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ORIGINAL ARTICLE

Low psoas muscle area is associated with postoperative complications in Crohn's disease

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Abstract

Background and aims Crohn's disease (CD) is associated with increased postoperative morbidity. Sarcopenia correlates with increased morbidity and mortality in various medical conditions. We assessed correlations of the lean body mass marker and psoas muscle area (PMA), with postoperative outcomes in CD patients undergoing gastrointestinal surgery.

Methods We included patients with CD who underwent gastrointestinal surgery between June 2009 and October 2018 and had CT/MRI scans within 8 weeks preoperatively. PMA was measured bilaterally on perioperative imaging.

Results Of 121 patients, the mean age was 35.98 ± 15.07 years; 51.2% were male. The mean BMI was 21.56 ± 4 kg/m2. The mean PMA was 95.12 ± 263.2cm^2. Patients with postoperative complications (N = 31, 26%) had significantly lower PMA compared with patients with a normal postoperative recovery (8.5 ± 2.26 cm2 vs. 9.85 ± 2.68 cm2, P = 0.02). A similar finding was noted comparing patients with anastomotic leaks to those without anastomotic leaks (7.48 ± 0.1 cm2 vs. 9.6 ± 2.51 cm2, P = 0.04). PMA correlated with the maximum degree of complications per patient, according to the Clavien-Dindo classification (Spearman's coefficient = −0.26, P = 0.004). Patients with major postoperative complications (Clavien-Dindo ≥ 3) had lower mean PMA (8.12 ± 2.75 cm2 vs. 9.71 ± 2.57 cm2, P = 0.03). Associations were similar when stratifying by gender and operation urgency. On multivariate analysis, PMA (HR = 0.72/cm2, P = 0.02), operation urgency (HR = 3.84, P < 0.01), and higher white blood cell count (HR = 1.14, P = 0.02) were independent predictive factors for postoperative complications.

Conclusion PMA is an easily measured radiographic parameter associated with postoperative complications in patients with CD undergoing bowel resection.

Keywords Crohn's · Bowel resection · Sarcopenia · Psoas · Surgery

Introduction

Crohn's disease (CD) is an idiopathic chronic inflammatory bowel disease with an annual incidence of 3–20 cases per 100,000 people [1] ,which has been continuously rising in prevalence in the western world [2].

Approximately 70–90% of individuals with Crohn's disease will require surgical intervention throughout of their lifetime [2] with some requiring more than one operation [3]. The increased risk of developing surgical complications posed by CD [4] raises debate regarding preoperative optimization [5, 6] and surgical approaches and timing [7]. Several risk factors for postoperative complications in patients with CD have been identified. These involve poor nutritional status [6], corticosteroids usage [8], and high neutrophil to lymphocyte ratios [9]. Evidence regarding the association between previous biologic treatment and post-operative complications are ambiguous [10, 11].

Sarcopenia was initially described in elderly patients. This condition is recognized as having prognostic value for low general well-being [12, 13], in the context of malignancy

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[14], organ transplantation [15], cirrhosis [16], and sepsis [17]. Sarcopenia is also an established marker and byproduct of chronic inflammation, mediated in part through several mechanisms [18]. These include upregulation of pro-inflammatory factors (TNF α, IL 1β , IL-6, COX-2, iNOS) [19], through the PI3K/Akt/mTOR [20–22]pathway and through apoptosis signaling [20, 21].

Recently, there has been an increased interest in investigating the prognostic value of sarcopenia in patients with CD or ulcerative colitis (UC). Most of these studies have examined the value of sarcopenia in assessing the need of surgical intervention in Crohn's patients [22–25]. However, not much is known on the effects of sarcopenia on postoperative complications in CD patients. Therefore, we aimed to study the perioperative and postoperative prognostic value of sarcopenia, as assessed through psoas muscle surface area (PMA), in individuals with CD undergoing bowel surgery.

Methods

We performed a single-center retrospective study. The study was approved by institutional ethics committee (approval No. SMC 1443-14). We included all the patients who underwent CD-related abdominal surgery between June 2009 and October 2018 in our department. All elective and semi-elective patients were presented in a multi-disciplinary board and decisions regarding operation made on basis of poorly controlled disease. We collected demographic, preoperative, intraoperative, and postoperative data. Complication severity was classified using the physicians' actions and escalation-based Clavien-Dindo system [26]. Major complications were defined as Clavien-Dindo ≥ 3. The urgency of operation was classified into three groups: urgent (up to 24 h from admission due to abdominal sepsis or bowel obstruction), semi-elective operation (from 24 h to 1 week from acute admission), and elective operation. Data regarding prior clinical preoperative optimization was not assessed due to missing data from cases that were referred from other institution or urgent/semi-urgent cases. Preoperative PMA was measured during the conduct of the study, in 2019, using available CT/MRI imaging obtained within 30 days prior to the operation. PACS software (Carestream Veu ver 11.3, Carestream health, Rochester, NY) was used to perform the PMA measurements. PMA was measured retrospectively, by blinded researchers from our team, in transverse section at the L5 level. We used the mean area of the right and left psoas for the statistical analysis. Psoas muscle index (PMI), a normalized PMA measurement (PMA/BMI) was also calculated. We examined associations between postoperative complications and PMA. Among other complications, we studied the incidence of anastomotic leak, intra-abdominal abscess, paralytic ileus, readmission within 30 days for discharge, and reoperation within 30 days from index operation. Following a preliminary analysis that demonstrated a significant difference in PMA, between male and female patients, we performed analyses with stratification by gender.

Statistical analysis

Statistical analysis was performed using SPSS (Version 25, IBM Corp, Armonk, NY) software. For continuous variables, Mann-Whitney tests and *t* tests were used for comparisons based on the normality of distribution. Categorical data were compared using Fisher's exact test and the chi-square test to evaluate differences between qualitative variables. Receiver operator curve (ROC) analysis was used to assess the robustness of associations between variables. Binary logistic regression was used for multivariate analysis. Also, binary logistic regression with 2 variables was used to calculate odds ratio (OR). A p value of < 0.05 was considered statistically significant.

Results

We reviewed the data of 121 patients who underwent bowel resection for CD during 2009–2018. All patients underwent abdominal CT/MRI 30 within 30 days before operation. The mean age was 35.98 ± 15.07 years; 62 (51%) were male. Basic demographic and clinical data are presented in Table 1. Incidences of postoperative complications are described in Table 2. Overall, 31 (26%) patients had a postoperative complication.

The incidence of postoperative complications is associated with PMA

The mean PMA was lower among patients who presented with postoperative complications than among those without complications (854.3 ± 226.3mm^2 vs. 984.5 ± 267.8mm^2, P = 0.02). Also, patients whose PMA values were within the lower quartile of the cohort had considerably higher rates of major and overall post-operative complications (Fig. 1). In addition, among the patients who were anastomosed, the mean PMA was lower among those presenting with post-surgical anastomotic leak (N = 6) than among those without leaks (N = 87) (P = 0.04, Fig. 2). The maximum degree of complications per patient, as ranked using the Clavien-Dindo classification, was shown to correlate inversely with PMA (Spearman's coefficient = −0.26, $P < 0.01$, Fig. 3). In a similar analysis, the mean PMA was lower among patients with major postoperative complications (Clavien-Dindo ≥ 3) than among those without major complications (8.12 ± 2.75cm^2 vs. 9.71 ± 2.57cm^2, P = 0.03). ROC analyses showed strong inverse association of PMA with the occurrence of postoperative complications

Table 1 Demographic characteristics, basic clinical data and postoperative data of patients with Crohn's disease who underwent bowel resection. $N = 121$.

Variable	Standard deviation/%
Mean age (years)	35.98 ± 15.07
Mean BMI (kg/m^2)	21.56 ± 4
Mean pre-operative albumin (mg/dl)	3.56 ± 0.67
Mean psoas muscle area (cm^2)	9.51 ± 2.63
Gender (F/M)	62 (51.2%) M/ 59(48.8%) F
Smokers (No.)	20 (16.5%)
Mean disease duration (years)	10.21 ± 6.99
Preoperative corticosteroids use (No.)	34 (29%)
Preoperative anti TNF-α use (No.)	23 (19%)
Indication for operation:	66(56%)
Failure on medical treatment	47(40%)
Bowel obstruction/stricture	27 (23%)
Symptomatic fistular disease	15 (13%)
Abscess/sepsis	10 (8%)
Bowel perforation	46 (31%)
Multiple indications	
Operation urgency:	36 (29.8%)
Urgent	21 (17.4%)
Semi-elective	62 (51.2%)
Elective	2 (1.6%)
Missing	
Mean length of stay (days)	14.26 ± 11.7

Data are presented as medians and ranges.*BMI* body mass index, *F* female, *M* male, *No.* number

(AUC 0.64, $P = 0.02$). Despite the low incidence of specific complications, PMA was significantly associated with paralytic ileus (AUC 0.73, $P = 0.04$) and pneumonia (AUC 0.8, $P = 0.04$) and with anastomotic leaks among patients who underwent surgical bowel anastomosis (AUC 0.78, $P = 0.03$) (Fig. 4). Univariate analysis of the association of postoperative complications with PMA and other factors is presented in Table 3. Preoperative corticosteroid use was surprisingly found to be inversely associated with complications ($P < 0.05$, OR 0.3). Suspecting possible selection bias, we analyzed the preoperative characteristics of corticosteroid users and found that the non-corticosteroid group was indeed enriched for significantly higher rates of preoperative abdominal abscess (20% vs. 0%) or active infections preventing the use of corticosteroids ($P < 0.005$). ROC analysis of PMI also was found to be associated with postoperative complications ($P < 0.05$); however the parameter was available for only 70% of the cohort due to incomplete BMI data.

Subset analyses based on sex and clinical urgency recapitulate the inverse correlations of PMA with postoperative complications

The mean PMA value for male patients was significantly higher than the mean value for female patients (10.45 ± 2.6cm^2 vs. 8.53 ± 2.31cm^2, $P < 0.01$). We therefore conducted sub-analyses that were stratified by sex.

Among female patients ($N = 59$), low preoperative PMA values were associated with an increased need for reoperations (5.7cm^2 vs. 8.74 cm^2, $P = 0.01$). Female patients who underwent urgent and semi-elective operations ($N = 32$) were found to have a correlation between low PMA and higher severity of complications (Spearman's coefficient = −0.47, $P < 0.01$). Furthermore, in female patients who underwent urgent operations ($N = 17$), PMA was also found to correlate with the length of hospital stay (LOS) (Pearson's coefficient = −0.639, $P < 0.01$). Additionally, in the subset of female patients who underwent elective operations ($N = 27$), lower PMAs were associated with postoperative abdominal abscess formation (6.07 ± 0.93mm^2 vs. 9.15 ± 2.42 mm^2, $P = 0.04$).

Analysis of male patients who underwent elective operations ($N = 33$) showed correlations of PMA with LOS (Spearman's ρ coefficient = −0.38, $P = 0.03$). Interestingly, in male patients who underwent urgent and semi-elective index-surgery settings ($N = 25$), lower PMA values were noted amongst those who required hospital readmission ($N = 11$)

Table 2 Incidence of postoperative complications among individuals with Crohn's disease who underwent bowel resection

Complication	Incidence
Patients presenting with postoperative complications.	31 (25.6%)
Anastomotic leaks among patients who were anastomosed ($N = 93$)	6 (6.5%)
Abscess	17 (14.0%)
Pneumonia	4 (3.3%)
Wound infections	16 (13.2%)
Renal failure	2 (1.7%)
Paralytic ileus	7 (5.8%)
Thromboembolic events	2 (1.7%)
Re-operation	11 (9.1%)
Re-admission within 30-days	32 (26.4%)
Major complication (Clavien-Dindo = > 3)	16 (13.2%)

Table 3 Univariate analysis of association between various factors including psoas muscle area (PMA) and post-operative complications incidence

	Post-operative complications		Post-operative major complications (Clavien-Dindo ≥ 3)	
	P value	Hazard ratio	*P* value	Hazard ratio
Psoas muscle area (measured in cm^2)	0.02	0.81 (0.68–0.97)	0.03	0.76 (0.6–0.98)
Operation urgency	> 0.01	2.644 (1.445–4.84)	0.33	0.733 (0.395–1.363)
Pre-operative white blood cell count (WBC)	0.241	1.037 (0.976–1.103)	0.11	1.055 (0.987–1.129)
Gender	0.96	0.98 (0.433–2.218)	0.86	0.909 (0.307–2.685)
Age (years)	0.04	1.028 (1.022–1.055)	0.75	0.994 (0.957–1.032)
Body mass index (kg/m^2)	0.27	1.075 (0.945–1.224)	0.57	1.047 (0.896–1.223)
Smoking history	0.29	1.5 (0.704–3.197)	0.63	1.274 (0.476–3.407)
Pre-operative hemoglobin level (g/dl)	0.6	1.062 (0.85–1.325)	0.65	1.069 (0.798–1.434)
Pre-operative albumin level (g/dl)	0.86	1.057 (0.56–1.997)	0.42	0.715 (0.318–1.605)
Pre-operative corticosteroids usage	0.03	0.303 (0.106–0.866)	0.66	0.756 (0.221–2.579)
Pre-operative TNF-α inhibitors usage	0.08	2.379 (0.9–6.288)	0.97	1.025 (0.264–3.979)

than among those ($N = 14$) who did not require readmission ($9.94 \pm 3mm^2$ vs. $12.7 \pm 2.4cm^2$, P = 0.02).

PMA and operation urgency are independent predictive factors for postoperative complications

In binary logistic regression, lower PMA (HR = $0.72/cm^2$, $P = 0.02$), operation urgency (HR = 3.8, $P < 0.01$), and higher white blood cell count (HR = 1.14, P = 0.02) were independent predictive factors for postoperative complications. These results indicate that for every 2 cm^2 of difference in the psoas muscle area the risk for postoperative complication increases by about twofold. Based on the regression model, the risk difference between patients with PMA values in the 10th percentile versus the 90th percentile was approximately 7.5-fold. Other factors such as female gender, older age, smoking history, low preoperative hemoglobin, pre-operative albumin levels, corticosteroids usage, and TNF-α inhibitors usage were not found to be independent predictors of postoperative complications (Table 4).

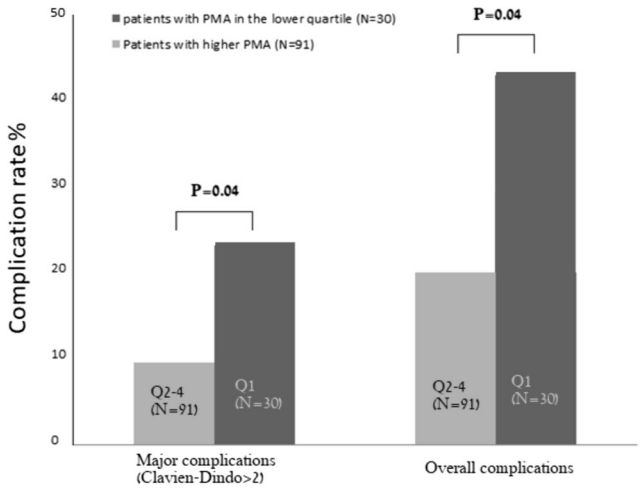

Fig. 1 Incidence of post-operative complications and major post-operative complications (Clavien-Dindo ≥ 3) among patients within the first quartile of psoas muscle area (PMA) in comparison with patients in quartiles 2–4 of PMA

Discussion

Surgical treatment plays a pivotal role in the management of CD. This is evidenced by the requirement of surgery by 70–90% of individuals with CD during their lifetime [1]. Unfortunately, CD is also a well-known risk factor for postoperative complications in gastrointestinal surgery [4]. This may be, at least in part, because this patient group is often referred to surgical intervention when the patients are already malnourished and after treatments with various types of anti-inflammatory and biological medications that may dysregulate the endogenous wound healing mechanisms [27]. This increased rate of postoperative complications has led researchers in recent years to explore preoperative interventions aimed to optimize the preparation of patients for surgery and thereby maximize the chances of achieving a successful surgical outcome.

Sarcopenia has been recognized as a prognostic marker in many medical conditions [12–17]. Of note, sarcopenia was also shown to strongly associate with chronic inflammation conditions. Several methods of quantitative assessment of sarcopenia have been previously described (e.g., Bioelectric Impedance Assessment, Dual energy X-ray Absorptiometry (DXA), etc.). However, in the context of IBD patients, CT and MRI have been more frequently used in clinical research to assess sarcopenia [13, 28, 29]. Psoas muscle area (overall and normalized to body mass) and psoas muscle density have been repeatedly

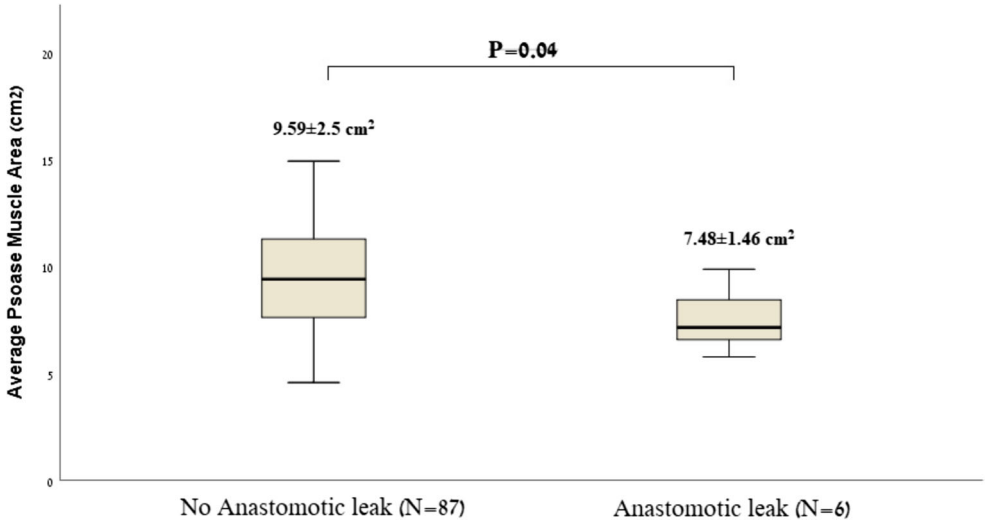

Fig. 2 Psoas muscle area (PMA) of patients with Crohn's disease who underwent bowel resection and who were anastomosed, according to the presentation of an anastomotic leak

employed and validated as sarcopenia markers, thereby making them a commonly used metric in sarcopenia assssment [28, 29].

Our study aimed to investigate the role of sarcopenia (assessed by PMA) as a prognostic factor in patients with CD undergoing abdominal operations. Our results showed a strong association between low PMA and postoperative complications, including anastomotic leak, paralytic ileus, and pneumonia. Concordantly, we found a correlation between PMA and hospital length of stay. A multivariate analysis showed PMA to be an independent prognostic factor for the incidence of overall complications.

Our findings concur with those of other studies of individuals with inflammatory bowel disease who underwent surgery. Zhang et al. described high rates of sarcopenia among 114 Chinese surgery-naïve patients with CD who underwent bowel resection. In their study, they assessed sarcopenia by measuring skeletal muscle area at the level of L3. Similar to our findings, their results showed a higher rate of major complications (Clavien-Dindo ≥ 3) among patients with sarcopenia [30]. O'Brien et al. have looked at a smaller cohort combined of 25 UC patients and 52 patients with CD [31]. Though they have not found sarcopenia to significantly increase the combined cohort's postoperative complication rates or length of hospital stay, and they have noted an increase in readmission rates. In a larger study, Pedersen et al. reviewed the combined data of 178 patients with CD or ulcerative colitis who underwent surgical operations. They reported that sarcopenia had significant prognostic value for blood transfusions, sepsis, the risk of deep venous thrombosis, increased LOS, and the risk for admissions to intensive care units among patients younger than 40 years [29]. However, similar to the study by O'Brien and colleagues, no comparisons were made in that study between the CD group and the UC group. Complementing these studies, Fujikawa et al. demonstrated higher incidence of surgical site infection and pelvic abscesses among 69 patients with UC and sarcopenia who underwent proctocolectomy [32].

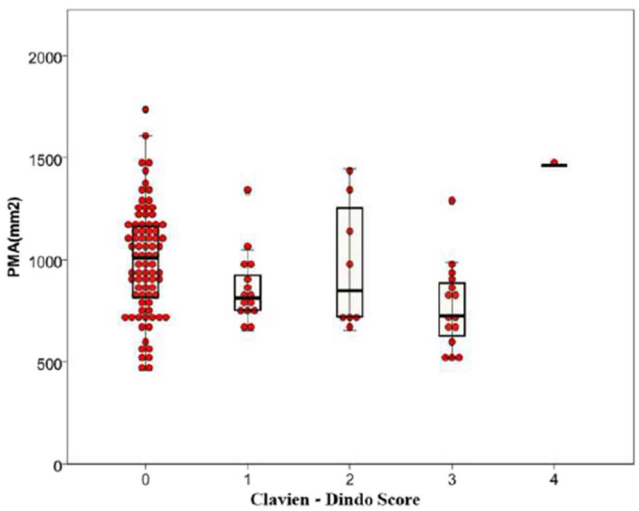

Fig. 3 Psoas muscle area (PMA) of patients with Crohn's disease who underwent bowel resection, according to Clavien-Dindo classification

Standard treatments of sarcopenia include physical exercise and nutritional enhancements. However, novel treatments for this condition have been discussed extensively in the literature [33]. Some noteworthy advances in the pharmacological management of sarcopenia include testosterone administration, anabolic steroids, selective androgen receptor modulators, ghrelin administration, myostatin, and and activin II receptor inhibitors [34]. Clinical studies are needed to assess the applicability of these treatments in the pre-surgical management of CD.

It should be mentioned that one of the outcomes our analysis was the unexpected decreased association of corticosteroids with incidence of post-operative complications (Table 3). This association was not preserved in the multi-variant analysis (Table 4). In our cohort, 34 (29%) patients were treated with corticosteroid before

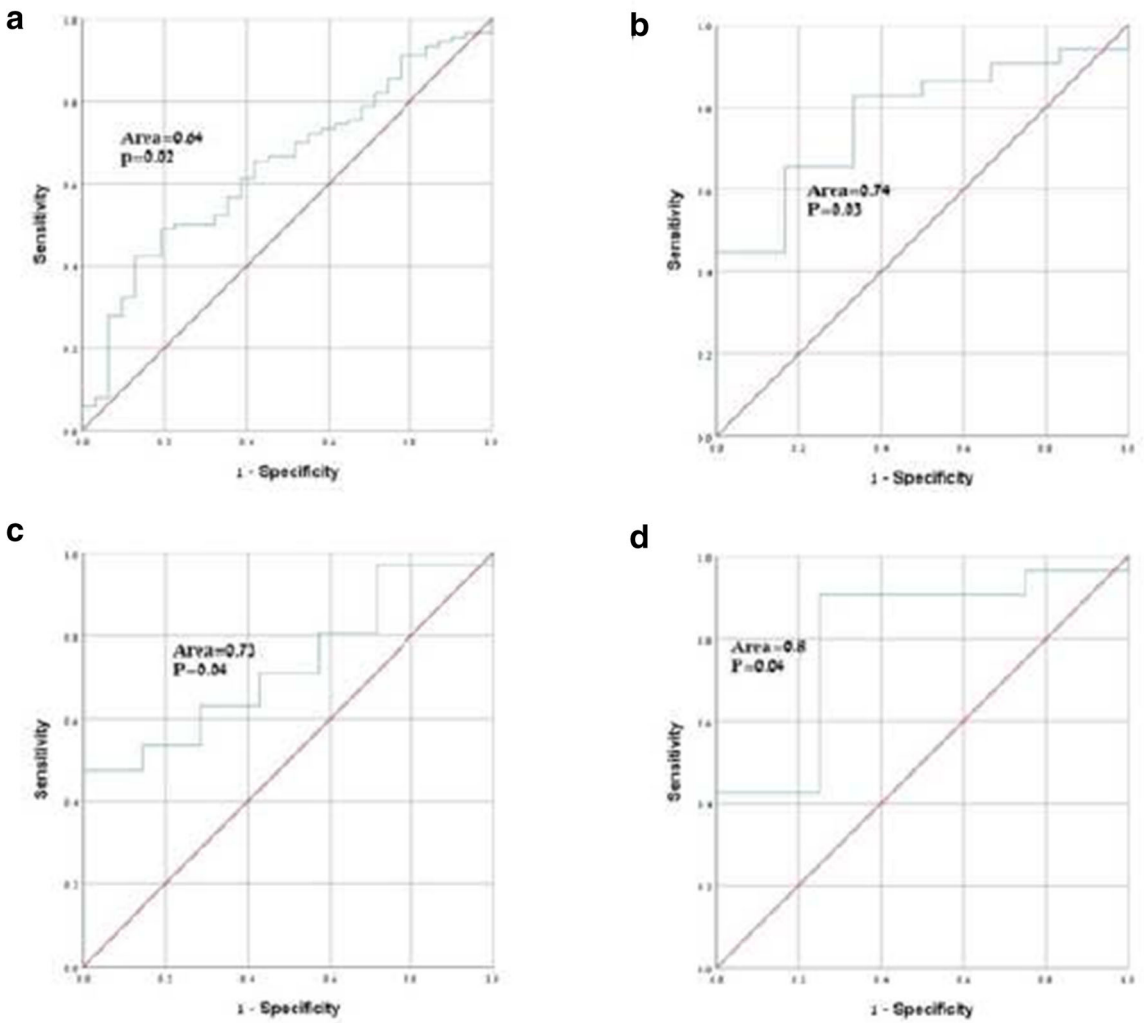

Fig. 4 Receiver operator curves of associations of psoas muscle area (PMA) with **a** postoperative complications, **b** surgical bowel anastomosis, **c** paralytic ileus. and **d** pneumonia

operation, and among them 24 patients (71%) continued corticosteroid treatment after operation. We further explored this seemingly paradoxical association to find that, at least partially, it is a result of selection bias caused

Table 4 Multivariate analysis of association between various factors, including psoas muscle area (PMA) and post-operative complications incidence

	Post-operative complications		Post-operative major complications (Clavien-Dindo ≥ 3)	
	P value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)
Psoas muscle area (pma)	0.02	0.72 (0.55–0.94)	0.07	0.64 (0.46–0.89)
Operation urgency	< 0.01	3.842 (1.48–9.974)	0.46	0.736 (0.326–1.662)
Pre-operative white blood cell count (WBC)	0.02	1.139 (1.023–1.267)	0.15	1.063 (0.979–1.154)
Gender	0.3	0.508 (0.142–1.817)	0.36	0.499 (0.112–2.222)
Age	0.91	0.912 (1.002–0.966)	0.28	0.975 (0.931–1.02)
Smoking history	0.73	1.213 (0.398–3.7)	0.75	1.219 (0.365–4.075)
Pre-operative hemoglobin level	0.76	0.946 (0.659–1.356)	0.28	1.235 (0.842–1.812)
Pre-operative albumin level	0.63	0.811 (0.35–1.879)	0.32	0.617 (0.23–1.654)
Pre-operative corticosteroids usage	0.11	0.315 (0.77–1.292)	0.25	0.408 (0.089–1.868)
Pre-operative TNF-α inhibitors usage	0.27	2.072(0.572–7.502)	0.94	0.932 (0.155–5.62)

by avoiding the usage of corticosteroids in patients with intra-abdominal abscesses which usually associated with more severe presentation.

Our study has several limitations. For one, the retrospective design enables only the identification of correlations and statistical associations, and not the assessment of causality. Similarly, this study design does not permit to explicitly determine if low PMA is a result of more aggressive CD or other comorbidities. Secondarily, due to the retrospective nature of the study, its lack of assessment of functionality as part of definition of sarcopenia [35], and therefore the study's definition for sarcopenia is relative and radiological and not functional. It is important to note that PMA is only one of several imaging methods for assessing sarcopenia each one having its own limitations and advantages. Physiologically, PMA measurement does not take into consideration body size or nutritional measures except for albumin. Our preliminary assessment of PMI, a BMI normalized PMA metric, has also shown association with postoperative complications. However, PMI was available for only a subset of our cohort due to incomplete or partial BMI data. PMA muscle density, another strong and validated sarcopenia marker, was not assessed in our study as density assessment is not easily translatable across the CT/MRI platforms. Our sample size (N = 121), while large enough to detect the significant association between PMA and postoperative complication, still merits caution in the interpretation of association to specific less common complications such as anastomotic leaks due to the small number of events in the study period. The study uses Clavian-Dindo classification for post-operative complications. This classification is limited in its ability to discuss multiple complications in the same patient. Furthermore, this study does not address whether PMA is a clinically modifiable factor and whether such a modification will correlate with a change in outcome.

Conclusions

Sarcopenia, as measured using PMA, is an easily calculated metric. It is significantly associated with postoperative complications in patients with CD undergoing bowel resection. Our findings support the use of PMA measurement in clinical decisions regarding the surgical management of CD. It is yet to be ascertained whether PMA can be used as a dynamic metric to assess the efficacy of preoperative optimization during the follow-up of patients with CD. Further prospective studies should be undertaken to validate PMA-based risk assessment and PMA-based evaluation of pre-operative optimization.

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Compliance with ethical standards

Conflict of interest The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript

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