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ORIGINAL ARTICLE

GNRI And Conut Scores: Simple Predictors of Sarcopenia in Metastatic Colorectal Cancer Patients

Zeynep Gülsüm Güç[1] · Canan Altay[2] · Hakan Abdullah Özgül[2] · Hülya Ellidokuz[3] · Tuğba Yavuzşen[4]

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Abstract

Objective To evaluate the correlation between sarcopenia and inflammation- and nutrition-based markers in metastatic colorectal cancer (mCRC) patients.

Materials and methods Age, body mass index (BMI), neutrophil/lymphocyte ratio (NLR), modified Glasgow prognostic score (mGPS), prognostic nutrition index (PNI), cachexia index (CIn), skeletal muscle index (SMI), controlling nutritional status (CONUT) score, and geriatric nutritional risk index (GNRI) were evaluated in 185 patients. Ideal cut-off values for the GNRI score were determined with the ROC curve analysis, and the patients were divided into two groups as low and high GNRI. Sarcopenia was diagnosed using CT scanning, the gold standard method. Univariate and multivariate Cox proportional hazard analyses were done based on the above-listed parameters to assess the correlation between sarcopenia and changes in immuno-nutrition and inflammatory response. Kaplan–Meier analysis was also done to evaluate survival.

Results Univariate analysis of the 185 patients based on the EGWSOP 2018 threshold values showed correlation between the presence of sarcopenia and male gender, diagnosed colon cancer, history of metastasectomy, BMI < 24, high mGPS score, PNI score ≥ 45, high CONUT score, and low GNRI score ($p < 0.05$). In multivariate analysis, low GNRI (*HR*: 2.40; 95% *CI*: 1.03–5.544; $p = 0.040$), and high-CONUT scores (*HR*: 2.01; 95% *CI*: 1.06–3.73; $p = 0.029$) were identified as independent prognostic factors for the presence of sarcopenia.

Conclusion GNRI and CONUT scores are elementary and practical predictors for sarcopenia, a condition which is associated with poor outcomes in mCRC patients.

Keywords Sarcopenia · Colorectal cancer · Nutrition scores · Inflammatory scores · Survival

Introduction

Sarcopenia is defined as a decline in skeletal muscle mass, strength, and function due to advanced age, reduced mobility, malnutrition, malignancy, chronic diseases, and cachexia [1]. Major clinical guidelines have included sarcopenia as a tool for assessing cachexia in cancer patients [1]. Albeit, sarcopenia is said to be a syndrome associated with malnutrition, and the condition has also been shown to occur in overweight and obese individuals [2]. Sarcopenia patients can have adverse nutritional and immunological factors and show lower adherence to successive anti-tumor treatments, such as radiotherapy, surgery, and chemotherapy [2, 3].

Sarcopenia has been identified as a poor prognostic factor in patients with solid tumors such as pancreatic cancer, melanoma, and hepatocellular carcinoma [2–4]. While different measurement techniques were used in different studies to identify sarcopenia, there are some overall challenges in the assessment of the condition. Computed tomography (CT) measurement of the skeletal muscle in the third lumbar vertebra (L3) region is a reference method due to its accuracy and reliability in the assessment of the condition [2, 3]. The method, however, is expensive, exposing individuals to a high dose of radiation, and measurement of the skeletal

✉ Zeynep Gülsüm Güç
zeynepgsevgen@hotmail.com

1 Department of Medical Oncology, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey

2 Department of Radiology, Dokuz Eylul University Medical Faculty, Izmir, Turkey

3 Department of Biostatistics and Medical Informatics, Dokuz Eylul University Medical Faculty, Izmir, Turkey

4 Department of Medical Oncology, Institute of Oncology, Dokuz Eylul University, Izmir, Turkey

muscle region is a labor-intensive process that requires an experienced radiologist.

The mechanisms underlying chemotherapy-induced sarcopenia in cancer patients have not been clearly differentiated. While impaired food intake, reduced physical activity due to fatigue, the direct effect of chemotherapy on the muscles, and malabsorption secondary to mucositis or anorexia are the possible causes of sarcopenia that emerge during chemotherapy; the catabolic sequelae of chemotherapy can also be a co-factor for chemotherapy-induced sarcopenia [2]. The presence of sarcopenia in cancer patients has been associated with increased postoperative complications, chemotherapy toxicity, and worse disease-free survival or overall survival [2, 3].

Increasing evidence suggest that systemic inflammatory response and malnutrition have a role in the development and progression of cancer [2]. The host's immune response to malignancy is characterized by systemic inflammation, which leads to changes in the levels of cells such as neutrophils, lymphocytes, monocytes and platelets, and markers such as C-reactive protein (CRP) and albumin. While systemic inflammation is characterized by an imbalance between pro-inflammatory and anti-inflammatory cytokines in malignant cases, inflammatory markers can be used to predict prognosis in various malignancies.

Immuno-nutritional parameters like the prognostic nutritional index (PNI), the controlling nutritional status (CONUT), and the geriatric nutritional risk index (GNRI) have been evaluated as predictive and prognostic factors in different malignancies. These parameters can be easily calculated based on the hematological and anthropometric data of patients used in everyday practice.

Recently, these immuno-nutritional parameters were defined as prognostic markers for various malignancies, including CRC [2–4]. There are, however, no studies that have examined whether these biomarkers could predict sarcopenia in mCRC patients. In our study, we aimed to assess the relationship between sarcopenia diagnosed with CT in mCRC patients and immuno-nutritional parameters.

Materials and methods

Data collection and follow-up

The method and procedure for the study were approved by the Ethics Committee of the University. All 185 mCRC patients that were treated at the Medical Oncology Clinic from April 2010 through March 2014 were included in the study and followed-up for at least 5 years. Patients' age, weight, height, body mass index (BMI), comorbidities, ECOG status, and demographic data were recorded. Patients who had severe comorbidities, or were receiving anti-inflammatory therapy, had active infection, inadequate organ function or no abdominal CT scan at the third lumbar vertebra level (L3) available for review were excluded. The Charlson comorbidity index (CCI) was used to determine and grade comorbidities, and patients with a CCI score ≥ 7 were excluded (a baseline score of 6 was accepted for all patients due to the presence of metastatic solid tumors). Absolute neutrophil and lymphocyte counts, serum albumin and C-reactive protein (CRP) levels, and serum total cholesterol levels were recorded at the time when metastasis was detected. The presence of sarcopenia was evaluated using the computed tomography (CT) images of patients that were taken one month before treatment.

Skeletal muscle index (SMI) and sarcopenia

The images were analyzed using the technique that is commonly used in sarcopenia studies: the third lumbar vertebra where transverse processes were visible was used as landmark axial level. Two consecutive images were chosen to measure muscle cross-sectional area. The psoas, paraspinal, oblique, and rectus muscle regions were quantified with dedicated renderings as a region of interest (ROI), using a Hounsfield unit (HU) threshold of 30 to þ150 to select skeletal muscle, but excluding fat, bone, and vasculature. The average of the cross-sectional areas was computed and corrected for height to calculate the muscle index (cm^2/m^2). Sarcopenia index (SI) was calculated as L3 SMA (cm^2)/height (m^2). Given the absence of studies from our country, the SI cut-off value was obtained by using EGWSOP-2018 [2].

Body mass index (BMI)

Height and weight of patients were measured with a regularly standardized stadiometer. Body weight was recorded to the nearest 0.1 kg and height to the nearest 0.1 cm. BMI was calculated by dividing the weight by the square of height (kg/m^2). Groups were classified as $BMI < 24$ kg/m^2 and $BMI \geq 24$ kg/m^2 for statistical analysis. Optimal BMI cut-off values were determined with ROC curve analysis and patients were separated into two groups as low (>24) and high (≥ 24) BMI.

Markers of systemic inflammation

Nine markers (absolute neutrophil count, NLR, serum albumin level, serum CRP level, mGPS, Cachexia Index (CIn), PNI scores, CONUT, and GNRI) were calculated using the laboratory data obtained. Any infections or chronic inflammatory conditions affecting these laboratory parameters were ruled out. mGPS, CIn, and PNI are given in Table 1. NLR cut-off value was accepted as the median value of patients' NLR measurements. The CONUT score was calculated using serum albumin concentration, peripheral lymphocyte count, and total cholesterol concentrations (12). In brief, each parameter was

Table 1 Inflammation-based prognostic scores and cut-off values of sarcopenia indexes

Prognostic Index (PI)	Score
CRP ≤ 10 mg/L and WBC ≤ 10×10^9	0
CRP ≤ 10 mg/L and WBC > 10×10^9	1
CRP > 10 mg/L and WBC ≤ 10×10^9	1
CRP > 10 mg/L and WBC > 10×10^9	2
Prognostic Nutritional Index (PNI)	Score
10×albumin (g/dL) + 0.005×lymphocyte count(per mm^3) ≥ 45	0
10×albumin (g/dL) + 0.005×lymphocyte count(per mm^3) < 45	1
Modified Glasgow Prognostic Score (mGPS)	Score
CRP < 10 mg/L and albumin ≥ 3.5 g/dL	0
CRP ≤ 10 mg/L and albumin < 3.5 g/dL	1
CRP > 10 mg/L	1
CRP > 10 mg/L and albumin < 3.5 g/dL	2
Sarcopenia Index (SI)*	Sarcopenia
L3 lumbar skeletal muscle area (cm^2)/height^2 (m^2)	
Women ≤ 32 and men ≤ 41.6 (cm^2/m^2)	Yes
Women > 32 and men > 41.6 (cm^2/m^2)	No
Cachexia Index (CIn)	Stage
SI (cm^2/m^2) × albumin (g/dL)/NLR ≥ 35	1
SI (cm^2/m^2) × albumin (g/dL)/NLR < 35	2

CRP C-reactive protein. *EGWSOP sarcopenia index cut-off value

scored as follows: albumin concentration: ≥ 3.5 mg/dL: 0 points, 3.0–3.49 mg/dL: 2 points, 2.5–2.99 mg/dL: 4 points, and < 2.5 mg/dL: 6 points. Total lymphocyte count: ≥ 1600/mm^3: 0 points, 1200–1599/mm^3: 1 point, 800–1199/mm^3: 2 points, and < 800/mm^3: 3 points. Total cholesterol levels were scored as: ≥ 180 mg/dL: 0 point, 140–179/mm^3: 1 point, 100–139/mm^3: 2 points, and < 100/mm^3: 3 points. The sum of these scores was defined as the CONUT score.

GNRI was calculated using serum albumin concentration and body weight as described elsewhere [2]. The GNRI formula was $GNRI = 14.87 \times$ serum albumin concentration (g/L) $+ 41.7 \times$ weight/ideal weight (kg). The ideal body weight was calculated as: ideal bodyweight = 22*x*square of height (m).

Statistical analyses

The Statistical Package for Social Sciences for Windows 20.0 (SPSS, Inc., Chicago, IL, USA) was used for analysis. Survival was defined as the time from diagnosis to death or last visit. Descriptive statistics summarized frequencies and percentages for categorical, mean, and standard deviation for continuous variables. Categorical variables were compared with the Independent Samples *T*-test and categorical parameters with the $\chi 2$ test. The power of the GNRI was analyzed using ROC curve analysis. A significant cut-off point was observed, and the sensitivity, specificity, and positive and negative predictive values were detected. Overall survival analyses of prognostic indexes and clinical and pathological features were calculated using the Kaplan–Meier method (log-rank test). Parameters that appeared significant in univariate analysis for survival and did not show multicollinearity were included in the Cox multivariate regression analysis. Also, inflammatory parameters that seemed significant for the presence of sarcopenia in the univariate analysis were included in the Cox multivariate regression analysis. Backward LR Strategy was applied in multivariate analysis. The 95% confidence interval (CI) was used to indicate the relationship between survival time and each independent factor. Statistical significance level was $p < 0.05$.

Results

The baseline characteristics of 185 mCRC patients are given in Table 2 and the mean values of clinical and laboratory parameters based on patient characteristics are shown in Table 3. Median age at presentation was 59 (range, 19–87) years. Males were predominant in the study population (58.4%). Of the 185 patients, 125 (67.6%) had colon cancer and 60 (32.4%) had rectal cancer. Median follow-up time was 38.4 (range, 2–120) months. While 81.1% of the patients were recorded as ECOG 0–1, 42.7% (79 patients) had a history of adjuvant chemotherapy and were found metastatic in the follow-up period. The most common site of metastasis was the liver with 53%.

The CONUT score of the patients was between 0 and 11 (4.03) and the GNRI score was between 64.20 and 142.07 (102.36). The ROC curve for GNRI showed an optimal cut-off value of 107.28 ($AUC = 0.805$; 95% *CI* 0.58–0.87, $p < 0.001$). ROC analysis provided 90% sensitivity and 74% specificity for this cut-off value (Fig. 1). Therefore, 107.28 was determined as the threshold value and the patients were separated into two different groups as low GNRI and high GNRI. According to the CONUT score, 114 patients (61.6%) were in the normal-to-light score group.

Univariate analysis was conducted to identify the potential risk factors for sarcopenia. In the univariate analysis with cut-off values of EGWSOP 2018, sarcopenia was found to be associated with male gender, colon cancer at diagnosis, history of metastasectomy, $NLR < 3.41$, $BMI < 24$, high mGPS, and PNI score ≥ 45. Sarcopenia was significantly more common among patients who had moderate-to-severe CONUT scores and low GNRI levels ($p < 0.001$). When patients were grouped by age, no difference was found with respect to the presence of sarcopenia between patients aged > 65 years and ≥ 65 years ($p = 0.145$) (Table 4).

In univariate analysis for survival, poor prognostic factors were found to be associated with poor ECOG performance status, weight loss > 10% in the past 6 months, $NLR > 3.41$, $BMI < 24$, high mGPS, high PI, CIn score < 35, PNI level < 45, SI positivity (EGWSOP), high CONUT, and

Table 2 Clinic and pathological features of patients

Parameters	Number of patients (%)
Age	
< 75	167 (90.3%)
≥ 75	18 (9.7%)
Gender	
Female	77 (41.6%)
Male	108 (58.4%)
Histology	
Adenocarcinoma	166 (89.7%)
Mucinous adenocarcinoma	16 (8.6%)
Signet-ring cell	3 (1.6%)
Grade	
Well differentiated	65 (35.1%)
Moderately differentiated	104 (56.2%)
Poorly differentiated	16 (8.6%)
ECOG	
ECOG 0–1	150 (81.1%)
ECOG 2–3	35 (18.9%)
Condition at diagnosis	
Metastatic	106 (57.3%)
Non-metastatic	79 (42.7%)
Site of metastasis	
Liver	98 (53%)
Peritoneum	25 (13.5%)
Lungs	37 (20%)
Other	25 (13.5%)
Metastasectomy	
Yes	58 (31.4%)
No	127 (68.6%)
Weight loss	
< 10%	129 (69.7%)
≥ 10%	56 (30.3%)

ECOG Eastern Cooperative Oncology Group

Table 3 Mean values of clinical and laboratory parameters

Parameters	(Mean ± SD)
Age (years)	59.41 ± 12.367
Weight (kg) Male/female	70.54 ± 13.01 72.62 ± 12.21/67.62 ± 13.6
BMI (kg/m^2) Male/female	25.72 ± 4.82 24.63 ± 3.77/27.25 ± 5.67
CRP (mg/L) Male/female	31.56 ± 40.36 36.75 ± 42.74/24.28 ± 35.77
Albumin (mg/dL) Male/female	3.60 ± 0.52 3.55 ± 0.52/3.68 ± 0.52
SMA (cm^2) Male/female	113.59 ± 27.66 126.43 ± 25.63/95.57 ± 19.11
SI (cm^2/m^2) Male/female	41.08 ± 8.44 42.99 ± 8.78/38.39 ± 7.16

BMI body mass index, *CRP* C-reactive protein, *SMA* skeletal muscle area, *SI* sarcopenia index, *SD* standard deviation

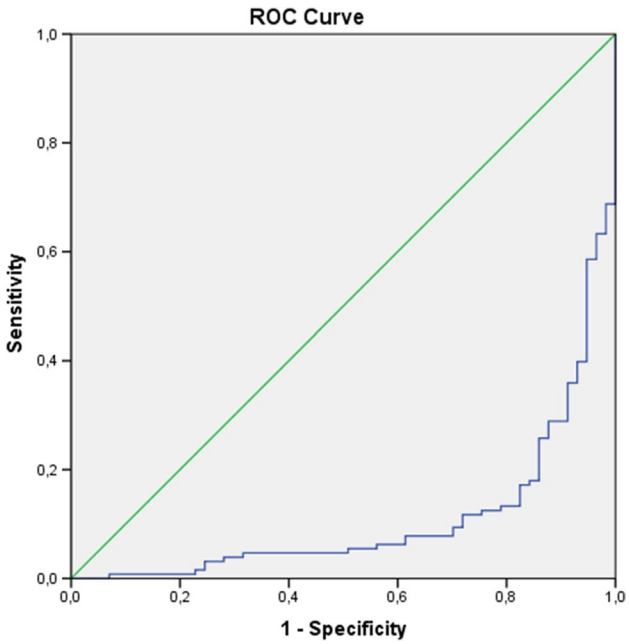

Fig. 1 ROC curve for the Geriatric Nutritional Risk Index

low GNRI scores (Table 5). In multivariate analysis, low GNRI score (HR: 2.22; 95% *CI*: 1.55–3.17; $p < 0.001$), high ECOG performance score (*HR*: 1.67; 95% *CI*: 1.11–2.49; $p = 0.012$), moderate-to-severe CONUT score (*HR*: 1.49; 95% *CI*: 1.04–2.14; $p = 0.027$), and presence of sarcopenia according to EGWSOP (*HR*: 1.62; 95% *CI*: 1.09–2.39, $p = 0.016$) retained significance (overall survival).

Multivariate analysis was done to determine the inflammatory/immuno-nutritional marker that best indicated the presence of sarcopenia. In multivariate analysis, low GNRI score (*HR*: 2.40; 95% *CI*: 1.03–5.544; $p = 0.040$) and moderate-to-severe CONUT score (*HR*: 2.01; 95% *CI*: 1.06–3.73; $p = 0.029$) were identified as independent prognostic factors for the presence of sarcopenia.

Discussion

In this study, we investigated the relationship between sarcopenia and inflammatory/immuno-nutritional parameters in mCRC patients. As a result, we showed—for the first time—that the condition of sarcopenia in mCRC patients is significantly correlated with immuno-nutritional parameters such as GNRI and CONUT scores. Our results showed that the decision of whether sarcopenia exists can be given simply based on laboratory parameters and anthropometric

Table 4 Association of clinical and laboratory parameters and prognostic indexes with sarcopenia

	Number of patients (%)	Sarcopenia (EGWSOP)		
		No	Yes	*p*-value
Gender				
Male	108 (58.4)	17 (15.7)	91 (84.3)	**< 0.001**
Female	77 (41.6)	40 (51.9)	37 (48.1)	
Age				
< 65	105 (56.8)	37 (35.2)	68 (64.8)	0.145
≥ 65	80 (43.2)	21 (26.3)	59 (73.7)	
Diagnosis				
Colon	123	31 (25.2)	92 (74.8)	**0.019**
Rectal	62	27 (41.7)	35 (58.3)	
Metastasectomy				
Yes	127	25 (43.1)	33 (56.9)	**0.012**
No	58	32 (25.2)	95 (74.8)	
ECOG status				
ECOG 0–1	150 (81.1)	48 (32)	102 (68)	0.305
ECOG 2–3	35 (18.9)	9 (25.7)	26 (74.3)	
Weight loss				
< 10%	129 (69.7)	45 (34.9)	84 (65.1)	0.055
≥ 10%	56 (30.3)	13 (21.8)	43 (78.2)	
BMI				
< 24	74 (40)	9 (12.2)	65 (87.8)	**< 0.001**
≥ 24	111 (60)	48 (43.2)	63 (56.8)	
NLR group				
< 3.41	108(58.4)	27 (25)	81 (75)	**0.031**
≥ 3.41	77(41.6)	30 (39)	47 (61)	
mGPS				
0	57 (30.8)	54 (94.7)	3 (5.3)	**< 0.001**
1	38 (20.5)	3 (7.9)	35 (92.1)	
2	90 (48.6)	0 (0)	90 (100)	
PNI				
≥ 45	73 (39.5)	31 (43.8)	41 (56.2)	**0.002**
< 45	112 (60.5)	25 (22.3)	87 (77.7)	
Cln				
< 35	68 (36.8)	16 (23.5)	52 (76.5)	0.070
≥ 35	117 (63.2)	41 (35)	76 (65)	
CONUT				
Normal-light	114 (61.6)	55 (48.2)	59 (51.8)	**< 0.001**
Moderate-severe	71 (38.4)	2 (2.8)	69 (97.2)	
GNRI				
High	69 (37.3)	47 (68.1)	22 (31.9)	**< 0.001**
Low	116 (62.7)	10 (8.6)	106 (91.4)	

BMI body mass index, *Cln* cachexia index, *ECOG* Eastern Cooperative Oncology Group, *EGWSOP* European Working Group on Sarcopenia in Older People, *mGPS* modified Glasgow prognostic score, *NLR* neutrophil–lymphocyte ratio, *PNI* prognostic nutritional index. The bold entries are statistical significance. $p < 0.05$ = statistical significance

Table 5 Association of clinical and laboratory parameters and prognostic indexes for OS

	Univariate analysis of OS		
	Number of patients (%)	Median OS in months (95% ***CI***)	*p*-value
ECOG			
0–1	150 (81.1)	37 (31.36–42.63)	**< 0.001**
2–3	35 (18.9)	21 (15.2–26.79)	
Age			0.204
< 65	105 (56.8)	30 (20.86–39.13)	
≥ 65	80 (43.2)	36 (26.24–45.75)	
BMI			**< 0.001**
< 24	74 (40)	21 (16.78–25.21)	
≥ 24	111 (60)	39 (33.35–44.64)	
NLR			**< 0.001**
< 3.41	108 (58.4)	43 (37.02–48.97)	
≥ 3.41	77 (41.6)	21 (16.76–25.23)	
SI (cm^2/m^2)*			
Yes	128 (69.2)	27 (21.26–32.73)	**0.026**
No	57 (30.8)	40 (32.75–47.24)	
Diagnosis			
Colon	123 (66.4)	30 (21.66–38.33)	0.194
Rectal	62 (33.6)	36 (25.25–46.74)	
Gender			
Male	108 (58.4)	31 (23.07–38.97)	0.117
Female	77 (41.6)	35 (22.84–47.11)	
WL	129 (69.7)	39 (32.92–45.07)	**< 0.001**
< 10% ≥ 10%	56 (30.3)	21 (17.37–24.62)	
mGPS			
0	57 (30.8)	40 (32.94–47.05)	
1	38 (20.5)	44 (36.13–51.87)	**0.006**
2	90 (48.6)	24 (18.19–29.8)	
PNI			
≥ 45	73 (39.5)	42 (37.72–46.27)	**0.013**
< 45	112 (60.5)	26 (20.51–31.48)	
PI			
0	55 (29.7)	40 (33.07–46.92)	
1	110 (59.4)	30 (21.87–38.13)	**0.002**
2	20 (10.9)	15 (8.45–21.54)	
Cln			
< 35	68 (36.8)	19 (15.38–22.61)	**< 0.001**
≥ 35	117 (63.2)	42 (37.07–46.92)	
CONUT			
Normal-light	114 (61.6)	40 (35.35–44.65)	**0.002**
Moderate-severe	71 (38.4)	23 (18.14–27.86)	
GNRI			
High	69 (37.3)	46 (30.86–61.13)	**< 0.001**
Low	116 (62.7)	23 (18.82–27.17)	

BMI body mass index, *Cln* cachexia index, *ECOG* Eastern Cooperative Oncology Group, *mGPS* modified Glasgow prognostic score, *NLR* neutrophil–lymphocyte ratio, *OS* overall survival, *PNI* prognostic nutritional index, *PI* prognostic index, *SI* sarcopenia index, *WL* weight loss, *CONUT* controlling nutritional status, *GNRI* Geriatric Nutritional Risk Index. The bold entries are statistical significance. $p < 0.05$ = statistical significance

measurements such as height-weight, without the need for skeletal muscle measurement with CT, and immuno-nutritional parameters such as the GNRI and the CONUT scores could predict sarcopenia.

Sarcopenia, which is characterized by the progressive loss of skeletal muscle mass, muscle strength, and physical performance [2], has been reported as a poor prognostic factor in various types of cancers and to predict survival [2–4]. A meta-analysis of 38 studies conducted with a total of 7,843 patients with solid tumors showed that, similar to our study, sarcopenia was associated with poor overall survival (*HR*: 1.44, 95% *CI*: 1.32–1.56, $p < 0.001$) [2]. Roxburgh et al. [2] reported a strong correlation between low skeletal muscle mass and systemic inflammatory response in CRC patients and indicated that this negatively affected the course of the cancer. As well as prognosis and survival, sarcopenia has been reported to also be an independent risk factor for complications after CRC surgery and mortality [2, 3]. In their review including 9138 cancer patients from 53 studies, Kazemi et al. [2] reported that sarcopenia negatively affected the outcome of cancer treatment, increased chemotherapy toxicity, length of hospitalization, and postoperative complications. Jung et al. reported sarcopenia to be associated with an increased risk of toxicity and poor prognosis of grade 3–4 chemotherapy in metastatic colon cancer patients [14].

The CONUT score is a relatively new immuno-nutritional biomarker based on total lymphocyte count, serum albumin concentration, and total serum cholesterol measurement [16]. Total lymphocyte count, total serum albumin concentration, total cholesterol concentration in the peripheral blood indicate decreased immune response, protein storage, and calorie deficiency, respectively: Cholesterol, a component of cellular membranes, plays an important role in immunity. It effectuates a range of biological activities, such as membrane fluidity and membrane protein activities, which, as well as the initiation and progression of cancer, may also be associated with immune response. The relationship between cytotoxic effect and cholesterol content in the cell membrane has been shown in apoptosis against cancer cells. Hypocholesterolemia may therefore lead to a poor prognosis in cancer [2]. Lymphocytes, on the other hand, play a role in the host's anticancer defense by both causing apoptosis and suppressing cancer cell proliferation, invasion, and migration [2]. Consequently, lymphocytopenia may contribute to tumor growth. Malnutrition or hypercatabolism may cause hypoalbuminemia in cancer patients, but low albumin may also be due to systemic inflammation, which can lead to hypercytokinemia and a weak immune response against cancer cells [2]. The CONUT score measures not only the nutritional status, but also systemic inflammation and immunological response. As a result, the CONUT score can be a good immuno-nutritional marker. The CONUT score has been demonstrated to have prognostic significance in lung cancer [2] and stomach cancer [2]. Our study is the first to demonstrate that the CONUT score can be used as an independent biomarker for predicting sarcopenia in mCRC patients. The CONUT score has also been proven to be an independent prognostic factor on overall survival.

Since the GNRI is based on serum albumin concentration and BMI, it is a marker that can reflect nutritional status. Serum albumin is a simple and valuable marker that can indicate malnutrition or cachexia in cancer patients. Low serum albumin levels have been associated with poor survival in mCRC and stomach cancer patients [2, 3]. Moreover, recent studies showed that increased BMI was associated with a better prognosis in mCRC patients [2–4]. GNRI, which consists of the combination of these two important parameters, may be one of the most valuable immuno-nutritional parameters. An effective nutrition screening tool should be simple, cost-free, computable with available data, and easy to use. GNRI can be easily calculated using routine laboratory data. The prognostic prediction ability of GNRI is superior to those of BMI and serum albumin levels alone [2]. The role of GNRI in patients with different types of cancers, including lung cancer [2], prostate cancer [2], head and neck cancer [2], and gastrointestinal cancer [2, 3] has been assessed in recent studies; however, the prognostic value of GNRI in CRC and its relationship to sarcopenia could not be fully identified. Our study is the first to show that GNRI has good differentiating power in predicting the presence of sarcopenia in mCRC patients and is an independent prognostic factor.

There are many studies that show the effects of the presence of sarcopenia on both survival and the treatment process, as well as hospitalizations, chemotherapy toxicity, and complications. In our study, we once again showed that the presence of sarcopenia in mCRC patients is an independent prognostic factor on overall survival. Even more important is the detection and monitoring of sarcopenia in this group of patients with a simple, bias-free, and practical method. Our study has shown, for the first time, that sarcopenia diagnosed with CT scanning can be independently predicted by immuno-nutritional parameters such as GNRI and CONUT scores. These scores, which can be easily calculated during diagnosis and follow-up, both are significant immuno-nutritional indicators and very important in the management of mCRC patients who are in dire need of treatment, including chemotherapy, radiotherapy, nutritional support, and conservative care.

The absence of a standardized definition of sarcopenia, in other words, lack of a generally accepted definition in CT-based measurements and standardized cut-off values, has been a major limiting factor in our study. Cut-off values for our country, on the other hand, were determined

in sarcopenia studies that included a general elderly population. Reported BIA (bioelectrical impedance analysis) measurements are 9.2 kg/m^2 for men and 7.4 kg/m^2 for women [2]; however, it was not possible to use these measurements in our analysis since our study was designed to investigate sarcopenia by CT. We therefore used the EGWSOP values. Another possible limitation of our study was that we did not have the opportunity to measure inflammation-related cytokine levels such as TNF-α, IL-1 and IL-6 in the blood of the patients but analyzed the parameters obtained in standard tests as inflammatory markers. And lastly, since our study was a single-center study, our results should be supported by prospective multi-center studies and the role of immuno-nutritional scores in patients' follow-up and treatment responses should be elucidated.

To conclude, our study showed both GNRI and CONUT scores to be effective independent prognostic factors for predicting sarcopenia, which is associated with poor outcome in mCRC patients. Based on our results, we recommend using both, as they are simple and inexpensive indicators that can be calculated with the parameters we use in daily practice. Prospective studies with larger numbers of patients, in which the two scores are tested in this aspect, are needed to investigate the superiority of these two scores over each other in specific situations.

Author contribution Study concept: ZGG, TY. Study design: ZGG, TY. Data acquisition: ZGG, HAÖ, CA. Quality control of data: ZGG, HAÖ, CA. Data analysis and interpretation: ZGG, HAÖ, CA. Statistical analysis: ZGG, HE. Manuscript editing: ZGG, TY. Manuscript review: ZGG, TY.

Data availability The authors confirm that the data supportting the findings of this study are available within the article. Row data that supportting the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval The study was approved by the Institutional Review Board at the Izmir Dokuz Eylül University.

Consent to participate All patients provided written informed consent to participate in the study.

Consent for publication Patients signed informed consent regarding publishing their data.

Conflicts of interest The authors declare no competing interests.

References

1. Rosenberg IH (1997) Sarcopenia: origins and clinical relevance. J Nutr 127:990S-991S. https://doi.org/10.1093/jn/127.5.990S
2. Fuggle N, Shaw S, Dennison E, Cooper C (2017) Sarcopenia. Best Pract Res Clin Rheumatol 31:218–242. https://doi.org/10.1016/j.berh.2017.11.007
3. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE (2008) Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 9:629–635. https://doi.org/10.1016/S1470-2045(08)70153-0
4. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC (2009) Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 15:6973–6979. https://doi.org/10.1158/1078-0432.CCR-09-1525
5. Narici MV, Maffulli N (2010) Sarcopenia: characteristics, mechanisms and functional significance. Br Med Bull 95:139–159. https://doi.org/10.1093/bmb/ldq008
6. Bozzetti F (2017) Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. Ann Oncol 28:21072118. https://doi.org/10.1093/annonc/mdx271
7. Sabel MS, Lee J, Cai S, Englesbe MJ, Holcombe S, Wang S (2011) Sarcopenia as a prognostic factor among patients with stage III melanoma. Ann Surg Oncol 18:3579–3585. https://doi.org/10.1245/s10434-011-1976-9
8. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, Ikeda T, Maehara Y, Nishie A, Yamanaka T (2013) Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg 100:1523–1530. https://doi.org/10.1002/bjs.9258
9. Heymsfield SB, Wang Z, Baumgartner RN, Ross R (1997) Human body composition: advances in models and methods. Annu Rev Nutr 17:527–558. https://doi.org/10.1146/annurev.nutr.17.1.527
10. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D (1985) Ross R (1998) Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol 85:115–122. https://doi.org/10.1152/jappl.1998.85.1.115
11. Kodera Y (2015) More than 6 months of postoperative adjuvant chemotherapy results in loss of skeletal muscle: a challenge to the current standard of care. Gastric Cancer 18:203–204. https://doi.org/10.1007/s10120-014-0381-z
12. Coelen RJS, van Gulik TM (2015) Preoperative sarcopenia negatively impacts postoperative outcomes following major hepatectomy with extrahepatic bile duct resection. World J Surg 39:2368–2369. https://doi.org/10.1007/s00268-015-3053-1
13. Jung HW, Kim JW, Kim JY, Kim SW, Yang HK, Lee JW, Lee KW, Kim DW, Kang SB, Kim KI, Kim CH, Kim JH (2015) Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. Support Care Cancer 23(3):687–694. https://doi.org/10.1007/s00520-014-2418-6
14. Luo H, Chen Y, Chuang Y, Cheng YT, Lee WC, Kang CH, Chiang PH (2014) Subclassification of upper urinary tract urothelial carcinoma by the neutrophil-to-lymphocyte ratio (NLR) improves prediction of oncological outcome. BJU Int 113:144–149. https://doi.org/10.1111/bju.12582
15. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, Rodríguez F, Fernández G (2005) CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp 20:38–45 (PMID: 15762418)
16. Pan QX, Su ZJ, Zhang JH, Wang CR, Ke SY (2015) A comparison of the prognostic value of preoperative inflammation-based scores and TNM stage in patients with gastric cancer. OncoTargets Ther 8:1375–1385. https://doi.org/10.2147/OTT.S82437

17. Kuroda D, Sawayama H, Kurashige J, Iwatsuki M, Eto T, Tokunaga R, Kitano Y, Yamamura K, Ouchi M, Nakamura K, Baba Y, Sakamoto Y, Yamashita Y, Yoshida N, Chikamoto A, Baba H (2018) Controlling Nutritional Status (CONUT) score is a prognostic marker for gastric cancer patients after curative resection. Gastric Cancer 21:204–212. https://doi.org/10.1007/s10120-017-0744-3
18. Cruz-Jentoft AJ, Bahat G, Bauer J et al (2018) Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. https://doi.org/10.1093/ageing/afy169
19. Hasselmann M, Alix E (2003) Tools and procedures for screening for malnutrition and its associated in risks in hospital. Nutr Clin Metabol 17:218–226. https://doi.org/10.1016/j.nupar.2003.09.004
20. Fox KM, Brooks JM, Gandra SR, Markus R, Chiou CF (2009) Estimation of cachexia among cancer patients based on four definitions. J Oncol 1-7. https://doi.org/10.1155/2009/693458
21. Sabel MS, Lee J, Cai S, Englesbe MJ, Holcombe S, Wang S (2001) Sarcopenia as a prognostic factor among patients with stage III melanoma. Ann Surg Oncol 18:3579–3585. https://doi.org/10.1245/s10434-011-1976-9
22. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, Ikeda T, Maehara Y, Nishie A, Yamanaka T (2013) Sarcopenia as a predictor of prognosis in patients following hepatectomy. Br J Surg 100:1523–1530. https://doi.org/10.1002/bjs.9258
23. Shachar SS, Williams GR, Muss HB, Nishijima TF (2016) Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. Eur J Cancer 57:58–67. https://doi.org/10.1016/j.ejca.2015.12.:26882087030
24. Roxburgh CS, Platt JJ, Leitch EF, Kinsella J, Horgan PG, McMillan DC (2011) Relationship between preoperative comorbidity, systemic inflammatory response, and survival in patients undergoing curative resection for colorectal cancer. Ann Surg Oncol 18:997–1005. https://doi.org/10.1245/s10434-010-1410-8 (PMID: 21042941)
25. Huang DD, Wang SL, Zhuang CL, Zheng BS, Lu JX, Chen FF, Zhou CJ, Shen X, Yu Z (2015) Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. Colorectal Dis 17:O256–O264. https://doi.org/10.1111/codi.13067
26. Huang DD, Chen XX, Chen XY, Wang SL, Shen X, Chen XL, Yu Z, Zhuang CL (2016) Sarcopenia predicts 1-year mortality in elderly patients undergoing curative gastrectomy for gastric cancer: a prospective study. J Cancer Res Clin Oncol 142:2347–2356. https://doi.org/10.1007/s00432-016-2230-4
27. Kazemi-Bajestani SMR, Mazurak VC, Baracos V (2016) Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Semin Cell Dev Biol 54:2–10. https://doi.org/10.1016/j.semcdb.2015.09.001
28. Lorent JH, Léonard C, Abouzi M, Akabi F, Quetin-Leclercq J, Mingeot-Leclercq MP (2016) α-Hederin induces apoptosis, membrane permeabilization and morphologic changes in two cancer cell lines through a cholesterol-dependent mechanism. Planta Med 82:1532–1539. https://doi.org/10.1055/s-0042-114780
29. Lim JA, Oh CS, Yoon TG, Lee JY, Lee SH, Yoo YB, Yang JH, Kim SH (2018) The effect of propofol and sevoflurane on cancer cell, natural killer cell, and cytotoxic T lymphocyte function in patients undergoing breast cancer surgery: an in vitro analysis. BMC Cancer 18:159. https://doi.org/10.1186/s12885-018-4064-8
30. Lucijanic M, Veletic I, Rahelic D, Pejsa V, Cicic D, Skelin M, Livun A, Tupek KM, Stoos-Veic T, Lucijanic T, Maglicic A, Kusec R (2018) Assessing serum albumin concentration, lymphocyte count and prognostic nutritional index might improve prognostication in patients with myelofibrosis. Wien Klin Wochenschr 130:126–133. https://doi.org/10.1007/s00508-018-1318-z
31. Jeon CH, Park KB, Jung YJ, Seo HS, Park CH, Song KY, Lee HH (2020) Modified controlling nutritional status score: a refined prognostic indicator depending on the stage of gastric cancer. Surg Oncol 34:261–269. https://doi.org/10.1016/j.suronc.2020.05.008
32. Wei Y, Xu H, Dai J, Peng J, Wang W, Xia L, Zhou F (2018) Prognostic significance of serum lactic acid, lactate dehydrogenase, and albumin levels in patients with metastatic colorectal cancer. Biomed Res Int 2018:1804086. https://doi.org/10.1155/2018/1804086PMID:30627541;PMCID:PMC6304480
33. Costa MD, Vieira de Melo CY, Amorim AC, Cipriano Torres Dde O, Dos Santos AC (2016) Association between nutritional status, inflammatory condition, and prognostic indexes with postoperative complications and clinical outcome of patients with gastrointestinal neoplasia. Nutr Cancer 68:1108–1114. https://doi.org/10.1080/01635581.2016.1206578
34. Mohamed Sad L, Elsaka AM, Abdelmonem Zamzam Y, Gharib Khairallah F (2010) Phase angle, body mass index and KRAS status of metastatic colorectal cancer in response to chemotherapy with and without target therapy: clinical impact and survival. J BUON 25:914–926 (PMID: 32521886)
35. Cybulska-Stopa B, Ługowska I, Wiśniowski R, Domagała-Haduch M, Rajczykowski M, Piejko K, Bar-Letkiewicz I, Suwiński R, Regulski K, Mackiewicz J (2020) Overweight is associated with better prognosis in metastatic colorectal cancer patients treated with bevacizumab plus FOLFOX chemotherapy. Contemp Oncol (Pozn) 24:34–41. https://doi.org/10.5114/wo.2020.94728
36. Aparicio T, Ducreux M, Faroux R, for FFCD investigators, et al (2018) Overweight is associated to a better prognosis in metastatic colorectal cancer: a pooled analysis of FFCD trials. Eur J Cancer 98:1–9. https://doi.org/10.1016/j.ejca.2018.03.031
37. Lidoriki I, Schizas D, Frountzas M, Machairas N, Prodromidou A, Kapelouzou A, Karavokyros I, Pikoulis E, Kales SN, Liakakos T (2021) GNRI as a prognostic factor for outcomes in cancer patients: a systematic review of the literature. Nutr Cancer 73:391–403. https://doi.org/10.1080/01635581.2020.1756350
38. Lee GW, Go SI, Kim DW, Kim HG, Kim JH, An HJ, Jang JS, Kim BS, Hahn S, Heo DS (2020) Geriatric Nutritional Risk Index as a prognostic marker in patients with extensive-stage disease small cell lung cancer: results from a randomized controlled trial. Thorac Cancer 11:62–71. https://doi.org/10.1111/1759-7714.13229
39. Okamoto T, Hatakeyama S, Narita S, Takahashi M, Sakurai T, Kawamura S et al (2019) Impact of nutritional status on the prognosis of patients with metastatic hormone-naive prostate cancer: a multicenter retrospective cohort study in Japan. World J Urol 37:1827–1835. https://doi.org/10.1007/s00345-018-2590-2
40. Nakayama M, Gosho M, Adachi M, Ii R, Matsumoto S, Miyamoto H, Hirose Y, Nishimura B, Tanaka S, Wada T, Tabuchi K (2021) The Geriatric Nutritional Risk Index as a prognostic factor in patients with advanced head and neck cancer. Laryngoscope 131:E151–E156. https://doi.org/10.1002/lary.28587
41. Migita K, Matsumoto S, Wakatsuki K, Ito M, Kunishige T, Nakade H, Sho M (2018) The prognostic significance of the Geriatric Nutritional Risk Index in patients with esophageal squamous cell carcinoma. Nutr Cancer 70:1237–1245. https://doi.org/10.1080/01635581.2018.1512640
42. Sugawara K, Yamashita H, Urabe M, Okumura Y, Yagi K, Aikou S, Seto Y (2021) Geriatric Nutrition Index influences survival outcomes in gastric carcinoma patients undergoing radical surgery. JPEN J Parenter Enteral Nutr 45:1042–1051. https://doi.org/10.1002/jpen.1978
43. Bahat G, Tufan A, Tufan F, Kilic C, Akpinar TS, Kose M, Erten N, Karan MA, Cruz-Jentoft AJ (2016) Cut-off points to identify sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP) definition. Clin Nutr 35:1557–1563. https://doi.org/10.1016/j.clnu.2016.02.002