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Nutritional and functional status as indices of short- and long-term prognosis in patients undergoing surgery due to colorectal cancer

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ABSTRACT

Introduction: Nutritional status and body composition parameters would seem to be reasonable prognostic factors in patients with colorectal cancer (CRC). The study aimed to investigate the relationships between numerous parameters of nutritional status and prognosis in patients undergoing surgery due to CRC.

Material and methods: Clinical nutritional assessment and biochemical determinations were performed on 110 patients who underwent elective surgery due to primary CRC. Body composition was also analyzed using bioelectrical impedance (BIA) and computed tomography (CT) scans at the third lumbar (L3) vertebra using OsiriX software.

Results: Patients who failed to attend a visit 3 months after surgery (n = 15; 13.6%) were more likely to be sarcopenic, with lower baseline functional status, handgrip strength, skeletal muscle (SM) parameters in BIA and a smaller SM area in CT. Compared to those who died during, on average, 3.6 years of follow-up (n = 33; 30%), patients who survived had, at baseline, a significantly higher Mini-Nutritional Assessment (MNA) score, lower waist-to-height ratio (WHtR), and higher scores on functional status scales. In a Cox's proportional-hazards model, in addition to an advanced WHO CRC stage, scores for MNA (HR; 95% CI: 0.85; 0.74–0.98; p = 0.021), Patient-Generated Subjective Global Assessment (PG-SGA), instrumental activities of daily living (IADL), and WHtR (3.68; 1.03–13.13; p = 0.049) were independent risk factors for death.

Conclusions: Patients' functional status 3 months after surgery due to CRC was related to baseline SM strength, mass, and functional performance, whereas 3.5-year mortality was associated with lower MNA and IADL scores and higher WHtR and PG-SGA scores.

Key words: colorectal cancer, nutritional status, body composition, computed tomography scans, sarcopenia

Introduction

Colorectal cancer (CRC) is recognized as nutrition-related cancer, and obesity, especially visceral obesity, is a risk factor for CRC-related morbidity and mortality [1–5]. However, the association is complex. On the one hand, overweight and obesity are linked to longer survival of CRC patients after treatment, which is mostly interpreted as the presence of the "obesity paradox" [6–9]. On the other, there is strong evidence that both malnutrition [10–14] and excess body fat, visceral adiposity, and sarcopenia (reduced skeletal muscle mass, strength and functional performance), especially when it coexists with obesity (sarcopenic obesity), contribute to worse short-, medium- and long-term outcomes of CRC treatment [1, 2, 6–8, 11–13, 15, 16]. Numerous explanations for associations between CRC surgery outcomes and patients' baseline nutritional status are proposed, including (a) the effect of adipocytokines (hormonal substances secreted by adipocytes and that induce insulin and insulin-like growth factor-1 [IGF-1] secretion), changes in appetite and energy expenditure, promotion of colonic cell proliferation, immune response, and angiogenesis [8, 17–22]; (b) possibility to perform of radical operation [1, 2, 4]; (c) the risk of perioperative complications [1, 2]; (d) the response to chemotherapy [23] and the risk of chemotherapy-associated hepatotoxicity due to liver steatosis [4]; and (e) the risk of post-surgery neoplasmatic cachexia and frailty [14, 24].

CRC is the second most prevalent neoplasm worldwide and the most common obesity-related neoplasm [1–5]. As a result of the development of new therapeutic methods, knowledge about prognosis after CRC surgery would seem to be very important in order to personalize patients' therapy with regard to different levels of aggressiveness. Therefore, the authors investigated the prognostic importance of numerous clinical, biochemical, and anthropometric nutritional status-related parameters of CRC patients undergoing surgery.

Material and methods

Patients

The study involved 110 consecutive inpatients with primary CRC who underwent elective surgery between 2016 and 2019 at the University Hospital. The exclusion criteria were lack of informed consent to participate in the study and the need for emergency surgery (e.g., due to bowel obstruction or haemorrhage).

During their first day of admission, a medical history was obtained from each of the patients enrolled on the study and a physical examination was performed that included an assessment of anthropometric parameters of nutritional status. After being discharged, the patients were invited to attend a follow-up visit 3 months after their operation. In a long-term follow-up (average 1298.5 ± 607.8 days), the patient's survival status was checked during a telephone visit.

Parameters of nutritional status and body composition assessment

The following parameters of nutritional and anthropometric status assessment were measured: Nutritional Risk Screening (NRS)-2002 (a score of 3 or more points in the questionnaire indicating a risk of malnutrition-related complications); Mini Nutritional Assessment (MNA, a 17–23.5 score in the questionnaire indicating a risk of malnutrition, and score < 17 diagnose malnutrition); Patient-Generated Subjective Global Assessment (PG-SGA) (a score of more than 4 points in the questionnaire indicating a risk of malnutrition-related complications); height (cm); body weight (kg); body mass index (BMI, kg/m^2), measured as the ratio of body weight and the square of height expressed in meters; waist circumference (WC, cm); waist-to-height ratio (WHtR), measured as the ratio of WC (cm) to height (cm); mid-arm circumference (MAC, cm); triceps skinfold (TSF, mm) and subscapular skinfold thickness (SST, mm), using the Harpenden MG-4800 manual skinfold caliper (BATY, UK); and the handgrip strength (HGS, kg) of the dominant and non-dominant hands using an electronic dynamometer (Kern, Germany). Body composition was determined using whole-body bioelectrical impedance analysis (BIA) and a TANITA BC 420 MA device (TANITA Corporation, Japan). The following BIA parameters were analysed: fat mass (FM, expressed as a percentage of total body weight [FM%] and as an absolute mass in kg [FM kg]); visceral adipose tissue (VAT) score (in the range 1–59, a level > 12 showing abdominal adiposity); fat-free mass (FFM, kg); skeletal muscle mass (SMM, expressed as a percentage of total body mass [SMM%] and as the absolute mass in kg [SMM kg]); basal metabolic rate (BMR, kcal); and metabolic age (MA, years). Moreover, because abdominal computed tomography (CT) was performed in every CRC patient before surgery (range of slice thickness: 1–5 mm), the regional densitometric quantification of skeletal muscle (SM, attenuation limit –30 to 150 Hounsfield units [HU]), visceral adipose tissue (VAT, attenuation limit –150 to –50 HU) and subcutaneous adipose tissue (SAT) and their cross-sectional areas at the third lumbar (L3) vertebra were manually selected as specific regions of interest (ROI) [25] and parameters of body composition using OsiriX software by Pixmeo SARL, Bernex, Switzerland (Fig. 1).

Functional status indices, such as Barthel, Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL), were also completed.

Biochemical determinations

Blood samples were taken from the ulnar vein of each patient between 7 am and 8 am on the day of admission while they were in a fasting state. For all the patients with CRC, the following biochemical determinations were performed in the hospital's diagnostic laboratory using standard methods: blood morphology with a detailed determination of white blood cell distribution (total lymphocyte count [TLC] and neutrophils), glucose, albumin, C-reactive protein (CRP), and carcinoembryonic antigen (CEA). The Preoperative Onodera's Prognostic Nutritional Index (OPNI) was also calculated according to the following formula: [10 × blood albumin concentration (g/l)] + [0.005 × TLC (G/l)] [7].

Outcomes measured

The following outcomes were measured in the perioperative period: length of stay and all-type post-operative complications, both surgical (e.g., surgical site infection [SSI], anastomotic leakage, fistula) and non-surgical (e.g., pneumonia, myocardial infarction,

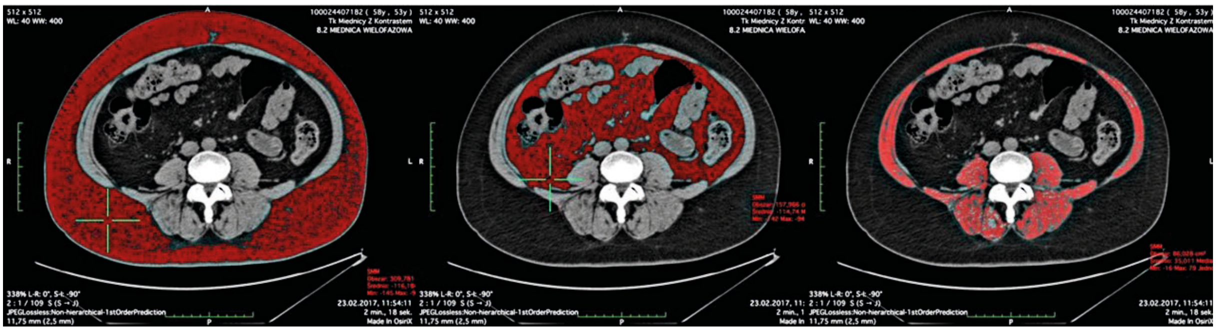

Figure 1. Example of computed tomography (CT) scans with the area-based densitometric quantification of tissues measured at spinal level L3 with regions of interest (ROI) containing (from left to right): A. subcutaneous adipose tissue (SAT) (threshold: –190 to –30 Hounsfield units [HU]); B. visceral adipose tissue (VAT) (threshold: –150 to –50 HU); and C. skeletal muscle area (SM, threshold: –30 to 150 HU)

stroke). At a 3-month visit, as at baseline, nutritional and functional status questionnaires were completed, and anthropometric parameters of nutritional status and BIA parameters of body composition were obtained. In the long-term follow-up, patients' survival was checked during a telephone visit.

Bioethics

The investigation was conducted in compliance with the Declaration of Helsinki for medical research, after receiving permission from the local Bioethical Committee (No. KB 595/2015).

Statistics

Statistical analysis was conducted using the licensed version of the statistical software Statistica, version 13.3, developed by Tibco Software, Inc. (2017). The normal distribution of the study variables was checked using the Kolmogorov-Smirnov test. Depending on the type of variable distribution, the results were presented as the median, interquartile range (IQR), mean ± standard deviation, or n, %, and the statistical significance of differences between groups was verified using the Mann-Whitney U non-parametric test, Kruskal Wallis ANOVA test, Student's t-test, and Chi^2 test. The statistical significance level was set at a p-value < 0.05. A Cox's hazards regression model and Kaplan-Meier curve were determined in the survival analysis. The optimal cut-offs for the respective significant parameters (e.g., MNA score, WHtR) were determined for maximal Youden indices by plotting receiver operating characteristic (ROC) curves in predicting patient deaths.

Table 1. Characteristics of the study population presented as number (%) or median (interquartile range, IQR)

Characteristic (n = 110)	
Age (years)	67 (20–86)
Gender, male (n, %)	67 (61)
Height (cm)	168.8 (149.00–195.00)
Weight (kg)	82.06 (54.00–140.00)
Size of tumour (cm)	4.44 (0.50–20.00)
CRC (WHO stage) (n, %)	
I	29 (26)
II	29 (26)
III	41 (38)
IV	11 (10)
Site of tumour (n, %)	
Rectum	43 (39)
Left colon	35 (32)
Right colon	32 (29)
Comorbidities (n, %)	
Diabetes mellitus	33 (30)
Coronary artery disease	13 (12)
Hypertension	74 (67)
CRP-to-albumin ratio	2.37 (0.06–18.70)
Total lymphocyte count (G/L)	1.98 (0.46–10.35)
Total cholesterol (mg/dl)	177.70 (88.00–316.00)
Patients with perioperative complications (n, %)	18 (16)
Length of in-hospital stay (days)	7 (7–8)
Death during follow-up (n, %)	33 (30)

Results

The analysis included 110 patients. Almost half of those CRC patients had advanced neoplasm (WHO stages III or IV), and the majority of the tumours were located in the left colon and the rectum (Tab. 1). Patients who failed to attend a visit 3 months after surgery (n = 15; 13.6%) due to poor functional status were more likely to be sarcopenic, with regard

Table 2. Nutritional status and body composition assessment of patients at baseline and postintervention

Variable	Before surgery (n = 110)	Data obtained for patients who attended a visit 3 months after surgery (n = 95,86%)	Baseline values for patients who failed to attend a 3-month visit (n = 15,14%)	Baseline values for patients who died during follow-up (n = 33,30%)
Age (years)	67.20 ± 11.41	66.87 ± 10.58	69.27 ± 16.06	70.88 ± 9.00†
Weight (kg)	82.06 ± 16.73	77.40 ± 16.77	75.60 ± 13.06	85.98 ± 17.62
PG-SGA (score)	5.12 ± 4.17	4.91 ± 5.01	6.13 ± 3.44	6.18 ± 5.24
MNA (score)	25.31 ± 2.89	25.16 ± 3.46	24.50 ± 2.45	24.27 ± 2.53‡
OPNI (score)	41.93 ± 4.56	–	40.39 ± 3.97	41.06 ± 3.99
Barthel scale (score)	98.91 ± 3.61	95.53 ± 14.08	99.00 ± 3.87	97.88 ± 5.00†
ADL (score)	5.96 ± 0.19	5.82 ± 0.82	6.0 ± 0.00	5.91 ± 0.29†
IADL (score)	23.28 ± 1.75	22.69 ± 2.93	23.07 ± 2.28	22.67 ± 2.33†
Handgrip strength (kg)	31.30 ± 12.07	29.68 ± 11.40	26.29 ± 10.88†	28.44 ± 12.62
WHtR	0.59 ± 0.08	0.59 ± 0.08	0.57 ± 0.08	0.62 ± 0.08‡
Fat mass (%)	29.01 ± 9.47	24.50 ± 10.45	27.77 ± 10.88	30.18 ± 9.40
Skeletal muscle mass (kg)	44.55 ± 12.19	32.46 ± 7.32	42.03 ± 8.79	43.45 ± 12.80
Skeletal muscle mass (%)	38.82 ± 6.21	54.90 ± 5.05	40.06 ± 7.62	37.96 ± 5.92
Visceral fat index (score)	12.42 ± 5.15	18.41 ± 16.92	12.80 ± 7.12	13.44 ± 5.64
TSF (mm)	15.29 ± 8.42	15.57 ± 7.38	14.59 ± 8.04	15.12 ± 8.33
Calf circumference (cm)	36.81 ± 3.69	39.36 ± 6.12	35.60 ± 4.24	36.83 ± 4.36
Arm circumference (cm)	28.40 ± 3.54	28.40 ± 3.93	27.67 ± 2.81	28.76 ± 3.4
MAC (cm^2)	23.49 ± 2.93	23.44 ± 3.52	22.86 ± 2.83	23.46 ± 3.24
AMA (cm^2)	44.61 ± 10.98	44.68 ± 13.41	42.18 ± 10.27	44.60 ± 12.22
AFA (cm^2)	21.96 ± 11.77	21.27 ± 10.29	19.73 ± 11.04	21.93 ± 10.94
BAMR (cm^2)	0.53 ± 0.31	0.52 ± 0.29	0.51 ± 0.33	0.54 ± 0.32
CT-SMM (cm^2)	99.73 ± 31.32	–	81.26 ± 31.64†	101.11 ± 35.01
CT-SAT (cm^2)	175.65 ± 78.81	–	137.84 ± 64.58	177.83 ± 85.62
CT-VAT (cm^2)	160.70 ± 82.06	–	148.45 ± 107.49	174 ± 86.19
SMM-to-SAT ratio	0.69 ± 0.46	–	0.76 ± 0.74	0.68 ± 0.36
SMM-to-VAT ratio	0.69 ± 0.46	–	1.02 ± 1.18	0.71 ± 0.41
CRP-to-albumin ratio	2.37 ± 3.85	–	4.52 ± 5.74†	2.03 ± 3.43
Total cholesterol (mg/dl)	177.70 ± 44.49	–	184.27 ± 52.11	158.27 ± 38.13‡

The results are expressed as mean ± standard deviation (SD); † — $p < 0.05$, ‡ — $p < 0.01$ in comparison to baseline values obtained for patients who attended a 3-month visit and those who survived the follow-up period. ADL — activities of daily living; AFA — arm fat area; AMA — arm muscle area; BAMR — brachial adipo-muscular ratio; CRP — C-reactive protein; CT — computed tomography; IADL — instrumental activities of daily living; MAC — mid-arm circumference; MNA — Mini Nutritional Assessment; OPNI — Preoperative Onodera's Prognostic Nutritional Index; PG-SGA — Patient-Generated Subjective Global Assessment; SAT — subcutaneous adipose tissue; SMM — skeletal muscle mass; TSF — triceps skinfold; VAT — visceral adipose tissue; WHtR — waist-to-height ratio

to lower baseline HGS and lower SM area in CT (81.3 ± 31.6 vs. 102.4 ± 30.5 cm^2; $p = 0.03$). They also had a higher CRP-to-albumin ratio (Tab. 2).

After 1298.5 ± 607.8 days of follow-up (an average of 3.6 years, median; IQR: 1293; 978–1792 days), 77 CRC patients (70%) survived. Compared to those who died, those patients who survived had at baseline significantly lower age and WHtR, as well as higher functional status scores (Barthel, ADL and IADL indices), and higher MNA and blood total cholesterol concentration scores (Tab. 2). In the Cox's proportional hazards model, in addition to the WHO CRC advancement stage, the other independent risk factors for death in the CRC patients studied were the scores of the MNA, PG-SGA and IADL indices, as well as WHtR (Tab. 3). However, the values of the parameters of instrumental body composition analysis (BIA, CT scans at L3) were not associated with patient prognosis during the 3.6 years

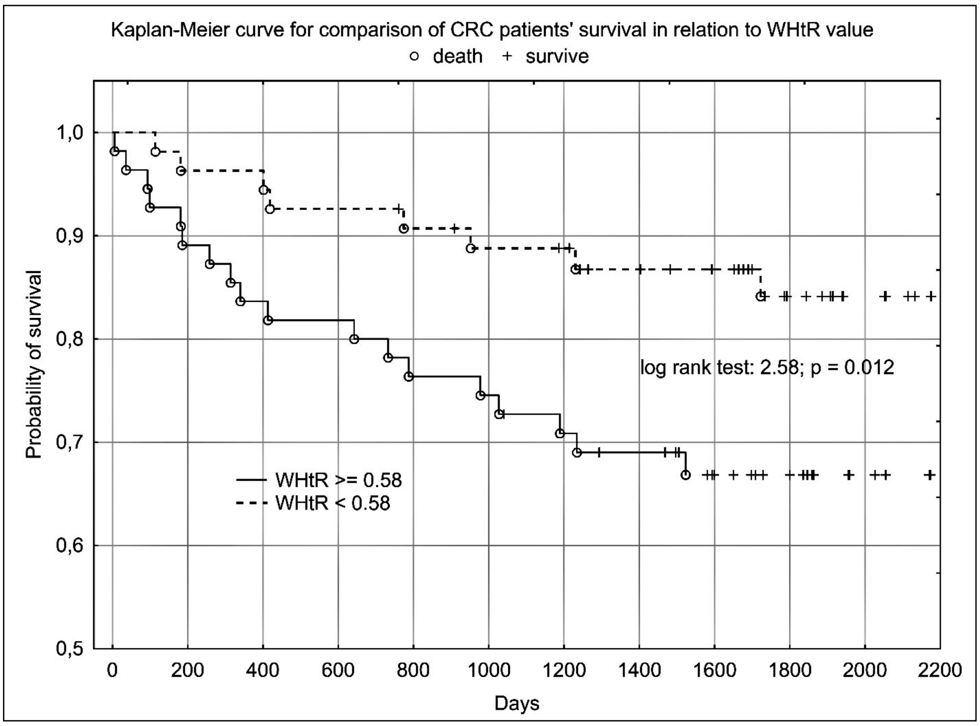

Figure 2. Kaplan-Meier curve for CRC patients' 3.6-year survival in relation to WHtR value

Table 3. Cox's hazards regression model for prediction of death; Chi-square = 22.26; p = 0.014

Baseline values of parameters	HR	95% CI	P-value
Age (years)	1.02	0.98–1.07	0.269
CRC (WHO stage)	1.94	1.26–3.00	0.003
MNA (score)	0.85	0.74–0.98	0.021
PG-SGA (score)	1.13	1.03–1.23	0.010
Barthel index (score)	0.97	0.88–1.06	0.515
IADL (score)	0.79	0.65–0.96	0.017
WHtR	3.68	1.03–13.13	0.049
OPNI (score)	0.96	0.89–1.04	0.358
CT-SMM (cm^2)	1.00	0.98–1.02	0.850
CT-SAT (cm^2)	0.99	0.99–1.00	0.544
CT-VAT (cm^2)	1.00	0.99–1.01	0.877
CT-SMM-to-CT-VAT ratio	0.54	0.12–2.35	0.409
Handgrip strength (kg)	0.81	0.31–2.10	0.660
SMM in BIA (%)	0.94	0.87–1.01	0.104
CRP-to-albumin ratio	0.92	0.81–1.05	0.219
Total cholesterol (mg/dL)	0.99	0.98–1.00	0.139

BIA — bioelectrical impedance analysis; CI — confidence interval; CRC — colorectal cancer; CRP — C-reactive protein; CT — computed tomography; CT-SAT — subcutaneous adipose tissue area in CT; CT-SMM — skeletal muscle mass area in CT; CT-VAT — visceral adipose tissue area in CT; HR — hazard ratio; IADL — instrumental activities of daily living; MNA — Mini Nutritional Assessment; PG-SGA — Patient-Generated Subjective Global Assessment; OPNI — Onodera's Prognostic Nutritional Index; WHO — World Health Organization; WHtR — waist-to-height ratio

of the follow-up period. The survival of CRC patients in relation to WHtR values below and greater than or equal to 0.58 is presented in Figure 2. The cut-off value for WHtR was obtained in ROC analysis (AUC 0.654; 0.95% CI: 0.542–0.765; p = 0.007).

Discussion

This study analysed the clinical and nutritional data of CRC patients with typical neoplasm distribution in the large intestine (Tab. 1). Patients who failed to attend the 3-month follow-up visit due to poor functional state were more likely to have lower HGS, and SM area in CT, and higher CRP-to-albumin ratio at baseline (Tab. 2), which showed that sarcopenia before CRC surgery is a risk factor for deterioration in patients' functional and performance status in the short-term period after an operation. However, with regard to patients' 3.6-year survival after CRC surgery, the multifactorial analysis showed that their risk of death was, in addition to the WHO CRC advancement stage, related to (a) worse baseline nutritional status, expressed by lower MNA and PG-SGA scores; (b) worse baseline functional status, expressed by a lower score on the IADL scale; and (c) higher visceral adiposity expressed by a higher WHtR (Tab. 3). Significantly, an association between abdominal fat distribution, expressed by WHtR $\geq$ 0.58, and a worse patient prognosis was also confirmed in the Kaplan-Meier analysis (Fig. 2).

Concerning deterioration in patients' functional status during the 3-month follow-up, other studies corroborate the obtained results, showing that people with malnutrition and/ or sarcopenia have a higher risk of in-hospital death and complications [11–13, 15–16] and need a longer hospital stay [26, 27]. Short-term outcomes after CRC surgery were discussed in earlier research [7]. According to the current definition of sarcopenia [28–30], this clinical condition should be diagnosed based on the confirmation, in order, of the following criteria: impairment in patient's performance (loss of skeletal muscle function), low skeletal muscle strength, and loss of muscle mass. This suggests that a lower IADL score, as an index of low functional performance, found in this study before CRC surgery to be a risk factor for death in a long-term follow-up (Tab. 3), might be considered as a surrogate for sarcopenia, or as a parameter at least partially related to preoperative sarcopenia. This is despite not confirming that low HGS and low SMM determined in BIA or CT are statistically significant predictors of CRC patient mortality (Tab. 3).

It seems surprising that advanced methods of body composition analysis (BIA, CT scans) failed to predict a 3.6-year risk of all-cause death in the CRC patients studied, in contrast to, for example, such simple anthropometric parameters as WHtR (Tab. 3), with a cut-off value amounting to 0.58 (Fig. 2). However, the present observation is consistent with the report by Nattenmueller et al. [25], who found that WHtR was a better predictor of adipose tissue compartments and SMM than BMI and waist-to-hip ratio (WHR), although, compared to the CT-based measurement, WHtR did not adequately capture differences according to age and gender. Nevertheless increased WHtR with different cut-offs is recognized as a risk factor and/or prognostic parameter in numerous clinical conditions, such as thyroid cancer (WHtR $\geq$ 0.5) [31], primary liver cancer [32, 33], prostate cancer (WHtR > 0.59 or $\geq$ 0.6 [34]), gallbladder cancer [35], breast cancer [1, 36], kidney cancer in postmenopausal women [37], all obesity-related cancers (WHtR $\geq$ 0.51 in men, and $\geq$ 0.57 in women) [1, 38], CRC (WHtR $\geq$ 0.55 [39] or $\geq$ 0.5 [40]), and prognosis after CRC surgery [41]. Moreover, increased WHtR is a better predictor for the risk of metabolic disorders (diagnostic value in descending order: WHtR > WHR > WC > BMI) [42]. In addition, WHtR is more strongly associated than BMI with obesity-associated mortality in patients with heart failure [43–45], and with diabetes, diabetic nephropathy, hypertension, and dyslipidaemia, [2, 46]. It should be underlined that some authors report that A Body Shape Index (ABSI) or Body Roundness Index (BRI) surpasses WHtR in relation to the usefulness of anthropometric nutritional parameters as prognostic and risk factors for cardiovascular and cancer mortality [32, 47].

Study limitations

As with the majority of studies, the present analysis has some shortcomings that may reduce the strength of the conclusions obtained. The small number of patients included in this study should be considered the main limitation. Nonetheless, this study unquestionably has strong points, which are the analysis of numerous nutritional parameters and the evaluation of their usefulness as mortality predictors among CRC patients who underwent surgery in one centre.

Conclusions

Patients' functional statuses 3 months after surgery due to CRC are related to baseline SM strength, mass, performance, and CRP-to-albumin ratio. Whereas, 3.5-year mortality among CRC patients after an operation, in addition to the preoperative WHO CRC stage, was also associated with higher nutritional risk (MNA, PG-SGA), impaired functional status (IADL), and greater visceral distribution of adipose tissue (WHtR) measured before surgery.

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