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Original article

Bone mineral density correlates with survival after resection of extrahepatic biliary malignancies

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SUMMARY

Background & aims: Osteopenia is a condition in which bone mineral density (BMD) is lower than normal, and it is an important determinant of bone fragility. However, the utility of osteopenia in assessing the risks of surgery is unclear. This study investigated the impact of preoperative low BMD on the outcomes in patients undergoing resection of extrahepatic biliary cancers.

Methods: A retrospective analysis was performed with 181 patients who underwent resections of extrahepatic biliary cancers between 2005 and 2015. Their BMD was measured on preoperative computed tomography images. Overall survival (OS) and recurrence-free survival (RFS) rates were compared according to BMD (normal vs. low), and the prognostic factors after surgery were assessed. Propensity score matching was used to minimize the bias in patient background.

Results: Older age and female were strongly associated with low BMD. These factors were used to construct the propensity score model, which yielded a matched cohort of 52 legs in each group. The OS (21.2% vs. 53.9% at 5 years, $p < .001$) and RFS (21.8% vs. 64.6% at 5 years, $p < .001$) rates were significantly lower in patients with low BMD (osteopenia) than in those with normal BMD (non-osteopenia). Multivariable analyses showed that low BMD was an independent factor predictive of poor OS (hazard ratio [HR]: 2.343, 95% confidence interval [CI]: 1.362–4.129, $p = .002$) and poor RFS (HR: 3.648, 95% CI: 1.986–6.990, p=<.001).

Conclusions: Preoperative low BMD is closely related to mortality and cancer recurrence after the resection of extrahepatic biliary cancers. BMD screening in patients with cancer should be further highlighted in the oncology field.

1. Introduction

Sarcopenia has been identified as a factor for poor prognosis in patients after several kinds of hepato-biliary-pancreatic surgery [1–3]. In addition to muscle mass, muscle quality and obesity also affect postoperative outcomes [4–11]. We have reported that decreased skeletal muscle quality and the accumulation of visceral adipose tissue are closely related to poor patient survival after liver transplantation [4,5] and resections for metastatic liver tumors [6], hepatocellular carcinoma (HCC) [7], pancreatic adenocarcinoma [8,9], and biliary malignancies [10,11]. With regard to extrahepatic biliary malignancies, preoperative sarcopenia, indicating a low quantity and quality of skeletal muscle, was found to be associated with poor postoperative survival following resection [10].

Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; DXA, dual-energy X-ray absorptiometry; HCC, hepatocellular carcinoma; HR, hazard ratio; HU, Hounsfield unit; IMAC, intramuscular adipose tissue content; PMI, psoas muscle mass index; PS, propensity score; RFS, recurrence free survival; ROC, receiver operating characteristic; ROI, region of interest; SMI, skeletal muscle mass index; VSR, visceral to subcutaneous adipose tissue area ratio.

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Osteopenia is a condition in which bone mineral density (BMD) is lower than normal but not as severely low as in osteoporosis, and it is an important determinant of bone fragility. Like osteoporosis, osteopenia occurs more frequently in post-menopausal women because of the loss of estrogen and the older age of the population. A recent study reported that approximately 80% of older cancer patients (aged ≥65 years) had osteopenia or osteoporosis [12]. Additionally, sarcopenia and osteopenia commonly co-exist in older adults [13]. However, the utility of osteopenia in assessing the risks of conditions other than fractures is unclear.

While a dual-energy X-ray absorptiometry (DXA) is currently the standard for diagnosing osteoporosis or osteopenia and has correlated with fracture risk, several studies suggested that quantitative computed tomography (CT) could be an alternative in terms of sensitivity and versatility [14,15]. Using this method, an association has recently been described for the first time between osteopenia and poor postoperative outcomes in the field of hepato-biliary-pancreatic surgery. Sharma et al. [16] reported that preoperative osteopenia, indicated by low BMD acquired from CT, predicted posttransplant survival of liver-transplanted recipients with HCC. However, the impact of osteopenia or low BMD on the outcome after the resection of extrahepatic biliary cancers and its association with sarcopenic factors remains unknown.

In the present study, preoperative osteopenia was evaluated by determining the BMD using preoperative plain CT imaging. The impact of low BMD on the outcome in patients undergoing resection of extrahepatic biliary cancers and its correlation with sarcopenic factors were investigated.

2. Materials and methods

2.1. Patient population

The data of 233 consecutive patients who underwent resection for extrahepatic biliary cancer with curative intent between 2005 and 2015 at Kyoto University were reviewed. Patients with ampullary cancer (n = 38) and stage 0 cancer (n = 6) were excluded from the analysis because of their better prognosis than those with other extra-hepatic biliary cancers or other stages. Those who only underwent a cholecystectomy (n = 8) were also excluded because of its low surgical stress that would not affect patients' prognosis. After excluding these patients, 181 patients were enrolled in this study. All study protocols were approved by the Ethics Committee of Kyoto University (Approval number: R1431), and all procedures were conducted in accordance with the Declaration of Helsinki of 1996.

2.2. Image analysis

Preoperative osteopenia was evaluated by determining the BMD using preoperative plain CT imaging because DXA was not routinely performed for screening of bone fragility in cancer patients. All preoperative CT imaging was obtained within 2 months prior to the operation with a multidetector CT scanner. We analyzed the cross-sectional non-contrast plain CT images at the level of the eleventh thoracic vertebra (Th11) with the region of interest (ROI) attenuations to measure BMD according to the methods outlined in a previous report [16]. BMD was only measured on the trabecular bone with the calculation of the average pixel density within a circle defined as the mid-vertebral core sample (Fig. 1). The values for BMD were described in hounsfield unit (HU). In addition, we analyzed the plain CT images at the level of the third lumbar vertebra (L3) with the Aquarius iNtuition Server (TeraRecon, Inc., San Mateo, CA, USA) to determine the areas of skeletal muscle, abdominal visceral and subcutaneous adipose tissue, as previously described [5].

2.3. Definitions

Patients were assigned into one of two groups: normal-BMD or low-BMD group. Low BMD was defined according to the cut-off value detected by receiver operating characteristic (ROC) curve analysis of the association between the BMD and overall mortality. Body composition components regarding muscularity and visceral adiposity, including psoas muscle mass index (PMI), skeletal muscle mass index (SMI), intramuscular adipose tissue content (IMAC), and visceral to subcutaneous adipose tissue area ratio (VSR), were graded according to the previous reports [5,17]. Post-hepatectomy liver failure, bile leakage, and pancreatic fistula was defined in accordance with the International Study Group of Liver Surgery criteria [18], the Clavian-Dindo classification [19], and the International Study Group of Pancreatic Fistula criteria [20], respectively. Adjuvant chemotherapy was administered to patients with stages II/III/IV or patients without R0 resection with gemcitabine, S-1, or both, for longer than 6 months.

2.4. Statistical analysis

As imbalances of background clinical characteristics may potentially confound the interpretation of outcomes, propensity score (PS) matching was used to minimize the bias for presenting low BMD. A PS model was constructed using logistic regression analysis. All preoperative factors were compared in the two groups (normal-BMD versus low-BMD), and factors found to be statistically different in univariate analysis were then used to construct the PS model. Continuous variables with normal and non-normal distributions are presented as the mean ± standard deviation and the median with the range, respectively. Categorical variables are presented as the number and percentage. Comparisons were performed by the t test or Mann–Whitney U test for continuous variables and by the χ^2 test or Fisher exact test for categorical variables. Cox regression analysis was used to examine the predictors of postoperative mortality. Factors with a significant

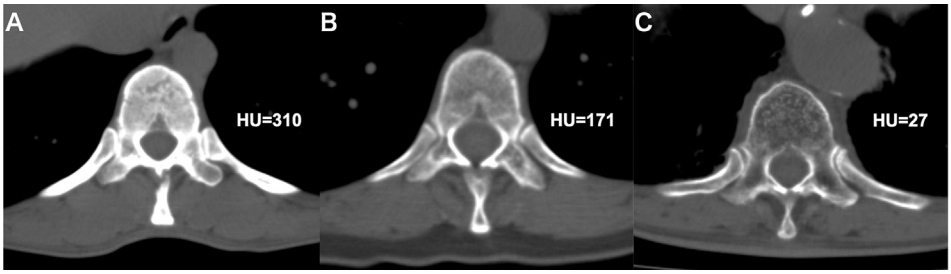

Fig. 1. Cross-sectional CT images at the level of the eleventh thoracic vertebra. Examples in three patients with different BMDs. A) A 45-year-old female with high BMD (310 HU). B) A 69-year-old male with normal BMD (171 HU). C) An 82-year-old male with low BMD (27 HU). BMD, bone mineral density; CT, computed tomography; HU, Hounsfield unit.

relationship in the univariable analysis were subsequently used in the multivariable analysis. The effect of a factor is presented as the hazard ratio (HR) and its 95% confidence interval (CI). The cumulative patient survival rate was calculated using Kaplan–Meier curves with a log-rank test. A p value of $< .05$ was considered statistically significant. JMP 12.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

3. Results

There were 98 men (54.1%) and 83 women (45.9%), and their median age was 68 years (range, 33–84). The distribution of preoperative BMD according to sex is presented in Fig. 2A (male) and Fig. 2B (female). The median BMD was greater in males than in females (155 vs. 140 HU, $p = .009$). The median BMD in the whole cohort was 152 HU (range, 27–310 HU). The locations of the tumors were perihilar bile duct, distal extrahepatic bile duct, and gallbladder, in 60, 78, and 43 patients, respectively. The median follow-up period was 33.0 months (range, 0.3–152.7). The distribution of preoperative BMD based on an age-matched study is presented in Supplementary Fig. 2.

3.1. Correlations between preoperative BMD and patient age and other sarcopenic factors

There was a significant negative correlation between BMD and patient age ($R = -0.402$, $p < .001$; Fig. 3A). Although the correlations were weak, there were also significant relationships between BMD and PMI ($R = 0.248$, $p < .001$; Fig. 3B), SMI ($R = 0.180$, $p = .015$; Fig. 3C), and IMAC ($R = -0.325$, $p < .001$; Fig. 3D). No significant correlations were observed between BMD and VSR ($R = 0.118$, $p = .115$; Fig. 4E) or body mass index ($R = -0.134$, $p = .072$; Fig. 3F).

3.2. Cut-off values for BMD

Because the ranges of BMD in male and female patients are quite different, cut-off values were established for each using ROC curve analysis. The cut-off values for BMD in males and females were both 169 HU (area under the curve [AUC], 0.600; sensitivity = 76%, specificity = 58% for males, AUC, 0.611; sensitivity = 88%, specificity = 44% for females). Based on these cut-off values, patients were assigned to one of two groups, low BMD ($n = 124$) or normal BMD ($n = 57$).

3.3. Preoperative characteristics of patients classified by BMD

The preoperative clinicopathologic characteristics of patients are shown in Table 1. The median age was significantly older (70 vs. 64 years, $p = .002$) and the ratio of females to males was significantly higher (52.4 vs. 31.6%, $p = .008$) in the low BMD group. With regard to tumor location, more gallbladder cancer was included in the low BMD group (29.8 vs. 10.5%). With regard to sarcopenic factors, more patients with high IMAC were included in the low BMD group (66.1 vs. 45.6%, $p = .009$). There were no differences in other patient-related factors or tumor-related factors between the two groups.

Age and sex were used to construct the PS model. These factors in addition to tumor location and IMAC were no longer statistically different following PS matching (Table 1). The AUC was 0.70, which indicated good predictive power and confirmed that the variables we selected in our PS model were highly predictive of the patient background characteristics presenting low BMD.

3.4. Postoperative outcomes of patients classified by BMD

Intraoperative characteristics and postoperative outcomes of PS-matched patients classified by BMD are shown in Table 2. There were no differences in the type of operations, operative time, intraoperative blood loss, resection curability, postoperative complications, operative mortality, or adjuvant chemotherapy between the two groups. With regard to postoperative complications, no differences were observed even after classifying by the type of operations.

3.5. Overall and recurrence-free survival rates after resection of extrahepatic biliary malignancies

Overall survival (OS) and recurrence-free survival (RFS) curves for patients classified by BMD in the PS-matched cohort are shown in Fig. 4A and B ($n = 104$). The OS (21.2% vs. 53.9% at 5 years, $p < .001$) and RFS rate (21.8% vs. 64.6% at 5 years, $p < .001$) were significantly lower in patients with low BMD compared to those with normal BMD. In addition, disease-specific survival (DSS) was investigated (Supplementary Fig. 2). Patients with low BMD had significantly lower DSS (36.1% vs. 70.3% at 5 years, $p < .001$).

3.6. Risk factors for a poor outcome after resection of extrahepatic biliary malignancies

Risk factor assessment was performed in the PS-matched cohort ($n = 104$). In addition to patient-related factors, operative factors, and tumor-related factors, the analysis included sarcopenic factors because these factors may affect survival. The variable 'adjuvant chemotherapy' was excluded from the multivariable analysis due to the correlation with nodal metastasis. The multivariable analysis identified high IMAC (HR: 2.050, 95% CI: 1.164–3.744, $p = .013$), low

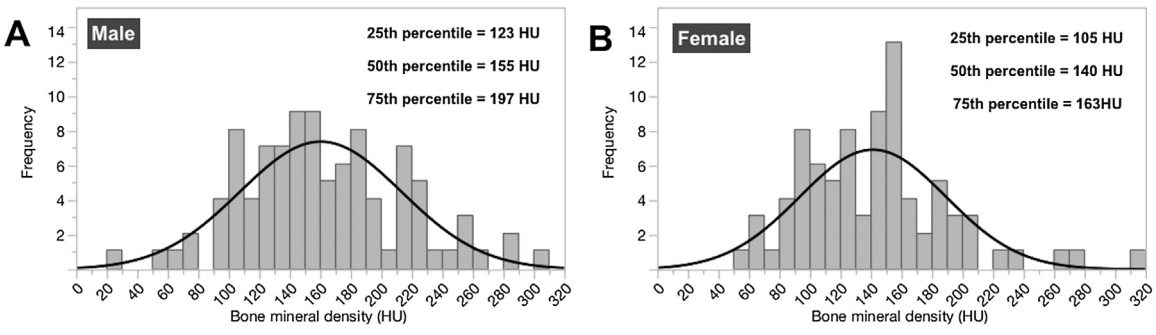

Fig. 2. Distribution of preoperative BMD among extrahepatic biliary cancer patients according to sex. A) Male. B) Female. BMD, bone mineral density; HU, Hounsfield Unit.

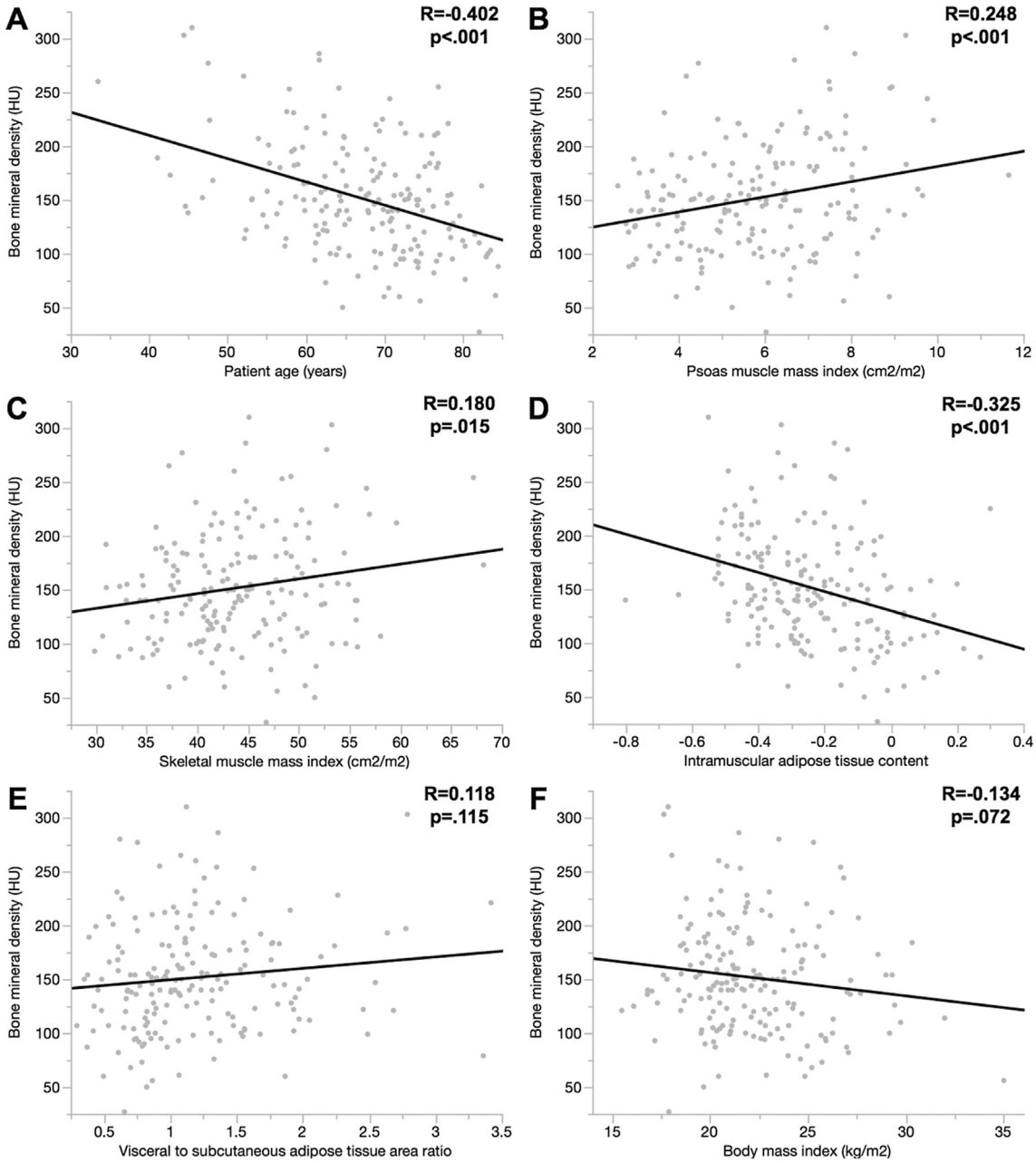

Fig. 3. The correlations between BMD and the perioperative factors. A) A significantly negative relationship was observed between BMD and patient age. B) A significant positive relationship was observed between BMD and PMI. C) A significant positive relationship was observed between BMD and SMI. D) A significant negative relationship was observed between BMD and IMAC. E) No significant correlation was observed between BMD and VSR. F) No significant correlation was observed between BMD and BMI. BMD, bone mineral density; BMI, body mass index; IMAC, intramuscular adipose tissue content; PMI, psoas muscle mass index; SMI, skeletal muscle mass index; VSR, visceral to subcutaneous adipose tissue area ratio.

BMD (HR: 2.343, 95% CI: 1.362–4.129, p = .002), large tumor burden (HR: 1.831, 95% CI: 1.010–3.465, p = .046), and nodal metastasis (HR: 2.020, 95% CI: 1.102–3.719, p = .023) as four significant independent risk factors for death after resection of biliary cancer, and high levels of CA19-9 (HR: 4.184, 95% CI: 2.232–7.776, p=<.001), low BMD (HR: 3.648 95% CI: 1.986–6.990, p=<.001), microvascular invasion (HR: 1.938, 95% CI: 1.023–3.672, p = .042), and nodal metastasis (HR:1.943, 95% CI: 1.076–3.526, p = .028) as four independent risk factors for the recurrence of extrahepatic biliary cancer after the operation (Table 3).

Thus, low BMD was identified as an independent risk factor for OS and RFS after the resection of extrahepatic biliary cancers.

4. Discussion

The present study showed that preoperative low BMD, in addition to the known tumor-specific prognostic factors and sarcopenia factors [10], was an independent risk factor for mortality in patients with extrahepatic biliary cancers after resection. This is the first study to identify the association between BMD and postoperative survival among biliary cancers.

Osteopenia is a condition represented by decreased BMD. While DXA is a widely accepted tool for defining osteoporosis or osteopenia, several previous studies reported the predominance of quantitative CT in predicting vertebral fractures and serial

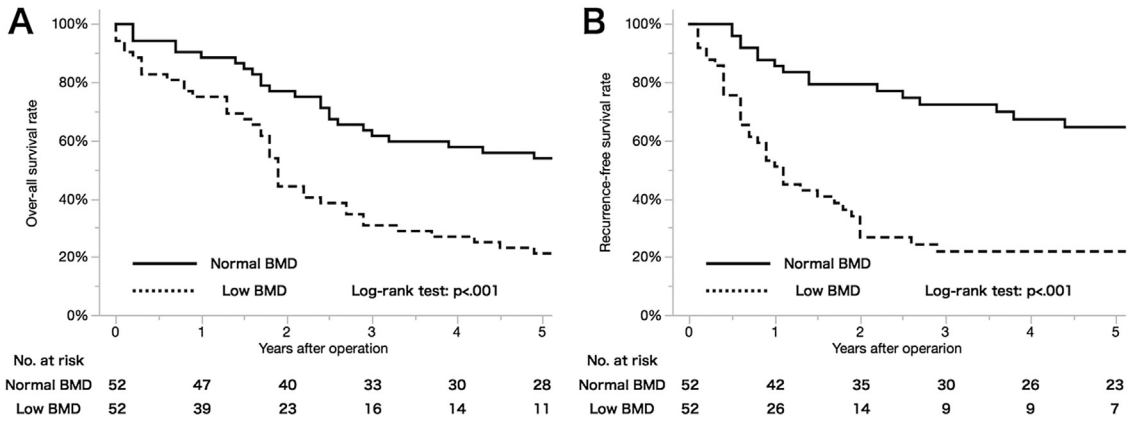

Fig. 4. Patient survival. A) Overall survival rates after operation, classified by BMD. B) Recurrence-free survival rates after operation, classified by BMD. BMD, bone mineral density.

Table 1
Clinicopathologic characteristics of patients with low BMD and normal BMD.

Variables	Unmatched			PS-matched		
	Low BMD n = 124	Normal BMD n = 57	p value	Low BMD n = 52	Normal BMD n = 52	p value
Patient preoperative factors						
Age, years	70 (44–84)	64 (33–78)	.002*	67 (44–80)	64 (41–78)	.587
Sex, female	65 (52.4)	18 (31.6)	.008*	13 (25.0)	18 (34.6)	.284
BMI, kg/m^2			.457			.274
BMI < 20	27 (21.8)	16 (28.1)		14 (26.9)	15 (28.9)	
BMI = 20-25	77 (62.1)	31 (54.4)		34 (65.4)	28 (53.9)	
BMI>25	20 (16.1)	10 (17.5)		4 (7.7)	9 (17.3)	
Albumin, g/dL	3.9 (2.3–4.8)	3.9 (2.9–5.0)	.101	3.9 (2.9–4.7)	3.9 (2.9–4.8)	.169
CRP, mg/dL	0.2 (0–10.9)	0.3 (0–6.6)	.921	0.3 (0–10.9)	0.3 (0–6.6)	.927
CA19–9, U/mL	55.7 (1–11684)	42.3 (1–9858)	.239	52.0 (1–11684)	43.2 (1–9858)	.448
Comorbidities						
Hypertension	36 (29.0)	13 (22.8)	.381	15 (28.9)	13 (25.0)	.658
Diabetes mellitus	18 (14.5)	9 (15.8)	.823	7 (13.5)	9 (17.3)	.587
Cardiac disease[a]	14 (11.3)	6 (10.5)	.879	6 (11.5)	6 (11.5)	1.000
Preoperative biliary drainage	94 (75.8)	50 (87.7)	.065	40 (76.9)	46 (88.5)	.120
Sarcopenic factors						
Low PMI	50 (40.3)	15 (26.3)	.064	24 (46.2)	15 (28.9)	.067
Low SMI[b]	8 (6.5)	5 (8.8)	.551	6 (11.5)	5 (9.6)	1.000
High VSR	72 (58.1)	31 (54.4)	.643	27 (51.9)	30 (57.7)	.554
High IMAC	82 (66.1)	26 (45.6)	.009*	31 (59.6)	26 (50.0)	.324
Tumor factors						
Tumor location, (PHBD/DBD/GB)	36/51/37	24/27/6	.009*	16/23/13	23/24/5	.083
UICC stage, I/II/III/IV						
Perihilar bile duct, I/II/III/IV	2/17/14/3	1/15/8/0	.276	0/7/8/1	1/14/8/0	.274
Distal bile duct, I/II/III/IV	15/33/1/2	11/15/0/1	.625	7/15/0/1	10/14/0/0	.381
Gallbladder, I/II/III/IV	1/10/13/13	0/3/2/1	.632	0/2/4/7	0/2/2/1	.357
Tumor burden >2 cm	82 (66.1)	29 (50.9)	.052	34 (65.4)	26 (50.0)	.112
Poorly differentiated tumor	20 (16.1)	7 (12.3)	.493	7 (13.5)	6 (11.5)	.767
Microvascular invasion	47 (37.9)	21 (36.8)	.891	21 (40.4)	20 (38.5)	.841
Nodal metastasis, yes	55 (44.4)	19 (33.3)	.158	26 (50.0)	17 (32.7)	.072

Values are either median ± range or numbers of patients (%).
*p value < .05.
BMD, bone mineral density; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CRP, C-reactive protein; DBD, distal bile duct; GB, Gallbladder; IMAC, intramuscular adipose tissue content; PHBD, perihilar bile duct; PMI, psoas muscle mass index; SMI, skeletal muscle mass index; VSR, visceral to subcutaneous adipose tissue area ratio; UICC, union for International Cancer Control.
[a] Cardiac disease is defined as history of myocardial infarction, chronic heart failure, angina pectoris, or arrhythmia.
[b] Fisher's exact test was applied. Other comparisons were performed by the χ^2 test for categorical variables.

measuring for bone fragility, with better sensitivity compared to DXA, as the trabecular bone can be selectively measured and overlying densities (such as aortic calcifications) can be excluded from the study [14,15,21]. Moreover, DXA is not widely available in all healthcare systems. In contrast, BMD can be assessed easily and accurately together with other important parameters, including PMI, SMI, IMAC, and VSR, from the CT scans obtained for other indications without exposing patients to additional ionizing radiation [16]. However, a recent systematic review has concluded that direct HU measurement from CT scans does not necessarily correlate with DXA and has the potential to be used opportunistically for screening [22]; further investigations are necessary for better defining osteopenia.

Low BMD had correlations not only with age and sex but also with sarcopenia factors such as low PMI, low SMI, and high IMAC in our analysis. The association between sarcopenia and low BMD has been cited in previous studies [13,23,24]. There is evidence that deterioration of the musculoskeletal system is characterized by

Table 2
Surgical outcomes of patients with low BMD and normal BMD.

Variables	PS-matched		
	Low BMD n = 52	Normal BMD n = 52	p value
Intraoperative characteristics			
Type of surgery			.548
PD	15 (28.9)	18 (34.6)	
HPD	8 (15.4)	6 (11.5)	
Major HTx[a]	21 (40.4)	24 (46.2)	
Minor HTx[b]	8 (15.4)	4 (7.7)	
Intraoperative blood loss, ml	1300 (116–1179)	1225 (77–3700)	.450
Operative time, min	488 (174–1156)	579 (376–1105)	.904
Resection curability, (R0/R1-2)	31/21	30/22	.842
Postoperative outcomes			
Postoperative complications[c]	24 (46.2)	21 (40.4)	.553
HPD[d]	4 (50.0)	5 (83.3)	.300
PD[d]	9 (60.0)	6 (33.3)	.170
Major HTx	10 (47.6)	9 (37.5)	.493
Minor HTx[d]	1 (12.5)	1 (25.0)	1.000
Liver failure	10 (19.2)	10 (19.2)	1.000
HPD[d]	4 (50.0)	3 (50.0)	1.000
Major HTx[d]	5 (23.8)	7 (29.2)	.746
Minor HTx[d]	1 (12.5)	0 (0)	1.000
Pancreatic fistula	12 (23.1)	8 (15.4)	.318
HPD[d]	3 (37.5)	3 (50.0)	1.000
PD[d]	8 (53.3)	5 (27.8)	.169
Major HTx[d]	1 (4.8)	0 (0)	.467
Bile leakage	7 (13.5)	11 (21.2)	.298
HPD[d]	0 (0)	2 (33.3)	.165
PD[d]	1 (6.7)	0 (0)	.455
Major HTx	6 (28.6)	8 (33.3)	.759
Minor HTx[d]	0 (0)	1 (25.0)	.333
Operative mortality ≤30 days[d]	3 (5.8)	0 (0)	.243
Adjuvant chemotherapy	26 (50.0)	22 (42.3)	.431

Values are either median ± range or numbers of patients (%).
HPD, hepatopancreatoduodenectomy; HTx, hepatectomy; PD, pancreatoduodenectomy; R0, grossly complete resection with microscopically negative margins; R1, grossly complete resection with microscopically positive margins; R2, incomplete resection with macroscopically residual tumor.
[a] Resection of ≥3 hepatic segments.
[b] Resection of <3 hepatic segments.
[c] Clavien-Dindo grade ≥3.
[d] Fisher's exact test was applied. Other comparisons were performed by the χ^2 test for categorical variables.

bone loss and muscle wasting in parallel and that these processes share common determinants. Both cause major personal morbidity, increase healthcare costs, and reduce quantity/quality of life. Moreover, both are multifactorial in origin, being caused by inflammation, hormonal and/or nutritional deficits, toxins, and sedentariness [25]. Pereira et al. [13] reported that older Latin American men (aged ≥60 years) with sarcopenia were more likely to have osteopenia than those with normal skeletal muscle mass, with an odds ratio of 9.0. Verschueren et al. [26] reported that European men (aged 40–79) with sarcopenia had increased risk for osteoporosis, with an odds ratio of 3.0. Thus, it could be argued that they are the same disease manifesting in different physiological systems [23].

Preoperative low BMD did not increase post-operative complications but correlated with reduced OS and RFS following the resection of biliary cancers. The etiology of bone loss in cancer patients is likely multifactorial, with age-related bone loss and cancer therapy-induced bone loss both playing roles [27]. Inflammation is a hallmark of cancer and results in accelerated bone loss [28]. Cyclooxygenase, prostaglandin E2, and other mediators have been identified for their role in cancer-associated inflammation and hastening of bone density decline [29]. Lifestyle factors commonly encountered in patients with advanced cancer such as fatigue, sedentariness, low dietary calcium intake, weight loss, frailty, and malnutrition will additionally contribute to rapid bone loss. Decreased mechanical loading also plays a role in cancer-related bone loss, often caused by cancer-related fatigue and sedentariness [30,31]. As sarcopenia has been identified in older adults as a contributing element in fracture risk [32], sarcopenia and osteopenia may affect or cause each other. We hypothesized that they both reflect chronic inflammation [33] or a weakened immune system [34] and as a result, enhanced carcinogenesis and that they negatively impact the survival of patients with cancer [35].

It is important to consider whether the present cut-off values for ROI-acquired BMD is adequate to define osteopenia. Pickhardt et al. [21] reported a trabecular ROI attenuation cut-off of 160 HU or less was 90% sensitive at L1 and a threshold of 110 HU was more than 90% specific for distinguishing osteoporosis from osteopenia and normal BMD (non-osteoporosis) in 1867 adults (1511 women, 356 men; mean age, 59.2 years). The aforementioned study by Sharma et al. [16] used 160 HU at Th11 as the cut-off value to evaluate osteopenia. Notably, both studies adopted the same threshold for both men and women, even though the distribution of BMD differed. In the present study, the cut-off values for BMD was determined based on ROC curves, which is considered to be a more accurate and objective method than the reported threshold or the use of standard deviation to set cut-off values. As a result, the cut-off value we set was reasonable, and ROI attenuation of approximately 160–170 HU might predict prognosis following major hepato-biliary surgery regardless of patient sex.

We acknowledge the limitations of our study. First, not only age and sex but also race may affect BMD. Generally, Asians have lower BMD than Caucasians or Africans regardless of age or sex [36–39]. As our cohort only included an Asian population, the distribution of BMD and cut-off values may differ between institutions in different countries. Our findings must be confirmed in other trials

Table 3
Univariable and multivariable analyses of risk factors for overall survival and recurrence-free survival following resection of extrahepatic biliary cancer (Cox proportional hazards model).

Variables	Risk factors for overall survival				Risk factors for recurrence-free survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Preoperative factors								
Age ≥70 year	0.856 (0.484–1.462)	.575			0.743 (0.407–1.302)	.305		
Sex, female	0.926 (0.514–1.603)	.789			0.866 (0.461–1.542)	.634		
Body mass index								
>25 kg/m^2 (vs. 20–25)	0.567 (0.214–1.253)	.171			0.787 (0.319–1.678)	.556		
<20 kg/m^2 (vs. 20–25)	0.691 (0.368–1.237)	.219			0.674 (0.342–1.250)	.216		
Albumin <3.5 g/dL	1.609 (0.763–3.072)	.198			1.365 (0.623–2.670)	.413		
CRP ≥1.0 mg/dL	1.762 (0.971–3.064)	.062			1.372 (0.705–2.501)	.337		
CA19-9 ≥200 U/mL	3.150 (1.429–6.213)	.006*	2.081 (0.906–4.369)	.082	5.797 (2.678–11.466)	<.001*	4.184 (2.232–7.776)	<.001*
Low PMI	1.711 (0.998–2.891)	.051			1.872 (1.072–3.227)	.028*	1.640 (0.893–2.985)	.110
Low SMI	0.420 (0.102–1.138)	.095			0.636 (0.192–1.558)	.353		
High VSR	1.141 (0.677–1.960)	.623			0.956 (0.557–1.656)	.871		
High IMAC	2.404 (1.398–4.299)	.001*	2.050 (1.164–3.744)	.013*	1.843 (1.066–3.268)	.029*	1.281 (0.700–2.400)	.425
Low BMD	2.488 (1.466–4.321)	<.001*	2.343 (1.362–4.129)	.002*	3.675 (2.080–6.753)	<.001*	3.648 (1.986–6.990)	<.001*
Operative factors								
Blood loss ≥1000 ml	1.785 (1.028–3.237)	.040*			1.633 (0.927–2.991)	.091		
Postoperative complication (Clavien-Dindo grade≥3)	1.552 (0.921–2.621)	.099			0.910 (0.517–1.567)	.736		
Oncological factors								
Location of tumor								
Distal bile duct (vs. perihilar bile duct)	1.412 (0.783–2.610)	.253			1.341 (0.734–2.517)	.343		
Gallbladder (vs. perihilar bile duct)	2.023 (0.967–4.117)	.061			1.799 (0.793–3.868)	.154		
Tumor burden >2 cm	2.623 (1.502–4.811)	<.001*	1.831	.046*	1.936 (1.114–3.466)	.019*	1.575 (0.828–3.057)	.167
Poorly differentiated tumor	1.806 (0.860–3.424)	.112			1.876 (0.856–3.667)	.110		
Microvascular invasion	1.938 (1.148–3.263)	.013*	1.409	.240	1.762 (1.015–3.031)	.044*	1.938 (1.023–3.672)	.042*
Nodal metastasis	3.104 (1.839–5.325)	<.001*	2.020	.023*	2.598 (1.510–4.492)	<.001*	1.943 (1.076–3.526)	.028*
Surgical radicality R1/2	1.990 (1.186–3.362)	.009*	1.484	.154	1.449 (0.836–2.486)	.184		
Adjuvant chemotherapy	1.309 (0.776–2.210)	.312			2.500 (1.438–4.478)	.001*	—[a]	—[a]

*p value < .05.
BMD, bone mineral density; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CRP, C-reactive protein; IMAC, intramuscular adipose tissue content; PMI, psoas muscle mass index; R0, grossly complete resection with microscopically negative margins; R1, grossly complete resection with microscopically positive margins; R2, incomplete resection with macroscopically residual tumor; SMI, skeletal muscle mass index; VSR, visceral to subcutaneous adipose tissue area ratio.
[a] Adjuvant chemotherapy' was excluded from the multivariate analysis due to the correlation with nodal metastasis.

at other institutions, preferably in a prospective manner. Second, the optimal anatomic landmark for evaluating BMD remains unclear. Samelson et al. [15] reported that the age-related decline in the spine is greater in the lumbar than the thoracic region, and therefore, the lumber spine BMD is more useful for predicting fracture. Considering this, the thoracic region would be suitable for measuring BMD in cancer patients for predicting prognosis because the thoracic region might reflect the influence of background diseases more accurately. Further, we should note that the incidence of vertebral fracture has a bimodal distribution with peak frequencies occurring at vertebral bodies T7-T8 and T12-L1 [40]. Third, this study did not provide clear information regarding osteopenia prevention as osteopenia is a new concept in the oncology field. While exercise and dietary intake of calcium and vitamin D are encouraged [41], their short-term and long-term effects in cancer patients remain unclear and need investigation. Finally, this study failed to distinguish osteoporosis from osteopenia; different stages of bone fragility were analyzed together. The possible different influences on cancer that osteoporosis and osteopenia possess should be investigated in another study with different design.

Despite these limitations, our study found a novel association between BMD and postoperative survival among biliary cancer patients. Given the growing number of older cancer patients, we would consider that a recommendation for BMD screening in population with cancer should be further highlighted in oncology and the supportive oncology field.

In conclusion, the preoperative BMD was related to postoperative survival in patients undergoing resection of extrahepatic biliary cancer. Along with tumor-specific prognostic factors and sarcopenia factors, preoperative evaluation of osteopenia may be useful for risk stratification and clinical decision making for patients with biliary cancer.

Statement of authorship

S.Yao and T.Kaido designed the study and wrote the draft. S.Yao, S.Okumura, S.Iwamura, Y.Miyachi, H.Shirai, A.Kobayashi, and Y.Hamaguchi acquired the data. N.Kamo and S.Yagi contributed to editing the manuscript. R.Uozumi revised the manuscript as an expert statistician. S.Uemoto supervised the study design, revised the manuscript and approved the version to be submitted.

Conflict of interest

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Appendix A. Supplementary data

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