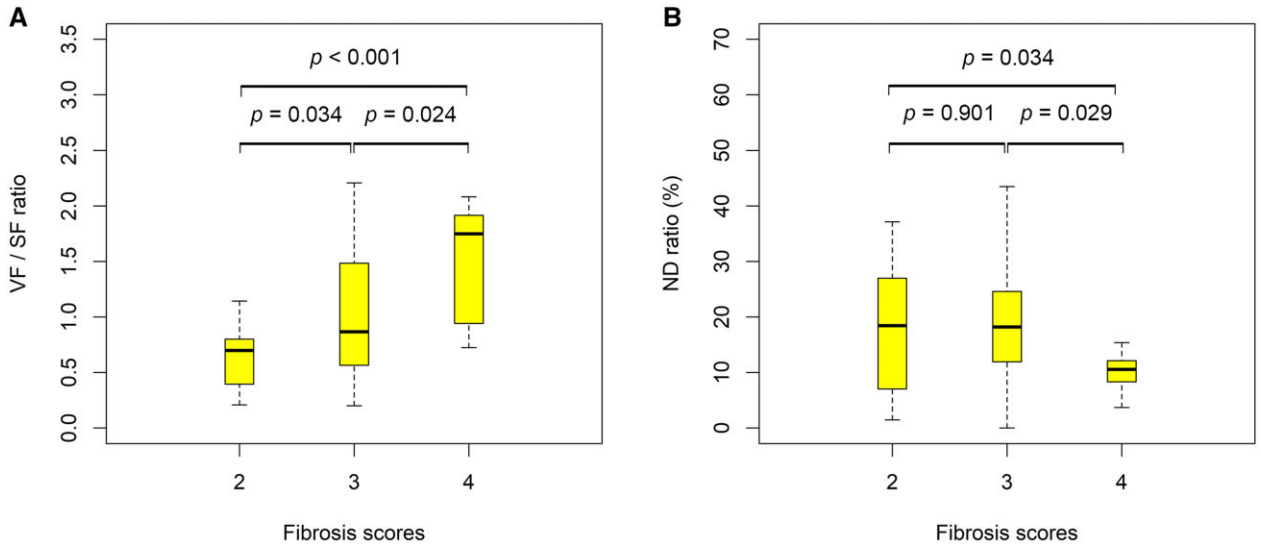

Figure 5. The correlation of the volume ratio of abdominal visceral fat to subcutaneous fat (VF/SF ratio) (A), the stenosis diameter/upstream intestinal dilatation diameter (ND ratio) (B) with different fibrosis scores of intestinal strictures. The overall *P*-values of VF/VS ratio and ND ratio among three subgroups are $P < 0.001$ and $P = 0.109$, respectively.

proliferative mesenteric fat uses intestinal fibrosis to block the spread of intestinal flora [25, 29]. More importantly, we used AI software to delineate the 3D shape of VF and calculate the volume with high accuracy and more convenience, which reduced the bias caused by subjectivity [8, 9].

This study also explored the relationships between typical CTE signs (including the hypervascularity, target sign, fat stranding, lymphadenopathy, narrowing, and dilatation) and stricture characteristics. We found that the degree of fibrosis was inversely correlated with the stenosis-to-dilation diameter ratio. When combined with the VF/SF volume ratio, the AUC for differentiating moderate from severe fibrosis was as high as 0.8. Using the Lemann score system [30], the sign of proximal intestinal dilatation was used to evaluate the degree of intestinal injury in CD patients. Proximal dilatation is suggestive of severe intestinal injury. Other studies have found that CD patients with proximal dilatation exhibited more severe fibrosis than those without proximal dilatation. Moreover, Michael *et al.* found a significant correlation between the pathological fibrous stenosis score and the severity of stenosis on CTE [31].

This study had several limitations. First, this was a single-center retrospective study with a limited sample size.

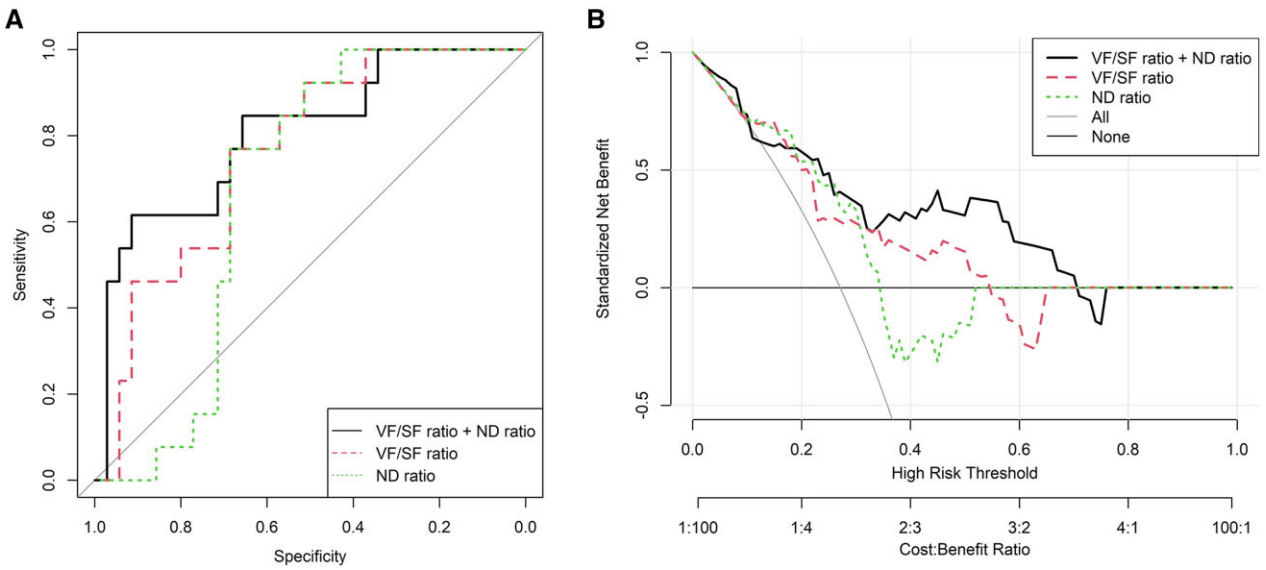

Figure 6. Receiver-operating characteristic curves (A) and decision curves (B) of VF/SF ratio, ND ratio, and combined (VF/SF + ND) ratio. The decision curve analysis reflected the net benefit of models. The horizontal lines across indicate that all samples were negative and none of them was intervened. The slanting one means that all the samples were positive and received the intervention, and the net benefit is a negative-slope backslash. The curves of net benefit of each model are compared and the slowest slope of the curve at the positive area indicates that the net benefit of the model is the best. ND ratio, 100 × narrow intestinal tube diameter/dilated intestinal segment diameter; VF/SF ratio, the volume ratio of abdominal visceral fat to subcutaneous fat.

Table 4. The diagnostic performance of each model for severe fibrosis (Grade 4)

Model	AUC (95% CI)	Sensitivity	Specificity	Accuracy	PPV	NPV
VF/SF ratio + ND ratio	0.804 (0.660–0.949)	61.5 (8/13)	91.4 (32/35)	83.3 (40/48)	72.7 (8/11)	86.5 (32/37)
VF/SF ratio	0.760 (0.619–0.902)	76.9 (10/13)	68.6 (24/35)	70.8 (34/48)	47.6 (10/21)	88.9 (24/27)
ND ratio	0.673 (0.523–0.822)	76.9 (10/13)	68.6 (24/35)	70.8 (34/48)	47.6 (10/21)	88.9 (24/27)

ND ratio, 100 × narrow intestinal tube diameter/dilated intestinal segment diameter; VF/SF ratio, the volume ratio of abdominal visceral fat to subcutaneous fat; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; AUC, the area under the curve.

Therefore, our conclusions must be verified by a multicenter study involving a larger sample size. Second, because of the lack of CD patients with mild fibrosis enrolled in this study, whether our conclusions can be applied to patients with mild fibrosis remains to be verified. Finally, the abdominal fat distribution is different among different races [32]; therefore, whether these results are applicable to other races, such as Caucasians, remains to be verified.

In conclusion, simple measurements of the VF/SF volume ratio using CTE can distinguish between moderate and severe fibrosis in CD patients. This ratio may serve as a novel method of evaluating the degree of intestinal fibrosis in CD patients.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

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Not applicable.

Authors' Contributions

Y.H. and G.Y. conceived the study. M.M.T., Y.Q., and Z.L.X. wrote the manuscript. G.Y. and M.H.C. revised the manuscript. Q.H.C. and Z.R.Z. evaluated the pathological and radiological parameters. M.H.C., Y.H., and S.P. critically reviewed the content of the paper and supervised the project. All authors have read and approved the final version of the manuscript.

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Conflict of Interest

None declared.

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