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Neutrophil-to-Lymphocyte Ratio Combined with Skeletal Muscle Mass Loss Predicts Survival in Patients with Metastatic Colorectal Cancer Receiving Palliative Chemotherapy

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Abstract

Aim: Increasing evidence indicates that a high Neutrophil-to-Lymphocyte Ratio (NLR) and Skeletal Muscle Mass (SMM) loss are associated with poor survival in patients with unresectable advanced/metastatic Colorectal Cancer (uCRC). We assessed the clinical outcomes in uCRC patients receiving chemotherapy in relation to the NLR and SMM loss.

Methods: In this study, we retrospectively enrolled 78 patients with uCRC who underwent systemic chemotherapy between December 2012 and June 2019. The bilateral psoas muscle cross-sectional area at the superior border of the fourth lumbar vertebra was measured using Computed Tomography (CT), and the Psoas Muscle Index (PMI) was determined. SMM loss was defined as a decrease in PMI of ≥ 5% when comparing pre-chemotherapy PMI values with values obtained 3 months after chemotherapy initiation. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count measured before chemotherapy. The NLR cutoff value was set as 3.0. Patients were divided into four groups according to NLR status and SMM loss: High NLR/SMM loss, high NLR/non-SMM loss, low NLR/SMM loss, and low NLR/non-SMM loss.

Results: Thirty-two patients had a high NLR; they exhibited significantly shorter Overall Survival (OS) than those with a low NLR (median 16.0 *vs*. 30.3 months; log-rank, p=0.001). The OS in patients with high NLR/SMM loss was significantly lower than that in all other groups (median 11.8 *vs*. 21.5 *vs*. 21.5 *vs*. 34.2 months; log-rank, p<0.001). In multivariate analysis, high NLR/SMM loss was an independent prognostic factor for shorter OS (hazard ratio: 3.44, 95% confidence interval: 1.45 to 8.12, p=0.0048).

Conclusion: There was a significant correlation between NLR status and SMM loss and prognosis in patients with uCRC who were receiving chemotherapy. Intensive supportive care, including exercise and nutrition, is needed for uCRC patients with a high NLR.

Keywords: Metastatic colorectal cancer; Chemotherapy; Skeletal muscle loss; Neutrophil-to-lymphocyte ratio

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Introduction

Colorectal Cancer (CRC) is ranks third in terms of incidence, with approximately 1.8 million patients affected in 2018, and is the second leading cause of cancer mortality, with 881,000 deaths in 2018 [1]. During the last 20 years, the clinical outcomes of patients with CRC, particularly of those with unresectable advanced/metastatic CRC (uCRC) have improved. The median survival duration in patients with uCRC is estimated to be nearly 30 months [2]. Advances in treatment have contributed to a more aggressive approach, including doublet or triplet chemotherapy combined with molecular targeting agents [3-5] and subsequently, conversion to resection of metastases [6].

Systematic Inflammatory Response (SIR) plays an important role in tumor initiation, promotion, malignant conversion, and progression [7,8]. The features of SIR include the increased production of proinflammatory cytokines such as Interleukin-6 (IL-6), IL-8, Tumor Necrosis Factor-α (TNF-α), and Macrophage-Colony Stimulating Factor (M-CSF) [7]. The Neutrophil/Lymphocyte Ratio (NLR) is an easily measurable parameter that is widely used as a marker of SIR and is correlated

with elevated circulating concentrations of the above-mentioned cytokines [9]. Moreover, its prognostic value has been validated through research in various cancers [10-12].

In 1989, Rosenberg defined sarcopenia as a decline in muscle mass and strength [13]. It is known to be an important prognostic factor in patients with various types of cancer [14-17]. Sarcopenia may be caused by a combination of reduced dietary intake, abnormal nutritional metabolism, and insufficient physical activity. A study showed that patients with non-metastatic CRC and a high NLR had a significantly lower skeletal muscle index, and those with both a high NLR and sarcopenia exhibited poor survival outcomes [18]. As cancer progresses, the release of inflammatory cytokines and protein degradation inducing factors increases, which may lead to cancer cachexia [19]. Cancer cachexia is defined as a multifactorial syndrome characterized by an ongoing loss of Skeletal Muscle Mass (SMM) with or without the loss of fat mass [20]. Some studies have shown that the loss of SMM during systemic chemotherapy was correlated with increased treatment toxicity and poor prognosis in patients with advanced colorectal cancer [21-23]. Similarly, the change in NLR during chemotherapy as an indicator of longitudinal SIR may be more accurate as a prognostic marker [24], but Granulocyte-Colony Stimulating Factor (G-CSF) administration makes it difficult to assess the change in NLR.

Hence, in this study, NLR was evaluated as an index of SIR before chemotherapy, and SMM changes were evaluated as an index of SIR during chemotherapy. The association between them and the clinical outcomes in patients receiving palliative chemotherapy for uCRC were then elucidated.

Materials and Methods

Patients

The study protocol was carried out in accordance with the ethical guidelines of the Helsinki Declaration and was approved by the Fukushima Medical University Ethics Committee. The need for written informed consent was waived because the opt-out approach was utilized.

Patients with Stage IV uCRC who were administered first-line chemotherapy between December 2012 and April 2019 at the Aizu Medical Center, Fukushima Medical University, were enrolled retrospectively. The inclusion criteria were as follows: i) uCRC, ii) histologically confirmed colorectal adenocarcinoma, and iii) availability of routine Computed Tomography (CT) scans of sufficient quality to accurately measure muscle area: One performed before chemotherapy and a second one performed within 3 months after chemotherapy initiation. Patients with clinically overt ascites or those who changed hospitals in the middle of chemotherapy were excluded from the study.

Skeletal muscle mass measurement

Skeletal muscle area was measured using the SYNAPSE SCOPE™ software (Fujifilm Medical, Tokyo, Japan) using CT scans that were taken before the administration of chemotherapy and routinely within 3 months after chemotherapy initiation. For each CT scan, a single axial slice at the superior border of the L4 level was chosen to measure the bilateral psoas muscle cross-sectional area. The cross-sectional area of the bilateral psoas muscle (cm^2) was measured by manual tracing using Hounsfield unit thresholds of - 29 to 150 for skeletal muscle tissue. Furthermore, the data were normalized by the square of the height (m^2) to obtain the Psoas Muscle Index (PMI, cm^2/m^2). The rate of PMI change (%) between the first and second scans was calculated, and the patients were divided into two groups, depending on whether they had lost muscle mass during chemotherapy. SMM loss, which was defined as a decrease in PMI of ≥ 5%, as described by Miyamoto et al. [22], was used to classify patients into two cohorts: Those with muscle loss (SMM loss) and those without muscle loss (non-SMM loss). Patients with less than median PMI were considered as those with sarcopenia, with a cutoff value of 3.9 for women and 5.5 for men. All measurements and calculations were performed independently by three authors (D.T., T.N., S.E.).

Neutrophil-to-lymphocyte ratio

White blood cells and leukocyte fractions were routinely measured. The NLR was calculated retrospectively from the ratio of peripheral blood absolute neutrophil and lymphocyte counts before chemotherapy. Based on the findings of previous studies [10,18,25], 3.0 was the cutoff value of NLR; the median NLR was 2.6 in this study. Finally, patients were classified into four groups according to NLR status and SMM loss: high NLR with SMM loss, high NLR and non-SMM loss, low NLR with SMM loss, and low NLR with non-SMM loss.

Toxicity assessment

Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 4.0. Patient toxicity was assessed using a self-assessment questionnaire administered before each cycle of chemotherapy, and a certified nurse reviewed this assessment.

Treatment response evaluation

The treatment response evaluation was performed according to the new response evaluation criteria in solid tumors criteria: Revised RECIST guidelines (version1.1) [26].

Statistical analysis

Statistical analyses were performed using SPSS software (version 27.0; IBM, Armonk, NY, USA). All results were presented as medians with ranges. For nominal data, statistical comparisons were performed using the chi-square test. For ordinal or evidently non-normal data, a Mann-Whitney U test was used to compare trends between groups. All p values were two-tailed, and $p<0.05$ indicated statistical significance. Overall Survival (OS) was defined as the time between the dates of chemotherapy initiation to the date of death from any cause. Survival curves were computed using Kaplan-Meier estimates with log-rank tests. Cox regression analysis was applied to test predictors of OS and calculate Hazard Ratios (HRs) with 95% Confidence Intervals (CIs).

Results

Patients

Seventy-eight consecutive patients were retrospectively enrolled in our study. The median follow-up time for all patients was 20.9 (3.8 to 74.4) months. There were 32 patients (41.0%) in the high NLR group and 46 (59.0%) in the low NLR group. Patient and treatment characteristics for both groups are shown in Table 1. BMI, pre-chemotherapy C-reactive protein levels, albumin, Lactate Dehydrogenase (LDH) levels, Prognostic Nutritional Index (PNI), and Carcinoembryonic Antigen (CEA) levels were significantly associated with a high NLR. Patients who showed a high NLR tended to have SMM loss during chemotherapy (p=0.06). There was no significant difference in any other variables, including pre-chemotherapy PMI and sarcopenia, between the two groups.

Table 1: Patient and treatment characteristics.

		Total (n=78)	High NLR (>3.0) (n=32)	Low NLR (≤ 3.0) (n=46)	*p*-value
Gender, n (%)	Male	56 (71.8)	20 (62.5)	36 (78.3)	0.20**
	Female	22 (28.2)	12 (37.5)	10 (21.7)	
Age, years		66 (37-84)	63 (37-84)	65 (45-80)	0.47*
BMI, kg/m^2		22.1 (16.1-28.9)	20.2 (16.1-27.0)	22.9 (16.6-28.9)	0.001*
Weight loss during chemotherapy		-0.3 (-12.1-9.5)	-0.2 (-12.1-8.8)	0.2 (-11.0-9.5)	0.69*
Location, n (%)	Right	26 (33.3)	11 (34.4)	15 (32.6)	0.23*
	Left	23 (29.5)	12 (37.5)	11 (23.9)	
	Rectum	29 (37.2)	9 (28.1)	20 (43.5)	
Number of metastatic organ/site	1	44 (56.4)	15 (46.9)	29 (63.0)	0.17**
	>1	34 (43.6)	17 (53.1)	17 (37.0)	
Pre-chemotherapy CRP, mg/dl		0.71 (0.02-12.12)	3.44 (0.11-12.12)	0.23 (0.02-3.44)	<0.001*
Pre-chemotherapy albumin, g/dl		3.7 (2.1-4.4)	3.2 (2.1-4.2)	3.9 (3.2-4.4)	<0.001*
Pre-chemotherapy LDH, U/L		220 (118-4068)	475 (118-4068)	210 (123-2453)	0.009*
Pre-chemotherapy PNI		46 (25-55)	39 (25-49)	47 (38-55)	<0.001*
Pre-chemotherapy CEA, ng/ml		21 (1.7-22527)	197 (7.4-22527)	11.1 (1.7-8980)	<0.001*
Pre-chemotherapy PMI, cm^2/m^2		4.9 (1.6-7.8)	4.4 (1.6-7.6)	5.0 (2.5-7.8)	0.14*
Pre-chemotherapy sarcopenia, n (%)		37 (47.4)	17 (53.1)	20 (54.1)	0.49**
The change of SMM during chemotherapy	SMM loss	31 (39.7)	17 (53.1)	14 (30.4)	0.060**
	non-SMM loss	47 (60.3)	15 (46.9)	32 (69.6)	
Resection of metastases, n (%)		10 (12.8)	6 (18.8)	4 (8.7)	0.30**
Tumor histology, n (%)	differentiated	74 (94.9)	29 (90.6)	45 (97.8)	0.30**
	undifferentiated	4 (5.1)	3 (9.4)	1 (2.2)	
RAS gene, n (%)	wild type	33 (42.3)	12 (37.5)	21 (45.7)	0.64**
	mutation type	36 (46.2)	17 (53.1)	19 (41.3)	
	unknown	9 (11.5)	3 (9.4)	6 (13.0)	
First-line chemotherapy, n (%)	FOLFOX base	36 (46.2)	14 (43.8)	22 (47.8)	0.28**
	FOLFILI base	33 (42.3)	12 (37.5)	21 (45.7)	
	FOLFOXIRI	9 (11.5)	6 (18.8)	3 (6.5)	
Combined target drug, n (%)	Anti-VEGF antibody	64 (82.1)	26 (81.3)	38 (82.6)	1.00**
	Anti-EGFR antibody	14 (17.9)	6 (18.8)	8 (17.4)	

*Wilcoxon signed-rank test, **Fisher's exact test

CRP: C-Reactive Protein; LDH: Lactate Dehydrogenase; PNI: Prognostic Nutritional Index; NLR: Neutrophil-to-Lymphocyte Ratio; PMI: Psoas Muscle Index; BMI: Body Mass Index; CEA: Carcinoembryonic Antigen; SMM: Skelatal Muscle Mass; VEGF: Vascular Endothelial Growth Factor; EGFR: Epidermal Growth Factor Receptor

PNI = [10 × albumin (g/dl)] + [0.005×total lymphocyte count (μl)]

Right: Cecum, ascending and transverse colon; Left: Descending, sigmoid colon and Rectosigmoid junction

Clinical outcomes according to NLR status

The disease control rate was significantly higher in the low NLR group than in the high NLR group (p=0.021, Table 2). According to the Kaplan-Meier analysis, patients in the high NLR group had significantly shorter OS than those in the low NLR group, and the median survival times were 16.0 and 30.3 months, respectively (Figure 1).

Clinical outcome according to NLR status and skeletal muscle mass loss

Patients were divided into four groups based on their NLR and SMM loss, and OS was compared among these groups. The disease control rate was significantly higher in the low NLR group with non-SMM loss than in the high NLR group with SMM loss (p=0.001) (Table 3). Patients with a high NLR and SMM loss had the worst survival outcomes, whereas those with a low NLR and non-SMM loss showed the longest survival (p<0.001); the high NLR/non-SMM loss group showed significantly better survival outcomes than the high NLR/SMM loss group (p<0.001), although there was no significant difference in OS in patients with a low NLR between the SMM loss and non-SMM loss groups (p=0.17) (Figure 2).

Cox regression analysis of overall survival

In the univariate Cox regression analysis, a high NLR and SMM loss were significantly associated with poor OS. In the multivariate Cox survival analysis adjusted for the number of baseline covariates, high NLR and SMM loss independently predicted shorter OS (HR=2.36; 95% CI, 1.38-4.03; p=0.0066; HR=2.38; 95% CI, 1.39-4.06;

Table 2: Clinical outcomes according to NLR status.

Outcomes	High NLR (>3.0) (n=32)	Low NLR (≤ 3.0) (n=46)	*p*-value
CR (%)	1 (3.1)	2 (4.3)	
PR (%)	12 (37.5)	19 (41.3)	
SD (%)	8 (25.0)	20 (43.5)	
PD (%)	11 (34.4)	5 (10.9)	
Response rate (%)	13 (40.6)	21 (45.7)	0.81*
Disease control rate (%)	21 (65.6)	41 (89.1)	0.021*
Median OS (months)	16.0	30.3	0.001**

*Fisher's Exact test, **log-rank test
CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; NLR: Neutrophil-to-Lymphocyte Ratio; OS: Overall Survival

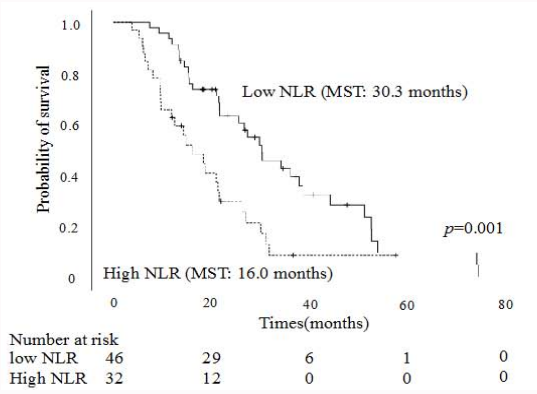

Figure 1: Overall survival according to Neutrophil-to-Lymphocyte Ratio (NLR) using an NLR cutoff of 3.0. Patients with high NLR had significantly lower OS compared with those with low NLR (median 16.0 *vs*. 30.3 months; log-rank p=0.001). OS: Overall Survival.

Table 3: Clinical outcomes according to NLR status with skeletal muscle mass loss.

Outcomes	High NLR/SMM loss (n=17)	High NLR/non-SMM loss (n=15)	Low NLR/SMM loss (n=14)	Low NLR/non-SMM loss (n=32)
CR (%)	0 (0)	1 (6.7)	2 (14.3)	0 (0)
PR (%)	5 (29.4)	7 (46.7)	5 (35.7)	14 (43.8)
SD (%)	4 (23.5)	4 (26.7)	4 (28.6)	16 (50.0)
PD (%)	8 (47.1)	3 (20.0)	3 (21.4)	2 (6.3)
Response rate (%)	5 (29.4)	8 (53.3)	7 (50.0)	14 (43.8)
Disease control rate (%)	9 (52.9)	12 (80.0)	11 (78.6)	30 (93.8)*
MST, months	11.8	21.6**	15.5†	34.3††

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; OS: Overall Survival; NLR: Neutrophil-to-Lymphocyte Ratio; SMM: Skelatal Muscle Mass; MST: Median Survival Time
*Low NLR/non-SMM loss *vs.* High NLR/SMM loss: p=0.001 in disease control rate
**High NLR/SMM loss *vs.* High NLR/non-SMM loss: p<0.001 in OS
†High NLR/SMM loss *vs.* Low NLR/SMM loss: p=0.012 in OS
††High NLR/SMM loss *vs.* Low NLR/non-SMM loss: p<0.001 in OS

p=0.0042, respectively; Table 4). When NLR was stratified by SMM change, the high NLR group, which had a poor OS, showed SMM loss estimated to be associated with worse survival outcomes (HR=3.24; 95% CI, 1.38-7.59; p=0.0066; Table 5). In the low NLR group, SMM loss did not exhibit significantly higher survival outcomes than non-SMM loss (HR=1.67; 95% CI, 0.79-3.53; p=0.17; Table 5).

Continuity of chemotherapy and toxicity

The incidence of discontinuation of second-line and third-line chemotherapy did not differ between the high NLR and low NLR groups, whereas the rate of treatment continuity with third-line chemotherapy tended to be higher in the high NLR group than in the other groups. The number of chemotherapy regimens administered was significantly higher in the low NLR group than in the high NLR group (2.0 *vs.* 3.0, p=0.022, Table S1). There was no significant difference in the incidence of adverse events of grade 3 or higher between the high NLR and low NLR groups; a similar finding was noted on comparison between the high NLR with SMM loss group and all other groups.

Discussion

This was the first study that examined the relationship between NLR status and SMM loss and prognosis in patients with uCRC who were receiving chemotherapy. This study demonstrated that patients with a high NLR had poorer OS than those with a low NLR, and NLR was associated with SMM loss during chemotherapy rather than with pre-chemotherapy sarcopenia. Furthermore, a high NLR was closely correlated with OS when accompanied by the loss of SMM. A high NLR with SMM loss was the most significant independent prognostic factor for poor survival outcomes. Independent measures of SIR and

Table 4: Univariate and multivariate analysis of the association between baseline characteristics and overall survival.

Variables		Univariate		Multivariable	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Gender	Female	1.74 (0.99-3.05)	0.053	1.51 (0.86-2.71)	0.14
	Male	Ref.		Ref.	
Age	≤ 70	0.97 (0.56-1.66)	0.91		
	>70	Ref.			
BMI	≤ 25	1.28 (0.91-1.81)	0.15		
	>25	Ref.			
Tumor location	Right	1.15 (0.86-1.53)	0.32		
	Left	Ref.			
No of metastatic organ/site	≥ 2	1.04 (0.80-1.35)	0.76		
	1	Ref.			
Prechemothearpy sarcopenia	Yes	1.30 (0.77-2.19)	0.32		
	No	Ref.			
Tumor histology	Undifferentiated	1.60 (0.96-2.69)	0.071	1.92 (0.67-5.49)	0.22
	Differentiated	Ref.		Ref.	
RAS gene	Wild	0.99 (0.56-1.75)	0.98		
	Mutant	Ref.			
First-line chemotharapy	Doblet	1.00 (0.60-1.68)	0.98		
	Triplet	Ref.			
Combined target drug	EGFR	1.20 (0.87-1.66)	0.25		
	VGFR	Ref.			
NLR	High	2.36 (1.38-4.03)	0.0016	2.15 (1.23-3.75)	0.0066
	Low	Ref.		Ref.	
SMM change	loss	2.38 (1.39-4.06)	0.0015	2.23 (1.28-3.86)	0.0042
	non loss	Ref.		Ref.	

BMI: Body Mass Index; NLR: Neutrophil-to-Lymphocyte Ratio; SMM: Skelatal Muscle Mass; VEGF: Vascular Endothelial Growth Factor; EGFR: Epidermal Growth Factor Receptor
Right: Cecum, ascending and transverse colon
Left: Descending, sigmoid colon, Rectosigmoid junction and Rectum
HR: Hazard Ratio; CI: Confidence Interval

Table 5: Multivariate analysis of overall survival in combined NLR status and SMM change.

Variables			Multivariable	
			HR (95% CI)	*p*-value
Gender	Female		1.43 (0.38-1.25)	0.23
	Male		Ref.	
Tumor histology	Undifferentiated		2.12 (0.73-6.18)	0.16
	Differentiated		Ref.	
NLR status and SMM loss	High NLR	SMM loss	3.24 (1.38-7.59)	0.0066
		non-SMM loss	Ref.	
	Low NLR	SMM loss	1.67 (0.79-3.53)	0.17
		non-SMM loss	Ref.	

NLR: Neutrophil-to-Lymphocyte Ratio; SMM: Skelatal Muscle Mass; HR: Hazard Ratio; CI: Confidence Interval

SMM are easily available in clinical situations and in combination, can serve as potent prognostic factors for patients with uCRC.

SMM loss and systemic inflammation have previously been correlated with prognosis in various cancers, including CRC, and most research studies have considered them individually [21,22,27]. The present study suggested that systemic inflammation may accelerate skeletal muscle loss, and the co-occurrence of inflammation and SMM loss of 5% or more were more likely to result in poor survival outcomes. Furthermore, chemotherapy induces skeletal muscle wasting through the activation of the transcription factor NF-κB (Nuclear Factor Kappa B), which up regulates ubiquitin and proteasomes, and increases proteolysis and the levels of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, which increases ubiquitin ligase expression (atrogin-1) and ubiquitin protein modification for proteolysis [28]. Cancer cachexia is characterized by a significant reduction in body weight, resulting

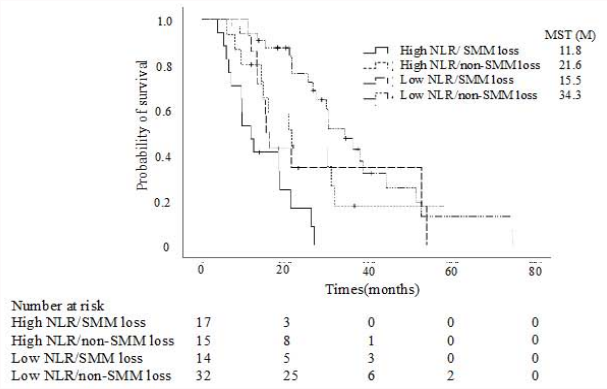

Figure 2: Overall survival according to Neutrophil-to-Lymphocyte Ratio (NLR) and Skeletal Muscle Mass (SMM) loss. Patients with high NLR/SMM loss was significantly lower than that in all other groups (median OS 11.8 *vs.* 21.5 *vs.* 21.5 *vs.* 34.2 months; log-rank, p<0.001). Patients high NLR/non-SMM loss showed significant better survival than those with high NLR/SMM loss (p<0.001), although patients with low NLR showed no significant difference in OS between SMM loss and non-SMM loss groups (p=0.17). OS: Overall Survival.

Supplemental Table 1: Continuity of chemotherapy and toxicity.

		High NLR (n=32)	Low NLR (n=46)	*P*-value	High NLR/SMM loss (n=17)	All others (n=61)	*p*-value
Continuity to 2nd line, n (%)	Yes	21 (65.6)	36 (78.3)	0.30**	10 (58.8)	47 (77.0)	0.21**
	No	11 (34.3)	10 (21.7)		7 (41.2)	14 (23.0)	
Continuity to 3rd line, n (%)	Yes	13 (61.9)	27 (75.0)	0.37	5 (29.4)	35 (57.4)	0.056**
	No	8 (38.1)	9 (25.0)		12 (70.6)	26 (42.6)	
Number of regimens		2.0 (1-5)	3.0 (1-7)	0.022*	2.0 (1 - 4)	3.0 (1 - 7)	0.027*
Grade 3/4 toxicity, n (%)		14 (43.8)	24 (52.2)	0.49**	8 (47.1)	30 (49.2)	1.00**

*Wilcoxon signed-rank test, **fisher's exact test, ***Log-Rank
NLR: Neutrophil-to-Lymphocyte Ratio; SMM: Skelatal Muscle Mass

predominantly from loss of skeletal muscle because of various metabolic dysfunctions. Systemic inflammation is known to underlie SMM loss in patients with cancer cachexia [19]. Markers of SIR such as NLR are associated with elevated circulating concentrations of proinflammatory cytokines and growth factors, such as IL-6, TNF-α, and M-CSF [29], and these lead to the activation of several catabolic pathways, inducing skeletal muscle protein loss and muscle atrophy. Additionally, such proinflammatory cytokines may play a critical role in eating disorders such as anorexia nervosa [30]. A high NLR was significantly associated with lower albumin and PNI baseline levels, which are known markers of nutritional status in patients with cancer. Poor nutritional status may accelerate skeletal muscle wasting and lead to poor prognosis [31]. Patients with a high NLR may be more likely to develop cancer cachexia owing to the synergistic effect of chemotherapy.

The present study revealed that the rate of chemotherapy continuity was not significantly different between the high and low NLR groups, but on combination with the status of SMM change, patients with a high NLR and SMM loss had worse treatment continuity than the others. The frequency of treatment toxicities was not significantly different between the groups. These findings suggest that SMM loss may be strongly associated with difficulty in continuing chemotherapy, and subsequent poor compliance could accelerate tumor activity. Furthermore, this may lead to cancer cachexia [32], which is probably the most severe condition of muscle atrophy and is associated with reduced tolerance to cancer treatment and decreased quality and length of life [19,33]. Therefore, prevention of cachexia is important for cancer patients receiving chemotherapy.

In recent studies, exercise interventions, including aerobic or resistance exercise, or both, in patients with advanced cancer have been evaluated, and these reports have suggested that supervised exercise interventions are safe and feasible [34]. In addition, it has been reported that exercise interventions can maintain or improve muscle strength and physical function and may improve quality of life of patients with advanced cancer [35,36]. However, not all patients can exercise because of fatigue and anorexia caused by chemotherapy. Supportive therapies, such as acupuncture and muscle electrical stimulation, may be more suitable and effective for such patients [37,38]. Nutritional support should also be considered because it is unlikely that muscle mass and body weight will increase or stabilize in the absence of adequate energy and nutrient supply [39-41]. Another possible intervention is administering drugs aimed at treating anorexia and enhancing food intake, while also stimulating anabolism to overcome the catabolic drive associated with cachexia, ultimately increasing lean body mass and body weight [42,43]. For instance, anamorelin, a novel ghrelin-receptor agonist, significantly improved anorexia and increased lean body mass in patients with advanced non-small-cell lung cancer [44]. Currently, a phase III randomized controlled trial of a multimodal intervention (exercise, nutrition, and anti-inflammatory medication) is underway across several international sites [45]. Further prospective studies with larger populations of uCRC patients are required to confirm our findings and to determine whether multiple interventions aimed at preventing cancer cachexia during treatment can effectively improve patient outcomes.

Our study has a few limitations. First, this was a retrospective study with a small number of patients from a single institute; therefore, we cannot exclude the possibility of selection bias. Second, our study population was heterogeneous with regard to the chemotherapy

regimens that were administered. This heterogeneity might have affected the physical and nutritional analyses. Skeletal muscle wasting may differ between patients who receive anticancer drugs and those who receive molecular targeted drugs: For example, platinum and topoisomerase inhibitors *vs.* vascular endothelial growth factor and epidermal growth factor receptor inhibitors. However, this difference had little impact on the endpoints of our study.

In conclusion, SMM loss during chemotherapy is likely to occur in uCRC patients with an elevation in the NLR. High pre-treatment NLR is associated with a poor prognosis. This association is stronger in patients with SMM loss among those with a high NLR. Preventive interventions should be provided to cachexia patients with both a high NLR and SMM loss on treatment initiation. A further randomized control study is needed to determine whether interventions including exercise, nutrition, and drugs may be useful for preventing muscle wasting and functional decline in patients with uCRC during chemotherapy.

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