Sarcopenia and major complications in patients undergoing oncologic colon surgery

Michael Schneider[1], Martin Hübner[1] iD, Fabio Becce[2] iD, Joachim Koerfer[2] iD, Jean-Aibert Collinot[2], Nicolas Demartines[1]* iD, Dieter Hahnloser[1] iD, Fabian Grass[1] iD & David Martin[1] iD

[1]Department of Visceral Surgery, Lausanne University Hospital CHUV, University of Lausanne (UNIL), Lausanne, Switzerland; [2]Department of Diagnostic and Interventional Radiology, Lausanne University Hospital (CHUV), University of Lausanne (UNIL), Lausanne, Switzerland

Abstract

Background Sarcopenia is a surrogate marker for malnutrition and frailty, which has been linked to higher complication rates and prolonged length of stay (LOS) after surgery. The study aim was to assess the correlation between computed tomography (CT)-based sarcopenia and short-term clinical outcomes after oncologic colon surgery.
Methods This retrospective study included consecutive patients operated between May 2014 and December 2019. Three radiological indices of sarcopenia were measured at the level of the third lumbar vertebra on preoperative CT scans: skeletal muscle area (SMA), skeletal muscle index (SMI) (both markers of muscle quantity), and skeletal muscle radiation attenuation (SMRA) (marker of muscle quality). Patients with major complications (grade $\geq$ 3b according to the Clavien classification) were compared with those without. Statistical correlation between sarcopenia indices, LOS, and comprehensive complication index (CCI) was tested with the Pearson correlation coefficient.
Results A total of 325 patients were included. Mean age was 67 years [standard deviation (SD) 14.3], mean body mass index was 26.0 kg/m^2 (SD 5.3), and 193 (59%) were male. Fifty patients (15.4%) had major complications, while 275 (84.6%) did not. Patients with major complications had more open surgery (52 vs. 21%, $P < 0.01$), intraoperative blood loss (257 vs. 102 mL, $P = 0.035$), and intraoperative complications (22 vs. 9%, $P = 0.012$). Patients with major complications had significantly increased CCI scores (53 vs. 6, $P < 0.01$), reoperations (74 vs. 0%, $P < 0.01$), and LOS (33 vs. 7, $P < 0.01$). SMA and SMI were comparable between both groups (126.0 vs. 125.2 cm^2, $P = 0.974$, and 43.4 vs. 44.3 cm^2/m^2, $P = 0.636$, respectively), while SMRA was significantly lower in patients with major complications (33.6 vs. 37.3 HU, $P = 0.018$). A lower SMRA was correlated with prolonged LOS ($r = -0.207$, $P < 0.01$) and higher CCI ($r = -0.144$, $P < 0.01$), while the other sarcopenia indices had no influence on surgical outcomes.
Conclusions Muscle quality (SMRA) as a specific sarcopenia marker was lower in patients with major complications and seems to prevail over muscle quantity (SMA and SMI) in the prediction of adverse outcomes after oncologic colon surgery.

Keywords Sarcopenia; Computed tomography; Colon cancer; Surgery; Outcomes

Introduction

Cancer patients can be exposed to sarcopenia, which has been recognized as a surrogate marker of vulnerability, frailty, and malnutrition.[1,2] According to the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is probable when low muscle strength is detected; the diagnosis is confirmed in the presence of low muscle quantity

or quality, and when low physical performance is demonstrated, sarcopenia is considered to be severe.[3,4] The prevalence of sarcopenia ranges from 12% to 60% in patients with colorectal cancer.[5–8] As a consequence, adjuvant multidisciplinary cancer therapy may be delayed, ultimately impacting patient survival.[9]

Several tests and tools are now available for characterizing sarcopenia in clinical research and practice.[10] Muscle mass and quality estimation represents a valuable diagnostic tool.[1] Computed tomography (CT) is considered the gold standard for the non-invasive assessment of muscle mass and quality.[3,11] In particular, density and cross-sectional area or volume of muscles on CT images of a specific lumbar vertebral landmark (L3) correlated significantly with whole-body muscle mass.[12] Skeletal muscle area (SMA), skeletal muscle index (SMI), and skeletal muscle radiation attenuation (SMRA) are different validated CT-based indices.[3]

Although previous studies have associated sarcopenia with higher post-operative morbidity and poorer oncological prognosis in surgical patients with colorectal cancer, most of them were limited by small sample sizes or short follow-up periods.[5,7,13] The clinical impact of sarcopenia on post-operative morbidity and mortality depends on the surgical procedures performed and the method of sarcopenia assessment.[14]

The aim of the present study was to investigate the correlation of three preoperative CT-based sarcopenia indices on clinical outcomes after oncologic colonic surgery.

Methods

Patients

This retrospective cohort study included consecutive patients undergoing elective oncologic colon resections between 1 May 2014 and 1 December 2020 at the Department of Visceral Surgery, Lausanne University Hospital CHUV, Lausanne, Switzerland. Patients undergoing emergency or non-oncologic resections and those undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were excluded. All patients were treated according to the ERAS protocol for colorectal surgery.[15,16] Surgical resection and reconstruction techniques were standardized: mechanical side-to-side aniso-peristaltic ileocolic anastomosis for right colectomies, manual end-to-end colocolic anastomosis for transverse colectomies, and mechanical end-to-end colorectal anastomosis for left colectomies.

Patient demographics, co-morbidities, and operative parameters were assessed. Post-operative outcomes included morbidity, mortality, reoperations, length of stay (LOS), and pathological results. Complications were graded according

to the Clavien classification until 30 post-operative days.[17] Major complications were defined as grade $\geq$ 3b. Only the highest grade was retained in patients presenting more than one complication. The comprehensive complication index (CCI) was calculated considering all complications, with a score ranging from 0 to 100.[18] Surgical site infections (SSI), ileus with need for nasogastric tube insertion, and radiologically confirmed anastomotic insufficiency were described separately. Tumour stage was assessed according to the Union for International Cancer Control (UICC) TNM classification.[19]

Computed tomography-based measurements of muscle mass and quality

Sarcopenia was defined according to the EWGSOP, based on CT muscle mass and quality.[3] Muscle mass or quantity was represented by the SMA (in cm^2), while muscle quality was reflected by the SMRA (in Hounsfield unit, HU) (*Figure 1*).[20] SMA was normalized for patient height to obtain the SMI (in cm^2/m^2). Both SMA and SMRA were quantified using a semi-automated method from a single axial preoperative CT image of the abdomen at the L3 vertebral level.[21] The deep-learning-based method was used and followed a traditional U-Net architecture, which was slightly modified by adding a second smaller U-Net to improve its accuracy.[22] Such methods have recently been tested and validated on large CT datasets and have proven to be accurate and reliable.[23,24] All automated muscle segmentations were secondarily reviewed and corrected where appropriate by an attending musculoskeletal radiologist, blinded to the patients' characteristics and interventions, using a custom free-hand image segmentation tool, as previously described.[25,26]
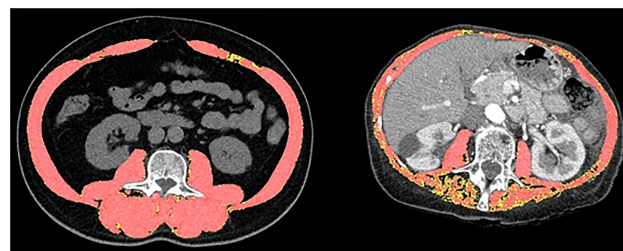

Figure 1 Computed tomography (CT) scan-based skeletal muscle area (SMA) and skeletal muscle radiation attenuation (SMRA). Representative abdominal CT scans showing different morphotypes of SMA and SMRA at the third lumbar vertebra. On the left: non-sarcopenic patient; on the right: sarcopenic patient. Red: healthy muscle; yellow: muscle infiltrated with fat.

Statistical analysis

Categorical variables were presented as frequencies (%) and compared with Pearson's chi-squared or Fisher's exact test, where appropriate. Continuous variables were presented as mean (standard deviation) or median (interquartile range) and compared with Student's *t* test or Mann–Whitney *U* test, where appropriate. Statistical correlation between different sarcopenia indices, CCI, and LOS was measured by use of the Pearson correlation coefficient and interpreted as follows: 0.00–0.09 negligible; 0.10–0.39 weak; 0.40–0.69 moderate; and 0.70–0.89 strong correlation.[27] Receiver operating characteristic (ROC) curves were used to assess the performance of sarcopenia indices as diagnostic tests of major complications. A fair diagnostic performance of a test was defined as a ROC curve having an area under the curve of at least 0.7. A *P*-value ≤ 0.05 was considered statistically significant, and analyses were performed using SPSS 26.0 software (SPSS Inc., Chicago, IL).

Ethics

The study was approved by the local ethics committee (protocol no. 2020-00677) and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave written informed consent, and the study has been conducted and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[28]

Results

A total of 325 patients were included, 50 (15.4%) with and 275 (84.6%) without major surgical complications. Patient demographics and surgical details are displayed in *Table* 1. Patients with major complications presented significantly more ASA grade III/IV and higher Charlson scores. Patients with major complications had more open surgery and more intraoperative blood loss and intraoperative complications. Post-operative surgical outcomes are described in *Table* 2. Patients with major complications had significantly increased CCI scores, colorectal specific complications, reoperations, and LOS, while cancer stages were not different.

Skeletal muscle radiation attenuation was significantly lower in patients with major complications (33.9 ± 10.4 vs. 37.3 ± 10.0 HU, *P* = 0.018), while SMA and SMI were comparable between both groups (125.4 ± 34.0 vs. 125.4 ± 31.0 cm^2, *P* = 0.974, and 43.4 ± 8.7 vs. 44.3 ± 9.4 cm^2/m^2, *P* = 0.636, respectively).

Lower SMRA correlated weakly with LOS (*r* = −0.207, *P* < 0.01, *Figure* 2) and CCI (*r* = −0.144, *P* < 0.01, *Figure* 3), while SMA and SMI had no correlation with these two outcomes (Supporting Information, *Figures* S1–S4). Sarcopenia

Table 1 Patient demographics and surgical details

	No major surgical complication (n = 275)	Major surgical complication (n = 50)	Total (n = 325)	P-value
Mean age, years (SD)	67 (14.1)	68 (15.4)	67 (14.3)	0.632
Male, n (%)	161 (59)	32 (64)	193 (59)	0.470
ASA III–IV (%)	110 (40)	32 (64)	142 (43.7)	**<0.01**
Mean BMI, kg/m^2 (SD)	25.9 (5.2)	26.5 (5.7)	26.0 (5.3)	0.549
Mean Charlson score (SD)	1.4 (2.3)	2.3 (2.5)	1.5 (2.3)	**<0.01**
Resection type, n (%)				0.058
Left colon	115 (42)	21 (42)	136 (42)	
Transverse colon	17 (6)	3 (6)	20 (6)	
Right colon	117 (43)	18 (36)	135 (41)	
Others	16 (6)	4 (8)	20 (6)	
Laparoscopy (%)	219 (79)	24 (48)	243 (75)	**<0.01**
Conversion rate (%)	27 (10)	1 (2)	28 (9)	0.098
Mean operative time, min (SD)	164 (94)	256 (163)	171 (112)	0.089
Mean blood loss, mL (SD)	102 (189)	257 (594)	122 (281)	**0.035**
Intraoperative complication (%)	24 (9)	11 (22)	35 (11)	**0.012**
Bleeding (%)	8 (3)	4 (8)	12 (4)	
Small bowel/colic serosal injury or enterotomies (%)	13 (5)	5 (10)	18 (6)	
Ureteral injury (%)	0 (—)	1 (2)	1 (0)	
Other (%)	3 (1)	1 (2)	4 (1)	
Anastomosis type (%)				0.057
Mechanical stapled (%)	223 (81)	35 (70)	258 (79)	
Manual suture (%)	47 (17)	14 (28)	61 (19)	
No anastomosis (%)	5 (2)	1 (2)	6 (2)	
Protective/permanent stoma (%)	12 (4)	2 (4)	14 (4)	1.000

BMI, body mass index; SD, standard deviation. Significant p values (<0.05) are displayed in bold characters.

Table 2 Post-operative surgical outcomes and pathological results

	No major surgical complication (*n* = 275)	Major surgical complication (*n* = 50)	Total (*n* = 325)	*P*-value
Mean LOS, in days (SD)	7 (5.8)S	33 (17.8)	11 (12.8)	<**0.01**
Mean CCI (SD)	6 (11.2)	53 (20.6)	13 (21.2)	<**0.01**
Type of complications				
Surgical site infections, *n* (%)	4 (2)	19 (38)	23 (7)	<**0.01**
Ileus, *n* (%)	42 (15)	23 (46)	65 (20)	<**0.01**
Anastomotic insufficiency, *n* (%)	2 (1)	20 (40)	22 (7)	<**0.01**
Reoperation, *n* (%)	1 (0)	37 (74)	38 (12)	<**0.01**
Cancer stage				0.344
UICC 0, *n* (%)	10 (4)	1 (2)	11 (3)	
UICC 1, *n* (%)	28 (10)	3 (6)	31 (10)	
UICC 2, *n* (%)	45 (16)	8 (16)	53 (16)	
UICC 3, *n* (%)	102 (37)	20 (40)	122 (38)	
UICC 4, *n* (%)	81 (29)	16 (32)	97 (30)	
Other cancer, *n* (%)	9 (3)	2 (4)	11 (3)	
R1 resection, *n* (%)	11 (4)	3 (6)	14 (4)	0.388

CCI, comprehensive complication index; LOS, length of stay; SD, standard deviation; UICC, Union for International Cancer Control. Significant *p* values (<0.05) are displayed in bold characters.
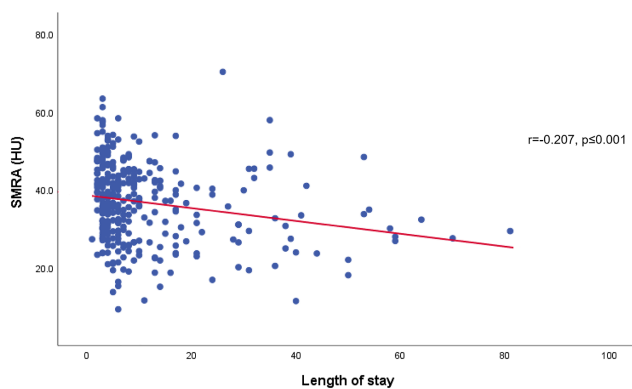
Figure 2 Correlation between skeletal muscle radiation attenuation (SMRA) and length of stay. HU, Hounsfield unit.
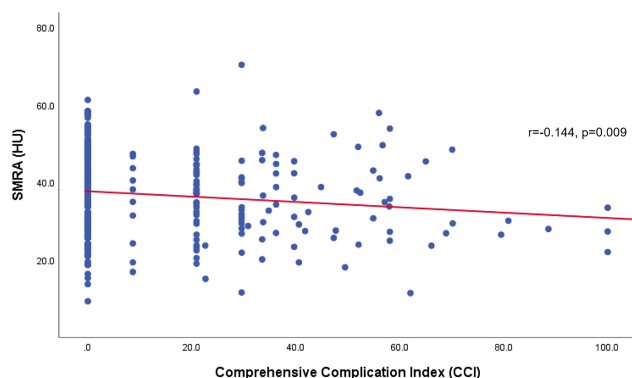
Figure 3 Correlation between skeletal muscle radiation attenuation (SMRA) and comprehensive complication index (CCI). HU, Hounsfield unit.

indices had a poor diagnostic performance in the detection of major complications according to the ROC curve analyses (*Figure* 4).
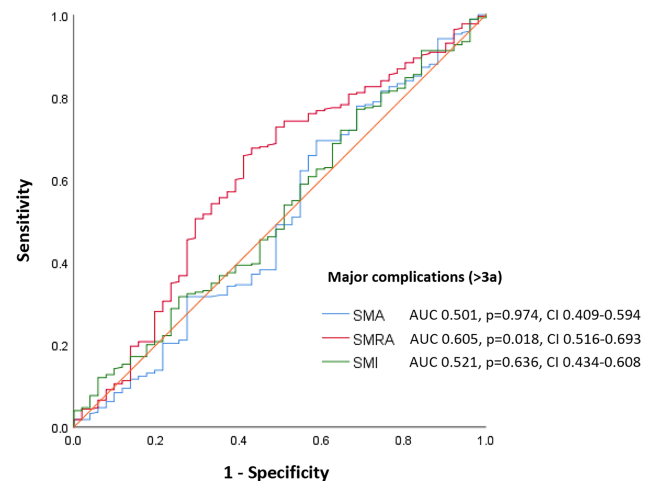
Figure 4 Receiver operating characteristic curves of sarcopenia indices and major complications. AUC, area under the curve; CI, confidence interval; SMA, skeletal muscle area; SMI, skeletal muscle index; SMRA, skeletal muscle radiation attenuation.

Discussion

This single-centre retrospective study identified preoperative SMRA as a weak predictor for adverse outcomes after oncologic colon surgery. Muscle quality (SMRA) as a specific sarcopenia marker seems to prevail over muscle quantity (SMA and SMI) in this cancer population.

Several methods have been described for the assessment of muscle mass and quality, namely, dual X-ray absorptiometry, CT scan, magnetic resonance imaging, or bioelectrical impedance analysis. More specifically in oncological surgery, CT scan is readily used insofar as it is performed routinely as part of the preoperative staging. In a review, multiple published reference values for discrepant parameters of skeletal muscle mass were identified.[29] Several authors suggested the use of

a unified nomenclature and methodology in order to facilitate comparison between studies. There is a difference between the quantity and the quality of muscle for CT-based sarcopenia assessment, and cut-off values vary depending on the population, gender, and race/ethnicity.[4] Several studies used pre-established or previously used cut-offs, while others relied on their cohort values, setting the limit of sarcopenia at the lowest gender-specific tertile or quartile.[30] Dividing a cancer patient population in subgroups may represent a limitation as patients could be all sarcopenic due to cancer. Using the reference range of a normal (or non-cancer) patient population should be considered in future studies. In the present study, quantitative and qualitative CT-based sarcopenia indices were assessed retrospectively, but no cut-off was used to define sarcopenia. When using ROC curve analysis, none of the indices had a clinically meaningful diagnostic performance to predict the occurrence of major complications. An interesting aspect was to observe if their values were impacted by the occurrence of major complications and avoiding bias of a methodology for defining sarcopenia that is not standardized and accepted.

A meta-analysis including 44 observational studies and 18 891 colorectal cancer patients showed that sarcopenia, mostly defined on the basis of the SMI (77% of studies), was a strong predictor of increased post-operative complications.[4] More specifically, sarcopenic patients had more severe post-operative complications [odds ratio (OR) = 1.72] and prolonged LOS (mean differences 0.77), while the rate of anastomotic leakage was similar (OR = 0.99).[4] On the contrary, the present study did not show difference in the rate of muscle quantity (SMA and SMI) in patients with major complications, and no correlation could be established with CCI and LOS. One of the hypotheses for this difference could be the fact that they may simply not have been sarcopenic enough, as could be expected in a cancer patient population. Previous studies on the association between sarcopenia and post-operative outcomes have mostly been conducted in Western countries with Western patient populations.[5,7,31,32] The situation is not necessarily similar in other populations. It has been reported that young Chinese men have 17% lower relative total skeletal muscle mass than that of White men.[33] When performing subgroup analyses, the pooled risk estimate did not demonstrate a significant increase in the risk of post-operative complications after colorectal surgery in studies from Europe, while this was the case for the populations of Asia and America.[4]

Muscle quality (SMRA) was significantly lower in patients with major complications, and weak correlations could be established with CCI and LOS in the present cohort. Similarly, a retrospective single-centre analysis of 185 patients undergoing elective laparoscopic right hemicolectomy for adenocarcinoma showed that muscle quality (average HU) had a higher prognostic accuracy for the prediction of overall and severe complications compared with muscle quantity (total

psoas muscle index on CT).[34] In 302 patients undergoing oncologic colectomy, psoas muscle density had a greater predictive value for complications compared with psoas muscle area.[35] Herrod et al. also found that psoas muscle density was highly predictive of complications after oncologic colorectal resection.[36] Muscle cross-sectional area or volume does not necessarily correlate with muscle quality.[37] It has also been shown that efforts to improve strength were associated with improved muscle quality rather than muscle size.[38] Further investigations of the difference between patient characteristics and sarcopenia indices are required. International and validated diagnostic criteria for sarcopenia, as published by international working groups, should be used in order to increase the quality of the comparisons and the generalization of results.[3,4,39] Sarcopenia is a dynamic process that should be assessed over time and not at a specific time point. It should also be determined when and how to intervene in case of low preoperative SMRA, as it may reflect a window of opportunity to mitigate muscle wasting in order to improve patient outcomes.

The majority of studies in colorectal cancer patients also included only skeletal muscle evaluation, as the unique parameter for the diagnosis of sarcopenia.[5,40] It is not sufficient to determine all aspects of the condition.[7] Muscle strength and physical performance are also important components of sarcopenia.[3] A meta-analysis showed that only four out of 44 studies (9%) realized the evaluation of physical strength and performance in addition to imaging measurements.[4] The correlation with these other measures was not assessed in the present study, as collecting these values retrospectively was not possible, insofar as patients did not perform them in the standard preoperative workup. For this reason, patients in this study may not be true sarcopenic, and vice versa, the patients considered to be sarcopenic on the basis of the radiological evaluation were possibly not in reality.

Several limitations of the present study need to be discussed beyond its retrospective study design. The sample size (n = 325) was relatively small, and the relationship between sarcopenia and complications should be interpreted with caution. Automated muscle segmentations were reviewed by one attending musculoskeletal radiologist, and no inter-rater reliability was assessed. Other aspects that could have an impact on major complications and sarcopenia, such as co-morbidities, body mass index, ASA score, nutrition, cardio-respiratory function, and chemotherapy, were not taken into consideration. They could potentially represent confounding factors, which were not adjusted in the stage of analysis.

In conclusion, muscle quality (SMRA) as a specific sarcopenia marker was lower in patients with major complications and seems to prevail over muscle quantity (SMA and SMI) in the prediction of adverse outcomes after oncologic colon surgery.

Acknowledgements

Conflict of interest

Funding

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Correlation between skeletal muscle area (SMA) and comprehensive complication index (CCI).
Figure S2. Correlation between skeletal muscle index (SMI) and CCI.
Figure S3. Correlation between SMA and length of stay (LOS).
Figure S4. Correlation between SMI and LOS.

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