

# ORIGINAL ARTICLE

## Prevalence of Bone Metastases Detected by Bone Scan in Patients with Hepatocellular Carcinoma

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### KEYWORDS

hepatocellular carcinoma; bone metastasis;  
bone scan; liver transplantation

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Received: January 15, 2026

Revised: March 31, 2026

Accepted: April 1, 2026

### ABSTRACT

Early-stage hepatocellular carcinoma (HCC) is curable by liver transplantation (LTx). However, donor scarcity necessitates a meticulous selection via Milan criteria. Although updated guidelines omit routine bone scans (BS) for staging, most Thai tertiary care centers still standardly perform them for LTx candidates with HCC. The aim of this study was to determine the prevalence of bone metastasis (BM) detected by BS among patients with HCC in northeastern Thailand and to assess the potential role of BS in the preoperative evaluation for LTx. This was a retrospective descriptive study of BS images of 101 patients with HCC who were referred to the Division of Nuclear Medicine, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. The prevalence of BS positivity and its potential associated factors were analyzed. A total of 16 patients had a positive BS (15.8%; 95% CI: 8.6–23.1) across multiple Barcelona Clinic Liver Cancer (BCLC) stages, including one patient in the very early stage (14.3%; 95% CI: 1.6–62.8). Among the 43 patients meeting the Milan criteria for LTx, three were found with positive BS (7.0%; 95% CI: 2.2–20.0). Bivariate analyses to determine the association between BS positivity and BCLC stage, Milan criteria, macrovascular invasion, largest tumor size, lymph node metastasis, and alpha-fetoprotein (AFP) level were performed, and tumors beyond the Milan criteria (crude OR 3.85; 95% CI: 1.02–14.5;  $p=0.046$ ), the presence of macrovascular invasion (crude OR 3.05; 95% CI: 1.02–14.5;  $p=0.046$ ), and N1 stage (crude OR 9.11; 95% CI: 1.81–45.8;  $p=0.007$ ) demonstrated a statistically significant association with BS positivity. However, upon further evaluation using multivariable logistic regression to adjust for potential confounders, no factors remained statistically significant in association with positive BS. These findings suggest that BS may still have a role in the preoperative evaluation of patients with HCC being considered for LTx.

### Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 80% of all cases<sup>1</sup>. It is also the sixth most common cancer worldwide and the third leading cause of cancer-related death<sup>2</sup>. In Thailand, HCC has the highest incidence, accounting for 15.2% of all cancers, and is also the leading cause of cancer-related death, with a mortality rate of 22.8%<sup>3</sup>. Significant risk factors for HCC include chronic viral hepatitis (hepatitis B virus [HBV] and hepatitis C virus [HCV]) infection, alcoholic liver disease, non-alcoholic steatohepatitis (NASH)/non-alcoholic fatty liver disease (NAFLD), and aflatoxin ingestion<sup>4</sup>.

The management strategy for HCC is dictated by the stage of the disease, for which the Barcelona Clinic Liver Cancer (BCLC) staging system<sup>5</sup> is widely accepted. For patients with early-stage disease, liver transplantation (LTx) offers a definitive curative option, as it addresses not only the malignancy, but also the underlying liver dysfunction. However, the scarcity of the organ donors necessitates a

meticulous patient selection process. The Milan criteria<sup>6</sup>—defined as unresectable HCC with limited tumor burden (a single tumor  $\leq 5$  cm or up to three tumors with none exceeding 3 cm and no imaging evidence of macrovascular invasion or extrahepatic spread)—are one of the most widely used standard criteria for selecting appropriate candidates and ensuring favorable post-LTx outcomes.

Previously, before patients were included on the LTx waiting list, international guidelines for LTx, such as those of the European Association for the Study of the Liver (EASL)<sup>7</sup> and the American Association for the Study of Liver Diseases (AASLD)<sup>8</sup> recommended comprehensive staging to exclude extrahepatic metastatic disease. This evaluation typically included the computed tomography (CT) scans of the chest to assess pulmonary metastasis and bone scans (BS) to detect bone metastasis (BM). However, recent updates to both EASL<sup>9</sup> and AASLD<sup>10</sup> clinical practice guidelines for the management of HCC no longer recommend BS to be routinely performed for staging. Despite this shift, there is

no clear statement on whether BS should be omitted from the preoperative work-up for LTx candidates. While BS is widely available and affordable for most patients, its diagnostic sensitivity is reportedly limited for the predominantly osteolytic lesions characteristic of HCC<sup>11–14</sup>. Nevertheless, routine BS remains the standard practice for all LTx candidates with HCC at our institution and in the majority of tertiary care centers in Thailand.

The prevalence of BM in patients with HCC ranges from 2% up to 20% in the literature<sup>12,13,15–29</sup>. This wide variation suggests that the risk profile may vary across different patient populations. Therefore, this study was undertaken to determine the prevalence of BM detected by BS among patients with HCC in northeastern Thailand and to assess the potential role of BS in the preoperative evaluation for LTx.

## Materials and Methods

### *Patient characteristics*

The authors retrospectively reviewed the medical records of all patients aged 18 years or older diagnosed with HCC who were referred for BS to the Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Khon Kaen University, between January 1, 2013, and December 31, 2020. The inclusion criteria comprised patients with HCC whose diagnosis was confirmed by radiological imaging (CT or magnetic resonance imaging [MRI]), with or without elevated alpha-fetoprotein (AFP) levels, who underwent BS either prior to diagnosis or within 12–16 weeks post-diagnosis. Patients were excluded from the study if they were diagnosed with other concomitant malignancies or if their medical or radiological records required for inclusion were incomplete. Demographic characteristics were collected from medical records, including age, sex, etiology, Child–Turcotte–Pugh (CTP) score, AFP levels, and Eastern Cooperative Oncology Group (ECOG) performance status. Afterward, patients were classified according to the BCLC staging system based on tumor size and number, macrovascular invasion, nodal involvement, and metastatic spread which were individually assessed by a diagnostic radiologist using the available imaging modalities.

### *Image acquisition*

Whole-body BS was performed approximately 3 hours after the intravenous injection of 555–740 megabecquerels (MBq) (15–20 millicuries [mCi]) of technetium-99m methylene diphosphonate (<sup>99m</sup>Tc-MDP). Anterior and posterior planar images were obtained using dual-headed (Vertex V60 EPIC HP [ADAC, CA, USA], Discovery NM/CT 670 [GE Healthcare, IL, USA], Discovery MN 830 [GE Healthcare, IL, USA] or Symbia Intevo 2 [Siemens AG, Berlin and Munich, Germany]) or single-headed (Genesys [ADAC, CA, USA]) gamma cameras. In cases where planar images were inconclusive, single-photon emission computed tomography with CT (SPECT/CT) was performed using hybrid systems (Discovery NM/CT 670 [GE Healthcare, IL, USA] or Symbia Intevo 2 [Siemens AG, Berlin and Munich, Germany]) to further characterize the lesions.

### *Image interpretation*

Two nuclear medicine physicians, blinded to the patients' identification, clinical history, laboratory results, and other imaging studies, independently interpreted the BS. Discrepancies were resolved by a third reader by consensus. BS were categorized as positive, negative or

equivocal. A positive planar scan was defined by the presence of solitary or multiple focal lesions, diffuse uptake (superscan), or photon-deficient lesions, after excluding benign etiologies such as bone fractures, infections, or degenerative changes. For SPECT/CT images, positivity was defined as increased or decreased radiotracer uptake corresponding to osteolytic, osteoblastic or mixed osteolytic/osteoblastic lesions on the CT portion. Equivocal results that could not be definitively classified were grouped with negative scans for the final analysis.

### *Statistical analysis*

Data analysis was performed using Stata version 13.1 (StataCorp LLC, TX, USA). Demographic characteristics were summarized using descriptive statistics; continuous variables were expressed as mean  $\pm$  standard deviation (SD) for normally distributed data or median and range for non-normally distributed data, while categorical variables were presented as numbers and percentages. The prevalence of positive BS was calculated and stratified by BCLC stage, Milan criteria eligibility, and the presence of macrovascular invasion. Analyses were conducted separately for planar studies and studies combined with SPECT/CT (if available). Results were reported as numbers, percentages, and 95% confidence intervals (95% CI). A sensitivity analysis was conducted to evaluate the impact of BS with equivocal results on prevalence estimates. Bivariate and multivariable logistic regression analyses were performed to calculate crude and adjusted odds ratios (ORs), respectively, to identify factors associated with BS positivity. Covariates included in the models were BCLC stage, Milan criteria status, presence of macrovascular invasion, tumor size, nodal metastasis, and AFP levels. A *p*-value of less than 0.05 was considered statistically significant.

## Results

### *Patient characteristics*

128 patients initially met the inclusion criteria based on a retrospective review of medical records between January 1, 2013, and December 31, 2020. However, after excluding 10 patients with concomitant malignancies and 17 patients with incomplete medical or radiological records, a total of 101 patients were included in the final analysis.

As detailed in Table 1, the majority of the patients were male (84.2%) with a mean age of 56.5 years (range, 33–81 years). The predominant etiology for HCC was HBV and/or HCV infection, accounting for 88.1% of cases. Only eight patients (7.9%) had alcoholic cirrhosis as the sole risk factor. Most patients (98.1%) had preserved liver function (CTP score A or B), but two patients presented with CTP score C (classified as BCLC stage D).

AFP levels were available for 100 patients, with a median of 54.9 ng/mL and a wide range of 2.5–269,853.0 ng/mL. Using a cut-off of 20 ng/mL<sup>30</sup>, 63.4% of patients had elevated AFP levels. Regarding staging using tumor–node–metastasis (TMN) system according to the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual<sup>31</sup>, most patients were classified as TNM stage I (33.7%) or stage II (29.7%). Macrovascular invasion was present in 28.7% of patients. Prior to the inclusion of BS, 13 patients (12.9%) were radiologically identified as having extrahepatic spread, consisting of pulmonary metastases in six patients and BM in seven patients. When classified by the BCLC staging system, the largest group was BCLC stage C (37.6%), followed by stage A (32.7%).

**Table 1** Demographic characteristics of the study population

| Characteristics                                | Total (n = 101)<br>n (%) |
|------------------------------------------------|--------------------------|
| Age at diagnosis, years, mean $\pm$ SD (range) | 56.5 $\pm$ 8.5 (33–81)   |
| Sex                                            |                          |
| Male                                           | 85 (84.2)                |
| Female                                         | 16 (15.8)                |
| Etiology                                       |                          |
| HBV alone                                      | 33 (32.6)                |
| HCV alone                                      | 43 (42.6)                |
| HBV+HCV                                        | 4 (4.0)                  |
| Others                                         | 17 (16.8)                |
| - Alcohol alone                                | 8 (7.9)                  |
| - Alcohol with HBV                             | 3 (2.9)                  |
| - Alcohol with HCV                             | 6 (5.9)                  |
| Not identified                                 | 4 (4.0)                  |
| ECOG score                                     |                          |
| 0                                              | 21 (20.8)                |
| 1                                              | 11 (10.9)                |
| 2                                              | 0 (0)                    |
| 3                                              | 1 (1.0)                  |
| 4                                              | 1 (1.0)                  |
| Not identified                                 | 67 (66.3)                |
| CTP score                                      |                          |
| A                                              | 54 (53.5)                |
| B                                              | 45 (44.6)                |
| C                                              | 2 (1.9)                  |
| AFP level, ng/mL, median (range)               | 54.9 (2.5–269,853.0)     |
| $\leq$ 20                                      | 36 (35.6)                |
| >20                                            | 64 (63.4)                |
| Not identified                                 | 1 (1.0)                  |
| T stage                                        |                          |
| T1                                             | 35 (34.6)                |
| - T1a                                          | 8 (7.9)                  |
| - T1b                                          | 27 (26.7)                |
| T2                                             | 32 (31.7)                |
| T3                                             | 5 (5.0)                  |
| T4                                             | 29 (28.7)                |
| N stage                                        |                          |
| N0                                             | 94 (93.1)                |
| N1                                             | 7 (6.9)                  |
| M stage                                        |                          |
| M0                                             | 88 (87.1)                |
| M1                                             | 13 (12.9)                |

**Table 1** Continued

| Characteristics             | Total (n = 101)<br>n (%) |
|-----------------------------|--------------------------|
| TNM stage                   |                          |
| Stage I                     | 34 (33.7)                |
| - Stage IA                  | 8 (7.9)                  |
| - Stage IB                  | 26 (25.8)                |
| Stage II                    | 30 (29.7)                |
| Stage III                   | 23 (22.7)                |
| - Stage IIIA                | 4 (3.9)                  |
| - Stage IIIB                | 19 (18.8)                |
| Stage IV                    | 14 (13.9)                |
| - Stage IVA                 | 2 (2.0)                  |
| - Stage IVB                 | 12 (11.9)                |
| Number of hepatic nodules   |                          |
| 1                           | 53 (52.5)                |
| 2–3                         | 29 (28.7)                |
| >3                          | 19 (18.8)                |
| The largest tumor size (cm) |                          |
| ≤2                          | 17 (16.8)                |
| >2–5                        | 50 (49.5)                |
| >5                          | 34 (33.7)                |
| Macrovascular invasion      |                          |
| No                          | 72 (71.3)                |
| Yes                         | 29 (28.7)                |
| BCLC staging system         |                          |
| 0                           | 7 (6.9)                  |
| A                           | 33 (32.7)                |
| B                           | 19 (18.8)                |
| C                           | 38 (37.6)                |
| D                           | 4 (4.0)                  |

### BS findings

As shown in Table 2, among the 101 patients, seven had evidence of BM prior to BS; all of these patients were classified as BCLC stage C and were beyond the Milan criteria. BS further identified additional positive cases of BM, bringing the total number of patients with BM to 16. Notably, positive BS results were detected across all BCLC stages, including one patient (14.3%; 95% CI: 1.6–62.8) in the very early stage (BCLC 0).

In the analysis of planar images, six cases were interpreted as equivocal. A one-way sensitivity analysis was performed to compare the impact of classifying these equivocal results as negative versus positive. The estimated prevalence of BM was 15.8% (95% CI: 8.6–23.1) using the first method (negative) and 21.8% (95% CI: 13.6–29.9) using the second (positive); this difference was not statistically

significant. Furthermore, SPECT/CT was performed in only 28 cases. In the majority of these cases (22/28), SPECT/CT results were concordant with the planar interpretation. Of the six equivocal planar cases, only one was reclassified as positive following SPECT/CT. Consequently, the final data analysis treated equivocal planar scans as negative.

Based on this analysis, the prevalence of BM detected by BS in patients with HCC was 15.8% (16/101; 95% CI: 8.6–23.1). Among patients meeting the Milan criteria, the prevalence was 7.0% (3/43; 95% CI: 2.0–20.0).

Additionally, two patients exhibited false-negative BS results. Both had osteolytic lesions confirmed on CT scans prior to BS but showed no corresponding abnormal radiotracer uptake on the planar images (see Figures 1 and 2). This resulted in a false-negative rate of 2.4% (2/85) among patients with negative scans.

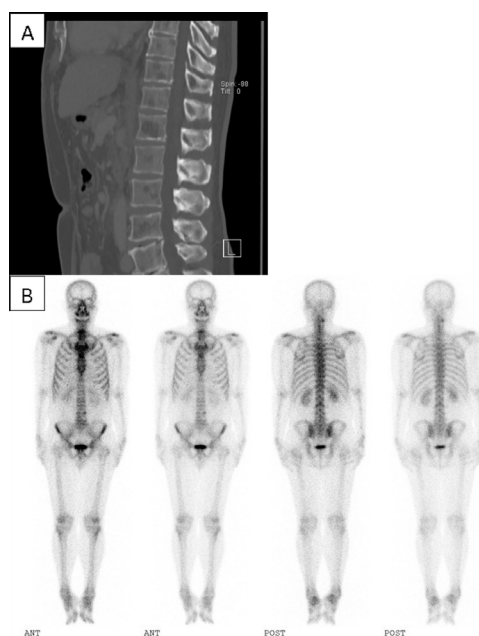
**Table 2** Bone metastasis in patients with hepatocellular carcinoma based on bone scan results

| Stage of hepatocellular carcinoma<br>(before bone scan) | Total<br>(n=101) | Bone metastasis detected<br>before bone scan<br>n (%; 95% CI) | Bone metastasis detected<br>after bone scan<br>n (%; 95% CI) |
|---------------------------------------------------------|------------------|---------------------------------------------------------------|--------------------------------------------------------------|
| BCLC (all stages)                                       | 101              | 7 (6.9, 1.9–12.0)                                             | 16 (15.8, 8.6–23.1)                                          |
| BCLC 0                                                  | 7                | 0 (0)                                                         | 1 (14.3, 1.6–62.8)                                           |
| BCLC A                                                  | 33               | 0 (0)                                                         | 3 (9.1, 2.9–25.3)                                            |
| BCLC B                                                  | 19               | 0 (0)                                                         | 2 (10.5, 2.5–35.1)                                           |
| BCLC C                                                  | 38               | 7 (18.4, 8.9–34.4)                                            | 10 (26.3, 14.6–42.8)                                         |
| BCLC D                                                  | 4                | 0 (0)                                                         | 0 (0)                                                        |
| Within Milan criteria                                   | 43               | 0 (0)                                                         | 3 (7.0, 2.2–20.0)                                            |
| Beyond Milan criteria                                   | 58               | 7 (12.1, 5.8–23.5)                                            | 13 (22.4, 13.3–35.2)                                         |
| No macrovascular invasion                               | 72               | 3 (4.2, 1.3–12.4)                                             | 8 (11.1, 5.6–20.9)                                           |
| Macrovascular invasion                                  | 29               | 4 (13.8, 5.1–32.1)                                            | 8 (27.6, 14.1–46.8)                                          |

### Factors associated with positive BS

Both bivariate and multivariable logistic regression analyses were performed to identify factors associated with positive BS. The variables evaluated included BCLC stage, Milan criteria status, presence of macrovascular invasion, largest tumor diameter, lymph node metastasis (N stage), and AFP level, as shown in Table 3.

In the bivariate analysis, three factors demonstrated statistically significant associations with positive BS: tumors beyond the Milan criteria (crude OR 3.85; 95% CI: 1.02–14.5;  $p=0.046$ ), presence of macrovascular invasion (crude OR 3.05; 95% CI: 1.02–9.13;  $p=0.046$ ), and nodal metastasis (N1 stage) (crude OR 9.11; 95% CI: 1.81–45.8;  $p=0.007$ ). However, upon further evaluation using multivariable logistic regression to adjust for potential confounders, no factors remained statistically significant in association with positive BS.



**Figure 1** A 71-year-old male with HCC. CT scan images prior to the BS (A) revealed multiple osteolytic lesions along the lower thoracic and lumbar vertebrae, suggestive of BM, whereas the planar BS (B) was interpreted as negative, showing only degenerative changes at the cervical and lumbar vertebrae.



**Figure 2** A 77-year-old male with HCC. CT scan images prior to the BS (A, B) revealed osteolytic lesions, suggestive of BM, with a pathologic fracture at the L1 vertebra. The planar BS (C) was interpreted as negative. The increased radiotracer uptake was considered to be due to an osteoporotic compression fracture rather than BM.

**Table 3** Factors associated with bone metastasis in hepatocellular carcinoma detected by bone scan

| Factors                     | No. of bone metastasis<br>(n (%)) | Crude OR<br>(95% CI) | p-value | Adjusted OR<br>(95% CI) | p-value |
|-----------------------------|-----------------------------------|----------------------|---------|-------------------------|---------|
| BCLC staging system         |                                   |                      |         |                         |         |
| 0                           | 1 (14.3)                          | 1                    |         | 1                       |         |
| A                           | 3 (9.1)                           | 0.60 (0.53–6.80)     | 0.680   | 0.82 (0.03–19.3)        | 0.901   |
| B                           | 2 (10.5)                          | 0.71 (0.54–9.27)     | 0.791   | 0.26 (0.004–15.3)       | 0.517   |
| C                           | 10 (26.3)                         | 2.14 (0.23–20.1)     | 0.504   | 0.35 (0.005–22.8)       | 0.623   |
| D                           | 0 (0)                             | N/A                  |         | N/A                     |         |
| Milan criteria              |                                   |                      |         |                         |         |
| Tumor within Milan criteria | 3 (7.0)                           | 1                    |         | 1                       |         |
| Tumor beyond Milan criteria | 13 (22.4)                         | 3.85 (1.02–14.5)*    | 0.046*  | 3.31 (0.18–61.7)        | 0.421   |
| Macrovascular invasion      |                                   |                      |         |                         |         |
| No                          | 72 (71.3)                         | 1                    |         | 1                       |         |
| Yes                         | 29 (28.7)                         | 3.05 (1.02–9.13)*    | 0.046*  | 0.97 (0.11–8.52)        | 0.979   |
| Largest tumor size          |                                   |                      |         |                         |         |
| ≤2 cm                       | 2 (11.8)                          | 1                    |         | 1                       |         |
| >2–5 cm                     | 3 (6.0)                           | 0.48 (0.07–3.14)     | 0.443   | 0.52 (0.05–5.93)        | 0.602   |
| >5 cm                       | 11 (32.4)                         | 3.59 (0.70–18.5)     | 0.127   | 2.88 (0.18–45.5)        | 0.454   |
| N stage                     |                                   |                      |         |                         |         |
| N0                          | 94 (93.1)                         | 1                    |         | 1                       |         |
| N1                          | 7 (6.9)                           | 9.11 (1.81–45.8)*    | 0.007*  | 3.83 (0.58–25.0)        | 0.162   |
| AFP level (ng/mL)           |                                   |                      |         |                         |         |
| ≤20                         | 5 (13.9)                          | 1                    |         | 1                       |         |
| >20                         | 11 (17.2)                         | 1.29 (0.41–4.05)     | 0.667   | 0.55 (0.13–2.36)        | 0.422   |
| Not identified              | 0                                 | N/A                  |         | N/A                     | N/A     |

## Discussion

This study observed a prevalence of BM of 15.8% (16/101 patients), which is higher than the 4.42% reported by Huang et al.<sup>23</sup>, who analyzed data from the Surveillance, Epidemiology, and End Results (SEER) Program<sup>32</sup>. However, our finding remains within the range of 2% to 20% range reported in other studies<sup>12,13,15–29</sup>.

In the case of the two patients with CTP score C who were initially classified as BCLC stage D, recent updates to the BCLC staging system regarding treatment stage migration suggest that such patients may still be considered for LTx if their liver function improves.

A key characteristic of our study population is the high prevalence of viral hepatitis, with 88.1% of patients having HBV or HCV as the etiology of HCC. Yang et al.<sup>33</sup> reported that HBV infection in HCC patients is associated with greater disease severity, characterized by earlier onset (by approximately 10 years), higher rates of cirrhosis, elevated AFP levels, higher CA19-9 levels, increased microvascular invasion, and significantly lower neutrophil-to-lymphocyte ratios (NLR) and platelet-to-lymphocyte ratios (PLR) compared with non-HBV patients. This etiological difference may explain why our study observed a higher prevalence of BM compared with studies involving predominantly Western populations<sup>15,20–23</sup>, where the prevalence is often less than 5%. In Western cohorts, HCC is more commonly associated with alcoholic cirrhosis, metabolic syndrome, and NASH<sup>34</sup>. Conversely, our results align more closely with studies from Asian populations<sup>12,18,19,26,27</sup>, where HBV/HCV prevalence is higher and BM rates range from 6.5% to 20%.

Crucially, this study identified positive BS in three patients (7.0%) who met the Milan criteria, which is comparable to the findings of Erhamamcı et al.<sup>35</sup>, who reported BM in 5 of 46 LTx candidates (10.9%). Considering the increasing trend of BM detection noted by Huang et al.<sup>36</sup> and Fukutomi et al.<sup>18</sup>, our findings suggest that BS cannot yet be safely omitted from the screening protocol for HCC patients listed for LTx.

Regarding false-negative results, two patients (2.4% of the negative scan group) presented with osteolytic lesions on CT scans (one involving the lower thoracic and lumbar vertebrae and the other an L1 vertebra with a pathologic fracture) but had negative planar BS. This highlights a limitation of BS in detecting purely osteolytic lesions, consistent with Chen et al.<sup>27</sup>, who reported a false-negative rate as high as 42.4% in patient-based analysis and 27.0% in lesion-based analysis.

Positive BS were observed across all BCLC stages, including the very early stage (BCLC 0). Although the highest number of positive cases was found in BCLC stage C (advanced stage), no positive cases were detected in BCLC stage D, likely due to the small sample size ( $n=4$ ) in that group. Multivariable logistic regression analysis revealed that the adjusted odds ratio did not significantly increase with advancing disease stage. This indicates that BM can occur at any stage of HCC, with a prevalence of 14.3% in BCLC 0, 9.1% in BCLC A, and 10.5% in BCLC B in our study. These findings support the necessity of routine BS for all HCC patients.

Previous literature suggests that factors such as tumor size, macrovascular invasion, lymph node metastasis, and tumor markers (e.g., AFP) are associated with BM<sup>19,21,26,36,37</sup>. Although the 2022 BCLC update<sup>5</sup>, Huang et al.<sup>36</sup>, and He et

al.<sup>37</sup> emphasize the relationship between AFP levels, disease stage, and survival, our study did not find a statistically significant association between AFP levels and positive BS in either bivariate or multivariable analyses. This may be attributed to the non-normal distribution of AFP data in our study.

While bivariate analysis showed that presence of macrovascular invasion, nodal metastasis (N1), and tumor beyond the Milan criteria were associated with positive BS, these factors did not retain statistical significance in the multivariable analysis. This contrasts with the study by Hu et al.<sup>22</sup>, which identified N1 stage, ethnicity, sex, histological grade, and T stage as significant factors. The discrepancy may be due to the descriptive nature of our study, which was not powered to calculate the sample size required for robust risk factor analysis.

This study has several limitations. Due to its retrospective design, some data were incomplete; not all patients underwent additional SPECT/CT beyond planar BS, and ECOG performance status was unavailable for a portion of patients, which may have influenced the accuracy of BCLC staging. BM from HCC are predominantly osteolytic and may occasionally result in false-negative BS findings, although only two such cases were observed in this cohort. In addition, the relatively small sample size and retrospective patient selection may limit the generalizability of the findings. Finally, histopathological confirmation of bone lesions was not routinely available, and therefore positive BS findings were interpreted based on imaging and clinical correlation.

## Conclusions

In this study, BM detected by BS were identified in 15.8% of patients with HCC and in 7.0% of those meeting the Milan criteria for LTx. Notably, BM were observed across multiple BCLC stages, including early-stage disease, and no significant predictors of positive BS were identified. These findings suggest that BS may still have a role in the preoperative evaluation of patients with HCC being considered for LTx. However, further studies with larger cohorts are warranted to better define its clinical value in this setting.

## Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Human Research Ethics Committee of Khon Kaen University (protocol code HE641433; approval date: 24 August 2021). Informed consent was obtained from all participants or their legal representatives.

## Acknowledgements

The author wishes to express gratitude to their advisor, Nantaporn Wongsurawat, M.D., and co-advisors, Assoc. Prof. Daris Theerakulpisut, M.D., Ph.D. of the Nuclear Medicine Division, and Anucha Ahooja, M.D. of the Division of Diagnostic Radiology, Department of Radiology, Faculty of Medicine, Khon Kaen University. Their invaluable guidance and support were essential to the successful completion of this research. Special thanks are also extended to Assoc. Prof. Charoonsak Somboonporn, M.D., Ph.D., and Asst. Prof. Yutapong Raruenrom, M.D. for their academic

mentorship, and to all the staff of the Division of Nuclear Medicine and the Medical Records Unit at Srinagarind Hospital for their assistance in data collection.

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