Osteosarcopenia is a potential predictor for the prognosis of patients who underwent hepatic resection for colorectal liver metastases

Kenei Furukawa | Koichiro Haruki | Tomohiko Taniai | Ryoga Hamura | Yoshihiro Shirai | Jungo Yasuda | Hironori Shiozaki | Shinji Onda | Takeshi Gocho | Toru Ikegami

Division of Hepatobiliary and Pancreas Surgery, Department of Surgery, The Jikei University School of Medicine, Minato-ku, Japan

Correspondence
Toru Ikegami, Department of Surgery, The Jikei University School of Medicine, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan.
Email: toruikegami@jikei.ac.jp

Abstract

Aim: We investigated the prognostic impact of osteosarcopenia, which is the combination of osteopenia and sarcopenia, in patients with colorectal liver metastases (CRLM) after hepatic resection.

Methods: One hundred and eighteen patients were analyzed retrospectively. Osteopenia was evaluated with computed tomographic measurement of pixel density in the midvertebral core of the 11th thoracic vertebra. Sarcopenia was evaluated with psoas muscle areas at the third lumbar vertebra. Osteosarcopenia was defined as the concomitant occurrence of osteopenia and sarcopenia.

Results: Osteosarcopenia was identified in 38 (32%) of the patients. In univariate analysis, the overall survival was significantly worse in patients with lymph node metastases (P < .01), extrahepatic lesion (P < .01), sarcopenia (P = .02), osteosarcopenia (P < .01), Glasgow Prognostic Score (GPS) 1 or 2 (P = .05), and curability R 1 or 2 (P = .04). In multivariate analysis, lymph node metastases (P < .01), osteosarcopenia (P < .01), and GPS 1 or 2 (P = .03) were independent and significant predictors of the overall survival. In patients with osteosarcopenia, there were more women than men and body mass index was lower compared to patients without osteosarcopenia.

Conclusion: Osteosarcopenia was the strong predictor for outcomes in patients who underwent liver resection for CRLM.

KEYWORDS
colorectal liver metastases, liver resection, osteopenia, osteosarcopenia, sarcopenia

1 | INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, with a yearly increase in incidence.1 Of these, 20%–25% of patients will have colorectal liver metastases (CRLM) at presentation and a further 40%–50% will develop metachronous CRLM after primary tumor resection.2 Hepatic resection is the only treatment that can provide the possibility of prolonged survival for patients with CRLM, and their 5-year survival rate has reached 30%–50%.3

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made. © 2021 The Authors. Annals of Gastroenterological Surgery published by John Wiley & Sons Australia, Ltd on behalf of The Japanese Society of Gastroenterological Surgery
Sarcopenia was introduced as an age-related involuntary loss of muscle mass in 1989. Recently, sarcopenia is defined as a complex syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength. Sarcopenia can predict survival in patients with various kinds of cancer or patients with liver cirrhosis and has been identified as a factor that indicates a poor prognosis after liver resection, including hepatocellular carcinoma (HCC), intrahepatic cholagiocarcinoma, and CRLM.

Sarcopenia has been linked to low bone mineral density (BMD), known as osteopenia, suggesting that a low muscle mass decreases the mechanical loading on the skeleton, leading to reduced bone formation. Sharma et al demonstrated that low BMD was independently associated with post-liver transplantation mortality in HCC patients.

Recently, the concept and term “osteosarcopenia” has been established, which is defined as the concomitant occurrence of sarcopenia and osteopenia. Osteosarcopenia, described as a “hazardous duet,” has more negative impacts on health-related quality of life and eventual prognosis, with an increased risk of falls, fractures, institutionalization, and mortality than sarcopenia and osteopenia alone. However, the impact of osteosarcopenia on the prognosis for malignancies has not been reported yet.

The aim of this study is to investigate the impact of preoperative osteosarcopenia on the outcomes of patients with CRLM after hepatic resection in conjunction with other nutritional markers including sarcopenia and osteopenia, as well as inflammatory parameters.

2 METHODS

2.1 Patients

Between May 2007 and October 2017, 118 consecutive patients with CRLM underwent initial hepatic resection at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. We performed a retrospective review of a prospectively maintained database of patients. This study was approved by the Ethics Committee of the Jikei University School of Medicine (27-177).

2.2 Treatment and patient management

All patients with no unresectable extrahepatic tumor underwent hepatic resection regardless of the size, number, or location of liver metastases as long as curative resection would leave sufficient remnant liver. Generally, parenchymal-sparing hepatectomy was performed and extent of hepatic resection was based on retention rate of indocyanine green at 15 minutes (ICG$_{R15}$). Percutaneous transhepatic portal embolization was performed for patients with estimated residual hepatic volume of less than 30%.

SSI was defined as a condition where purulent discharge was observed with or without microbiological evidence in the incision or in an organ or space. Organ or space infection was determined by radiologic evidence of a fluid collection necessitating antibiotic therapy or drainage.

Recurrence of colorectal cancer after hepatic resection for CRLM was defined as newly detected local, hepatic, lung or extrahepatic tumors by ultrasonography, contrast-enhanced computed tomography (CT), or gadoxetic acid-enhanced magnetic resonance imaging (EOB-MRI) with or without increase in serum carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA19-9). For recurrent liver metastasis, repeated hepatic resection or systemic chemotherapy was performed. For lung metastasis, limited partial lung resection or systemic chemotherapy was performed. For local recurrence, tumor resection, radiotherapy, or systemic chemotherapy was performed. As with systemic chemotherapy, the patients received infusional 5-fluorouracil/l-leucovorin with oxaliplatin (FOLFOX) and/or infusional 5-fluorouracil/l-leucovorin with irinotecan (FOLFIRI).

2.3 Definition of osteopenia, sarcopenia, and osteosarcopenia

Osteopenia was defined as actual bone mineral density (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).

FIGURE 1 (A) Measurement of bone mineral density (BMD) on trabecular bone with calculation of the average pixel density within a circle in midvertebral core at 11th thoracic vertebral level. (B) Kaplan-Meier curve for overall survival after hepatic resection for colorectal liver metastases.
women). BMD was measured in trabecular bone by calculating average pixel density within a circle in midvertebral core at the bottom of 11th thoracic vertebra (Th11) on preoperative CT \(^{13}\) (Figure 1A). Sarcopenia was defined as psoas muscle mass area (PMA) below the established sex-specific median size and PMA was calculated using the formula \((\text{radii of the major axes} \times \text{radii of the minor axes} \times \pi)\) at the level of the third lumbar vertebra \(^{10}\) (Figure 2A). Osteosarcopenia was defined as the concomitant occurrence of osteopenia and sarcopenia.

### 2.4 Nutrition and inflammation markers

Hemogram and chemistry profile were measured preoperatively. The nutrition and inflammation-based biomarkers examined in this study were the following: Glasgow Prognostic Score (GPS), which is a combination of C-reactive protein (CRP) and albumin (Alb); patients with a normal Alb level (≥3.5 mg/dL) and a normal CRP level (<10 mg/L) were allocated a score of 0, patients with a low Alb level (<3.5 mg/dL) or an elevated CRP (≥10 mg/L) were allocated a score of 1, and patients with both a low Alb level (<3.5 mg/dL) and an elevated CRP (≥10 mg/L) were allocated a score of 2 \(^{16}\); prognostic nutritional index (PNI) which is calculated by the formula \(10 \times \text{Alb (g/dL)} + 0.005 \times \text{lymphocyte count/μL}^{17}\) neutrophil-lymphocyte ratio (NLR) \(^{18}\); and platelet-lymphocyte ratio (PLR) \(^{19}\).

### 2.5 Analyses of risk factors for recurrence and overall survival

We investigated the relation between clinicopathologic variables and disease-free or overall survival after initial liver resection by univariate and multivariate analyses. The variables include diabetes mellitus, cardiovascular disease, alcohol drinking, smoking, regional lymph node metastases of primary colorectal cancer, timing of tumor (synchronous or metachronous CRLM), neoadjuvant chemotherapy, tumor number, tumor size, extrahepatic lesion, osteopenia, sarcoopenia, osteosarcopenia, GPS, PNI, NLR, PLR, serum CEA level, and curability (R1, 2 or R0). Continuous variables were classified into two groups for the Cox proportional hazard regression model based on the previous literature as follows: tumor size ≥50 or <50 mm \(^{20}\), PNI ≥ 45 or <45 \(^{21}\), NLR ≥ 3 or <3 \(^{22}\), PLR ≥ 150 or <150 \(^{23}\) and serum CEA ≥ 20 or <20 ng/mL \(^{20}\).

Next, we investigated the relation between clinical variables and osteosarcopenia by univariate analysis. The variables include age, gender, body mass index, diabetes mellitus, cardiovascular disease, regional lymph node metastases of primary colorectal cancer, timing of tumor, neoadjuvant chemotherapy, extrahepatic lesion, tumor number, BMD, PMA, GPS, PNI, NLR, PLR, operation time, intraoperative blood loss, postoperative SSI, adjuvant chemotherapy, and treatment for recurrence.

### 2.6 Statistical analysis

The data were expressed as the median (inter quartile range). Univariate analysis were performed using the Mann-Whitney U test and chi-square test. Univariate and multivariate analyses of disease-free and overall survival was performed using the Cox proportional regression model. Survival curve was calculated using the Kaplan-Meier method with the Log-rank test. All P-values were considered statistically significant when the associated probability was less than .05.

### 3 RESULTS

#### 3.1 Patient characteristics

The mean age was 67.5 years with a range 28-90 years. The median value of BMD was 139 Hounsfield units (HU) and osteopenia was diagnosed in 66 patients (56%) according to the calculated standard BMD values. The median PMA was 23.1 cm\(^2\) for men and 11.9 cm\(^2\) for women and sarcopenia was diagnosed in 61 patients (52%) and osteosarcopenia was diagnosed in 38 patients (32%). In this study, the 3-year disease-free and overall survival rate after hepatic resection for CRLM was 28.7% and 71.5%, respectively.
### TABLE 1 Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after hepatic resection for colorectal liver metastases

| Variables                        | N  | DFS univariate analysis | DFS multivariate analysis |
|----------------------------------|----|-------------------------|---------------------------|
|                                  |    | Hazard ratio (95% CI)   | P-value                   | Hazard ratio (95% CI) | P-value |
| **DFS univariate analysis**      |    |                         |                           |
| **DFS multivariate analysis**    |    |                         |                           |
| Lymph node metastases            |    |                         |                           |
| Yes                              | 74 | 1.68 (1.04-2.69)        | .03                       | 1.52 (0.93-2.49)      | .09     |
| No                               | 44 |                         |                           |                       |         |
| Timing of tumor                  |    |                         |                           |
| Synchronous                      | 74 | 1.37 (0.86-2.18)        | .18                       |                       |         |
| Metachronous                     | 44 |                         |                           |                       |         |
| Neoadjuvant chemotherapy         |    |                         |                           |
| Yes                              | 41 | 1.37 (0.88-2.15)        | .17                       |                       |         |
| No                               | 77 |                         |                           |                       |         |
| Tumor number                     |    |                         |                           |
| Multiple                         | 61 | 1.99 (1.28-3.11)        | <.01                      | 2.06 (1.31-3.23)      | <.01    |
| Solitary                         | 57 |                         |                           |                       |         |
| Tumor size, mm                   |    |                         |                           |
| ≥50                              | 25 | 0.93 (0.54-1.61)        | .79                       |                       |         |
| <50                              | 93 |                         |                           |                       |         |
| Extrahepatic lesion              |    |                         |                           |
| Yes                              | 19 | 2.10 (1.21-3.64)        | <.01                      | 2.53 (1.44-4.44)      | <.01    |
| No                               | 99 |                         |                           |                       |         |
| Osteopenia                       |    |                         |                           |
| Yes                              | 66 | 1.30 (0.83-2.01)        | .25                       |                       |         |
| No                               | 52 |                         |                           |                       |         |
| Sarcopenia                       |    |                         |                           |
| Yes                              | 61 | 1.53 (0.98-2.39)        | .06                       |                       |         |
| No                               | 57 |                         |                           |                       |         |
| Osteosarcopenia                  |    |                         |                           |
| Yes                              | 38 | 1.42 (0.90-2.23)        | .13                       |                       |         |
| No                               | 80 |                         |                           |                       |         |
| GPS                              |    |                         |                           |
| 1 or 2                           | 31 | 1.35 (0.83-2.20)        | .22                       |                       |         |
| 0                                | 87 |                         |                           |                       |         |
| PNI                              |    |                         |                           |
| ≥45                              | 66 | 0.78 (0.50-1.20)        | .26                       |                       |         |
| <45                              | 52 |                         |                           |                       |         |
| NLR                              |    |                         |                           |
| ≥3                               | 38 | 1.29 (0.82-2.03)        | .28                       |                       |         |
| <3                               | 80 |                         |                           |                       |         |
| PLR                              |    |                         |                           |
| ≥150                             | 58 | 1.59 (1.03-2.47)        | .04                       | 1.64 (1.04-2.59)      | .04     |
| <150                             | 60 |                         |                           |                       |         |
| Serum CEA, ng/mL                 |    |                         |                           |
| ≥20                              | 46 | 1.32 (0.85-2.05)        | .22                       |                       |         |
| <20                              | 72 |                         |                           |                       |         |
| Curability                       |    |                         |                           |
| R1 or 2                          | 16 | 1.80 (0.99-3.29)        | .05                       |                       |         |
| R0                               | 102|                         |                           |                       |         |

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; DFS, disease-free survival; GPS, Glasgow Prognostic Score; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PNI, prognostic nutrition index.
3.2 Univariate and multivariate analyses of clinicopathological variables in relation to disease-free survival after hepatic resection for CRLM

Table 1 lists the association between the clinicopathological variables and disease-free survival after hepatic resection for CRLM. In univariate analysis, the disease-free survival was significantly worse in patients with lymph node metastases (\( P = .03 \)), multiple tumors (\( P < .01 \)), extrahepatic lesion (\( P < .01 \)), and PLR \( \geq 150 \) (\( P = .04 \)). In multivariate analysis, multiple tumors (hazard ratio 2.06, 95% confidence interval 1.31-3.23, \( P < .01 \)), extrahepatic lesion (hazard ratio 2.53, 95% confidence interval 1.44-4.44, \( P < .01 \)), and PLR \( \geq 150 \) (hazard ratio 1.64, 95% confidence interval 1.04-2.59, \( P = .04 \)) were independent and significant predictors of the disease-free survival.

3.3 Impact of osteopenia, sarcopenia, and osteosarcopenia for overall survival after hepatic resection for CRLM

The overall survival of patients with osteopenia was significantly lower than that of patients without osteopenia (\( P = .05 \); 3-year survival, 60.5% vs 82.2%) (Figure 1B). The overall survival of patients with sarcopenia was significantly lower than that of patients without sarcopenia (\( P = .02 \); 3-year survival, 63.9% vs 77.7%) (Figure 2B). The overall survival of patients with osteosarcopenia was significantly lower than that of patients without osteosarcopenia (\( P < .01 \); 3-year survival, 47.9% vs 81.2%) (Figure 3A). The Kaplan-Meier curve separated by gender showed that male patients not female patients with osteosarcopenia had significantly worse overall survival than those without osteosarcopenia (\( P < .01 \), \( P = .07 \), respectively) (Figure 3B, C).

The overall survival of patients with osteosarcopenia was significantly lower than that of patients with osteopenia alone and sarcopenia alone (\( P = .03 \), .0497, respectively) (Figure 4).

3.4 Univariate and multivariate analyses of clinicopathological variables in relation to overall survival after hepatic resection for CRLM

Table 2 lists the association between the clinicopathological variables and overall survival after hepatic resection for CRLM. In univariate analysis, the overall survival was significantly worse in patients with lymph node metastases (\( P = .01 \)), extrahepatic lesion (\( P < .01 \)), and GPS 1 or 2 (\( P = .05 \)). In multivariate analysis, lymph node metastases (hazard ratio 2.60, 95% confidence interval 1.26-5.38, \( P < .01 \)), osteosarcopenia (hazard ratio 3.17, 95% confidence interval 1.38-7.25, \( P < .01 \)) and GPS 1 or 2 (hazard ratio 2.11, 95% confidence interval
| Variables                        | N   | OS univariate analysis | OS multivariate analysis |
|---------------------------------|-----|-------------------------|--------------------------|
|                                 |     | Hazard ratio (95% CI)   | P-value                  |
|                                 |     | Hazard ratio (95% CI)   | P-value                  |
| Diabetes mellitus               |     |                        |                          |
| Yes                             | 20  | 0.78 (0.31-1.99)        | .61                      |
| No                              | 98  |                        |                          |
| Cardiovascular disease          |     |                        |                          |
| Yes                             | 17  | 0.64 (0.25-1.62)        | .34                      |
| No                              | 111 |                        |                          |
| Alcohol drinking                |     |                        |                          |
| Yes                             | 10  | 0.84 (0.26-2.72)        | .77                      |
| No                              | 108 |                        |                          |
| Smoking                         |     |                        |                          |
| Yes                             | 38  | 1.05 (0.57-1.95)        | .87                      |
| No                              | 80  |                        |                          |
| Lymph node metastases           |     |                        |                          |
| Yes                             | 74  | 2.43 (1.20-4.90)        | .01                      |
| No                              | 44  | 2.60 (1.26-5.38)        | <.01                     |
| Timing of tumor                 |     |                        |                          |
| Synchronous                     | 74  | 1.20 (0.64-2.24)        | .58                      |
| Metachronous                    | 44  |                        |                          |
| Neoadjuvant chemotherapy        |     |                        |                          |
| Yes                             | 41  | 1.77 (0.99-3.19)        | .06                      |
| No                              | 77  |                        |                          |
| Tumor number                    |     |                        |                          |
| Multiple                        | 61  | 1.50 (0.83-2.70)        | .18                      |
| Solitary                        | 57  |                        |                          |
| Tumor size, mm                  |     |                        |                          |
| ≥50                             | 25  | 1.32 (0.67-2.61)        | .42                      |
| <50                             | 93  |                        |                          |
| Extrahepatic lesion             |     |                        |                          |
| Yes                             | 19  | 2.28 (1.18-4.40)        | .01                      |
| No                              | 99  | 1.84 (0.93-3.65)        | .08                      |
| Osteopenia                      |     |                        |                          |
| Yes                             | 66  | 1.81 (0.99-3.29)        | .05                      |
| No                              | 52  |                        |                          |
| Sarcopenia                      |     |                        |                          |
| Yes                             | 61  | 2.13 (1.14-4.00)        | .02                      |
| No                              | 57  | 0.95 (0.41-2.21)        | .91                      |
| Osteosarcopenia                 |     |                        |                          |
| Yes                             | 38  | 2.54 (1.41-4.56)        | <.01                     |
| No                              | 80  | 3.17 (1.38-7.25)        | <.01                     |
| GPS                             |     |                        |                          |
| 1 or 2                          | 31  | 1.86 (1.00-3.45)        | .05                      |
| 0                               | 87  | 2.11 (1.06-4.20)        | .03                      |
| PNI                             |     |                        |                          |

(Continues)
1.06-4.20, $P < .01$) were independent and significant predictors of the overall survival.

### 3.5 Association between clinical variables and osteosarcopenia

Table 3 lists the association between clinical variables and osteosarcopenia. In patients with osteosarcopenia, female patients were significantly more common and body mass index, BMD, and PMA was significantly lower compared to patients without osteosarcopenia ($P = .03$, $< .01$, $< .01$ and $< .01$, respectively). GPS, PNI, NLR, PLR, adjuvant chemotherapy, and treatment for recurrence were comparable between the two groups.

### 4 DISCUSSION

In the present study, we evaluated the impact of preoperative osteosarcopenia on the outcomes after hepatic resection for CRLM. To the best of our knowledge, this is the first report to demonstrate the impact of preoperative osteosarcopenia on prognosis for malignancies and to compare with other preoperative nutritional predictors of prognosis, including GPS, PNI, NLR, PLR, and patients’ status of sarcopenia and osteopenia. Multivariate analysis using the Cox proportional regression model showed that osteosarcopenia was independently associated with poor overall survival after hepatic resection for CRLM. And overall survival in patients with osteosarcopenia was significantly worse those with sarcopenia alone or osteopenia alone.

Sarcopenia plays an important role as a prognostic factor for various tumors. Inflammatory conditions, nutritional factors, and aging have been postulated as the molecular mechanism. On the other hand, there are few reports to show the prognostic value of osteopenia.

It is not clear whether the bone loss promotes cancer development or whether stable bone density prevents cancer invasion. Gender, low body mass index, comorbidities, such as diabetes and kidney dysfunction, low levels of Vitamin D, reduced insulin-like growth factor-1, and malnutrition have been associated with osteosarcopenia. Our findings showed that in patients with osteosarcopenia, female patients were significantly more common and body mass index was significantly lower compared to patients without osteosarcopenia. On the other hand, there were no differences in comorbidities (diabetes and cardiovascular disease), serum creatinine level (0.77 vs 0.79 mg/dL; $P = .32$), serum calcium level (9.2 vs 9.1 mg/dL; $P = .44$), serum Alb level (3.9 vs 3.8 g/dL; $P = .72$), serum prealbumin level (23.6 vs 23.9 mg/dL; $P = .59$), serum transferrin level (227 vs 245 mg/dL; $P = .17$), and serum retinol-binding protein level (2.8 vs 2.9 mg/dL; $P = .49$) including the nutrition and inflammation-based biomarkers such as GPS, PNI, NLR, and PLR between patients with and without osteosarcopenia. Chen et al. reported that women with a lower body weight at colorectal cancer diagnosis had an increased mortality risk, which is the same as the present study. According to the Kaplan-Meier curve separated by gender, the overall survival of female patients with osteosarcopenia was not significantly worse than that of female patients without osteosarcopenia. However, female patients with osteosarcopenia were likely to have poorer prognosis than those without osteosarcopenia ($P = .07$), and we could explain this discrepancy but the sample size was too small to show the statistical significance.

The BMD measurement is a surrogate cumulative exposure to multiple factors, including vitamin D and estrogen. Vitamin D and
TABLE 3 Univariate analysis of clinical variables in relation to osteosarcopenia

| Variables                                      | Osteosarcopenia | P-value |
|------------------------------------------------|----------------|---------|
| Age, y                                         | Yes (n = 38) | 68 (61-75) | 66 (60-74) | .61 |
| Gender, female                                 | No (n = 80) | 66 (60-74) | 66 (60-74) | .61 |
| Body mass index, kg/m²                         | Yes (n = 38) | 21 (19-23) | 23 (21-25) | <.01 |
| Diabetes mellitus                              | No (n = 80) | 7 (18%) | 13 (16%) | .77 |
| Cardiovascular disease                         | Yes (n = 38) | 6 (16%) | 11 (14%) | .77 |
| Lymph node metastases, yes                     | No (n = 80) | 24 (63%) | 50 (63%) | .94 |
| Timing of tumor, synchronous                   | Yes (n = 38) | 23 (61%) | 51 (64%) | .74 |
| Neoadjuvant chemotherapy, yes                  | No (n = 80) | 14 (37%) | 27 (34%) | .74 |
| Extrahepatic lesion, yes                       | Yes (n = 38) | 9 (24%) | 10 (13%) | .12 |
| Tumor number                                   | No (n = 80) | 1 (1-2) | 2 (1-3) | .52 |
| Tumor size, mm                                 | Yes (n = 38) | 27 (18-45) | 26 (17-43) | .60 |
| BMD, HU                                        | No (n = 80) | 113 (90-126) | 156 (128-196) | <.01 |
| PMA, cm²                                       | Yes (n = 38) | 11 (10-19) | 24 (18-30) | <.01 |
| GPS, 1 or 2                                    | No (n = 80) | 9 (24%) | 22 (28%) | .66 |
| PNI                                            | Yes (n = 38) | 46 (40-49) | 46 (42-49) | .58 |
| NLR                                           | No (n = 80) | 2 (2-3) | 2 (2-3) | .99 |
| PLR                                           | Yes (n = 38) | 170 (121-211) | 144 (101-206) | .11 |
| Operation time, min mL                         | No (n = 80) | 385 (275-469) | 375 (290-475) | .90 |
| Intraoperative blood loss, mL                  | Yes (n = 38) | 340 (100-980) | 495 (198-1.101) | .29 |
| Postoperative SSI, yes                         | No (n = 80) | 3 (8%) | 12 (15%) | .30 |
| Adjuvant chemotherapy, yes                     | Yes (n = 38) | 25 (66%) | 48 (60%) | .55 |
| Treatment for recurrence, none                 | Yes (n = 38) | 10:0:15:5 | 20:3:21:8 | .51 |

Abbreviations: BMD, bone mineral density; CEA, carcinoembryonic antigen; GPS, Glasgow Prognostic Score; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PMA, psoas muscle mass area; PNI, prognostic nutrition index; SSI, surgical site infection.

Interestingly, in this study, there was no significant difference in the disease-free survival between the patients with and without osteosarcopenia. Toshima et al and Sharma et al also demonstrated that osteopenia was independently associated with post-liver transplantation survival in HCC patients, but not recurrence. They pointed out how effective treatments for recurrence were done might be related to osteopenia; however, the present study showed that treatment for recurrence was comparable between them. In addition, most patients with osteosarcopenia (21/22 patients) died of colorectal cancer-related death (one patient died of interstitial pneumonia), which could suggest that osteosarcopenia only affected cancer-related death. This discrepancy should be investigated in the future.

Several limitations must be considered when interpreting the present findings. The study was retrospective and conducted in a single institution with a relatively small sample size. Our results should be confirmed in larger prospective studies. The prognostic impact of sarcopenia and osteopenia on survival for malignancies has been demonstrated in several studies. Although varying cutoff points regarding skeletal muscle mass and BMD have been used, the definitions of sarcopenia and osteopenia remain controversial, with a variety of claimed appropriate diagnostic cutoff values. In our study, we based the cutoff values on the median PMA of the population for sarcopenia and the standard BMD with age for osteopenia.

Interventions such as supportive therapy focusing on nutrition and rehabilitation would be applicable for patients with osteosarcopenia to improve outcomes after hepatic resection for CRLM. Perioperative nutritional therapy such as synbiotics, micronutrients, branched-chain amino acid, and immunonutrition formulas in liver transplant recipients who have decreased skeletal muscle mass and malnutrition have been considered essential interventions to improve outcomes after liver transplantation. For osteosarcopenia, vitamin D, calcium, osteoporotic drugs such as teriparatide, denosumab and bisphosphates, exercises are needed to improve musculoskeletal health.

In conclusion, we demonstrated that preoperative osteosarcopenia was more closely related to postoperative survival than sarcopenia and osteopenia alone in patients who underwent hepatic resection for CRLM. The evaluation of skeletal muscle and BMD may be useful for risk stratification and clinical decision-making for patients with CRLM. Early interventions such as nutritional support and physical exercise may improve outcomes after hepatic resection for CRLM.

DISCLOSURE
Conflict of Interest: The authors have no conflicts of interest and funding to declare.

ORCID
Kenei Furukawa https://orcid.org/0000-0002-5081-6417
Koichiro Haruki https://orcid.org/0000-0002-1686-3228
Ryoga Hamura https://orcid.org/0000-0003-1670-4435
Toru Ikegami https://orcid.org/0000-0001-5792-5045
REFERENCES

1. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67:177–93.

2. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006;244:254–9.

3. Adam R, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. Ann Gastroenterol Surg. 2019;3:50–6.

4. Rosenberg IH. Sarcopenia: origins and clinical relevance. Clin Geriatr Med. 2011;27:377–9.

5. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–23.

6. Sabel MS, Lee J, Cai S, Englesbe MJ, Holcombe S, Wang S. Sarcopenia as a prognostic factor among patients with stage III melanoma. Ann Surg Oncol. 2011;18:3579–85.

7. Tan BH, Birdsell LA, Martin L, Englesbe MJ, Holcombe S, Wang S. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15:6973–9.

8. Tandon P, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. Liver Transpl. 2012;18:1209–16.

9. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg. 2013;100:1523–30.

10. Yugawa K, Itoh S, Kurihara T, Yoshiya S, Mano Y, Takeishi K, et al. Skeletal muscle mass predicts the prognosis of patients with intrahepatic cholangiocarcinoma. Am J Surg. 2019;218:952–8.

11. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg. 2012;99:550–7.

12. Verschueren S, Gielen E, O’Neill TW, Pye SR, Adams JE, Ward KA, et al. Sarcopenia and its relationship with bone mineral density in middle-aged and elderly European men. Osteoporos Int. 2013;24:87–98.

13. Sharma P, Parikh ND, Yu J, Barman P, Derstine BA, Sonnenday CJ, et al. Bone mineral density predicts posttransplant survival among hepatocellular carcinoma liver transplant recipients. Liver Transpl. 2016;22:1092–8.

14. Kirk B, Zanker J, Duque G. Osteosarcopenia: epidemiology, diagnosis, and treatment-facts and numbers. J Cachexia Sarcopenia Muscle. 2020;11:609–18.

15. Toshima T, Yoshizumi T, Kosai-Fujimoto Y, Inokuchi S, Yoshiya S, Takeishi K, et al. Prognostic impact of osteopenia in patients who underwent living donor liver transplantation for hepatocellular carcinoma. World J Surg. 2020;44:258–67.

16. Forrest LM, McMillan DC, Mcardle CS, Angerson WJ, Dunlop DJ. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2003;89:1028–30.

17. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi. 1984;85:1001–5.

18. Zahorec R. Ratio of neutrophil to lymphocyte counts–rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001:102:5–14.

19. Liaw FY, Huang CF, Chen WL, Wu LW, Peng TC, Chang YW, et al. Higher platelet-to-lymphocyte ratio increased the risk of sarcopenia in the community-dwelling older adults. Sci Rep. 2017;7:16609.

20. Haruki K, Shiba H, Hirochi T, Sakamoto T, Gocho T, Fujiyara Y, et al. Impact of the C-reactive protein to albumin ratio on long-term outcomes after hepatic resection for colorectal liver metastases. Am J Surg. 2017;214:752–6.

21. Chan AW, Chan SL, Wong GL, Wong VWS, Chong CCN, Lai PBS, et al. Prognostic nutritional index (PNI) predicts tumor recurrence of very early/early stage hepatocellular carcinoma after surgical resection. Ann Surg Oncol. 2015;22:4138–48.

22. Chiang SF, Hung HY, Tang R, Changchien CR, Chen JS, You YT, et al. Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? Int J Colorectal Dis. 2012;27:1347–57.

23. He W, Yin C, Guo G, Jiang C, Wang F, Qiu H, et al. Initial neutrophil-lymphocyte ratio is superior to platelet lymphocyte ratio as an adverse prognostic and predictive factor in metastatic colorectal cancer. Med Oncol. 2013;30:439.

24. Okamura H, Ishikawa K, Kudo Y, Matsuoka A, Maruyama H, Emori H, et al. Risk factors predicting osteosarcopenia in postmenopausal women with osteoporosis: a retrospective study. PLoS One. 2020;15:e0237454.

25. Chen CW, Tsai HL, Yeh YS, Lin HL, Huang CW, Chen CF, et al. Osteoporosis self-assessment tool for Asians as a simple risk index of identifying a poor prognosis in women surgically treated for colorectal cancer. J Surg Res. 2013;181:242–9.

26. Ng K, Meyerhardt JA, Wu K, Feskanich D, Hollis BW, Giovannucci EL, et al. Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer. J Clin Oncol. 2008;26:2984–91.

27. Rennert G, Rennert HS, Pinchev M, Lavie O, Gruber SB. Use of hormone replacement therapy and the risk of colorectal cancer. J Clin Oncol. 2009;27:4542–7.

28. Hendifar A, Yang D, Lenz F, Lurje G, Pohl A, Lenz C, et al. Gender disparities in metastatic colorectal cancer survival. Clin Cancer Res. 2009;15:6391–7.

29. Hammad A, Kaido T, Aliyev V, Mandato C, Uemoto S. Nutritional therapy in liver transplantation. Nutrients. 2017;9:1126.

How to cite this article: Furukawa K, Haruki K, Tanai T, et al. Osteosarcopenia is a potential predictor for the prognosis of patients who underwent hepatic resection for colorectal liver metastases. Ann Gastroenterol Surg. 2021;5:390–398. https://doi.org/10.1002/ags3.12428