World J Surg (2019) 43:920–928
https://doi.org/10.1007/s00268-018-4861-x

ORIGINAL SCIENTIFIC REPORT

Bone Mineral Density as a Risk Factor for Patients Undergoing Surgery for Hepatocellular Carcinoma

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Published online: 21 November 2018

Abstract

Background We have reported the impact of sarcopenia and body composition on patients undergoing hepatectomy for hepatocellular carcinoma (HCC). However, the impact of bone mineral density (BMD) on outcomes after hepatectomy for HCC and correlation with other parameters including sarcopenia are unclear.

Methods We retrospectively analyzed 465 patients who underwent primary hepatectomy for HCC between April 2005 and March 2015. We analyzed the plain CT images at the level of the eleventh thoracic vertebra with the region of interest and defined as preoperative BMD.

Results In this cohort, male (n = 367) and female (n = 98) patients showed significant heterogeneity in age, body composition markers, tumor factors, peri-operative parameters and so on. The median preoperative BMD in male and female patients was 155 and 139 HU, respectively ($P = 0.005$). BMD was negatively correlated with age in female ($r = -0.590$, $P < 0.001$) and intramuscular adipose tissue content in both male and female ($r = -0.332$ and -0.359, respectively, $P < 0.001$). For males, BMD < 160 HU was associated with worse cancer-specific survival post-hepatectomy ($P = 0.015$). In contrast, females were not ($P = 0.135$). For male patients, multivariate analysis identified low BMD as an independent risk factor for death (hazard ratio 1.720, 95% confidence interval 1.038–2.922, $P = 0.035$) after hepatectomy for HCC.

Conclusion Preoperative low BMD was an independent risk factor for cancer-specific mortality after hepatectomy for HCC.

Abbreviation

AFP	Alpha-fetoprotein
AUC	Area under the curve
BMD	Bone mineral density
CI	Confidence interval
CT	Computed tomography
DXA	Dual-energy X-ray absorptiometry
HBs Ag	Hepatitis B virus antigen
HCC	Hepatocellular carcinoma
HCV Ab	Hepatitis C virus antibody
HU	Hounsfield unit
IMAC	Intramuscular adipose tissue content
IQR	Interquartile range
PMI	Psoas muscle index
ROC	Receiver operating characteristic
ROI	Region of interest
SD	Standard deviation
Th11	Eleventh thoracic vertebra
VSR	Visceral-to-subcutaneous adipose tissue ratio

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Introduction

Predicting the prognosis of patients with hepatocellular carcinoma (HCC) is imperative for the accurate assignment of treatment strategy [1–3]. In the past, factors associated with the long-term outcomes of HCC could be classified into three categories: (1) tumor variables (size, multi-nodularity, vascular invasion), (2) underlying liver function (Child–Pugh score) and (3) physiologic reserve (i.e., Eastern Cooperative Oncology Group performance status) [1, 4–9]. In addition, postoperative complications [10], portal venous pressure [11] and bile duct tumor thrombus [12] have been proposed as risk factors for death after hepatectomy.

Sarcopenia, defined as a progressive and generalized loss of skeletal muscle mass and strength [13], has recently been recognized as a new risk factor that adversely affect the postoperative outcome for patients with HCC [14–17]. Moreover, we previously reported that preoperative body composition, including psoas muscle mass, muscle quality and visceral adiposity, were closely related to outcomes after various types of surgeries, including liver transplantation, hepatectomy and pancreatectomy [18–22]. Most recently, we demonstrated that preoperative sarcopenic obesity was an independent risk factor for death and recurrence after surgery for HCC [23].

The World Health Organization defines bone mineral density (BMD) as a T-score evaluated by dual-energy X-ray absorptiometry (DXA) of the spine or hip [24, 25]. Currently, Sharma et al. reported that low BMD measured by the CT attenuation value in the trabecular bone at the eleventh thoracic vertebral (Th11) was an independent predictor of post-liver transplant mortality in HCC patients [26]. However, the relationship between preoperative BMD level and outcome after hepatectomy for HCC is unclear.

In the present study, therefore, we investigated the relationship between preoperative BMD and body composition markers and the clinical significance of low BMD in patients undergoing hepatectomy for HCC.

Patients and methods

A total of 522 patients underwent primary hepatectomy for HCC at Kyoto University Hospital between April 2005 and March 2015. Fifty-seven patients who did not undergo preoperative abdominal plain computed tomography (CT) at umbilical level were excluded from this study. As a result, 465 patients (367 males, 98 females) were enrolled in this study. Patients were followed until November 31, 2017. The study was approved by the Ethics Committee of Kyoto University and was conducted in accordance with the Declaration of Helsinki of 1996.

Data collection

The following data were retrospectively collected from patient charts: demographic data (age, sex, body mass index [BMI]); date and type of hepatectomy; date of HCC recurrence and last follow-up or death; Child–Pugh classification; preoperative alpha-fetoprotein (AFP), serum total bilirubin, serum albumin, prothrombin time and platelet counts; status of hepatitis B virus antigen (HBs Ag) and hepatitis C virus antibody (HCV Ab); preoperative imaging data, including size and number of lesions; postoperative complications according to Clavien–Dindo classification; BMD; and intramuscular adipose tissue content (IMAC), psoas muscle index (PMI) and visceral-to-subcutaneous adipose tissue ratio (VSR). The measurements of IMAC, PMI and VSR have been described previously [18, 23].

BMD measurements were taken as follows. All preoperative CT imaging was obtained within 2 months before surgery with a multi-detector CT scanner (Aquilion 64, Toshiba Medical Systems, Tochigi, Japan). We analyzed cross-sectional, non-contrast plain CT images at the level of the Th11 vertebra with region of interest (ROI) attenuations. BMD was measured according to the methods outlined in the previous reports [26, 27]. BMD was measured using the trabecular bone, calculating the average pixel density within a circle ROI [26, 27]. We avoided placing the ROI near the posterior venous plexus, focal heterogeneity, lesions, such as compression fractures or imaging-related artifacts [27].

Analyzed parameters

First, the characteristics of 465 patients were summarized and the difference of background factors between male and female was evaluated. Second, the correlations between BMD and age or other body composition markers (IMAC, PMI and VSR) were investigated. Third, postoperative survival and recurrence-free survival were investigated according to BMD. For long-term postoperative survival, we chose cancer-specific survival, instead of overall survival, to focus on the factors associated with HCC. Finally, the prognostic factors associated with worse postoperative survival were analyzed.

Statistical analysis

Continuous data are expressed as the median and interquartile range (IQR) and were compared using the

Wilcoxon rank-sum test. Categorical data are expressed as counts and percentages and were compared with the Chi-square test. For the analysis of correlation, correlation coefficients less than −0.3 or more than 0.3 were defined as statistically significant. Cancer-specific and recurrence-free survival rates were calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. Any variables identified as significant ($P < 0.05$) or with $P < 0.10$ in the univariate analysis were considered a candidate for multivariate Cox regression analysis. The results of the multivariate analysis are shown as hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical data were generated using JMP Pro 13.0.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The baseline characteristics for the patients ($n = 465$) are shown in Table 1. In this cohort, male ($n = 367$) and female ($n = 98$) patients showed significant heterogeneity in terms of preoperative parameters (age, BMI, platelet counts, AFP, positive HCV Ab, PMI, IMAC and VSR) tumor factors (size ≥ 3 cm), intra-operative parameters (more than segmentectomy, operation time and blood loss) and postoperative parameters (pathological stage ≥ III). Also, there was a significant difference in preoperative BMD between male and female patients (155 HU vs. 139 HU, $P < 0.001$).

Correlation between BMD and various parameters

Among the total cohort (including male and female patients), BMD had a significant negative correlation with age ($r = -0.364$; Fig. 1a). When separated by gender, BMD was not correlated with age in male patients ($r = -0.298$; Fig. 1b). In contrast, significant correlation was found in female patients ($r = -0.590$; Fig. 1c). As to body composition markers, BMD was negatively correlated with IMAC among the total cohort ($r = -0.355$; Fig. 2a), male ($r = -0.332$; Fig. 2b) and female patients ($r = -0.359$; Fig. 2c) separately. However, there was no significant correlation between BMD and PMI or VSR for total cohorts ($r = 0.147$ and −0.119), male ($r = 0.084$ and −0.155) or females ($r = 0.214$ and −0.280).

Cutoff value of BMD and survival after hepatectomy

According to the previous reports [27], we set the cutoff value of BMD less than 160 HU in order to evaluate the association between preoperative BMD and cancer-specific survival after hepatectomy. The cancer-specific survival among total cohort was significantly lower in patients with BMD < 160 HU than patients with BMD ≥ 160 HU ($P = 0.038$; Fig. 3a). When separated by gender, low BMD was associated with worse cancer-specific survival in male patients ($P = 0.015$; Fig. 3b) and not in female patients ($P = 0.135$; Fig. 3c). However, low BMD was not associated with worse recurrence-free survival after hepatectomy in total ($P = 0.523$), male ($P = 0.809$) and female patients ($P = 0.402$).

Comparison of patient characteristics between low and normal BMD in male

Next, in order to evaluate the factors associated with worse postoperative survival, we compared the various parameters between low and normal BMD among male patients (Table 2). The median age of the patients with low BMD was 4 years higher than the patients with normal BMD ($P < 0.001$). The patients with low BMD had lower PMI ($P = 0.045$) and higher VSR ($P = 0.002$) than patients with normal BMD. IMAC was also higher in patients with low BMD ($P < 0.001$). Conversely, the patients with equal or more than four tumors ($P = 0.016$) and, though the difference did not reach statistical significance, liver cirrhosis and chronic hepatitis ($P = 0.072$) were more frequent in patients with normal BMD. Other than these factors, there was no significant difference between low and normal BMD in male.

Risk factors for mortality after hepatectomy for HCC

Finally, we assessed the risk factors for mortality in male patients. According to the previous reports [1, 4–8, 10], we included the following factors into the univariate analysis: age, Child–Pugh class, tumor size, the number of tumors, pathological stage, postoperative complications and body compositions (PMI, VSR and BMD) [15–18, 28]. IMAC was not included in the analysis because it already has a significant correlation with BMD in male patients. The cutoff values of PMI [19] and VSR [15] were determined by previous reports. The univariate analysis showed that the number of tumors ≥ 4 ($P = 0.024$), pathological stage ≥ III ($P < 0.001$), postoperative complication of Clavien–Dindo ≥ III ($P = 0.087$), VSR ≥ 1.33 ($P = 0.007$) and BMD < 160 HU ($P = 0.025$) were potential risk factors for mortality in males. In the multivariate analysis, the number of tumors ≥ 4 (HR 2.282, 95% CI 1.021–4.583, $P = 0.045$), pathological stage ≥ III (HR 2.484, 95% CI 1.475–4.329, $P < 0.001$), VSR ≥ 1.33 (HR 1.695, 95% CI 1.054–2.737, $P = 0.035$) and BMD < 160 HU (HR 1.720, 95% CI 1.038–2.922,

Table 1 Patients' characteristics

	Total (n = 465)	Male (n = 367)	Female (n = 98)	P
Preoperative parameter				
Age, years†	69 (62–75)	68 (61–75)	71 (63–76)	0.026*
BMI, kg/m^2†	23 (21–25)	23 (21–25)	22 (19–28)	0.030*
Child–Pugh class, n (%)				
A	421 (91)	225 (91)	86 (88)	0.303
B	44 (9)	32 (9)	12 (12)	
C	0 (0)	0 (0)	0 (0)	
Platelet count, × 10^3/μl†	145 (105–193)	151 (109–198)	123 (85–163)	<0.001*
Total bilirubin, mg/dl†	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.930
Albumin, g/dl†	3.9 (3.6–4.2)	3.9 (3.6–4.3)	3.9 (3.6–4.1)	1.000
AFP, ng/ml†	21.9 (5.7–236.7)	16.5 (4.9–177.3)	61.5 (10.3–1316.7)	<0.001*
Prothrombin time, s†	12.3 (11.9–12.8)	12.3 (11.8–12.9)	12.4 (12–12.8)	0.654
Positive HBs Ag, n (%)	85 (18)	67 (18)	18 (19)	0.092
Positive HCV Ab, n (%)	222 (48)	158 (43)	64 (65)	<0.001*
BMD, HU†	151 (120–185)	155 (123–188)	139 (104–170)	0.005
PMI, cm^2/m^2†	6.5 (5.3–7.6)	6.9 (5.7–7.8)	4.8 (4.1–5.8)	<0.001*
IMAC†	−0.3 (−0.4 to − 0.2)	−0.3 (−0.4 to −0.3)	−0.2 (−0.3 to −0.1)	<0.001*
VSR†	1.1 (0.8–1.5)	1.2 (0.9–1.6)	0.7 (0.5–1.0)	<0.001*
Tumor factors				
Size ≥ 3 cm, n (%)	309 (66)	259 (71)	50 (51)	<0.001*
The number of tumor ≥ 4, n (%)	35 (8)	27 (7)	8 (8)	0.829
Intra-operative parameter				
More than segmentectomy, n (%)	175 (38)	151 (41)	24 (24)	0.002*
Laparoscopic procedure, n (%)	69 (15)	52 (14)	17 (17)	0.427
Operation time, min†	369 (281–453)	388 (298–466)	307 (250–393)	<0.001*
Blood loss, ml†	752 (358–1400)	810 (385–1542)	497 (243–900)	<0.001*
Postoperative parameter				
Clavien–Dindo grade ≥ III, n (%)	85 (18)	73 (19)	12 (12)	0.105
Pathological stage ≥ III, n (%)	218 (47)	187 (51)	31 (31)	0.001*
Hospital death, n (%)	4 (1)	4 (1)	0 (0)	0.584

BMI Body mass index; *AFP* alpha-fetoprotein; *HBs Ag* hepatitis B surface antigen; *HCV Ab* hepatitis C virus antibody; *BMD* bone mineral density; *PMI* psoas muscle index; *IMAC* intramuscular adipose tissue content; *VSR* visceral-to-subcutaneous adipose tissue ratio. †Data are presented as medians and IQRs. *P < 0.05

P = 0.035) were independent risk factors for cancer-specific mortality in males (Table 3).

Discussion

In this retrospective study, we first showed preoperative low BMD as an independent prognostic factor of mortality after hepatectomy for HCC in male patients, together with the number of tumors ≥ 4, pathological stage ≥ III and VSR ≥ 1.33. On the other hand, for female patients, preoperative low BMD was not associated with long-term prognosis after hepatectomy.

BMD is the most important determinant of bone fragility and susceptibility to fracture [25]. Although the gold standard of BMD measurement is DXA [24], recent studies have considered BMD evaluated with HU from CT scans as an alternative indicator of osteopenia or osteoporosis [27, 29]. Pickhardt and colleagues reported that the CT attenuation threshold of the first lumbar vertebra of less than 160 HU had 90% sensitivity to distinguish osteoporosis from osteopenia and normal BMD as evaluated with DXA [27].

To the best of our knowledge, Sharma et al. were the first to investigate the relationship between low BMD and outcome after liver transplantation for HCC [26]. Their

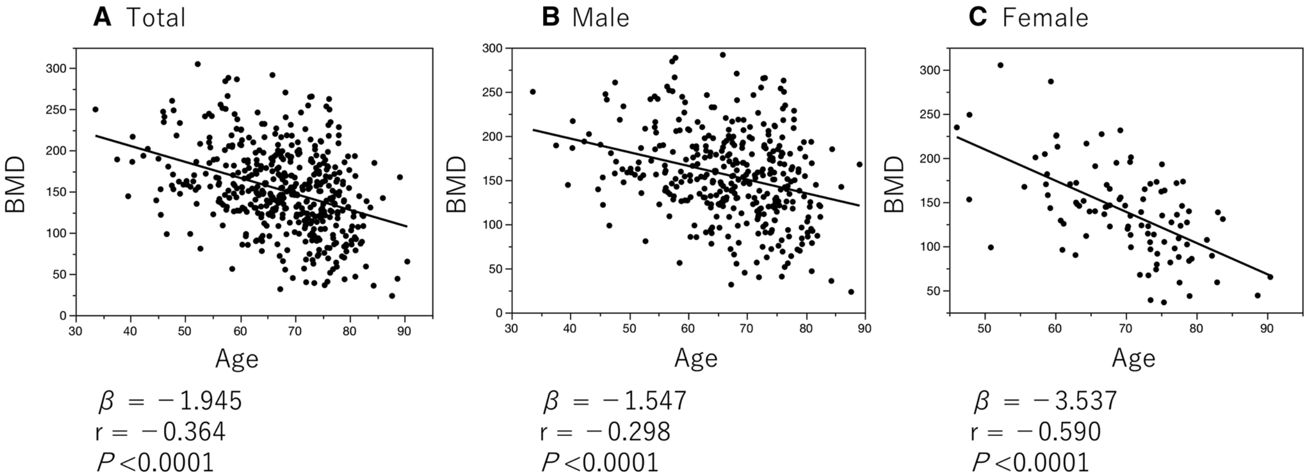


Fig. 1 Correlation between BMD and patients age. Significant negative relationship was observed between BMD and **a** total cohort ($r = -0.364$, $P < 0.001$). **b** The correlation did not reach statistical significance in male ($r = -0.298$, $P < 0.001$). **c** Female patients showed strong correlation between BMD and age ($r = -0.590$, $P < 0.001$)

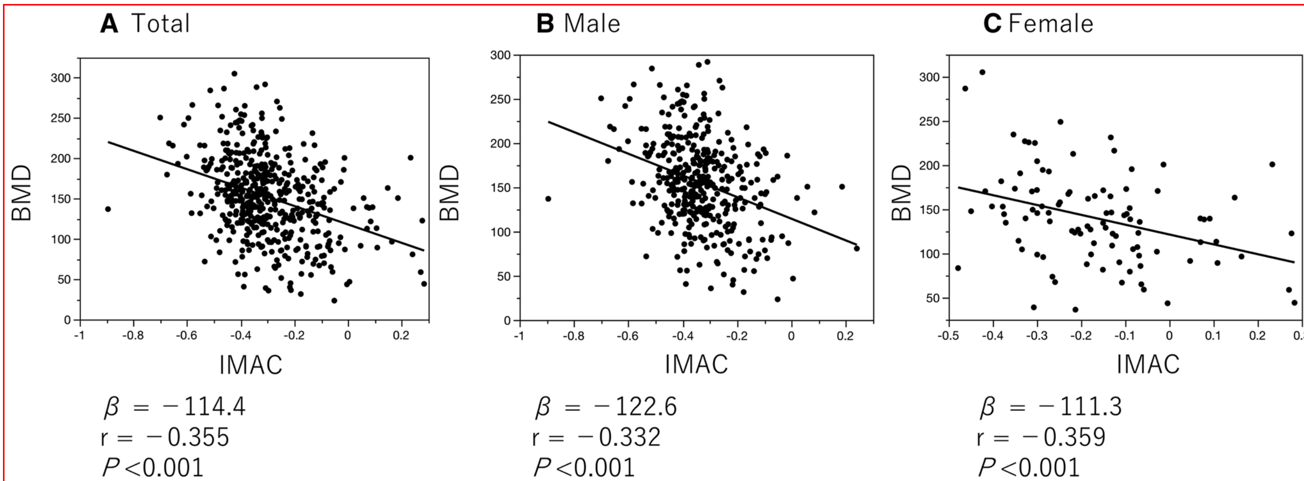
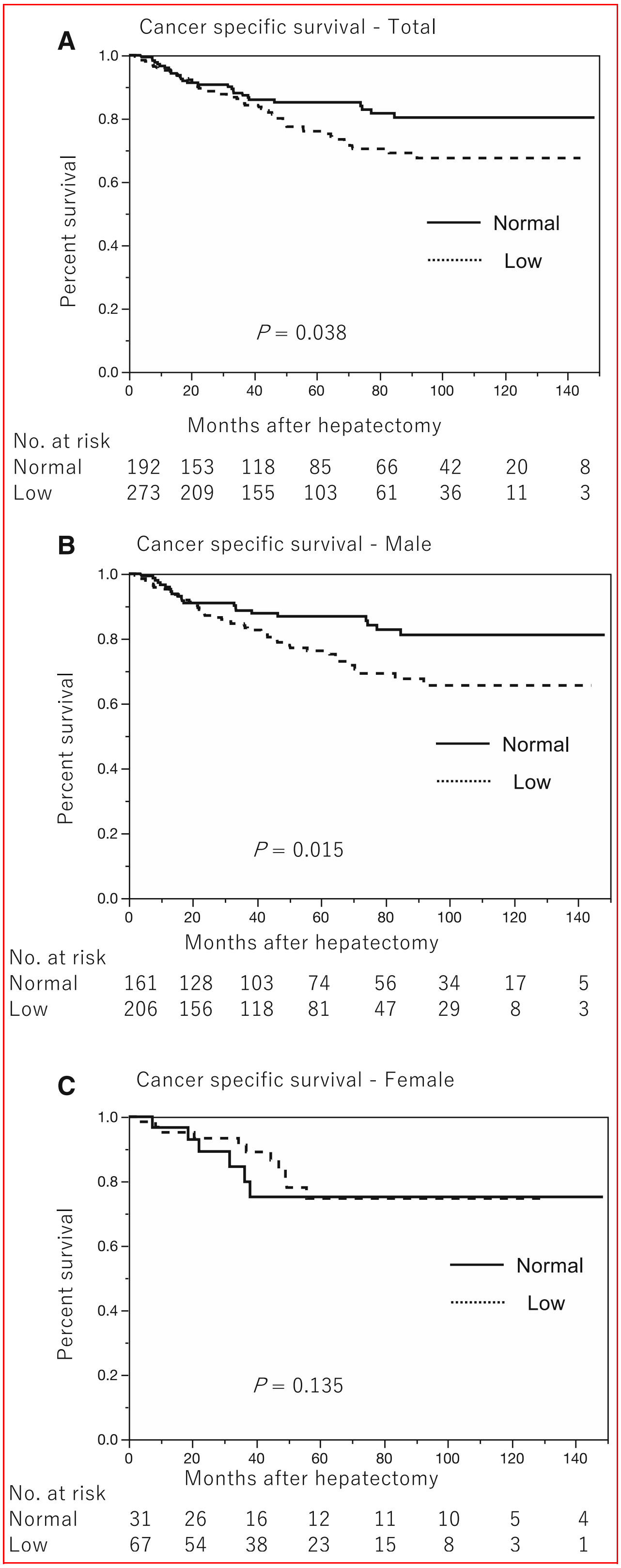


Fig. 2 Correlation between BMD and IMAC. Significant negative relationship was observed between BMD and **a** total ($r = -0.355$, $P < 0.001$), **b** male ($r = -0.332$, $P < 0.001$) and **c** female patients ($r = -0.359$, $P < 0.001$)

results showed that BMD < 160 HU, they set this cutoff value according to the report by Pickhardt et al. [27], and at Th11, trabecular bone was associated with a 2.8-fold higher hazard of mortality in patients who underwent liver transplantation for HCC than those with BMD > 160 HU [26].

In this present study, we used the same cutoff value of BMD (160 HU) as Sharma et al. [26] and showed the association between low BMD and worse cancer-specific postoperative survival for entire cohort. However, we split the cohort by genders and evaluate them separately. This is due to the significant heterogeneity in the various preoperative parameters between male and female (Table 1). As a result, for male patients, BMD less than 160 HU was associated with a 1.7-fold higher hazard of mortality, whereas low BMD was not associated with worse outcomes after hepatectomy for female patients.

One hypothesis for this gender discordance could be the characteristics of bone as an internal organ. Bone is strongly affected by age [25, 30], and the influence of aging varies depending on gender and parts of the body [30, 31]. Age-related changes are reportedly greater in female than male and in the lumbar spine than the thoracic spine [30]. Women lose their bone density and strength at both the thoracic and lumbar spine [30]. In contrast, men lose bone strength only at the lumbar spine [30]. The median age of our female patients was 71 years; therefore, even at the thoracic spine, the BMD of our female patients was so



◀**Fig. 3** Cancer-specific survival rates according to normal (> 160 HU) and low (≤ 160 HU) BMD. Low BMD was associated with worse outcome for **a** total ($P = 0.038$) and **b** male patients ($P = 0.015$). **c** However, the survival rate did not reach statistical significance for female patients ($P = 0.135$)

strongly affected by aging that its effect on postoperative survival may be diminished.

We also evaluated the factors associated with worse postoperative survival in male patients with low BMD. The patients with low BMD had higher age and worse body composition markers (lower PMI, higher IMAC and VSR) compared to the patients with normal BMD. IMAC was well correlated with BMD (Fig. 2b). Although the correlation with BMD did not reach statistical significance, VSR ≥ 1.33 was an independent risk factor associated with postoperative survival (Table 3). Pereira et al. showed even pre-sarcopenia, which is defined by the European Working Group on Sarcopenia in Older People [13], was strongly associated with abnormal BMD [32]. These results may suggest that low BMD reflects the earliest hallmark of the so-called bone loss–sarcopenia–frailty spectrum [26].

The influence of low BMD on worse prognostic outcome may be immunologic matter. Recent studies have investigated the potential cross talk between bone and the immune system, deemed "osteoimmunology" [33, 34]. Interestingly, several investigators have shown that some anti-resorptive drugs, like bisphosphonates or denosumab—a human monoclonal antibody against receptor activator of nuclear factor-kB ligand—have a significant anti-tumor effect through the immune system [35, 36]. Honda et al. showed that zoledronic acid, a nitrogen-containing bisphosphonate, not only suppresses the progression of bone metastasis but can also prevent growth of primary HCC in vitro [37].

From the above, our findings suggest that BMD could not only be used to predict but also improve the outcome of male patients undergoing hepatectomy for HCC. Currently, several medications and exercise are used to increase bone mass and prevent fractures in patients with osteoporosis [38–40]. Although it takes some time before these interventions lead to an increase in BMD, maintaining preoperative BMD levels may contribute to better prognosis after hepatectomy.

This study has several limitations. First, this study was retrospective and conducted in a single institution. Our results should be confirmed in multicenter prospective studies. Second, the number of female patients was limited compared to males. A strong negative correlation was observed between BMD and patient age especially in females. Therefore, for female patients, it might be necessary to investigate the impact of BMD on postoperative survival with consideration of age. For this purpose, we

Table 2 Comparison of patient characteristics between low and normal BMD in male

	Low BMD (n = 206)	Normal BMD (n = 161)	P
Patient factors			
Age, years†	70 (64–75)	66 (58–74)	<0.001*
BMI, kg/m^2†	23 (21–26)	23 (21–25)	0.494
Child–Pugh class, n (%)			
A	186 (90)	149 (93)	0.447
B	20 (10)	12 (7)	
C	0 (0)	0 (0)	
Platelet count, × 10^3/μl†	157 (112–202)	145 (104–192)	0.184
Total bilirubin, mg/dl†	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.457
Albumin, g/dl†	3.9 (3.6–4.2)	4.0 (3.7–4.3)	0.394
AFP, ng/ml†	13.4 (4.9–180.9)	21.9 (4.9–161.6)	0.507
Prothrombin time, s†	12.3 (11.8–12.9)	12.3 (11.9–12.9)	0.886
Positive HBs Ag, n (%)	31 (15)	36 (23)	0.089
Positive HCV Ab, n (%)	86 (42)	72 (45)	0.816
BMD, HU†	127 (98–155)	192 (177–218)	
PMI, cm^2/m^2†	6.6 (5.5–7.8)	7.0 (6.0–7.8)	0.045*
IMAC†	−0.321 (−0.393 to −0.226)	−0.366 (−0.442 to −0.308)	<0.001*
VSR†	1.3 (0.9–1.7)	1.1 (0.8–1.4)	0.002*
Operative factors			
More than segmentectomy, n (%)	88 (42)	63 (39)	0.522
Laparoscopic procedure, n (%)	29 (14)	23 (14)	0.955
Operation time, min†	400 (31–476)	375 (296–445)	0.061
Blood loss, ml†	832 (407–1790)	800 (351–1347)	0.182
Clavien–Dindo grade ≥ III, n (%)	47 (23)	26 (16)	0.116
Tumor factors			
Size ≥ 3 cm, n (%)	152 (73)	107 (66)	0.135
The number of tumor ≥ 4, n (%)	9 (4)	18 (11)	0.016*
Pathological stage ≥ III, n (%)	105 (51)	82 (51)	1.000
Positive portal vein invasion, n (%)	59 (29)	49 (30)	0.818
Positive venous invasion, n (%)	19 (9)	22 (14)	0.243
Positive surgical margin, n (%)	16 (9)	14 (9)	0.925
Poor or undifferentiated tumor, n (%)	59 (28)	37 (23)	0.233
Liver cirrhosis or chronic hepatitis, n (%)	145 (70)	127 (79)	0.072

BMI Body mass index; *AFP* alpha-fetoprotein; *HBs Ag* hepatitis B surface antigen; *HCV Ab* hepatitis C virus antibody; *BMD* bone mineral density; *PMI* psoas muscle index; *IMAC* intramuscular adipose tissue content; *VSR* visceral-to-subcutaneous adipose tissue ratio. †Data are presented as medians and IQRs. *$P < 0.05$

need further investigation using more female patients undergoing hepatectomy for HCC. Third, we also should consider whether the evaluation of BMD using CT attenuation values in Th11 was adequate and reliable. Sharma et al. reported that they chose this anatomic landmark for measuring BMD, because it has the highest likelihood of being available on all abdominal and chest CT scans [26]. In contrast, several authors used lumbar vertebra for measurements of BMD to define osteoporosis [27, 29]. However, as mentioned earlier, the lumbar vertebra is strongly affected by the age-related decline in bone mass more so than the thoracic vertebra in both males and females [30]. Thus, evaluating BMD at the lumbar spine may not be suitable for predicting postoperative outcomes after hepatectomy, particularly in older patients.

In conclusion, this study reveals preoperative low BMD as an independent risk factor for long-term outcomes after hepatectomy in male patients with HCC. This knowledge may help to select appropriate treatment options for

Table 3 Uni- and multivariate analysis of factors associated with survival after hepatectomy

Factors	Univariate analysis		P	Multivariate analysis		P
	Hazard ratio	95% CI		Hazard ratio	95% CI	
Patient age, per 1 year†	0.988	0.965–1.011	0.294			
Child–Pugh class						
A	1.037	0.337–2.164	0.936			
B	0.964	0.462–2.966				
Tumor size, cm						
≥5	1.437	0.892–2.298	0.135			
<5	0.696	0.435–1.121				
Number of tumors						
≥4	2.462	1.139–4.712	0.024*	2.282	1.021–4.583	0.045*
≤3	0.406	0.212–0.878		0.438	0.218–0.980	
Pathological stage						
≥III	2.913	1.761–5.006	<0.001*	2.484	1.475–4.329	<0.001*
≤II	0.343	0.200–0.568		0.403	0.231–0.678	
Postoperative complication						
Clavien–Dindo ≥ III	1.631	0.929–2.733	0.087	1.395	0.786–2.365	0.246
Clavien–Dindo ≤ II	0.613	0.366–1.077		0.717	0.423–1.272	
PMI, cm^2/m^2						
≤6.089	1.344	0.825–2.157	0.231			
>6.089	0.744	0.464–1.212				
VSR						
≥1.33	1.915	1.197–3.075	0.007*	1.695	1.054–2.737	0.030*
<1.33	0.522	0.325–0.835		0.717	0.365–0.949	
BMD, HU						
≤160	1.742	1.073–2.902	0.025*	1.720	1.038–2.922	0.035*
>160	0.574	0.345–0.932		0.581	0.342–0.963	

PMI Psoas muscle index; *IMAC* intramuscular adipose tissue content; *VSR* visceral-to-subcutaneous adipose tissue ratio; *BMD* bone mineral density. † The factor was evaluated as continuous variables. *$P < 0.05$

patients with low BMD before hepatectomy to improve BMD levels, particularly in male patients.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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