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Potential value and advances in research on bone mineral density (BMD) measurement in the auxiliary clinical assessment of hepatocellular carcinoma

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SUMMARY Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer death worldwide and its prognosis is highly heterogeneous, being related not only to underlying chronic liver disease but also to the severity of cancer cachexia. Nutritional factors play a crucial role in influencing the prognosis of HCC. Despite musculoskeletal imbalance being consistently reported as a predictor of perioperative mortality in patients with HCC, this condition is often overlooked in clinical management. Bone mineral density (BMD), which serves as a marker of nutritional status, can be assessed through CT by measuring the pixel density of the vertebral bone. Recent clinical studies have indicated that BMD serves not only as a significant risk factor for development of HCC in cirrhotic patients but also potentially functions as an independent prognostic indicator for post-treatment outcomes in patients with HCC. Preoperative abdominal CT scans provide a convenient and cost-effective method to measure BMD, offering significant assistance in prognostic evaluation of patients with HCC. A thorough grasp of the liver-bone connection, along with the conduct of higher-quality studies and the establishment of standardized methods and cutoff values for BMD measurement, could enhance approaches to manage HCC.

Keywords hepatocellular carcinoma (HCC), bone mineral density, osteopenia, prognosis, liver-bone axis

1. Introduction

Liver cancer is recognized as the second most common cancer worldwide and constitutes the fourth leading cause of cancer-related deaths. According to estimates, there are between 500,000 and 1,000,000 new cases annually, resulting in approximately 600,000 fatalities, with hepatocellular carcinoma (HCC) being the primary type (*1*). The majority of HCC cases arise in the context of chronic liver diseases, notably viral hepatitis, non-alcoholic fatty liver disease (NAFLD), and cirrhosis. Despite advances in screening and therapeutic interventions, the prognosis for liver cancer remains unfavorable due to its aggressive nature and the high incidence of cancer cachexia (*2*). The overall health status of patients with HCC, encompassing their nutritional status, performance status, and the presence of systemic complications, are significantly correlated with their prognosis (*3,4*).

Over the past few years, the investigation of bone mineral density (BMD) has gained considerable prominence within the context of liver diseases, and particularly HCC. The relationship between liver cirrhosis, which often precedes HCC, and the subsequent development of cancer cachexia is closely associated with musculoskeletal nutritional status, encompassing conditions such as sarcopenia and osteoporosis (*5*). A significant volume of research has identified sarcopenia as a vital prognostic factor for HCC (*6*). However, evidence suggests that a low BMD frequently occurs prior to the manifestation of sarcopenia, leading to an increasing emphasis on the prognostic implications of bone changes in the context of liver cancer (*7,8*).

Recent studies have indicated that BMD is not only correlated with the incidence of HCC but also functions as a prognostic marker for HCC outcomes when assessed prior to treatment (*9,10*). A study has indicated that chronic liver disease (CLD) -HCC-cachexia can influence bone degradation and remodeling through various mechanisms, including inflammatory

processes, nutritional status, and hormonal fluctuations (*5*). Moreover, changes in bone may also influence liver function *via* the liver-bone axis (*11*).

The aim of this review was to synthesize the existing literature regarding the prognostic role of BMD in the progression of HCC, while also providing a brief description of the mechanisms involved in the liver-bone axis. Through the assessment of the overall health status of patients diagnosed with HCC and the adoption of integrated treatment approaches, this work seeks to promote additional research in this area and improve patient prognosis.

2. Predicting the development of HCC based on BMD

BMD is typically assessed with dual-energy X-ray absorptiometry (DXA), using T-scores to classify individuals as having osteopenia (1-2.5 standard deviation (SD) below the mean for a young woman at either the femur neck or the lumbar spine) or osteoporosis (more than 2.5 SD below the normal). Both conditions are influenced by various factors, including age, genetic predisposition, hormonal fluctuations, and lifestyle (*12*). In addition, computed tomography (CT)-derived Hounsfield Units (HUs) and quantitative computed tomography (QCT) are widely used diagnostic techniques (*13*). The prevalence of osteoporosis is notably elevated in patients with CLD, with an incidence of 34.5%, and is largely attributable to musculoskeletal malnutrition (*14*). As CLD progresses to HCC, the cumulative impact of cancer cachexia and therapeutic interventions for the tumor significantly aggravate bone health concerns. This situation may suggest the potential use of BMD as a predictive indicator.

A point worth noting is that individuals diagnosed with osteoporosis exhibit an elevated risk of developing liver cancer compared to those without this condition. Moreover, male patients with osteoporosis have a significantly higher risk of liver cancer than their female counterparts. Notably, more pronounced findings were identified in individuals age 64 or younger (*15*). In a retrospective-prospective analysis, BMD at the level of the 12th thoracic vertebra was found to be a risk factor for cirrhosis to progress to HCC in both training Asian (n = 126, P = 0.044) and validation American (n = 274, P = 0.030) populations (*9*). A Kaplan-Meier analysis of 347 cirrhotic patients was performed for BMD at L5 and T12 in association with the time to development of HCC, and the BMD of L5 was found to be an independent predictor, with a cutoff value of 161 HU (HR = 1.676, 95% CI: 1.022-2.748, P = 0.041) (*16*). Both studies suggest that BMD and its decline may be indicative of a higher risk for development of HCC. Researchers hypothesize that reduced BMD, akin to increased visceral fat and obesity, may act as a comprehensive marker of lifestyle factors and impaired liver function. BMD can be combined with other high-risk factors, such as active hepatitis, to create a risk model for HCC. This enables the modification of follow-up strategies for high-risk individuals, promoting the early identification of HCC. While these studies are limited in scale and retrospective in nature, they stimulate discourse regarding the correlation between nutritional status, as reflected by BMD, and the incidence of HCC. Moreover, findings suggest that vertebral BMD is a more significant predictor of HCC risk compared to femoral BMD, which is conventionally utilized to diagnose osteoporosis. The fact that various clinical studies choose different vertebral BMD and cutoff values suggests that there is still a need for more clinical evidence to standardize BMD assessment.

3. Predicting the prognosis of HCC based on BMD

The value of BMD assessment lies not only in the development of HCC but also in predicting its prognosis. Sharma *et al*. first discovered that a low BMD may indicate post-transplant survival in 118 adult recipients of living donor liver transplantation (LDLT) for HCC (HR = 0.90, 95%IC: 0.83-0.99, P = 0.03). After adjusting for sex, dorsal muscle area, number of lesions and age, a BMD below 160 HU was associated with a 2.8-fold higher hazard of post-LT mortality compared to recipients with a BMD higher than 160 HU (HR = 2.87; P = 0.018) (*10*). As shown in Table 1, recent studies increasingly corroborate these findings. Japanese studies on HCC have indicated that BMD is linked to reduced overall survival (OS) and disease-free survival (DFS) not only in LDLT patients (*17*) but also in those undergoing hepatic resection (*18,19*). Osteopenia was confirmed to be an independent risk factor for a lower OS in HCC. Studies involving 102 patients with Barcelona Cancer Liver Classification Stage A (BCLC A) HCC and 227 patients who underwent elective hepatic resection concluded that preoperative osteosarcopenia was a significant independent predictor of DFS (*20*), and osteopenia served as a risk factor for DFS and OS in univariate analysis (*21*). Moreover, studies focusing on patients with intrahepatic cholangiocarcinoma have also indicated the prognostic value of preoperative BMD in outcome assessment (*22,23*). In addition, German studies involving 151 patients who underwent partial hepatectomy for HCC and 908 patients underwent transarterial chemoembolization (TACE) confirmed that osteopenia was an independent risk factor for OS (*24,25*). These studies utilized routine pre-operative CT scans of patients with HCC to evaluate mean pixel density in the mid-vertebral core of the 11th thoracic vertebra. This approach has been proven to be equivalent to DXA and can be used without incurring additional costs, making it a recommended approach (*13*). A CT-attenuation threshold of 160 HU or less was 90% sensitive at the first lumbar vertebra and a threshold of 110 HU was more than 90% specific at distinguishing osteoporosis from osteopenia and normal BMD, which is the reason

Table 1. Summary of clinical studies on BMD reflecting liver cancer prognosis

Country (*Ref.*)	Patient characteristics	Study type	Methodology	Main findings
USA, 2016 Sharma P (*10*)	Adult patients who underwent LDLT for HCC (n = 118)	Retrospective	Preoperative BMD was evaluated with CT of pixel density in the mid-vertebral core of T11. The cutoff value of BMD was less than 160 HU.	BMD was an independent risk factor for post-LT mortality (HR = 0.90, 95%CI: 0.83-0.99, P = 0.03).
Japan, 2020 Toshima T (*17*)	Adult patients who underwent LDLT for HCC (n = 193)	Retrospective	BMD was evaluated with CT in the mid-vertebral core of the T11. Osteopenia was defined as BMD below the standard (308.82–2.49×Age in men and 311.84–2.41×Age in women).	Osteopenia was an independent risk factor for mortality after LDLT (HR = 2.106, 95%CI: 1.102–4.241, P = 0.024).
Japan, 2019 Miyachi Y (*18*)	Adult patients who underwent primary hepatectomy for HCC (n = 465)	Retrospective	BMD was evaluated with CT in the mid-vertebral core of T11. The cutoff value of BMD was less than 160 HU.	For male patients (n = 367), low BMD was an independent risk factor for cancer-specific mortality (HR = 1.720, 95%CI: 1.038–2.922, P = 0.035).
Germany, 2022 Meister FA (*24*)	Adult patients who underwent partial hepatectomy for HCC (n = 151)	Retrospective	BMD was evaluated with CT-based segmentation. Osteopenia was defined as a BMD cut-off of < 175 HU for females, <160 HU for male patients with HCC.	Osteopenia was confirmed to be an independent risk-factor for inferior overall survival (HR = 7.743, 95%CI: 2.186–27.431, P = 0.002)
Japan, 2023 Yanagaki M (*21*)	Adult patients who underwent elective hepatic resection for HCC (n = 227)	Retrospective	BMD was evaluated with CT in the mid-vertebral core of T11. Osteopenia was defined as BMD below the standard BMD (308.82–2.49×Age in men and 311.84–2.41×Age in women).	Patients with osteopenia had a worse DFS (HR = 1.67, P = 0.008) and OS (HR = 2.24, P = 0.004) according to univariate analysis. Osteosarcopenia was an independent predictor of DFS and OS.
Japan, 2024 Ishida T (*19*)	Consecutive adult patients who underwent hepatectomy (n = 188)	Retrospective	BMD was evaluated with CT in the mid-vertebral core of the T11. The cutoff value of osteopenia was 160 HU	Osteopenia was an independent risk factor in OS (HR2.52, P = 0.004) and DFS (HR1.68, P = 0.023), possibly due to mechanisms mediated *via* microvascular portal vein invasion.
Japan, 2024 Abe K (*20*)	Adult patients who underwent surgical resection (n = 45) or RFA (n = 57) for BCLC A HCC	Retrospective	BMD was evaluated with CT in the mid-vertebral core of the T11. The cutoff value of osteopenia was 160 HU. Osteosarcopenia was defined as the concomitant development of osteopenia and sarcopenia.	No significant differences in DFS (P = 0.22) and OS (P = 0.09) were noted for osteopenia. Osteosarcopenia was a significant independent predictor of DFS and OS.
Germany, 2023 Müller L (*25*)	Adult patients with HCC who underwent TACE (n = 908)	Retrospective	BMD was evaluated with CT in the mid-vertebral core of T11. The cutoff value for BMD was less than 114 HU.	Low BMD remained an independent risk factor in median OS (HR1.7, 95%CI: 1.4–2.1, P < 0.001).
*China, 2021 Zheng X (*27*)	Adult patients who underwent TACE for HCC (n = 75)	Retrospective	QCT workstation (Mindways Software) indicated the mean BMD for the first and second lumbar vertebra before and after TACE.	Changes in BMD were not associated with OS. Muscle changes and the area of subcutaneous and visceral fat were independent risk factors for HCC after TACE.
*Germany, 2023 Sven H. L (*26*)	Adult patients who underwent TACE for HCC (n = 89)	Retrospective	BMD was measured at the level of the third lumbar vertebra in a single slice CT in the venous phase. The cutoff value for BMD was the median (159.5 HU).	A low BMD was not associated with OS.
# Japan, 2023 Miki A (*22*)	Adult patients with ICC who underwent hepatectomy (n = 71)	Retrospective	BMD was evaluated with CT in the mid-vertebral core of T11. The cutoff value for osteopenia was 160 HU.	Osteopenia (HR 3.66, P = 0.0258) was an independent factor associated with OS but not an independent prognostic factor for DFS.
# Japan, 2023 Taniai T (*23*)	Adult patients who underwent hepatic resection for ICC (n = 41)	Retrospective	BMD was evaluated with CT in the mid-vertebral core of T11. Osteopenia was defined as BMD below the standard (308.82–2.49 × Age in men and 311.84–2.41 × Age in women). Osteosarcopenia was defined as the concomitant development of osteopenia and sarcopenia.	Osteosarcopenia was an independent predictor of OS (HR 6.46, P < 0.01) and DSF (HR 3.38, P < 0.01).

*Studies with negative results on the prognostic implications of BMD; # Studies on ICC. HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; BMD, bone mineral density; T11, the 11th thoracic vertebra; HU, Hounsfield unit; BCLC, Barcelona Cancer Liver Classification stage; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; ICC, intrahepatic cholangiocarcinoma; QCT, quantitative computed tomography; OS, overall survival; DFS, recurrence-free survival, HR, hazard ratio; CI, confidence interval.

some studies have established that cutoff value (*10,19*). There is a discrepancy among studies regarding which vertebrae to measure. In two other studies on TACE conducted in China and Germany, different methods and thresholds were used, yet both concluded that changes in BMD were not related to OS in patients with HCC (*26,27*). This conclusion, different research strategies yield varying results, and the mixing of effects may have shifted the final result of the study in one direction or the other.

Considering the differences in populations and detection equipment, some studies have used different cutoff values to avoid age and sex biases, which hampered the determination of overall osteopenia incidence in patients with HCC and multi-center horizontal comparisons. Research in various countries reflects the similar predictive value of preoperative BMD for a poor prognosis for HCC, but subgroup analyses yield varying results, particularly in terms of sex grouping, tumor staging, and recurrence. Age and sex are crucial factors affecting BMD (*12*). Patients with HCC are predominantly middle-aged and elderly, with long-term cirrhosis and tumor conditions possibly impacting bone quality more than age differences (*25*). Due to the influence of female estrogen, changes in BMD are more useful in predicting the prognosis of HCC in males (*18*). Some studies, and especially those on LDLT, have found no correlation between BMD and DFS (*10,17,18*) or progression (*25*), suggesting that BMD is an independent factor reflecting the overall condition of the body while not being correlated with the cancer grade. However, Yanagaki *et al*. and Ishida *et al*. found that after sex differentiation, BMD has a predictive role in the DFS of patients with HCC (*19,21*). This contradiction may necessitate more precise population-specific cutoff values to yield more accurate results.

Surgical procedures and pharmacological treatments for HCC often temporarily exacerbate the burden on the liver, leading to increased bone loss and a heightened risk of pathological fractures. There is a lack of recent studies addressing the prognostic implications of BMD in patients with HCC undergoing targeted therapies. Evidence regarding immune checkpoint inhibitors (ICIs) suggests that a lower baseline BMD is correlated with poorer clinical outcomes in patients receiving ICIs for other malignancies (*28*). Further study is warranted to validate the role of changes in BMD in evaluating the efficacy of immunotherapy in HCC.

4. Regulation of the liver-bone axis in HCC

Whether BMD loss clearly promotes the progression of HCC or whether a consistent BMD prevents cancer invasion is unclear. Conclusive biological evidence to substantiate the predictive role of BMD has not yet been obtained (*17*). The pathophysiological mechanisms underlying osteopenia associated with liver cancer are intricate, and particularly in individuals with NAFLD, end-stage CLD, or cachexia.

Proposed molecular mechanisms that may elucidate the relationship between BMD and CLD-HCC include the receptor activator of nuclear factor kappa (RANK) - RANK ligand (RANKL) - osteoprotegerin (OPG) signaling pathway, the upregulation of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α), as well as variations in levels of erythropoietin (EPO), testosterone, and insulin-like growth factor (IGF) (*29*) . In addition, deficiencies in nutritional elements such as vitamin D, calcium, and vitamin K have been linked to osteoblast apoptosis, osteoclast differentiation, and osteoporosis in cachectic patients (*5*) (Figure.1).

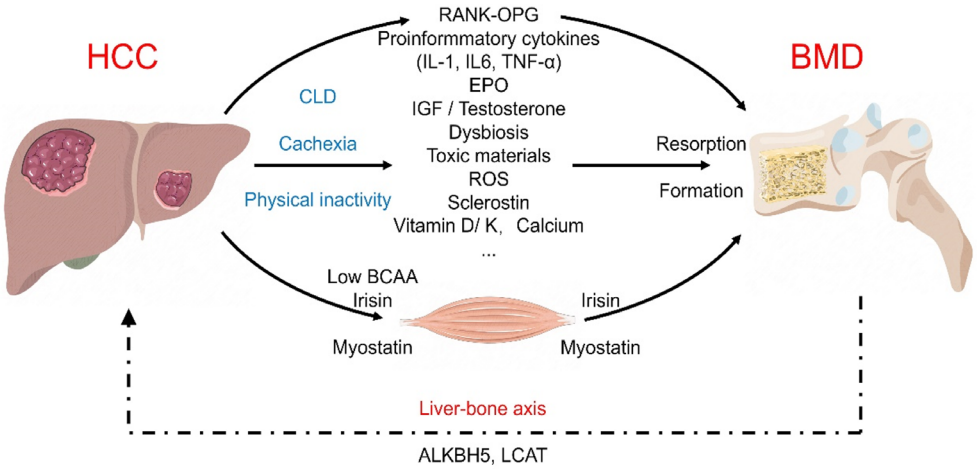

Figure 1. Diagram of the potential signaling mechanisms of bone density changes in patients with HCC. Shown are the possible signaling pathways between HCC and bone destruction and remodeling, as well as the intermediary regulatory role of muscles in the liver-bone axis. HCC, hepatocellular carcinoma; BMD, bone mineral density; CLD, chronic liver disease; RANK, the receptor activator of nuclear factor kappa; RANKL, RANK ligand; OPG, osteoprotegerin; IL-1, interleukin-1; TNF-α, tumor necrosis factor alpha; EPO, erythropoietin; ROS, reactive oxygen species; BCAA, branch-chain amino acid; GDF11, insulin-like growth factor 11, ALKBH5, AlkB homolog 5; LCAT, hepatokine lecithin-cholesterol acyltransferase.

The bidirectional regulation of the liver-bone axis has garnered considerable scholarly attention, which may be crucial to understanding the role of BMD in the progression of HCC. Lu *et al*. indicated that during osteoporosis, the downregulation of hepatokine lecithin-cholesterol acyltransferase can disrupt bone homeostasis and intensify liver fibrosis by hindering cholesterol transport from the bone to the liver, thereby highlighting the reciprocal regulatory relationship inherent in the liver-bone axis (*11*). Moreover, extracellular vesicles derived from bone-metastasized HCC cells have the capacity to target orthotopic HCC cells *via* AlkB homolog 5, thereby promoting and initiating prometastatic cascades (*30*). These findings underscore the bidirectional interplay between liver health and bone status, wherein various factors can concurrently impact both bone health and the progression of HCC.

5. BMD and therapeutic strategies for HCC

There is a lack of clinical evidence demonstrating a significant effect of improved BMD on the prognosis of HCC. Nevertheless, enhancing bone quality through exercise and nutritional interventions is not incompatible with the supportive therapies necessary for HCC management (*31*). The relationship between atezolizumab and osteoporosis appears to be particularly pronounced compared to other ICIs, necessitating special consideration for female patients due to their increased vulnerability (*32*). A study has suggested that osteoporosis therapies, such as denosumab, combined with ICIs may enhance clinical outcomes for patients with bone metastases (*33*). In addition, a reduction in fracture incidence is associated with improvement of quality of life (*5,34*). Identifying factors linked to a low BMD prior to treatment and those associated with BMD loss during treatment would be useful. Future research should aim to further elucidate the impact of treatment-related changes in BMD.

6. Conclusion

In summary, evaluating BMD may improve the assessment of prognosis in HCC. BMD has been found to be a prognostic risk factor in digestive cancers (*7*), but the current evidence from small-scale retrospective studies and limited etiopathogenesis research is insufficient to conclusively demonstrate a direct impact of BMD on the prognosis of HCC. Nevertheless, as a manifestation of overall nutritional status, BMD warrants attention during the screening and treatment of HCC. This focus may potentially contribute to improved patient outcomes, which highlights the urgent need for further interdisciplinary research. Conducting higher-quality research and establishing standardized methods of measuring BMD and cutoff values could significantly enhance its clinical use in patients with HCC.

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