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RESEARCH ARTICLE

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Imbalance between skeletal muscle and intermuscular fat predicts treatment failure in Crohn's disease: an imaging biomarker for risk stratification

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ABSTRACT

Background: Sarcopenia is prevalent in Crohn's disease (CD) patients, but the prognostic value of skeletal muscle-to-intermuscular adipose tissue (IMAT) balance in penetrating CD remains unexplored.
Objective: To determine whether skeletal muscle-IMAT imbalance predicts non-surgical treatment failure in CD.
Methods: This retrospective study included CD patients undergoing computed tomography enterography (CTE, 2013–2022), stratified by disease behavior (penetrating vs. non-penetrating). Automated CTE segmentation algorithm quantified skeletal muscle and IMAT volumes at baseline. Skeletal muscle ratio was calculated as skeletal muscle/(skeletal muscle + IMAT). Sarcopenia was defined by the skeletal muscle area at the third lumbar vertebra. Patients received ≥1 year of non-surgical therapy, with outcomes categorized as 'maintenance therapy' or 'treatment escalation'. Cox proportional hazards analysis identified predictors of escalation; mediation analysis evaluated inflammatory-nutritional pathways.
Results: Among 157 patients (penetrating: $n=42$; non-penetrating: $n=115$), treatment escalation rates were 64.3% (27/42) and 53.0% (61/115) respectively, without significant intergroup difference ($p=0.21$). Skeletal muscle ratio predicted escalation in both cohorts (penetrating: AUC = 0.822 [0.673, 0.923], non-penetrating: AUC = 0.922 [0.857, 0.964]), outperforming conventional sarcopenia metrics ($p=0.002$ and $p<0.001$). Cox regression confirmed skeletal muscle ratio as an independent protective factor (penetrating: HR = 0.098 [0.014 – 0.680], $p=0.02$; non-penetrating: HR = 0.597 [0.442 – 0.804], $p=0.001$; combined: HR = 0.637 [0.493 – 0.823], $p=0.001$), while penetrating disease as risk factor (HR = 3.778 [1.281 – 11.14], $p=0.02$). Body mass index mediated 6.9% of the skeletal muscle ratio-treatment escalation relationship in non-penetrating CD.
Conclusions: Skeletal muscle-IMAT imbalance independently predicts treatment escalation in CD, offering superior prognostic utility to traditional sarcopenia measures.

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Introduction

Penetrating complications affects up to 50% of Crohn's disease (CD) patients over their disease course, manifesting as free perforation, intra-abdominal abscess, and fistula formation [1]. Current therapeutic strategies primarily include surgical intervention, long-term medication, and supportive care. However, surgical management, while providing immediate symptomatic relief, is associated with high postoperative recurrence rates ranging from 48% to 93% [2], and inadequate treatment increases mortality and disability risks [3]. Non-surgical management is a crucial component in the treatment of penetrating CD, although its efficacy remains controversial. A study revealed comparable five-year recurrence rates between medical and surgical management in CD patients with intra-abdominal abscesses, while

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anti-tumor necrosis factor therapy independently reduced recurrence risk [4]. Longitudinal data showed that 65% of medically managed patients required surgery within one year despite initial 50% three-month response rates [5]. Therefore, accurately predicting treatment outcomes and optimizing personalized therapeutic strategies are pivotal to advancing clinical research.

Beyond clinical and surgical approaches, lifestyle factors also influence disease course and patient well-being. However, population-based studies have demonstrated that patients with inflammatory bowel disease generally exhibit low baseline levels of physical activity, with over 40% classified as completely inactive due to perceived barriers such as fear of disease reactivation and limited social support [6]. Physical inactivity—linked to obesity and sarcopenia—combines with other modifiable risks like smoking to perpetuate inflammation, drive metabolic dysfunction, and worsen outcomes, representing critical management targets.

Emerging imaging biomarkers have gain increasing attention in CD assessment. Computed tomography enterography (CTE) provides comprehensive evaluation of both intestinal manifestations and body composition features, demonstrating prognostic utility for therapeutic responses. Existing evidence indicates that visceral obesity caused by abnormal visceral adipose tissue (VAT) accumulation independently predicts poor anti-tumor necrosis factor treatment outcomes in CD patients [7,8], while CTE-based intestine and adipose tissue quantification can identify potential biologic therapy responders [9]. In addition, multi-parametric models integrating intestinal features and skeletal muscle metrics stratify treatment failure risk [10]. Despite these advances, current imaging biomarkers predominantly target non-penetrating phenotypes, leaving a critical gap in complex CD management.

Intermuscular adipose tissue (IMAT) regulates skeletal muscle insulin sensitivity through lipid-mediated signaling. This specialized depot independently alters the local metabolic environment and accelerates fat deposition [11]. Notably, IMAT demonstrates methylation patterns analogous to VAT, with higher expression of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α than subcutaneous adipose tissue (SAT) [12]. CT-quantified muscle attenuation, as a surrogate for IMAT infiltration, shows multi-disease prognostic capacity: From pulmonary decline in asthma to hepatocellular carcinoma progression [13,14]. Previous CD studies also associate this imaging biomarker with complex behaviors and severity [15,16], yet its predictive power remains unproven in penetrating CD. Investigating the role of IMAT in CD treatment outcomes might uncover underlying molecular mechanisms and identify new therapeutic targets.

Therefore, the purpose of this study is to develop CT-derived skeletal muscle adiposity biomarkers from baseline CTE data, investigating their relationships with clinical indicators and treatment outcomes in both penetrating and non-penetrating CD patients, and comparing their prognostic value with established risk factors.

Methods

Study population

This retrospective study was conducted in a tertiary referral center spanning three campuses and the research protocol was approved by the ethics committee of Tongji Hospital (TJ-IRB20230890) with a waiver of informed consent.

Adult CD patients who underwent baseline and follow-up CTE scans from May 28, 2013, to September 8, 2022, were enrolled, with follow-up ending on August 30, 2023. The inclusion criteria were as follows: (a) diagnosis was confirmed by a multidisciplinary team following the World Gastroenterology Organisation 2015 guidelines [17]; (b) baseline and follow-up CTE data were available; (c) a follow-up of at least one year. The exclusion criteria were as follows: (a) concomitant metabolic disease or malignancy; (b) poor CT image quality due to artifacts (respiratory/metal artifacts impeding bowel or body composition assessment). Enrolled patients were classified into penetrating and non-penetrating groups. Penetrating CD was identified by endoscopic or cross-sectional imaging showing intestinal fistulas, intra-abdominal abscesses, or perforation, with inflammatory exudation around diseased segments. After excluding those who underwent immediate bowel resection during their initial hospitalization, the remaining patients receiving conservative treatment were included for further analysis.

Collection of clinical and laboratory data

Baseline patient information was retrieved from the electronic medical record system, including demographic data (sex, age, height, weight, body mass index [BMI]), symptoms such as acute or chronic abdominal pain, smoking history, and surgical history. The Montreal classification and laboratory results, including C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), albumin, hematocrit, and hemoglobin, were also documented [18]. For patients receiving conservative treatment, specific treatments, such as biologics, immunomodulators, and exclusive enteral nutrition, were documented.

Assessment of ileocolonoscopy and CTE images

For patients with ileocolonoscopy data, their images and reports were reviewed by a senior gastroenterologist (F.X.), and the simple endoscopic score of CD (SES-CD) was calculated for each patient [19]. To address potential subjectivity and enhance the reliability of the endoscopic assessment, a second, independent review was performed on a randomly selected subset of the data. Specifically, among the 124 patients who completed ileocolonoscopy (out of the 157 enrolled), 30 patients (24.2%) were randomly selected. The ileocolonoscopy data for these 30 patients were then reviewed by a second gastroenterologist (J.H.), who was blinded to all patient clinical information as well as to the initial SES-CD scores and findings reported by the first reviewer. Meanwhile, the severity and length of inflammation within the distal 20 cm of the terminal ileum was measured on the baseline CTE by a senior radiologist (Y.S.) using the CTE scoring system mentioned in a previous study [20]. The severity of ileal inflammation was scored as follows: 0: none; 1: hyperenhancement with no or equivocal wall thickening (3–5mm); 2: wall thickening ≥5 mm (at thickest region) with hyperenhancement; 3: wall thickening ≥5 mm with hyperenhancement, fat stranding, ulcers; or wall thickening >10 mm. For those with disease confined to the colon, a CTE score of 0 was assigned. Similarly, to ensure the reliability of radiological assessments, the baseline CTE images of these same 30 patients were independently reviewed by a second radiologist (Z.X.), blinded to clinical data, endoscopic results, and initial CTE assessments. The original scoring protocol was rigorously followed.

Measurement of imaging metrics in fat and skeletal muscle

Utilizing a previously developed automatic segmentation algorithm [21,22], VAT, SAT, IMAT, and skeletal muscle in CTE images were automatically identified and segmented to obtain the volume of interests for each tissue. Subsequently, an abdominal radiologist checked volume of interests using open-source software (ITK-SNAP, version 3.8.0) and corrected any errors to get the final volume of interests for the extraction of fat and skeletal muscle metrics. The information extracted from volume of interests includes the volumes (cm^3) of each tissue in the lumbar region (from the upper edge of the first lumbar vertebra to the lower edge of the fifth lumbar vertebra), as well as CT attenuation (HU) (including median, 5th percentile, and 95th percentile). Based on the volumes, the visceral-to-subcutaneous fat ratio (VSR = VAT/SAT) and the skeletal muscle ratio (SMR = skeletal muscle/(skeletal muscle + IMAT) × 100%) were calculated.

In addition, the skeletal muscle area (SMA, cm^2) at the level of the third lumbar vertebra (L3) was calculated, which was normalized by the square of height to derive the skeletal muscle index (SMI, cm^2/m^2). Considering the age range (18 to 59 years) and ethnicity (Han Chinese) of the study participants, we applied the sarcopenia definition proposed by Zeng et al. [23]: males with SMI less than 44.77 cm^2/m^2 or females with SMI less than 32.50 cm^2/m^2.

Follow-up and treatment outcomes definition

Patients were categorized into a 'maintenance therapy' group and a 'treatment escalation' group based on whether the treatment regimen was modified during follow-up and the endoscopic or imaging assessments at follow-up completion. The definition is as follows:

Maintenance therapy group: Patients who consistently adhered to their initial treatment plan and showed either endoscopic response (SES-CD score decreased by ≥50% from baseline), endoscopic remission (SES-CD score ≤2), radiological improvement (inflammation length reduction of ≥5 cm or CTE score reduction of ≥2 points), or radiological remission (no wall thickening, enhancement, or other signs of inflammation) at the end of the follow-up [24,25]. Treatment escalation group: Patients who experienced either no improvement or disease progression, necessitating intensification of therapy beyond the initial treatment plan (including addition of biologics, corticosteroids, or immunomodulators; dose escalation; or bowel resection). Specifically, 'no improvement' was defined as: SES-CD score reduction <50% or SES-CD score ≥3, or radiological inflammation length change <5 cm or CTE score change <2 points. 'Disease progression' was characterized by radiological evidence of inflammation length increase ≥5 cm or CTE score increase ≥1 points, or development of new inflammatory segments (≥5 cm), strictures, or penetrating complications [25].

For patients in the treatment escalation group, the end point of follow-up was the time of treatment escalation; and for patients in the maintenance therapy group, it was August 30, 2023. The time from the baseline to the end point of follow-up was defined as escalation-free survival.

Statistical analysis

Statistical analyses were performed using SPSS (Version 26.0, SPSS Inc., Chicago, IL, USA) or Python (Version 3.11.4, Python Software Foundation, <http://python.org>). Automatic segmentation and extraction of imaging metrics were carried out using Python. Comparison between the penetrating and non-penetrating groups, as well as among different treatment outcome groups, was conducted using the Student's t-test, the Mann-Whitney U test, or the Chi-square test based on the distribution of the data. Based on the comparison results, receiver operating characteristic (ROC) curves were employed to assess the value of skeletal muscle indicators (SMR, attenuation values, and sarcopenia), CTE scores, and SES-CD scores in discriminating patients with different treatment outcomes.

To identify independent predictors of treatment escalation, clinical, endoscopic, imaging, and imaging quantitative indicators were considered as candidate predictors. Univariate Cox regression analysis was conducted firstly, and factors with a P-value <0.20 were subsequently included in the multivariate analysis. In the Cox analysis, time-zero was defined as the date of first hospital admission for diagnostic workup. Right-censoring was applied at: last documented clinical follow-up for patients in the maintenance therapy group; the date of treatment escalation for patients switching to advanced therapies. Furthermore, based on the Youden index of SMR, patients were stratified into low-risk and high-risk subgroups for skeletal muscle adiposity. Kaplan-Meier methods were used to assess escalation-free survival, and log-rank tests were utilized to compare survival distributions between subgroups. Time-dependent ROC curves, along with corresponding areas under the curve (AUC), sensitivity, and specificity, were employed to investigate performance at different time points (6, 12, 18, 24, 30, 36, 42 and 48 months). Furthermore, post-hoc power analyses were conducted in G*Power 3.1 based on the observed effect sizes and event rates.

A mediation analysis was conducted to explore the associations between skeletal muscle adiposity (SMR, independent variable), inflammatory markers (CRP and ESR, mediating variables), nutritional indicators (BMI and Album, mediating variables), and treatment escalation (dependent variable). To evaluate inter-rater reliability, consistency analyses were performed. For the ileocolonoscopy assessment (SES-CD), agreement between the two gastroenterologists was assessed in a randomly selected subset of 30 patients using Cohen's κ coefficient. For radiological assessments, inter-rater agreement was evaluated using weighted Cohen's κ coefficient for categorical inflammation severity scores and intraclass correlation coefficient (ICC) for continuous measures of inflammation length. For κ, values of ≤0.20 indicated slight agreement, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and 0.81–1.00 excellent. For ICC, ≤0.20 indicated slight reliability, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 almost perfect reliability.

A two-sided P-value of <0.05 indicates statistical significance, except in the univariate Cox regression analysis ($p < 0.20$).

Results

The inclusion process is summarized in Figure 1. A total of 195 CD patients were enrolled, comprising 60 penetrating and 135 non-penetrating cases. Of these, 38 patients underwent immediate bowel resection

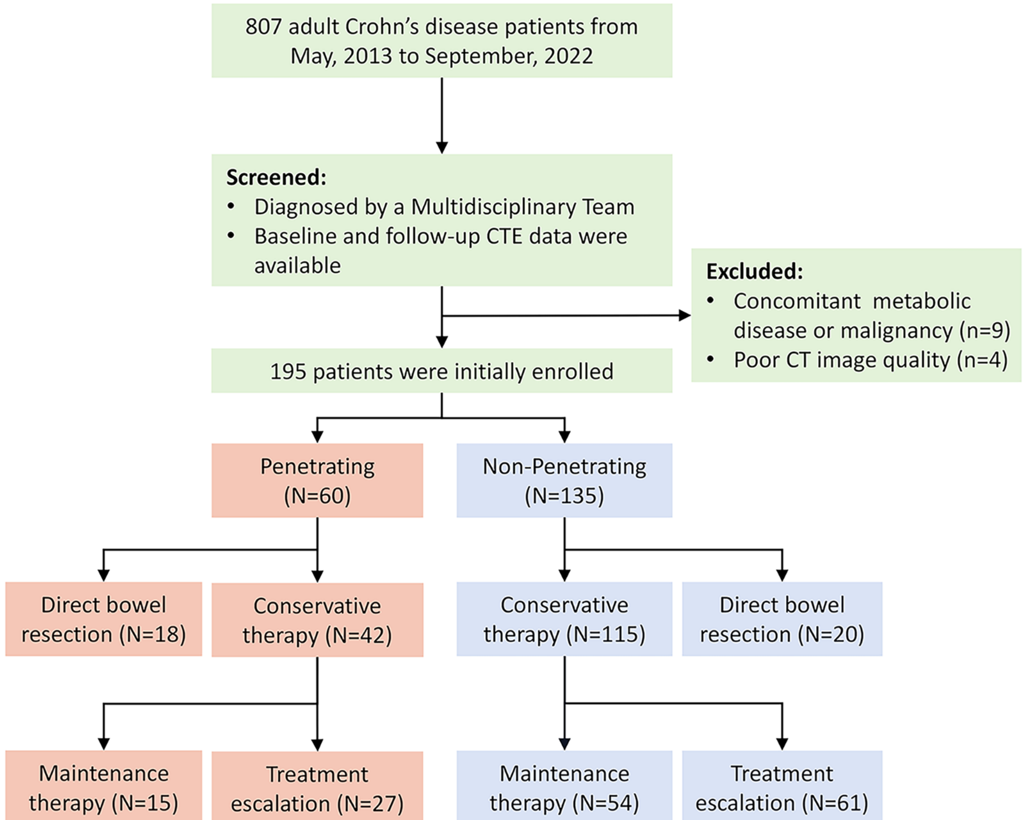

Figure 1. Overall flowchart of the patient inclusion and exclusion process. CTE, computed tomography enterography.

during their initial hospitalization (including 18 penetrating and 20 non-penetrating cases), while the remaining 157 received conservative treatment. Among the 157 patients, 88 required treatment escalation during follow-up. More specifically, 23 of those 88 patients underwent bowel resection, 52 changed to biologic therapy, and 13 increased glucocorticoids or immunomodulators use. Ttreatment escalation rates were 64.3% (27/42) and 53.0% (61/115) for the penetrating and non-penetrating groups, respectively, with no significant difference ($p = 0.21$).

Comparison of baseline characteristics between penetrating and non-penetrating groups

Table 1 summarizes the comparison of baseline features between the penetrating and non-penetrating groups. Active smoker (20% vs. 8.1%, $p = 0.03$), acute abdominal pain (43.3% vs. 14.8%, $p < 0.001$) and previous bowel resection (16.7% vs. 4.4%, $p = 0.008$) were more common in the penetrating group. The distribution of lesions significantly differed between the two groups ($p < 0.001$), with the penetrating group having a higher proportion of ileal lesions. The incidence of intestinal stricture (50.0% vs. 31.9%, $p = 0.02$) and CRP level ($p = 0.001$) was higher in the penetrating group. Ileocolonoscopy data for both groups were incomplete, with a lower acceptance rate in the penetrating group (41.7% vs. 79.3%, $p < 0.001$). Among patients undergoing ileocolonoscopy, SES-CD scores were comparable between the two groups ($p = 0.93$). In radiological evaluation, the affected ileum was more severe and longer in the penetrating patients. While more patients in the penetrating group required immediate or subsequent surgery (30.0% vs. 14.8%, $p = 0.003$), over half (51.7%) remained on conservative treatment.

Comparison of baseline characteristics among patients with different outcomes

Table 2 summarizes the comparisons between different outcome groups. Patients in the treatment escalation group were older in both the penetrating ($p = 0.15$) and non-penetrating groups ($p = 0.018$), though the difference was only significant in the latter. In the treatment escalation group, a higher proportion

Table 1. Comparison between penetrating and non-penetrating patients.

	Penetrating ($n=60$)	Non-penetrating ($n=135$)	P value
Sex (male/female)	44/16	98/37	>0.99
Age, yrs	33.3 ± 11.0	30.8 ± 10.6	0.13
BMI, kg/m^2	18.6 ± 3.1	19.0 ± 2.8	0.40
Active smoker, n (%)	12 (20%)	11 (8.1%)	**0.03**
Abdominal pain, n (%)			**<0.001**
Acute	26 (43.3%)	20 (14.8%)	
Chronic	30 (50.0%)	72 (53.3%)	
Disease duration, yrs	1.00 (0.10, 3.00)	0.75 (0.17, 2.00)	0.72
Previous bowel resection, n (%)	10 (16.7%)	6 (4.4%)	**0.008**
Location†, n (%)			**<0.001**
L1	31 (51.7%)	36 (26.7%)	
L2	2 (3.3%)	24 (17.8%)	
L3	27 (45.0%)	75 (55.6%)	
L4†, n (%)	6 (10.0%)	22 (16.3%)	0.35
Perianal disease, n (%)	29 (48.3%)	81 (60.0%)	0.17
Intestinal stricture, n (%)	30 (50.0%)	43 (31.9%)	**0.02**
Laboratory results			
CRP, mg/L	69.6 (18.9, 125.5)	31.5 (11.0, 61.8)	**0.001**
ESR, mm/hr	30.5 (18.3, 46.3)	25.0 (12.0, 40.5)	0.19
Albumin, g/L	34.9 ± 5.6	36.1 ± 7.0	0.26
Hematocrit, %	34.1 ± 5.7	34.8 ± 6.3	0.48
Hemoglobin, g/L	107.5 ± 21.7	110.3 ± 23.9	0.44
SES-CD	12.6 ± 6.7 ($n=25$)	13.7 ± 6.6 ($n=107$)	0.93
Radiological assessment			
CTE Score			**<0.001**
0	1 (1.7%)	15 (11.1%)	
1	0 (0.0%)	30 (22.2%)	
2	0 (0.0%)	46 (34.1%)	
3	59 (98.3%)	44 (32.6%)	
Length#,cm	20.0 (15.3, 20.0)	10.6 (5.7, 15.5)	**<0.001**
Treatment			**0.003**
Immediate bowel resection	18 (30.0%)	20 (14.8%)	
Continuous conservative therapy	31 (51.7%)	103 (76.3%)	
Follow-up bowel resection	11 (18.3%)	12 (8.9%)	

†L1: ileal, L2: colonic, L3: ileocolonic; L4; upper gastrointestinal tract.
#Lesion length within 20 cm of the terminal ileum.
BMI: Body mass index; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; SES-CD: Simple Endoscopic Score for Crohn's Disease, CTE: Computed tomography enterography.

of females was observed, along with significantly lower BMI, albumin, hematocrit, and hemoglobin levels (all $p<0.001$), which serve as markers of nutritional status, whereas ESR levels were significantly higher ($p<0.001$) in these patients. The proportion of intestinal strictures and the type of drug treatment showed no significant differences between different outcome groups. Of these patients, 45.2% (19/42) of the penetrating cases and 91.3% (105/115) of the non-penetrating cases underwent ileocolonoscopy, and no significant difference in SES-CD scores was observed between different outcome groups ($p=0.25$ and 0.23). The ileal CTE scores showed differences only in the non-penetrating group ($p=0.008$).

Table 3 summarizes the comparison of fat and skeletal muscle metrics between different outcome groups. In the penetrating group, no significant differences in fat metrics were observed, and among the various skeletal muscle metrics, only SMR showed statistical differences ($p<0.001$). However, in the non-penetrating group, patients in the treatment escalation group not only had higher fat attenuation values, but also had significantly greater VSR ($p=0.04$); in addition, they had lower skeletal muscle volumes, attenuation values, and ratios.

Predictive performance of skeletal muscle and fat metrics on treatment outcomes

Table 4 summarizes the performance of skeletal muscle metrics (SMR, attenuation, SMI_{L3}, and sarcopenia) and VSR in predicting treatment outcomes. In both the penetrating (AUC = 0.822 [0.673, 0.923], $p<0.001$, Figure 2a) and non-penetrating groups (AUC = 0.922 [0.857, 0.964], $p<0.001$, Figure 2b), SMR demonstrated the best predictive performance; and the cut-off values were 98.1% and 97.8%, respectively. The AUC for SMR was higher than attenuation ($p=0.03$ and $p<0.001$), SMI_{L3} (both $p<0.001$), sarcopenia ($p=0.002$ and $p<0.001$) and VSR ($p=0.011$ and $p<0.001$). In addition, we evaluated the AUC, sensitivity, and specificity of SMR in predicting treatment escalation at multiple time points (Figure 3), and found

Table 2. Comparison of clinical, radiological, and endoscopic results in patients with different outcomes.

	Penetrating ($n=42$)			Non-penetrating ($n=115$)		
	Maintenance therapy ($n=15$)	Treatment escalation ($n=27$)	P value	Maintenance therapy ($n=54$)	Treatment escalation ($n=61$)	P value
Sex (male/female)	11/4	19/8	>0.99	47/7	36/25	**0.002**
Age, yrs	29.1 ± 8.8	34.3 ± 12.0	0.15	27.8 ± 8.3	32.3 ± 11.7	**0.018**
BMI, kg/m^2	18.4 ± 3.1	18.9 ± 3.3	0.64	19.8 ± 2.6	18.0 ± 2.5	**<0.001**
Active smoker, n (%)	5 (33.3%)	4 (14.8%)	0.24	2 (3.7%)	5 (8.2%)	0.44
Acute pain, n (%)	5 (33.3%)	11 (40.7%)	0.89	6 (11.1%)	7 (11.5%)	>0.99
Disease duration, yrs	0.50 (0.17, 3.00)	1.00 (0.17, 4.00)	0.62	0.46 (0.17, 2.00)	1.00 (0.25, 3.00)	0.056
Previous bowel resection, n (%)	3 (20.0%)	4 (14.8%)	0.69	0 (0.0%)	1 (1.6%)	>0.99
Disease location†, n (%)			>0.99			0.89
L1	8 (53.3%)	15 (55.6%)		13 (24.1%)	13 (21.3%)	
L2	0 (0.0%)	1 (3.7%)		9 (16.7%)	12 (19.7%)	
L3	7 (46.7%)	11 (40.7%)		32 (59.3%)	36 (59.0%)	
Perianal disease, n (%)	6 (40.0%)	17 (63.0%)	0.27	38 (70.4%)	38 (62.3%)	0.47
Intestinal stricture, n (%)	6 (40.0%)	12 (44.4%)	>0.99	12 (22.2%)	21 (34.4%)	0.22
Treatment, n (%)						
Bowel resection	0 (0.0%)	11 (40.7%)	**0.004**	0 (0.0%)	12 (19.7%)	**0.002**
Biologics	10 (66.7%)	16 (59.3%)	0.89	41 (75.9%)	46 (75.4%)	>0.99
Immunomodulator	4 (26.7%)	2 (7.4%)	0.16	12 (22.2%)	17 (27.9%)	0.63
Exclusive enteral nutrition	11 (73.3%)	20 (74.1%)	>0.99	34 (63.0%)	40 (65.6%)	0.92
Laboratory results						
CRP, mg/L	98.9 (20.6, 137.9)	66.5 (24.7, 95.1)	0.36	27.6 (8.3, 45.0)	38.0 (13.7, 66.0)	0.06
ESR, mm/hr	31.5 (19.5, 45.0)	30.0 (9.5, 47.5)	0.63	18.0 (7.5, 33.8)	31.5 (20.0, 47.8)	**<0.001**
Albumin, g/L	35.7 ± 4.2	35.0 ± 5.4	0.67	39.1 ± 5.8	33.4 ± 6.8	**<0.001**
Hematocrit, %	34.1 ± 6.1	35.4 ± 6.0	0.48	38.8 ± 5.1	31.8 ± 5.1	**<0.001**
Hemoglobin, g/L	107.0 (90.0, 121.0)	106.0 (100.0, 119.0)	0.82	129.0 (116.3, 139.0)	99.0 (88.0, 111.0)	**<0.001**
CTE score			>0.99			**0.008**
0	0 (0.0%)	1 (3.7%)		6 (11.1%)	9 (14.8%)	
1	0 (0.0%)	0 (0.0%)		19 (35.2%)	6 (9.8%)	
2	0 (0.0%)	0 (0.0%)		17 (31.5%)	21 (34.4%)	
3	15 100.0%)	26 (96.3%)		12 (22.2%)	25 (41.0%)	
Involved Length, cm	20.0 (20.0, 20.0)	20.0 (15.0, 20.0)	0.12	8.2 (4.7, 15.0)	12.0 (7.3, 17.0)	0.056
SES-CD	10.3 ± 3.9 ($n=4$)	14.7 ± 7.2 ($n=15$)	0.25	12.9 ± 7.0 ($n=50$)	14.5 ± 6.2 ($n=55$)	0.23
Follow-up, mon	15.2 (7.9, 23.4)	18.5 (9.1, 36.8)	0.44	30.0 (21.0, 39.1)	26.3 (13.3, 38.6)	0.09

†L1: ileal, L2: colonic, L3: ileocolonic; L4; upper gastrointestinal tract. BMI: Body mass index; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; CTE: Computed tomography enterography, SES-CD: Simple Endoscopic Score for Crohn's Disease.

that the AUC ranged from 0.76 to 0.87 in the penetrating group and from 0.68 to 0.89 in the non-penetrating group.

Identification of independent predictors of treatment escalation

Table S1 and Table S2 summarizes the results of univariate and multivariate cox proportional hazards regression, respectively. SMR was identified as the independent predictor of treatment escalation in both groups (penetrating group: hazard ratio (HR) = 0.098 [0.014 – 0.680], $p=0.02$; non-penetrating group: HR = 0.597 [0.442 – 0.804], $p=0.001$). Additionally, BMI (HR = 0.449 [0.212 – 0.950], $p=0.04$), active smoking (HR = 0.032 [0.002 – 0.593], $p=0.02$), and VSR (HR = 0.052 [0.004 – 0.653], $p=0.02$) were identified as protective factors against treatment escalation in patients with penetrating disease, although they did not demonstrate statistically predictive power in non-penetrating patients. According to the cut-off values, the patients with SMR ≤98.1% in the penetrating group were at high risk of skeletal muscle adiposity, while those in the non-penetrating group were SMR ≤ 97.8%. According to the Kaplan-Meier curves, high-risk patients had a shorter median escalation-free time than low-risk patients in both penetrating (Figure 4a, $p=0.04$) and non-penetrating groups (Figure 4b, $p<0.001$). Figure 5 displays CT images of a low-risk penetrating patient and a high-risk non-penetrating patient, with skeletal muscle and IMAT

Table 3. Comparison of fat and skeletal muscle metrics in patients with different outcomes.

	Penetrating ($n=42$)			Non-penetrating ($n=115$)		
	Maintenance therapy ($n=15$)	Treatment escalation ($n=27$)	P value	Maintenance therapy ($n=54$)	Treatment escalation ($n=61$)	P value
Fat metrics						
VAT volume, cm^3	1710.34 (935.24, 2240.81)	1650.36 (562.49, 3302.54)	0.87	1401.11 (955.47, 2115.13)	1274.48 (686.16, 2217.15)	0.21
SAT volume, cm^3	1976.06 (258.43, 2838.61)	1856.17 (517.23, 4423.82)	0.57	1866.62 (1065.41, 3479.37)	1604.44 (489.66, 2617.86)	**0.02**
IMAT volume, cm^3	90.33 (39.44, 107.92)	60.33 (46.28, 116.98)	0.82	64.29 (43.08, 100.34)	61.91 (39.94, 99.27)	0.87
VSR	1.21 (0.76, 2.38)	1.12 (0.75, 1.68)	0.57	0.70 (0.57, 1.04)	1.02 (0.59, 2.15)	**0.04**
VAT_{median}, HU	−66.87 ± 18.46	−71.37 ± 22.97	0.52	−74.11 ± 14.68	−67.10 ± 21.16	**0.04**
VAT_{5th}, HU	−119 (−125, −109)	−119 (−130, −99)	0.69	−120 (-128, −112)	−115 (−125, −99)	**0.013**
VAT_{95th}, HU	5.00 ± 13.52	−1.41 ± 18.80	0.21	5 (−2.5, 13.3)	8 (−14.5, 18)	0.528
SAT_{median}, HU	−95 (−99, −55)	−95 (−109, −64)	0.54	−90 (−101.5, −76.8)	−83 (−104, −54.5)	0.13
SAT_{5th}, HU	−127 (−132, −97)	−126 (−138, −102)	0.56	−124 (−133.3, −115.3)	−118 (−135, −97)	0.12
SAT_{95th}, HU	−28.40 ± 20.45	−32.81 ± 21.12	0.52	−33.80 ± 13.96	−26.67 ± 22.67	**0.04**
$IMAT_{median}$, HU	−62.13 ± 9.57	−61.52 ± 9.23	0.84	−64.5 (−67, −60)	−63 (−67, −56)	0.07
$IMAT_{5th}$, HU	−110.27 ± 12.76	−109.26 ± 12.22	0.80	−113 (−117.3, −108)	−111 (−117.5, −104)	0.05
$IMAT_{95th}$, HU	−4.93 ± 6.67	−4.96 ± 7.45	0.99	−6.52 ± 7.23	−2.95 ± 7.69	**0.012**
Skeletal muscle metrics						
SMI_{L3}, cm^2/m^2	39.07 ± 6.15	39.46 ± 7.90	0.87	43.83 ± 7.84	37.80 ± 6.43	**<0.001**
Sarcopenia†	10 (66.7%)	17 (63.0%)	>0.99	25 (46.3%)	40 (65.6%)	0.058
Volume, cm^3	4327.39 (3122.12, 5020.51)	3235.52 (2904.75, 5061.30)	0.27	5384.96 (3693.26, 6625.63)	3557.78 (2814.52, 4730.51)	**<0.001**
SMR, %	98.32 ± 0.80	96.99 ± 1.21	**<0.001**	98.85 (98.36, 99.20)	97.00 (96.00, 97.79)	**<0.001**
$Attenuation_{median}$, HU	51 (46, 58)	49 (46, 52)	0.17	55 (52.8, 57)	49 (44.5, 54.5)	**<0.001**
$Attenuation_{5th}$, HU	−9.67 ± 10.47	−14.78 ± 9.88	0.12	−9.59 ± 10.24	−14.84 ± 11.27	**0.011**
$Attenuation_{95th}$, HU	85.20 ± 6.53	81.96 ± 6.39	0.13	87 (83, 91)	86 (81.5, 89)	0.10

†The cutoff values for male and female patients are 44.77cm^2/m^2 and 32.50cm^2/m^2 respectively.
VAT: Visceral adipose tissue; SAT: Subcutaneous adipose tissue; IMAT: Intermuscular adipose tissue; VSR: The ratio of visceral fat to subcutaneous fat; SMI: Skeletal muscle index; SMR: Skeletal muscle ratio.

Table 4. Performance of skeletal muscle and visceral fat metrics in predicting treatment outcomes in penetrating and non-penetrating patients.

	AUC [95% CI]	Sensitivity (%)	Specificity (%)	P value	Cut-off value
Penetrating (n = 42)					
SMR, %	0.822 [0.673, 0.923]	92.6	66.7	**<0.001**	≤98.1
SM $attenuation_{median}$, HU	0.630 [0.467, 0.773]	96.3	33.3	0.18	≤55
SMI_{L3}, cm^2/m^2	0.502 [0.344, 0.660]	55.6	60.0	0.98	≤38.15
Sarcopenia	0.519 [0.359, 0.675]	37.0	66.7	0.81	no
VSR	0.553 [0.392, 0.706]	96.3	26.7	0.61	≤2.3
Non-penetrating (n = 115)					
SMR, %	0.922 [0.857, 0.964]	77.1	92.6	**<0.001**	≤97.8
SM $attenuation_{median}$, HU	0.750 [0.661, 0.826]	67.2	75.9	**<0.001**	≤52
SMI_{L3}, cm^2/m^2	0.744 [0.654, 0.821]	75.4	72.2	**<0.001**	≤41.58
Sarcopenia	0.596 [0.501, 0.687]	65.6	53.7	**0.04**	yes
VSR	0.612 [0.517, 0.702]	34.4	92.6	**0.03**	>1.49

AUC: Area under the curve; SMR: Skeletal muscle ratio; SM: Skeletal muscle; SMI: Skeletal muscle index; VSR: The ratio of visceral fat to subcutaneous fat.

annotated on the images. In addition, we conducted univariate and multivariate Cox regression analyses on all patients combined (Table S3). The results showed that penetrating disease (HR = 3.778 [1.281 – 11.14], $p=0.02$) and SMR (HR = 0.637 [0.493 – 0.823], $p=0.001$) were independent predictors of treatment escalation. Post-hoc power analysis results (Table S4) demonstrated 92.5% power for the non-penetrating group, 93% for the combined cohort, but only 65% for the penetrating subgroup.

Inflammatory and nutritional indicators mediate skeletal muscle adiposity and treatment escalation

Table S5 summarizes the mediation analysis results for penetrating and non-penetrating patients. In the penetrating group, only a direct effect of SMR on treatment escalation was observed, with no

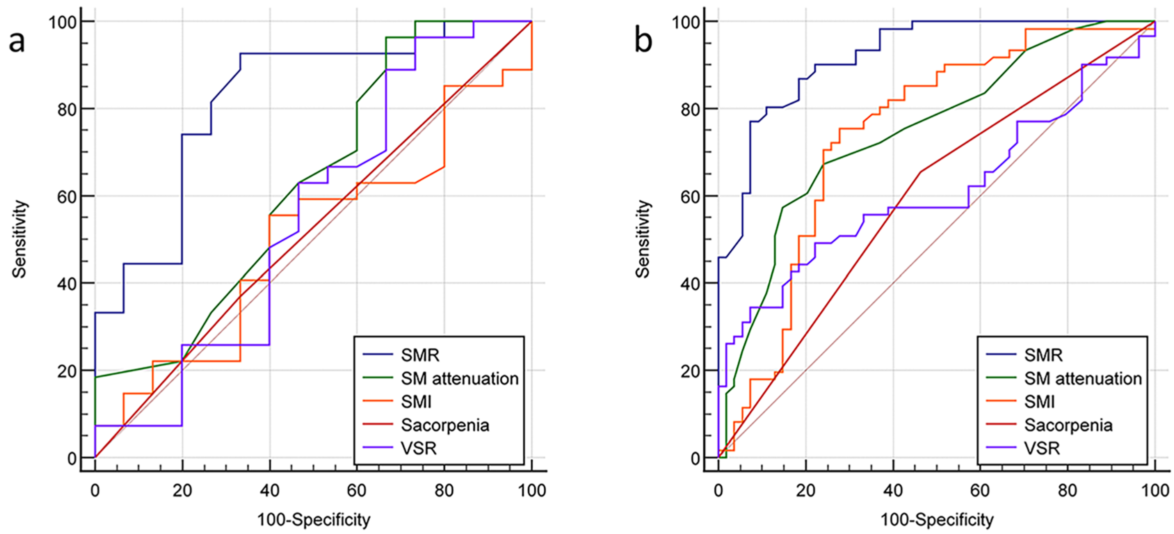

Figure 2. Performance of imaging metrics in predicting outcomes in penetrating (a) and non-penetrating (b) patients. SMR demonstrated the best predictive performance in both the penetrating (AUC = 0.822 [0.673, 0.923], $p<0.001$) and non-penetrating groups (AUC = 0.922 [0.857, 0.964], $p<0.001$). AUC, area under the curve; SMR, skeletal muscle ratio; SM, skeletal muscle; SMI, skeletal muscle index; VSR, the ratio of visceral fat to subcutaneous fat.

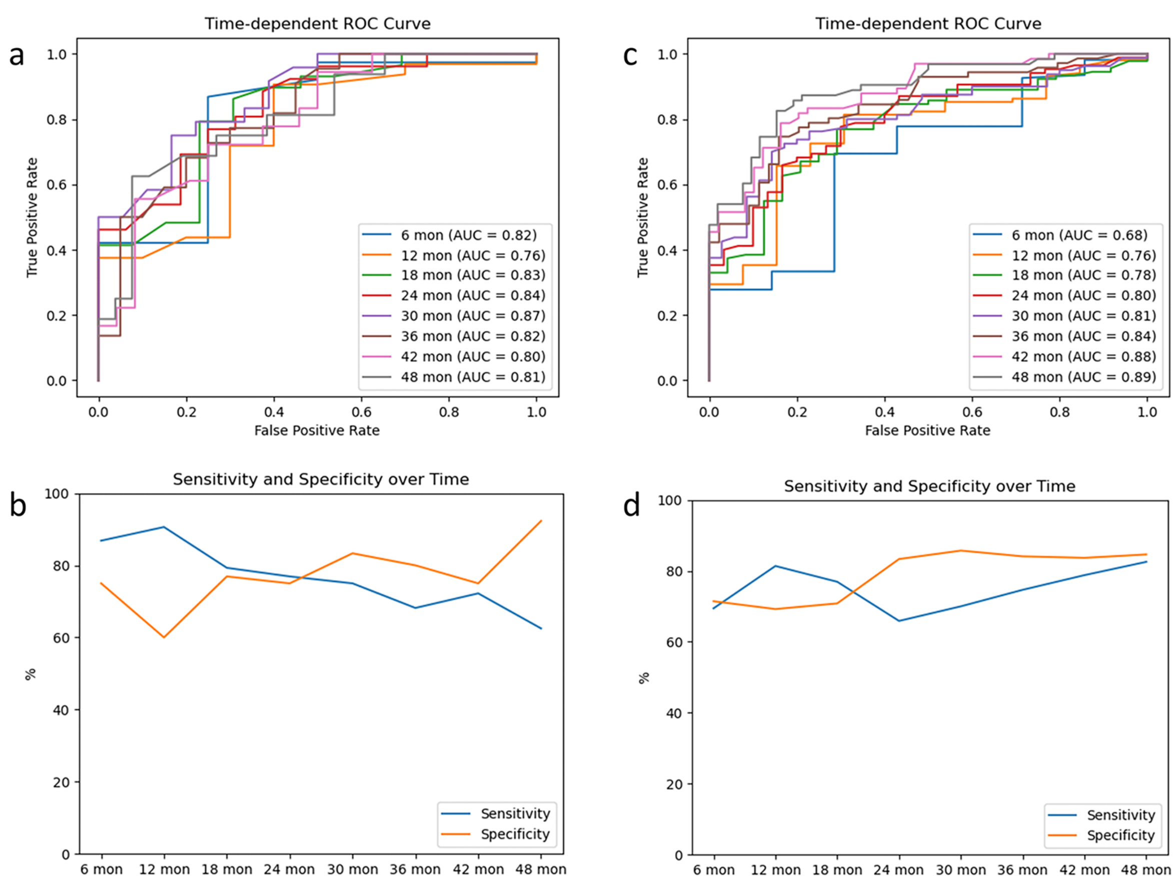

Figure 3. Time-dependent ROC curves for SMR in predicting treatment escalation in the penetrating (a–b) and non-penetrating (c–d) patients. AUCs for 6, 12, 18, 24, 30, 36, 42 and 48 months were used for escalation prediction. SMR, skeletal muscle ratio; ROC, receiver operation characteristic; AUC, area under the curve.

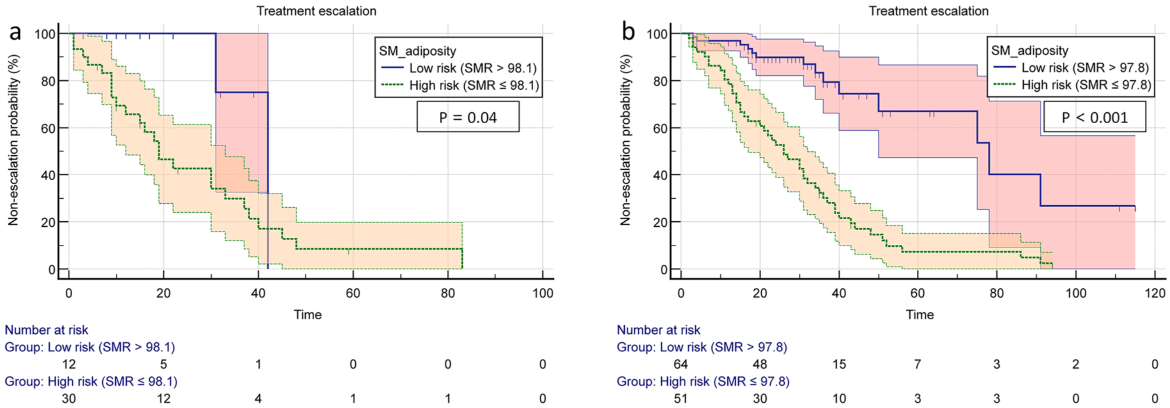

Figure 4. Kaplan-Meier Survival curves of escalation-free survival for the SMR in the penetrating (a) and non-penetrating (b) patients. High-risk patients had a shorter median escalation-free time than low-risk patients in both penetrating ($p = 0.04$) and non-penetrating groups, $p < 0.001$). SMR, skeletal muscle ratio; SM, skeletal muscle.

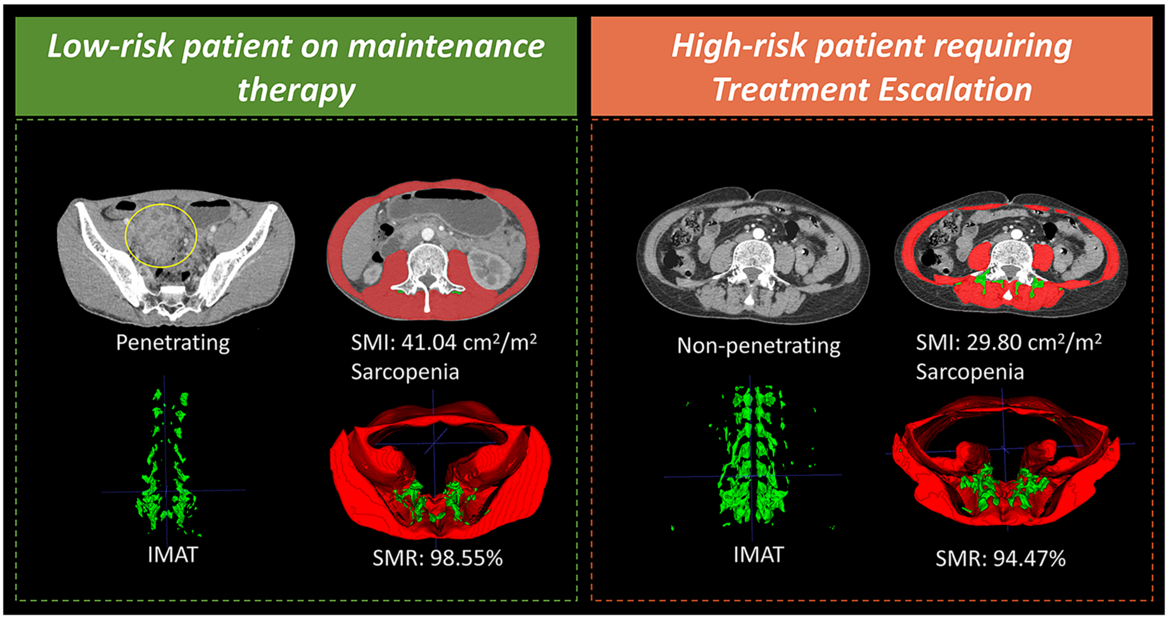

Figure 5. Comparison of skeletal muscle and IMAT measurements in low-risk and high-risk of skeletal muscle adiposity. Case 1: a 35-year-old male with baseline CTE score = 3, SES-CD score = 9, SMR = 98.55% (low risk), penetrating lesions, and sarcopenia. The patient maintained biologics therapy and demonstrated endoscopic remission (SES-CD = 1) after 15 months of follow-up. Case 2: a 53-year-old female with baseline CTE score = 3, SES-CD score = 6, SMR = 94.47% (high risk), and sarcopenia. The patient underwent surgery for a newly developed inter-intestinal fistula at the 8th month of follow-up. CTE, computed tomography enterography; SMR, skeletal muscle ratio; SES-CD, simple endoscopic score for crohn's disease.

significant mediation effects. In the non-penetrating group, significant associations were observed between SMR and all mediators, except for CRP, with BMI accounting for a partial mediating effect (6.9%) on the relationship between SMR and treatment escalation. Figure 6 illustrates the relationships among them.

Inter-rater agreement

For the ileocolonoscopy assessments, the inter-rater agreement of SES-CD scores between the two gastroenterologists was excellent ($\kappa = 0.936$ [0.909 – 0.963]). Similarly, the radiological evaluations by the two

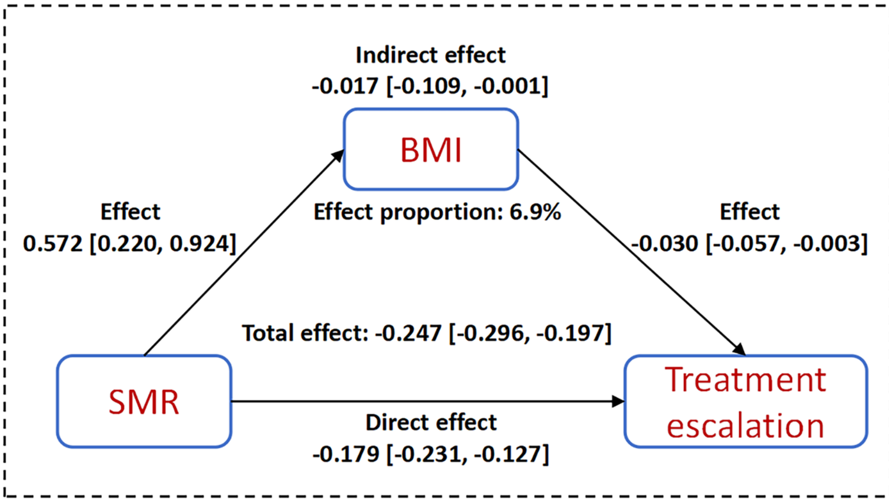

Figure 6. Schematic diagram of the mediating effect of BMI. Among non-penetrating patients, BMI acted as a mediator variable, partially mediating the association between the independent variable (SMR) and the dependent variable (treatment escalation). BMI, body mass index; SMR, skeletal muscle ratio.

radiologists demonstrated excellent consistency for both imaging scores (κ = 0.958 [0.877 – 0.999]) and inflammatory bowel segment length measurements (ICC = 0.954 [0.907 – 0.978]).

Discussion

This study identified SMR, a CT-derived imaging biomarker reflecting skeletal muscle adiposity, as the strongest predictor of treatment escalation in CD, outperforming clinical, endoscopic, and other body composition metrics. SMR showed robust prognostic accuracy across patient subgroups, notably maintaining its predictive value in the penetrating group, where other biomarkers often fail. Multivariable analysis confirmed that SMR was independently associated with treatment escalation, while mediation analysis revealed that 6.9% of this association was mediated by BMI. These findings position SMR as a novel imaging biomarker that could enhance risk stratification in CD management.

Sarcopenia, an age-related progressive skeletal muscle loss, commonly occurs in CD patients and is significantly associated with disease activity, postoperative complications and treatment durability [26–32]. The overall prevalence of sarcopenia in our cohort was 58.6% (92/157), with similar rates observed across different outcome groups, especially in penetrating cases (66.7% vs. 63.0%, $p > 0.99$). Subsequent ROC analysis revealed significantly lower AUC values for sarcopenia compared to other skeletal muscle and fat indicators. These findings suggest that skeletal muscle content alone may not sufficiently capture the complexity of therapeutic outcomes. IMAT, characterized by fatty infiltration within skeletal muscle, modulates local metabolic homeostasis through its paracrine lipid signaling pathways and is an important factor influencing skeletal muscle metabolism and quality [11]. Its excessive accumulation can manifest as skeletal muscle adiposity [13]. Current research primarily employs non-invasive imaging techniques, including CT and magnetic resonance imaging, for quantitative assessment of body composition, including skeletal muscle, IMAT, and VAT. Notably, reduced skeletal muscle attenuation values on CT images serve as an indirect biomarker for increased skeletal muscle adiposity. Published studies have demonstrated that skeletal muscle attenuation hold significant predictive value for the decline in lung function among asthma patients and for vascular invasion in hepatocellular carcinoma cases [13,14]. Furthermore, a strong correlation has been identified between the values and both complex disease behaviors and the disease severity in CD patients [15,16]. However, these studies have not yet achieved the direct and precise quantification of IMAT. Additionally, there remains a lack of in-depth exploration into the role of skeletal muscle fatty infiltration in CD treatment outcomes.

Our study utilized a validated automated segmentation algorithm to perform voxel-wise quantification of skeletal muscle and IMAT components through multiplanar 3D volumetric analysis [21,22].

Using these body composition metrics, we established the SMR as a novel, clinically relevant imaging biomarker to quantify muscle-to-IMAT balance. Our findings demonstrated that elevated SMR levels serves as an independent protective factor against treatment escalation requirements in CD patients. Moreover, risk stratification based on SMR thresholds revealed that high-risk patients (characterized by excessive skeletal muscle adiposity) experienced shorter treatment escalation-free survival period compared to low-risk counterparts. Notably, while skeletal muscle attenuation demonstrated moderate predictive capacity, SMR demonstrated superior prognostic value through its enhanced precision in assessment. Existing literature offers mechanistic support for these findings. One epigenetic study indicated that IMAT and VAT share highly similar functional characteristics, both acting as repositories for pro-inflammatory factors, with nearly identical DNA methylation patterns and functional traits [12]. Another study further characterized the molecular features of IMAT, showing significantly downregulated mRNA levels associated with oxidative metabolism and upregulated mRNA levels related to inflammatory cytokines [33,34]. These findings suggest that IMAT actively participates in the development of inflammation through the secretion of pro-inflammatory cytokines, thereby profoundly impacting skeletal muscle function. The adverse effects of VAT on CD have been well-documented, with multiple studies demonstrating that abnormal VAT accumulation and metabolic changes accelerate disease progression, resulting in poor outcomes [15,35,36]. Given the high functional similarity between IMAT and VAT, it is reasonable to hypothesize that IMAT influences treatment outcomes through analogous mechanisms. Interestingly, our analysis revealed that the VSR plays strikingly divergent roles in penetrating versus non-penetrating CD phenotypes: it acted as a protective factor in patients with penetrating disease but emerged as a risk factor in those with non-penetrating disease. This paradox likely stems from phenotype-specific pathophysiology. In non-penetrating disease, high VSR (excess VAT) exacerbates inflammation and metabolic dysfunction. Conversely, in penetrating disease, mesenteric VAT may confer protection through the physical sequestration of inflammatory mediators within adipose tissue, while potentially modulating immune responses or providing structural support.

This study explored the potential mediating roles of inflammatory and nutritional indicators in the SMR-treatment escalation relationship. Although inflammatory markers showed no mediating effect, SMR negatively influenced ESR. As a key marker of chronic inflammation, ESR could link skeletal muscle adiposity and chronic inflammatory processes. Importantly, BMI partially mediated the SMR-treatment escalation relationship, accounting for 6.9% of the total effect through indirect pathways. Prior cohort studies have shown BMI's mediating effects on adverse outcomes. Shen et al. reported BMI accounted for 36%-53% of the mediating effect linking night shift work to accelerated aging [37], while Li et al. found BMI mediated 11.45% of the effect linking adverse life events to chronic kidney disease risk [38]. In our study, while BMI correlates with SMR ($r = 0.572$, $p < 0.01$), its inability to differentiate muscle gain from fat accumulation limits clinical utility—a patient with high BMI could have either protective muscle mass or detrimental visceral fat. In contrast, SMR specifically quantifies muscle-fat balance, making it superior for guiding interventions. For CD patients, maintaining muscle mass through adequate protein intake and light resistance exercises, while controlling fat infiltration *via* balanced anti-inflammatory diets, may help optimize their SMR profile. Regular monitoring of body composition changes during clinical follow-ups could further personalize these nutritional approaches. These findings highlight the importance of integrating inflammatory, nutritional, and radiological metrics in disease management and offer novel insights into SMR's role in predicting treatment outcomes.

This study has several limitations. First, the retrospective design restricts the generalizability of findings to specific drug regimens, necessitating further prospective research. Second, as the study was conducted in a tertiary referral center rather than a community setting, the patient population likely represents more severe cases, potentially introducing selection bias. Third, the non-significant mediation analysis in the penetrating group ($n = 42$) may result from low statistical power attributable to the small subgroup size. Although this cohort represents the maximum feasible sample of penetrating CD patients meeting criteria that could be retrospectively collected at a single center within a reasonable timeframe—given only 3.9–14.0% present with penetrating disease at diagnosis—future larger multi-center cohorts are essential for validation [39]. Finally, incomplete endoscopic data may have influenced the analysis, though performing comprehensive ileocolonoscopies for all patients, particularly those with strictures, is not feasible in clinical practice.

In conclusion, for patients choosing non-surgical treatment, skeletal muscle adiposity substantially influences treatment outcomes in both penetrating or non-penetrating CD patients. The imaging biomarker SMR provides an objective and precise assessment of the fatty infiltration with skeletal muscle, outperforming traditional measures. Furthermore, SMR is readily accessible through routine CTE scans, underscoring its clinical practicality as an effective evaluation biomarker.

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Ethical considerations

This retrospective study followed the Declaration of Helsinki, and obtained the consent of the ethics committee of Tongji Hospital (TJ-IRB20230890), informed consent was waived due to the anonymity of the data.

Disclosure statement

All authors declare no conflict of interest in present study.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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