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ORIGINAL ARTICLE

Prognostic significance of osteosarcopenia in older adults with colorectal cancer

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Abstract

Aim: Osteopenia and sarcopenia, features of the aging process, are recognized as major health problems in an aging society. This study investigated the prognostic impact of osteosarcopenia, the coexistence of osteopenia and sarcopenia, in older adults undergoing curative resection for colorectal cancer.

Methods: We retrospectively reviewed data of older adults aged 65–98 y who had undergone curative resection for colorectal cancer. Osteopenia was evaluated by bone mineral density measurement in the midvertebral core of the 11th thoracic vertebra on preoperative computed tomography images. Sarcopenia was evaluated by measuring the skeletal muscle cross-sectional area at the third lumbar vertebra level. Osteosarcopenia was defined as the coexistence of osteopenia and sarcopenia. We explored the relationship of preoperative osteosarcopenia with the disease-free and overall survival after curative resection.

Results: Among the 325 patients included, those with osteosarcopenia had significantly lower overall survival rates than those with osteopenia or sarcopenia alone ($P < 0.01$). In the multivariate analysis, male sex ($P = 0.045$), C-reactive protein-to-albumin ratio ($P < 0.01$), osteosarcopenia ($P < 0.01$), pathological T4 stage ($P = 0.023$), and pathological N1/N2 stage ($P < 0.01$) were independent predictors of disease-free survival, while age ($P < 0.01$), male sex ($P = 0.049$), C-reactive protein-to-albumin ratio ($P < 0.01$), osteosarcopenia ($P < 0.01$), pathological T4 stage ($P = 0.036$), pathological N1/N2 stage ($P < 0.01$), and carbohydrate antigen 19–9 ($P = 0.041$) were independent predictors of overall survival.

Conclusion: Osteosarcopenia was a strong predictor of poor outcomes in older adults undergoing curative resection for colorectal cancer, suggesting an important role of osteosarcopenia in an aging society.

KEYWORDS
colorectal cancer, older adults, osteopenia, osteosarcopenia, sarcopenia

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1 | INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related death worldwide.[1] With the steady growth of the older population, the number of older adults requiring surgery for CRC increases.[2] However, the care and treatment for these patients are often difficult and complicated by age-related factors.[3] Therefore, in an aging society, identifying risk factors for poor outcomes in older adults with CRC is crucial for proper perioperative management.

Sarcopenia and osteopenia, which are strongly associated with aging, have been recognized as prognostic factors in several types of cancer.[4,5] Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength,[6] while osteopenia is defined as decreased bone mineral density (BMD) that is not as low as that in osteoporosis.[7] Recent studies have explored the mechanism of bone–muscle crosstalk and proposed the concept of "osteosarcopenia," defined as the coexistence of sarcopenia and osteopenia.[8]

Osteosarcopenia has been reported in 25%–40% of older adults,[9] and its prevalence will inevitably increase in an aging society.[8] Previous study has reported that osteosarcopenia has been associated with poor survival in patients with colorectal liver metastases.[10] Based on this evidence, we hypothesized that osteosarcopenia might be a strong predictor of postoperative poor outcomes in older adults with primary CRC.

The aim of the present study was to evaluate the utility of osteosarcopenia for predicting the prognosis in older adults after colorectal resection for CRC.

2 | MATERIALS AND METHODS

2.1 | Study design and population

We retrospectively analyzed data of consecutive patients with stage I-III CRC aged 65–98 y who underwent curative resection at Tokyo General Hospital and Kasai Shoikai Hospital between January 2014 and December 2020. Among them, 136 patients have been studied previously.[11]

Patient data included age, sex, body mass index (BMI), comorbidities (hypertension, diabetes mellitus, and cardiovascular disease), American Society of Anesthesiologists physical status (ASA-PS) score,[12] blood test results, surgical approach, tumor type and location, postoperative complications, and pathological findings. Additionally, we examined the following nutritional indices: neutrophil-to-lymphocyte ratio (NLR),[13] prognostic nutritional index (PNI),[14] and C-reactive protein to albumin (CRP/Alb) ratio.[15] Blood tests were performed within 4 wk before surgery. The study was approved by the Ethics Committee of Tokyo General Hospital (approval No. 22–4) and Kasai Shoikai Hospital (approval No. R4-1), and conducted in accordance with the tenets of the Declaration of Helsinki.

2.2 | Definitions of sarcopenia, osteopenia, and osteosarcopenia

Sarcopenia and osteopenia evaluation was performed using preoperative and 6 mo postoperative plane computed tomography (CT) images. The presence of sarcopenia was determined based on the skeletal muscle index (SMI),[16] which was calculated by measuring the cross-sectional area (cm^2) of skeletal muscle at the level of the third lumbar vertebra and normalizing it by the patient's height (cm^2/m^2) (Figure 1A). Sarcopenia was defined as SMI below the cutoff value (≤43.75 cm^2/m^2 for men and ≤41.10 cm^2/m^2 for women).[17]

Osteopenia was defined as BMD below the calculated standard BMD, which was calculated as previously reported (308.82–2.49 × age in men and 311.84–2.41 × age in women).[18] BMD was measured using the average pixel density (Hounsfield unit, HU) within a circle in the midvertebral core at the bottom of the Th11 on the preoperative plain CT image, as previously described[19] (Figure 1B).

Osteosarcopenia was defined as the coexistence of osteopenia and sarcopenia,[8] and penia-free was as neither of them.

2.3 | Patient follow-up

Postoperative complications were defined as those occurring within 30 d after primary surgery. Patients with Clavien–Dindo grade II or higher complications were included in the complication group.[20]

Postoperatively, the patients were followed up every 3 mo for 3 y, and then every 6 mo until 5 y. Routine blood tests and tumor biomarker measurements, including serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19–9, were performed at

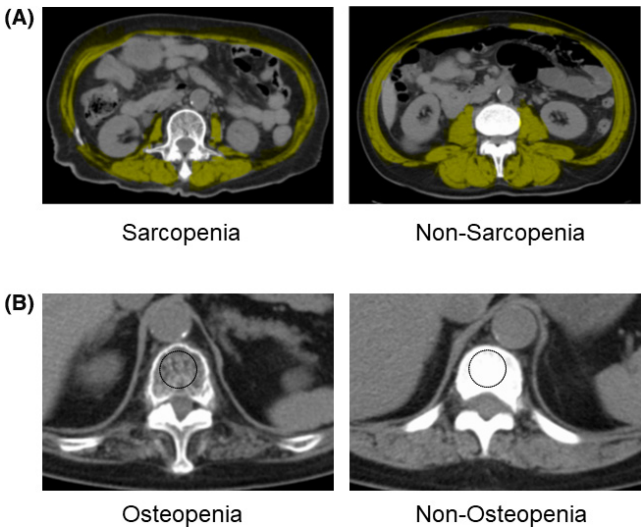

FIGURE 1 Measurement of (A) the cross-sectional area of skeletal muscle at the level of the third lumbar vertebra, and (B) bone mineral density with calculation of the average pixel density within a circle in midvertebral core at the bottom of the 11th thoracic vertebra

each follow-up. Contrast-enhanced CT or magnetic resonance imaging and colonoscopy were performed during the follow-up period.

2.4 | Statistical analysis

All statistical analyses were conducted using EZR software v. 1.51 (Saitama Medical Center, Jichi Medical University, Japan), and GraphPad Prism software (San Diego, CA,USA, v. 9). All *P*-values were two-sided with an α level of 0.05.

Data are expressed as a median value or numbers with percentages. Continuous and categorical variables were compared using the Mann–Whitney *U*-test or the chi-square test, as appropriate. Paired categorical data were compared using McNemar's test. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify the variables affecting the disease-free and overall survival. For these analyses, clinical continuous variables were classified into two groups based on the cutoff value or the previously defined standard value (above and below). The optimal cutoff value was determined by receiver operating characteristics (ROC) curve analyses to the overall survival event. The area under the curve (AUC) of the ROC was used to assess the prognostic ability and the multivariate ROC curve was constructed to compare with individual factors.

The multivariate Cox regression model initially included age (≥80 vs <80 y), sex (male vs female), ASA-PS (≥3 vs <3), NLR (≥3.03 vs <3.03), PNI (<40 vs ≥40), CRP/Alb (≥0.070 vs <0.070), preoperative osteopenia (yes vs no), preoperative sarcopenia (yes vs no), preoperative osteosarcopenia (yes vs no), surgical approach (laparoscopic vs open), tumor location (rectum vs colon), pathological T stage (T4 vs T1-3), pathological N stage (N1/2 vs N0), serum CEA (≥5.0 vs <5.0 ng/mL), serum CA 19–9 (≥37 vs <37 U/mL), and postoperative complications (yes vs no). The backward elimination stepwise approach was used with a threshold *P*-value of 0.05 to select variables for the final model. The Kaplan–Meier method was used to estimate cumulative survival probabilities, and the differences between groups were compared using the log-rank test.

3 | RESULTS

3.1 | Patients' characteristics

The demographic and clinicopathological characteristics of the patients according to the presence of preoperative osteosarcopenia are shown in Table 1. A total of 325 patients (185 men) with a median age of 76 (65–98) y were included. The median BMD and SMI were 134 HU and 43.7 cm^2/m^2, respectively. Among all, 115 (35%)

TABLE 1 Patients characteristics

Variables	All ($n = 325$)	Osteosarcopenia ($n = 84$)	Non-osteosarcopenia ($n = 241$)	*P*-value
Sex (male)	185 (57%)	77 (65–93)	76 (65–98)	0.86
Age (y)	76 (65–98)	42 (50%)	143 (59%)	0.16
BMI (kg/m^2)	22.0 (12.1–34.2)	20.3 (13.2–34.2)	22.4 (12.1–32.4)	<0.01
Hypertension	158 (49%)	34 (40%)	124 (51%)	0.099
Diabetes mellitus	84 (26%)	19 (23%)	65 (27%)	0.47
Cardiovascular disease	74 (23%)	20 (24%)	54 (22%)	0.77
ASA-PS ≥3	44 (14%)	13 (15%)	31 (13%)	0.58
Hemoglobin (g/dL)	11.2 (7.5–18.7)	11.5 (8.1–16.8)	12.1 (7.5–18.7)	0.057
Albumin (g/dL)	3.9 (1.8–5.0)	3.8 (1.9–4.8)	3.9 (1.9–5.0)	0.057
BMD (HU)	134 (58.8–265)	96.1 (58.9–142)	149 (58.8–265)	<0.01
Osteopenia	115 (35%)	84 (100%)	31 (13%)	<0.01
SMI (cm^2/m^2)	43.7 (21.1–64.8)	37.4 (21.1–43.6)	43.2 (23.4–64.9)	<0.01
Sarcopenia	186 (57%)	84 (100%)	102 (42%)	<0.01
Surgical approach (laparoscopic)	203 (62%)	46 (55%)	157 (65%)	0.12
Tumor location (rectum)	109 (34%)	32 (38%)	77 (32%)	0.35
Pathological T 4 stage	54 (17%)	22 (26%)	32 (13%)	0.010
Pathological N1/N2 stage	115 (35%)	39 (46%)	76 (32%)	0.017
Obstructive CRC	33 (9.2%)	15 (18%)	18 (7.4%)	0.011
Postoperative complication, yes	99 (30%)	36 (43%)	63 (26%)	<0.01

Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; BMD, bone mineral density; BMI, body mass index; CAR/Alb ratio, C-reactive protein/albumin ratio; HU, Hounsfield unit; NLR, neutrophil to lymphocyte ratio; PNI, prognostic nutritional index; SMI, Skeletal muscle.

patients had osteopenia, 186 (57%) had sarcopenia, and 84 (26%) had osteosarcopenia. Also, 45% (84/186) of patients with sarcopenia were diagnosed with osteopenia, while among patients with osteopenia, 73% (84/115) were diagnosed with sarcopenia. The 5-y disease-free and overall survival rates after curative resection for CRC were 65.7% and 75.2%, respectively.

Compared with those without osteosarcopenia, patients with osteosarcopenia had significantly lower BMI ($P < 0.01$) and PNI ($P = 0.031$). Furthermore, the proportion of patients with pathological T4 stage ($P = 0.010$), pathological N1/N2 stage ($P = 0.017$), obstructive CRC ($P = 0.011$), and postoperative complications ($P < 0.01$) was significantly higher in the osteosarcopenia than in the non-osteosarcopenia group.

Subdividing the patients into Stages I, II, and III disease groups, the histograms of osteosarcopenia, sarcopenia alone, osteopenia alone and penia-free are shown (Figure 2). The proportion of penia-free and osteopenia alone decreased and that of osteosarcopenia increased with increasing Stage (Figure 2A,B,D). The proportion of sarcopenia alone was higher in Stage II than Stage III (35% vs 30%) (Figure 2C), but the proportion of osteosarcopenia was reversed in Stage II and III (24% vs 34%) (Figure 2C,D).

3.2 | Osteosarcopenia impact on survival

Preoperative osteosarcopenia was significantly associated with the disease-free (Figure 3A, $P < 0.01$) and overall survival (Figure 3B, $P < 0.01$) after curative resection for CRC. The multivariate ROC curve showed that integrated factors (osteopenia and sarcopenia) had an AUC of 0.664 (95% confidence interval [CI] 0.593–0.734), which was significantly larger than that of osteopenia alone (vs 0.606; 95% CI 0.540–0.673, $P = 0.011$) and sarcopenia alone (vs 0.619; 95% CI 0.559–0.679, $P = 0.035$) (Figure S1). The overall survival of patients with osteosarcopenia was significantly lower than that of patients with osteopenia or sarcopenia alone (Figure 3C, $P < 0.01$).

3.3 | Clinicopathological variables associated with disease-free survival

Table 2 shows the relationship between clinicopathological variables and disease-free survival after curative resection for CRC. In the univariate analysis, the disease-free survival was significantly

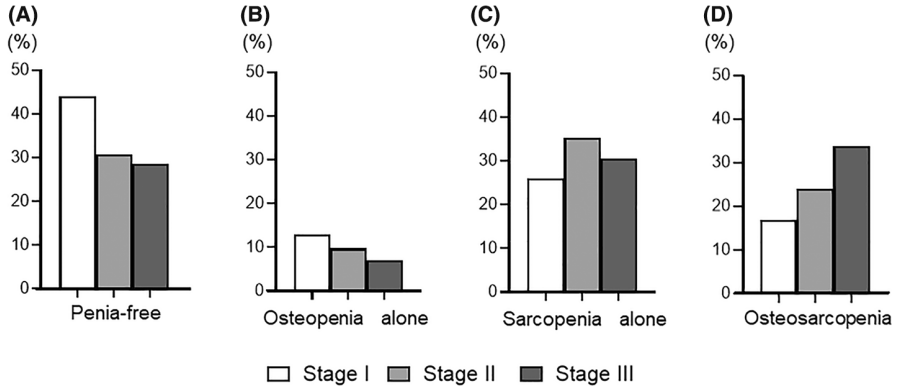

FIGURE 2 The histograms of (A) penia-free, (B) osteopenia alone, (C) sarcopenia alone, and (D) osteosarcopenia between stages

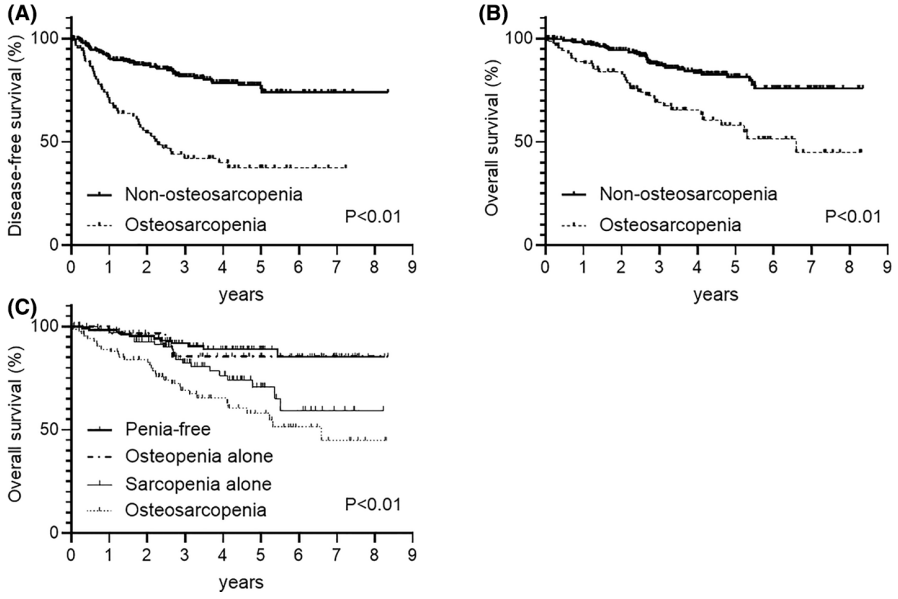

FIGURE 3 Kaplan–Meier curves for (A) disease-free survival and (B) overall survival in patients with or without osteosarcopenia, and (C) overall survival in patients with osteopenia or sarcopenia alone compared to osteosarcopenia after curative resection for colorectal cancer

TABLE 2 Univariate and multivariate analyses of factors associated with disease-free survival

	Univariate		Multivariate[a]	
Variables	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age (≥80 y)	1.61 (1.06–2.43)	0.023		N.S.
Sex (male)	1.45 (0.95–2.22)	0.087	1.65 (1.01–2.69)	0.045
ASA-PS ≥3	1.25 (0.71–2.21)	0.44		N.S.
NLR (≥3.03)	2.17 (1.41–3.35)	<0.01		N.S.
PNI (<40)	2.03 (1.27–3.25)	<0.01		N.S.
CRP/Alb ratio (≥0.070)	2.68 (1.73–4.14)	<0.01	2.12 (1.33–3.40)	<0.01
Osteopenia	2.86 (1.90–4.33)	<0.01		N.S.
Sarcopenia	2.63 (1.65–4.21)	<0.01		N.S.
Osteosarcopenia	3.83 (2.54–5.78)	<0.01	4.34 (2.66–7.08)	<0.01
Surgical approach (laparoscopic)	0.63 (0.41–0.94)	0.025		N.S.
Tumor location (rectum)	1.25 (0.82–1.90)	0.31		N.S.
Pathological T 4 stage	2.82 (1.80–4.42)	<0.01	1.84 (1.09–3.12)	0.023
Pathological N1/N2 stage	3.27 (2.16–4.95)	<0.01	2.44 (1.51–3.93)	<0.01
Obstructive CRC	2.25 (1.31–3.87)	<0.01		N.S.
Serum CEA (≥5.0 ng/mL)	1.52 (0.98–2.35)	0.063		N.S.
Serum CA19-9 (≥37 ng/mL)	1.64 (0.94–2.86)	0.082		N.S.
Postoperative complication, yes	1.58 (1.04–2.41)	0.033		N.S.

Abbreviations: CAR, C-reactive protein to albumin ratio; CA19-9, carbohydrate antigen19-9; CEA, carcinoembryonic antigen; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; NLR, neutrophil to lymphocyte ratio; N.S., not significant; PNI, prognostic nutritional index.

Note: A backward elimination was conducted with a threshold *P* of 0.05 to select variables for the final models.

[a]The multivariable Cox regression model included age (≥80 vs <80 y), sex (male vs female), ASA-PS (≥3 vs <3), NLR (≥3.03 vs <3.03), PNI (<40 vs ≥40), CRP/Alb ratio (≥0.070 vs <0.070), osteopenia (yes vs no), sarcopenia (yes vs no), osteosarcopenia (yes vs no), surgical approach (laparoscopic vs open), tumor location (rectum vs colon), pathological T (T4 vs T1-3), pathological N (N1/2 vs N0), obstructive CRC (yes vs no), serum CEA (≥5.0 vs <5.0 ng/mL), serum CA19-9 (≥37 vs <37 U/mL) and postoperative complications (yes vs no).

worse in patients with age ≥80 y ($P = 0.023$), NLR ≥3.03 ($P < 0.01$), PNI <40 ($P < 0.01$), CRP/Alb ratio ≥0.070 ($P < 0.01$), osteopenia ($P < 0.01$), sarcopenia ($P < 0.01$), osteosarcopenia ($P < 0.01$), surgical approach ($P = 0.025$), pathological T4 stage ($P < 0.01$), pathological N1/N2 stage ($P < 0.01$), obstructive CRC ($P < 0.01$), and postoperative complications ($P = 0.033$). In the multivariate analysis, male sex ($P = 0.045$), CRP/Alb ratio ($P < 0.01$), osteosarcopenia ($P < 0.01$), pathological T4 stage ($P = 0.023$), and pathological N1/N2 stage ($P < 0.01$) were independent predictors of disease-free survival.

3.4 | Clinicopathological variables associated with overall survival

Table 3 shows the relationship between clinicopathological variables and overall survival after curative resection for CRC. In the univariate analysis, the overall survival was significantly worse in patients with age ≥80 y ($P < 0.01$), NLR ≥3.03 ($P < 0.01$), PNI <40 ($P < 0.01$), CRP/Alb ratio ≥0.070 ($P < 0.01$), osteopenia ($P < 0.01$), sarcopenia ($P < 0.01$), osteosarcopenia ($P < 0.01$), pathological T4 stage ($P < 0.01$), pathological N1/N2 stage ($P < 0.01$), obstructive CRC ($P < 0.01$), and serum CA 19–9 ≥ 37 U/mL ($P < 0.01$). In the multivariate analysis, age ≥80 y ($P < 0.01$), male sex ($P = 0.049$), CRP/Alb ratio ($P < 0.01$), osteosarcopenia ($P < 0.01$), pathological T4 stage ($P = 0.036$), pathological N1/N2 stage ($P < 0.01$), and serum CA 19–9 ≥ 37 U/mL ($P = 0.041$) were independent predictors of overall survival.

3.5 | The change of osteosarcopenia status in older adults after CRC surgery

Table 4 shows the proportion of preoperative and postoperative osteosarcopenia. In the analyses, the proportion of postoperative osteosarcopenia was higher than that of preoperative (29% vs 26%, $P = 0.015$) and a similar change was observed in sarcopenia (60% vs 57%, $P < 0.01$). Also, the proportion of postoperative osteopenia tended to be higher than that of preoperative, which was not

TABLE 3 Univariate and multivariate analyses of factors associated with overall survival

	Univariate		Multivariate[a]	
Variables	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (≥80 y)	2.89 (1.78–4.71)	<0.01	3.15 (1.76–5.64)	<0.01
Sex (male)	1.42 (0.86–2.34)	0.17	1.82 (1.00–3.30)	0.049
ASA-PS ≥3	1.84 (0.99–3.44)	0.056		N.S.
NLR (≥3.03)	2.62 (1.57–4.36)	<0.01		N.S.
PNI (<40)	3.92 (2.36–6.49)	<0.01		N.S.
CRP/Alb ratio (≥0.070)	3.63 (2.15–6.13)	<0.01	2.52 (1.42–4.50)	<0.01
Osteopenia	2.08 (1.29–3.36)	<0.01		N.S.
Sarcopenia	2.92 (1.66–5.13)	<0.01		N.S.
Osteosarcopenia	2.83 (1.75–4.58)	<0.01	2.79 (1.55–5.03)	<0.01
Surgical approach (laparoscopic)	0.66 (0.40–1.06)	0.087		N.S.
Tumor location (rectum)	0.90 (0.54–1.50)	0.69		N.S.
Pathological T 4 stage	3.53 (2.13–5.86)	<0.01	1.92 (1.04–3.52)	0.036
Pathological N1/N2 stage	3.01 (1.85–4.90)	<0.01	2.19 (1.25–3.85)	<0.01
Obstructive CRC	2.28 (1.22–4.27)	<0.01		N.S.
Serum CEA (≥5.0 ng/mL)	1.25 (0.73–2.12)	0.41		N.S.
Serum CA19-9 (≥37 ng/mL)	2.88 (1.61–5.15)	<0.01	2.00 (1.03–3.90)	0.041
Postoperative complication, yes	1.51 (0.93–2.47)	0.099		N.S.

Abbreviations: CAR, C-reactive protein to albumin ratio; CA19-9, carbohydrate antigen19-9; CEA, carcinoembryonic antigen; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; NLR, Neutrophil to lymphocyte ratio; N.S., not significant; PNI, prognostic nutritional index.

Note: A backward elimination was conducted with a threshold *P* of 0.05 to select variables for the final models.

[a]The multivariable Cox regression model included age (≥80 vs <80 y), sex (male vs female), ASA-PS (≥3 vs <3), NLR (≥3.03 vs <3.03), PNI (<40 vs ≥40), CRP/Alb ratio (≥0.070 vs <0.070), osteopenia (yes vs no), sarcopenia (yes vs no), osteosarcopenia (yes vs no), surgical approach (laparoscopic vs open), tumor location (rectum vs colon), pathological T (T4 vs T1-3), pathological N (N1/2 vs N0), obstructive CRC (yes vs no), serum CEA (≥5.0 vs <5.0 ng/mL), serum CA19-9 (≥37 vs <37 U/mL) and postoperative complications (yes vs no).

TABLE 4 Comparison of the proportion of pre- and postoperative osteopenia, sarcopenia, and osteosarcopenia

	Preoperative		Postoperative 6 M		
Variables	Yes	No	Yes	No	*P*-value
Osteopenia	115 (35%)	210 (65%)	123 (38%)	202 (62%)	0.20
Sarcopenia	186 (57%)	139 (43%)	196 (60%)	129 (40%)	<0.01
Osteosarcopenia	84 (26%)	241 (74%)	95 (29%)	230 (71%)	0.015

Abbreviation: M, months.

significant (38% vs 35%, $P = 0.20$). The multivariate ROC curve revealed no significant difference in the prognostic ability of osteosarcopenia between preoperative and postoperative periods (0.664; 95% CI 0.593–0.734 vs 0.642; 95% CI 0.568–0.716, $P = 0.071$) (Figure S2).

4 | DISCUSSION

We found a significant association between preoperative osteosarcopenia and poor prognosis in older adults who underwent curative resection for CRC. Namely, osteosarcopenia was an independent risk factor for poor disease-free and overall survival. Furthermore, the overall survival in patients with osteosarcopenia was significantly poorer than that in patients with sarcopenia or osteopenia alone. These findings suggest the utility of osteosarcopenia as a prognostic factor for poor postoperative outcomes in older adults, which is particularly significant in an aging society.

Our results were consistent with the findings of a previous study in patients who underwent hepatic resection for colorectal liver metastases, which also demonstrated poorer survival in patients with osteosarcopenia compared with that in patients with sarcopenia or

osteopenia alone.[10] Considering the high rate of coexistence of osteopenia and sarcopenia in older adults, osteosarcopenia should be investigated if either condition (sarcopenia or osteopenia) is identified. However, the relationship between malignancy and osteosarcopenia has not been well investigated due to the novelty and uniqueness of osteosarcopenia.

In patients with sarcopenia, skeletal muscle-derived inflammatory cytokines, such as interleukin-6 (IL-6), activate an inflammatory cascade via the signal transducer and activator of the transcription 3 (STAT3) pathway.[21] The STAT3 pathway, in turn, activates osteoclastogenesis in stromal/osteoblastic cells by induction of the receptor activator of the NF-kappaB ligand (RANKL) pathway, leading to osteopenia.[22] Furthermore, the STAT3 and RANKL pathways promote epithelial mesenchymal transition-mediated invasion and metastasis in CRC.[23,24] Therefore, patients with sarcopenia may be at higher risk of osteopenia and CRC progression. In the present study, 73% of patients with osteopenia were diagnosed with sarcopenia and the overall survival rate of the osteopenia alone group was comparable to that of penia-free. Furthermore, the proportion of osteosarcopenia increased with increasing stage.

In addition, recent studies have described the mechanism of muscle–bone crosstalk that can promote the development of sarcopenia and osteopenia.[8] Muscle-derived myokines, such as myostatin, follistatin, and irisin, have direct effects on bone remodeling, inducing osteoclastogenesis and bone resorption inhibition.[8] On the other hand, bone-derived osteokines, such as osteocalcin and connexin, have modulating effects on muscle anabolism and catabolism, respectively.[8] Hence, the inflammatory cascade induced by increased expression of IL-6 and subsequent activation of the RANKL pathway could be more active through the muscle–bone crosstalk.[25,26] These findings may explain why patients with osteosarcopenia had poorer survival than those with sarcopenia or osteopenia alone.

Given the increased proportion of osteosarcopenia after CRC surgery, preoperative risk assessment and therapy may be needed to prevent osteosarcopenia. Osteopenia and sarcopenia have common risk factors such as aging, sex, and hormone.[6,7] Vitamin D is an immunomodulatory hormone, which has been associated with the occurrence of osteopenia and sarcopenia.[7,27] Previous study has shown that an adequate intake of vitamin D and calcium present a protective role against the development of osteosarcopenia.[28] Furthermore, postoperative vitamin D deficiency was associated with poor disease-free survival in patients who underwent curative surgical resection for CRC.[29] Thus, routine supportive therapy focusing on nutrition such as vitamin D and calcium would be applicable for older adults to prevent osteosarcopenia and improve outcomes after colorectal resection for CRC.

The present study has several limitations. First, this was the retrospective observational study with a limited sample size; therefore, the confounding factors cannot be completely excluded. Osteosarcopenia might be confounded by several factors including age, sex, nutritional status, and cancer stage, which may have influenced the results. Second, the criteria of osteosarcopenia are not consistent. As there is no available standard method for osteopenia and sarcopenia evaluation, the cutoff value for these two conditions differs across studies. Taken together, further multicenter prospective studies are warranted to validate our findings.

5 | CONCLUSION

Osteosarcopenia was a strong predictor of poorer disease-free and overall survival compared with those in sarcopenia and osteopenia alone in patients with CRC. In an aging society, osteosarcopenia may be an integral component of the geriatric assessment in surgery for CRC.

AUTHOR CONTRIBUTIONS

YT, KK, and EK are responsible for the study concept, data collection, and writing the article. The other authors collected data, reviewed and corrected the article. The authors read and approved the article.

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The authors have no funding to declare.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

ETHICS STATEMENT

The present study was approved by the Ethics Committee of Tokyo General Hospital (approval No. 22–4) and Kasai Shoikai Hospital (approval No. R4-1), and was carried out in compliance with the Helsinki Declaration.

ANIMAL STUDIES

N/A.

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

ORCID

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SUPPORTING INFORMATION

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

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