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Combined Bone Mineral Density (BMD) and Monocyte-to-Lymphocyte Ratio (MLR) Predicts Recurrence and Prognosis in Hepatocellular Carcinoma Patients Following Liver Resection

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Background: Bone mineral density (BMD) and monocyte-to-lymphocyte ratio (MLR) were recently identified as novel risk factors for patients with several malignancies. The objective of this study was to validate the role of preoperative BMD/MLR as a potential prognostic biomarker in patients with hepatocellular carcinoma (HCC) undergoing liver resection.

Methods: This investigation enrolled 442 adult patients diagnosed with HCC who underwent liver resection. The patients were classified into high- and low-BMD/MLR groups based on the median, and forward stepwise logistic regression was employed to identify independent predictors for early HCC recurrence. To mitigate the impact of confounding factors, a propensity score matching (PSM) analysis was conducted between patients in the high- and low-BMD/MLR groups. The Kaplan-Meier method was employed to assess and compare the disease-free survival (DFS) and overall survival (OS) between the two cohorts.

Results: The study categorized patients into high-BMD/MLR and low-BMD/MLR groups. Forward stepwise logistic regression analysis revealed that low BMD/MLR ($P < 0.001$), tumor size > 50 mm ($P < 0.001$), and AFP > 200 ug/L ($P = 0.001$) were significantly associated with the early recurrence of HCC. Moreover, the results suggested that DFS and OS were significantly shorter in the low-BMD/MLR group compared to the high-BMD/MLR group, both before and after PSM ($P < 0.05$).

Conclusion: Preoperative BMD/MLR held promise as a prognostic biomarker for early recurrence and prognosis in patients with HCC who underwent liver resection. Furthermore, the integration of tumor size, AFP level, and BMD/MLR demonstrated a robust predictive capacity for early recurrence within this patient population.

Keywords: hepatocellular carcinoma, resection, bone mineral density, recurrence, prognosis

Introduction

Liver cancer is the sixth most lethal type of cancer worldwide, and hepatocellular carcinoma (HCC) accounts for more than 80% of primary liver cancer cases.[1] Liver resection is considered the primary method for achieving curative treatment of HCC and is widely endorsed in multiple guidelines.[2,3] Following the Barcelona Clinic Liver Cancer (BCLC) staging system, the Western practice guidelines recommend liver resection for patients with very early- to early-stage HCC, while Asian practice guidelines reserve liver resection for those with intermediate-stage HCC.[4–7] Overall, patients with HCC who undergo liver resection exhibit varying outcomes, with 5-year survival rates ranging from 35% to 70%.[8–11] The observed variations can be ascribed to disparities in tumor burden, histopathological status, immune response status, and nutrition status.[12,13] To optimize risk stratification and improve prognostic accuracy, it is crucial to identify effective prognostic biomarkers for patients with HCC undergoing liver resection.

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In the realm of cancer progression, the significant contributions made by inflammatory response and immunonutrition are widely recognized as crucial elements that impact tumor priming, proliferation, angiogenesis, and migration.[14,15] Reports indicate that HCC induces an environment characterized by inflammation, immunosuppression, and nutritional deficiencies both locally and systemically.[16–19] These circumstances present considerable obstacles which can adversely affect clinical outcomes and the effectiveness of therapeutic interventions.[18,19] To date, peripheral blood inflammatory markers, such as the monocyte-to-lymphocyte ratio (MLR) and neutrophil-to-lymphocyte ratio (NLR), have been recognized as dependable predictors for prognosticating the clinical outcomes of patients with HCC.[16,20] Bone mineral density (BMD) has been established as an indicator of immunonutrition and has shown considerable prognostic value for HCC patients undergoing liver transplantation and resection.[21,22] Simultaneously, reduced BMD is significantly correlated with sarcopenia, which is intimately linked to unfavorable prognostic outcomes in patients with HCC.[23–25] To summarize, an elevated MLR and decreased BMD contribute to tumor promotion, while a reduced MLR and increased BMD contribute to tumor suppression. Therefore, the newly proposed biomarker BMD/MLR combines the advantages of BMD and MLR, potentially enhancing predictive accuracy.

Given the indeterminate prognostic implications of preoperative BMD/MLR in patients with HCC undergoing liver resection, this study aims to appraise the prognostic utility of BMD/MLR in this specific patient population and ascertain its suitability as a biomarker for HCC prognosis.

Materials and Methods

Study Population

The primary objective of this study was to assess the prognostic significance of preoperative BMD/MLR in patients with HCC undergoing liver resection. The aim was to ascertain whether BMD/MLR can function as a reliable biomarker for prognosticating HCC outcomes within this specific cohort. The inclusion criteria were: (1) age > 18 years; (2) an Eastern Cooperative Oncology Group performance status of 0; and (3) no macrovascular invasion or extrahepatic metastasis. The exclusion criteria were: (1) lost to follow-up data; (2) fever or infection at the time of liver resection; and (3) periodical administration of non-steroidal anti-inflammatory drugs or steroids. There were 442 patients included in this study. The flowchart of the study population is shown in Figure 1. This retrospective study was approved by the institutional review

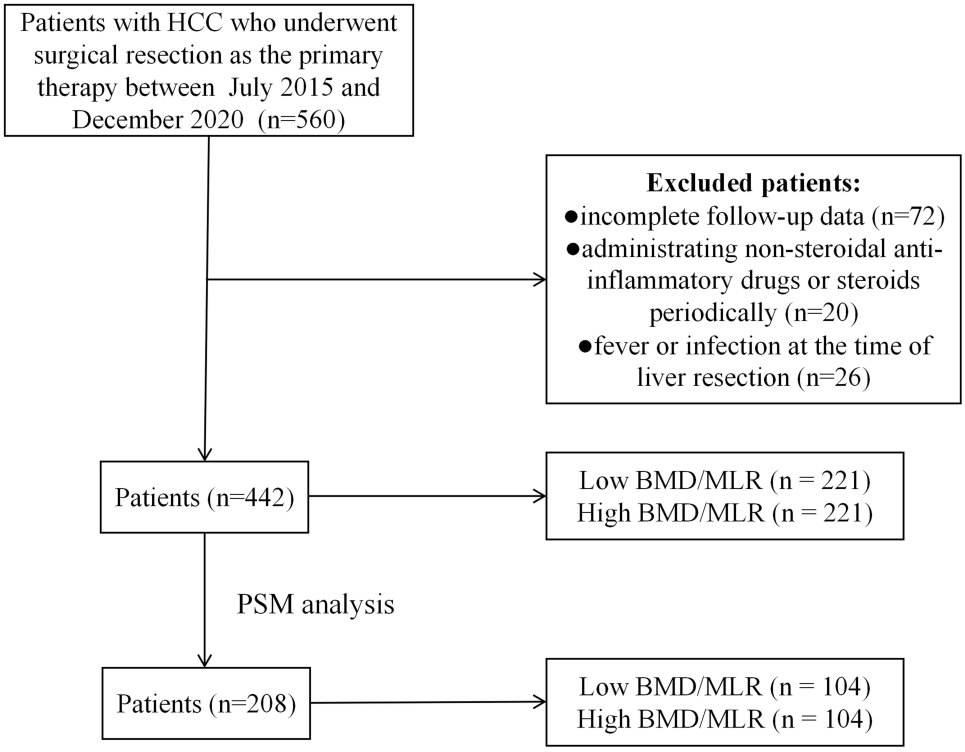

Figure 1 Diagram of the study population.

boards of the Second Xiangya Hospital of Central South University, in accordance with the principles outlined in the Declaration of Helsinki. Given the retrospective nature of the study and the anonymization and de-identification of patient data prior to analysis, the need for written consent was waived by the institutional review boards of the Second Xiangya Hospital of Central South University.

Data Collection

Patient-specific clinical data, including age, gender, Child-Pugh class, BCLC stage, underlying liver disease, tumor size, alpha-fetoprotein (AFP) level, and BMD were gathered. Additionally, peripheral blood testing encompassing neutrophil, lymphocyte, and platelet counts were obtained within one week before liver resection. BMD was evaluated by measuring the Hounsfield units (HU) of the 11th thoracic vertebra on CT scan prior to treatment, as previously documented (Figure 2).[21]

In this study, a standardized approach was employed to position a region of interest with a diameter ranging from 12 to 18 mm within the trabecular midvertebral core, specifically cranial to the base plate of the vertebral body. The calculated values of NLR, PLR, MLR, SII, and SIRI were obtained using the subsequent formulas: NLR = N/L, PLR = P/L, MLR = M/L, SII = N × P/L, SIRI = N × M/L. (Note: P = platelet count; N = neutrophil count; L = lymphocyte count; M = monocyte count).

Early Recurrence Evaluation and Follow-Up

The CT and MRI scans were evaluated by two radiologists with over 10 years of experience in abdominal radiology. Early recurrence of HCC was defined as the emergence of new lesions within two years following liver resection.[26] The study population was categorized into two groups: those who encountered early recurrence and those who did not. Disease-free survival (DFS) was determined from the date of diagnosis until tumor recurrence. Likewise, overall survival (OS) was determined from the date of diagnosis until the date of the last follow-up or death from any cause. DFS and OS were calculated both before and after one-to-one propensity score matching (PSM).

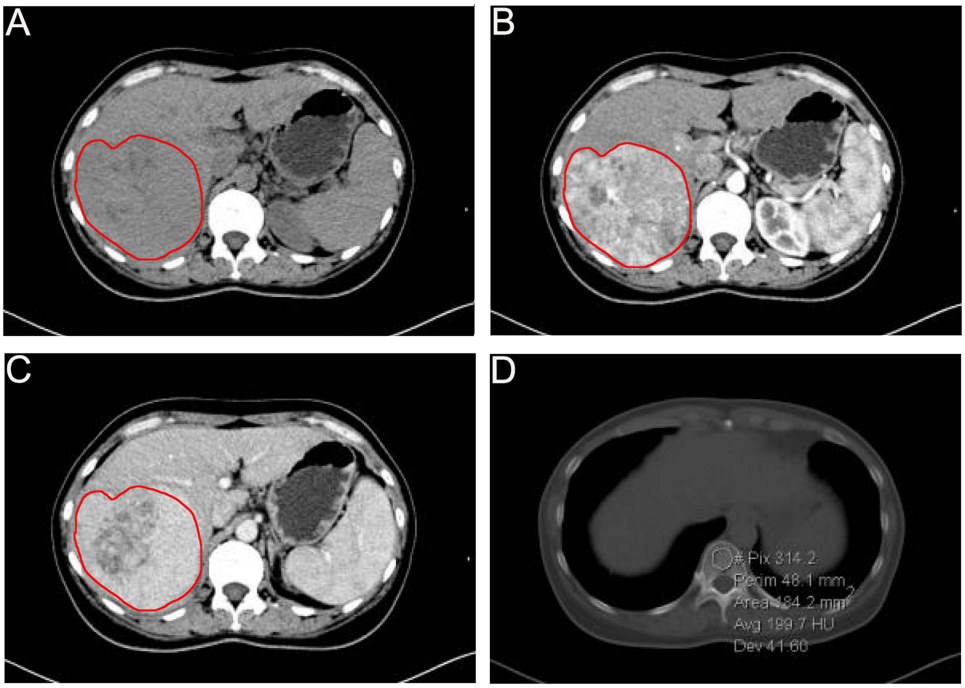

Figure 2 Plain scanning phase of HCC in contrast-enhanced CT (**A**); Arterial phase of HCC in contrast-enhanced CT (**B**); Portal phase of HCC in contrast-enhanced CT (**C**); Measurement of the BMD (**D**). Note: The red marker denotes the tumor's location and indicator # represents the regions of interest for bone density analysis.

Statistical Analysis

The current study employed the median as the statistical measure for SII, SIRI, NLR, MLR, PLR, and BMD/MLR in screening for patients with a higher probability of recurrence within a two-year period. The data was presented either as the median with interquartile range or as frequencies. Non-normally distributed numerical variables were compared using the Mann–Whitney *U*-test, while categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. A forward stepwise logistic regression model was employed to determine the most efficacious marker using both univariate and multivariate analyses. Furthermore, a one-to-one PSM analysis was utilized to mitigate the impact of confounding variables between the high- and low-BMD/MLR groups. The Kaplan-Meier method and log rank test were employed to compare the disparities in OS and DFS between the high- and low-BMD/MLR groups before and after PSM. The discriminatory capacity of the combination of BMD/MLR, AFP level, and tumor size in predicting early HCC recurrence was assessed using receiver operating characteristic (ROC) curve analysis.

Statistical analyses were performed using SPSS 26.0 statistical software, while the determination of statistical significance was based on a two-tailed P value of less than 0.05. The effect size and statistical power of this study were assessed using G-power 3.1.9.7 software.

Results

Demographic, Radiological and Laboratorial Characteristics

A total of 442 patients, consisting of 377 males (85.29%) and 65 females (14.71%), were included in the present study. The statistical power for this sample size was determined to be 0.99, employing a post-hoc power analysis with an effect size of 0.25, α error probability of 0.05, and n = 442. Among the patients, three hundred and thirty-one patients were with hepatitis B virus infection (74.89%). Four hundred and twenty-five patients (96.15%) had Child-Pugh A classification, while 17 (3.85%) had Child-Pugh B classification. Furthermore, two hundred and twenty-three patients (50.45%) had a tumor size ≤ 50 mm, while 219 (49.55%) had a tumor size > 50 mm. Tables 1 and 2 provide the detailed characteristics.

Table 1 The Demographic, Radiological and Laboratorial Characteristics of the Patient

Characteristics	Total (n = 442)
Age (y), Mean ± SD	52.35 ± 10.91
Gender, n (%)	
Male	377 (85.29)
Female	65 (14.71)
BCLC, n (%)	
0	34 (7.69)
A	373 (84.39)
B	35 (7.92)
Hepatitis, n (%)	
No	55 (12.44)
HBV	331 (74.89)
HCV	7 (1.58)
Alcohol	14 (3.17)
Other	35 (7.92)
Child-Pugh, n (%)	
A	425 (96.15)
B	17 (3.85)
Diameter (mm), n (%)	
≤ 50.00	223 (50.45)
> 50.00	219 (49.55)

(*Continued*)

Table 1 (Continued).

Characteristics	Total (n = 442)
Neutrophils (×10^9/L), (IQR)	3.40 (2.49, 4.40)
Lymphocytes (×10^9/L), (IQR)	1.36 (1.07, 1.75)
Platelet (×10^9/L), (IQR)	158.50 (117.00, 222.00)
Monocytes (×10^9/L), (IQR)	0.32 (0.24, 0.43)
Albumin (g/L), n (%)	
≤ 35.00	76 (17.19)
> 35.00	366 (82.81)
TBil (umol/L), n (%)	
≤ 17.10	306 (69.23)
> 17.10	136 (30.77)
AFP (ug/L), n (%)	
≤ 200.00	279 (63.12)
> 200.00	163 (36.88)
NLR (IQR)	2.37 (1.77, 3.15)
PLR (IQR)	109.94 (83.00, 154.56)
MLR (IQR)	0.22 (0.18, 0.31)
SII (IQR)	375.34 (230.31, 582.74)
SIRI (IQR)	0.73 (0.49, 1.19)
BMD (HU), (IQR)	171.10 (145.22, 201.75)
BMD/MLR (IQR)	734.83 (497.77, 1032.66)
BMD/SIRI (IQR)	226.63 (131.15, 364.96)
BMD/SII (IQR)	0.46 (0.28, 0.79)
BMD/NLR (IQR)	71.75 (51.48, 98.30)
Recurrence within two years, n (%)	
No recurrence	205 (46.38)
Recurrence	237 (53.62)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HBV, *Hepatitis B Virus*; HCV, *Hepatitis C Virus*; TBil, Total bilirubin; AFP, alpha fetoprotein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, Systemic Immune-Inflammation; SIRI, systemic inflammation response index; BMD, Bone mineral density; HU, Hounsfield unit; IQR, interquartile range.

Table 2 The Demographic, Radiological and Laboratorial Characteristics of the Low BMD/MLR and High BMD/MLR Patients

Characteristics	Total (n = 442)	Low BMD/MLR (n = 221)	High BMD/MLR (n = 221)	P value
Age (y), Mean ± SD	52.35 ± 10.91	54.63 ± 10.37	50.07 ± 10.98	< 0.001
Gender, n (%)				0.007
Male	377 (85.29)	199 (90.05)	178 (80.54)	
Female	65 (14.71)	22 (9.95)	43 (19.46)	
BCLC, n (%)				0.828
0	34 (7.69)	16 (7.24)	18 (8.14)	
A	373 (84.39)	186 (84.16)	187 (84.62)	
B	35 (7.92)	19 (8.60)	16 (7.24)	
Hepatitis, n (%)				0.136
No	55 (12.44)	30 (13.57)	25 (11.31)	
HBV	331 (74.89)	155 (70.14)	176 (79.64)	
HCV	7 (1.58)	5 (2.26)	2 (0.91)	
Alcohol	14 (3.17)	10 (4.52)	4 (1.81)	
Other	35 (7.92)	21 (9.50)	14 (6.33)	

(*Continued*)

Table 2 (Continued).

Characteristics	Total (n = 442)	Low BMD/MLR (n = 221)	High BMD/MLR (n = 221)	P value
Child-Pugh, n (%)				0.048
A	425 (96.15)	208 (94.12)	217 (98.19)	
B	17 (3.85)	13 (5.88)	4 (1.81)	
Diameter (mm), n (%)				< 0.001
≤ 50.00	223 (50.45)	87 (39.37)	136 (61.54)	
> 50.00	219 (49.55)	134 (60.63)	85 (38.46)	
Albumin (g/L), n (%)				<0.001
≤ 35.00	76 (17.19)	53 (23.98)	23 (10.41)	
> 35.00	366 (82.81)	168 (76.02)	198 (89.59)	
TBil (umol/L), n (%)				0.257
≤ 17.10	306 (69.23)	147 (66.52)	159 (71.95)	
> 17.10	136 (30.77)	74 (33.48)	62 (28.05)	
AFP (ug/L), n (%)				0.430
≤ 200.00	279 (63.12)	135 (61.09)	144 (65.16)	
> 200.00	163 (36.88)	86 (38.91)	77 (34.84)	
NLR (IQR)	2.37 (1.77, 3.15)	2.97 (2.23, 4.03)	1.97 (1.61, 2.62)	< 0.001
PLR (IQR)	109.94 (83.00, 154.56)	122.66 (96.39, 187.34)	97.44 (76.72, 131.45)	< 0.001
MLR (IQR)	0.22 (0.18, 0.31)	0.31 (0.26, 0.39)	0.18 (0.15, 0.21)	< 0.001
SII (IQR)	375.34 (230.31, 582.74)	496.07 (294.77, 821.23)	302.22 (210.10, 423.68)	< 0.001
SIRI (IQR)	0.73 (0.49, 1.19)	1.16 (0.77, 1.71)	0.56 (0.39, 0.72)	< 0.001
BMD (HU), (IQR)	171.10 (145.22, 201.75)	152.70 (132.80, 179.70)	188.50 (165.70, 220.90)	< 0.001
BMD/MLR (IQR)	734.83 (497.77, 1032.66)	497.06 (416.18, 615.25)	1034.36 (865.41, 1205.76)	< 0.001
Recurrence within two years, n (%)				< 0.001
No recurrence	205 (46.38)	81 (36.65)	124 (56.11)	
Recurrence	237 (53.62)	140 (63.35)	97 (43.89)	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HBV, *Hepatitis B Virus*; HCV, *Hepatitis C Virus*; TBil, Total bilirubin; AFP, alpha fetoprotein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, Systemic Immune-Inflammation; SIRI, systemic inflammation response index; BMD, Bone mineral density; HU, Hounsfield unit; IQR, interquartile range.

Potential Predictive Factors for Early HCC Recurrence

Early recurrence of HCC was operationally defined as reappearance within two years after liver resection.[26] Among the study population, a total of 237 individuals (53.62%) experienced recurrence within this two-year period, while 205 (46.38%) did not. ROC curves were employed to assess the diagnostic efficacy of various biomarkers and determine their respective cutoff points. The cutoff point for the ROC analysis was established as the median value of the potential biomarkers. The area under the curve (AUC) values for the NLR, MLR, PLR, SII, SIRI, BMD, and BMD/MLR were 0.602, 0.608, 0.542, 0.569, 0.607, 0.614, and 0.648, respectively (Figure 3). In the univariate analysis, a significant correlation was observed between the early recurrence of HCC and various factors, including BCLC stage ($p = 0.002$), tumor diameter > 50 mm ($p < 0.001$), AFP > 200 ug/L ($p < 0.001$), MLR > 0.22 ($p < 0.001$), SIRI > 0.73 ($p < 0.001$), BMD > 171.10 hU ($p = 0.004$), and BMD/MLR > 734.83 ($p < 0.001$). A forward stepwise multivariate analysis was subsequently conducted using the significant risk factors identified in the univariate analysis, revealing that tumor diameter > 50 mm, AFP > 200 ug/L, and BMD/MLR > 734.83 were independent biomarkers correlated with early HCC recurrence following liver resection. The odds ratios and 95% confidence intervals for these biomarkers were presented in Table 3.

Impact of Low and High BMD/MLR on DFS and OS

The results obtained from the logistic regression model suggested that several factors, including BCLC stage, tumor diameter, AFP, MLR, SIRI, BMD, and BMD/MLR, were associated with the early recurrence of HCC in the univariate

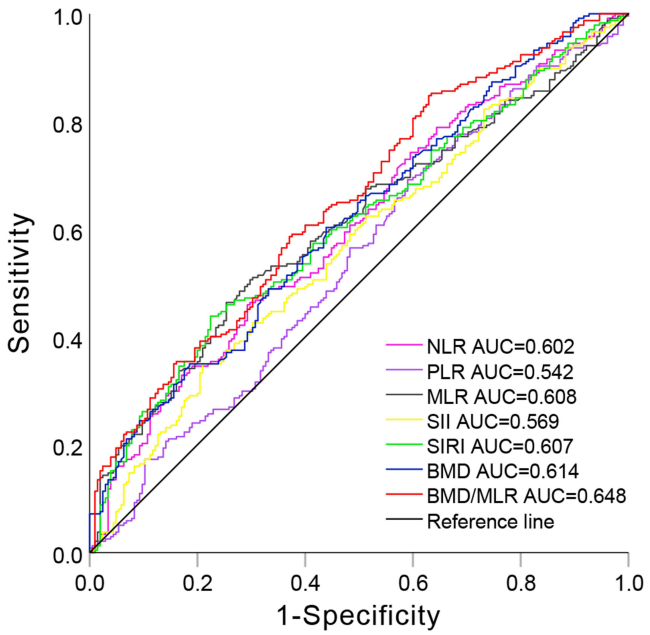

Figure 3 Comparison of the AUCs for NLR, MLR, PLR, SII, SIRI, BMD and BMD/MLR in predicting early recurrence of HCC after liver resection.

analysis. However, in the multivariate analysis, only tumor diameter, AFP, and BMD/MLR showed a significant association with early HCC recurrence. Moreover, the log rank test was used to assess the disparities in DFS and OS among patients categorized as having low and high BMD/MLR. In comparison to the low-BMD/MLR group, the high-BMD/MLR cohort exhibited a greater tumor diameter and higher AFP levels. The Kaplan-Meier survival curves illustrating DFS and OS in patients with low and high BMD/MLR are presented in Figure 4. Compared to the low-BMD/MLR group, the high-BMD/MLR group had a significantly longer median DFS (high BMD/MLR, 52.2 months

Table 3 Assessment of Potential Risk Factors for Early Recurrence of HCC After Liver Resection

Characteristics	Total (n = 442)	No recurrence (n = 205)	Recurrence (n = 237)	P value	
				Univariate	Multivariate
Age(y), Mean ± SD	52.35 ± 10.91	51.81 ± 10.72	52.82 ± 11.07	0.332	
Gender, n (%)				0.476	
Male	377 (85.29)	178 (86.83)	199 (83.97)		
Female	65 (14.71)	27 (13.17)	38 (16.03)		
BCLC, n (%)				0.002	
0	34 (7.69)	23 (11.22)	11 (4.64)		
A	373 (84.39)	173 (84.39)	200 (84.39)		
B	35 (7.92)	9 (4.39)	26 (10.97)		
Hepatitis, n (%)				0.418	
No	55 (12.44)	28 (13.66)	27 (11.39)		
HBV	331 (74.89)	157 (76.59)	174 (73.41)		
HCV	7 (1.58)	3 (1.46)	4 (1.69)		
Alcohol	14 (3.17)	6 (2.92)	8 (3.38)		
Other	35 (7.92)	11 (5.37)	24 (10.13)		
Child-Pugh, n (%)				0.760	
A	425 (96.15)	196 (95.61)	229 (96.62)		
B	17 (3.85)	9 (4.39)	8 (3.38)		

(*Continued*)

Table 3 (Continued).

Characteristics	Total (n = 442)	No recurrence (n = 205)	Recurrence (n = 237)	P value	
				Univariate	Multivariate
Diameter (mm), n (%)				< 0.001	0.000 (OR, 2.627; 95% CI: 1.755–3.932)
≤ 50.00	223 (50.45)	132 (64.39)	91 (38.40)		
> 50.00	219 (49.55)	73 (35.61)	146 (61.60)		
Albumin (g/L), n (%)				0.001	
≤ 35.00	76 (17.19)	22 (10.73)	54 (22.78)		
> 35.00	366 (82.81)	183 (89.27)	183 (77.22)		
TBil (umol/L), n (%)				0.769	
≤ 17.10	306 (69.23)	140 (68.29)	166 (70.04)		
> 17.10	136 (30.77)	65 (31.71)	71 (29.96)		
AFP (ug/L), n (%)				< 0.001	0.001 (OR, 2.032; 95% CI: 1.333–3.096)
≤ 200.00	279 (63.12)	147 (71.71)	132 (55.70)		
> 200.00	163 (36.88)	58 (28.29)	105 (44.30)		
NLR, n (%)				0.036	
≤ 2.37	221 (50.00)	114 (55.61)	107 (45.15)		
> 2.37	221 (50.00)	91 (44.39)	130 (54.85)		
PLR, n (%)				0.340	
≤ 109.94	221 (50.00)	108 (52.68)	113 (47.68)		
> 109.94	221 (50.00)	97 (47.32)	124 (52.32)		
MLR, n (%)				< 0.001	
≤ 0.22	221 (50.00)	121 (59.02)	100 (42.19)		
> 0.22	221 (50.00)	84 (40.98)	137 (57.81)		
SII, n (%)				0.056	
≤ 375.34	221 (50.00)	113 (55.12)	108 (45.57)		
> 375.34	221 (50.00)	92 (44.88)	129 (54.43)		
SIRI, n (%)				0.001	
≤ 0.73	221 (50.00)	120 (58.54)	101 (42.62)		
> 0.73	221 (50.00)	85 (41.46)	136 (57.38)		
BMD (HU), n (%)				0.004	
≤ 171.10	221 (50.00)	87 (42.44)	134 (56.54)		
> 171.10	221 (50.00)	118 (57.56)	103 (43.46)		
BMD/MLR, n (%)				< 0.001	0.000 (OR, 0.348; 95% CI: 0.217–0.558)
≤ 734.83	221 (50.00)	81 (39.51)	140 (59.07)		
> 734.83	221 (50.00)	124 (60.49)	97 (40.93)		
BMD/SIRI, n (%)				< 0.001	
≤ 226.63	221 (50.00)	83 (40.49)	138 (58.23)		
> 226.63	221 (50.00)	122 (59.51)	99 (41.77)		
BMD/SII, n (%)				0.001	
≤ 0.46	221 (50.00)	85 (41.46)	136 (57.38)		
> 0.46	221 (50.00)	120 (58.54)	101 (42.62)		
BMD/NLR, n (%)				< 0.001	
≤ 71.75	221 (50.00)	84 (40.98)	137 (57.81)		
> 71.75	221 (50.00)	121 (59.02)	100 (42.19)		
BMD/PLR, n (%)				0.004	
≤ 1.53	221 (50.00)	87 (42.44)	134 (56.54)		
> 1.53	221 (50.00)	118 (57.56)	103 (43.46)		

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HBV, *Hepatitis B Virus*; HCV, *Hepatitis C Virus*; TBil, Total bilirubin; AFP, alpha fetoprotein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, Systemic Immune-Inflammation; SIRI, systemic inflammation response index; BMD, Bone mineral density; HU, Hounsfield unit; IQR, interquartile range.

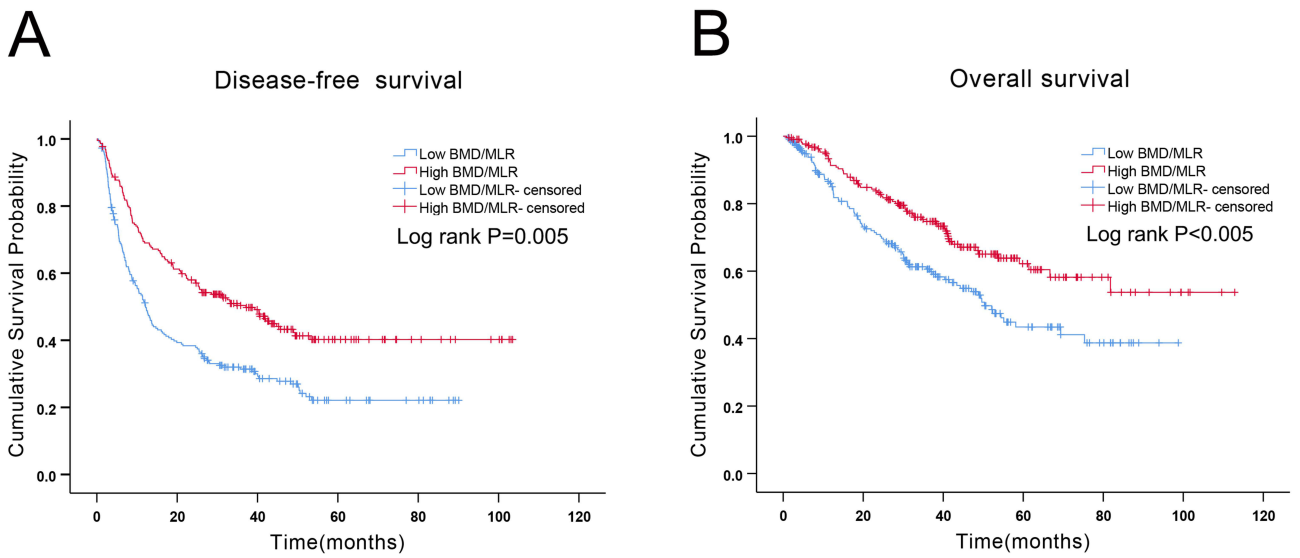

Figure 4 Log rank tests were used to compare DFS (**A**) and OS (**B**) between high BMD/MLR and low BMD/MLR groups before PSM.

[95% CI: 46.1–58.3] vs low BMD/MLR, 30.7 months [95% CI: 25.9–35.5]; P < 0.001) (Figure 4A) and OS (high BMD/MLR, 77.3 months [95% CI: 70.2–84.4] vs low BMD/MLR, 56.4 months [95% CI: 50.3–62.4]; P < 0.001) (Figure 4B). Furthermore, a one-to-one PSM analysis was executed to address potential selection bias resulting from confounding variables among distinct cohorts. The PSM investigation encompassed a total of 208 participants, with 104 individuals exhibiting low BMD/MLR and another 104 displaying high BMD/MLR. The PSM analysis found no noticeable disparities in baseline characteristics, including age, gender, tumor diameter, AFP levels, BCLC stage, and Child-Pugh score between the two cohorts (Table 4). As a result, the high-BMD/MLR group exhibited a significantly higher median DFS (high BMD/MLR, 28.5 months [95% CI: 10.7–46.3] vs low BMD/MLR, 12.0 months [95% CI: 9.9–14.1];

Table 4 Demographic, Radiological and Laboratorial Characteristics of the Patients After Propensity Score Matching

Characteristics	Total (n = 208)	Low BMD/MLR (n = 104)	High BMD/MLR (n = 104)	P value
Recurrence within two years, n (%)				0.035
No recurrence	88 (42.31)	36 (34.62)	52 (50.00)	
Recurrence	120 (57.69)	68 (65.38)	52 (50.00)	
Age (y), Mean ± SD	51.57 ± 10.06	51.50 ± 9.61	51.64 ± 10.55	0.918
Gender, n (%)				1.000
Male	179 (86.06)	90 (86.54)	89 (85.58)	
Female	29 (13.94)	14 (13.46)	15 (14.42)	
BCLC, n (%)				0.560
0	19 (9.13)	11 (10.58)	8 (7.69)	
A	170 (81.74)	82 (78.84)	88 (84.62)	
B	19 (9.13)	11 (10.58)	8 (7.69)	
Hepatitis, n (%)				0.463
No	21 (10.10)	12 (11.53)	9 (8.66)	
HBV	161 (77.40)	75 (72.12)	86 (82.69)	
HCV	3 (1.44)	2 (1.92)	1 (0.96)	
Alcohol	7 (3.37)	5 (4.81)	2 (1.92)	
Other	16 (7.69)	10 (9.62)	6 (5.77)	

(*Continued*)

Table 4 (Continued).

Characteristics	Total (n = 208)	Low BMD/MLR (n = 104)	High BMD/MLR (n = 104)	P value
Child-Pugh, n (%)				1.000
A	203 (97.60)	102 (98.08)	101 (97.12)	
B	5 (2.40)	2 (1.92)	3 (2.88)	
Diameter (mm), n (%)				1.000
≤ 50.00	107 (51.44)	54 (51.92)	53 (51)	
> 50.00	101 (48.56)	50 (48.08)	51 (49)	
Albumin (g/L), n (%)				0.394
≤ 35.00	25 (12.02)	15 (14.42)	10 (9.62)	
> 35.00	183 (87.98)	89 (85.58)	94 (90.38)	
TBil (umol/L), n (%)				0.767
≤ 17.10	141 (67.79)	69 (66.35)	72 (69.23)	
> 17.10	67 (32.21)	35 (33.65)	32 (30.77)	
AFP (ug/L), n (%)				0.203
≤ 200.00	124 (59.62)	57 (54.81)	67 (64.42)	
> 200.00	84 (40.38)	47 (45.19)	37 (35.58)	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HBV, *Hepatitis B Virus*; HCV, *Hepatitis C Virus*; TBil, Total bilirubin; AFP, alpha fetoprotein.

P = 0.012) (Figure 5A) and OS (high BMD/MLR, 66.7 months [95% CI: 49.1–84.2] vs low BMD/MLR, 50.3 months [95% CI: 28.2–72.4]; P = 0.026) (Figure 5B).

Combining BMD/MLR and Clinical Markers to Predict Early Recurrence of HCC

ROC curves for BMD/MLR, AFP level, tumor size, and the combination of BMD/MLR, AFP level, and tumor size in their ability to predict early HCC recurrence were illustrated in Figure 6. The corresponding AUC values for these predictors were 0.609, 0.581, 0.630, and 0.703, respectively. A higher AUC value indicates a greater predictive capacity for early recurrence of HCC. In this study, the combination of BMD/MLR, AFP level, and tumor size demonstrated superior discriminatory power in predicting early recurrence of HCC compared to BMD/MLR, AFP level, and tumor size alone.

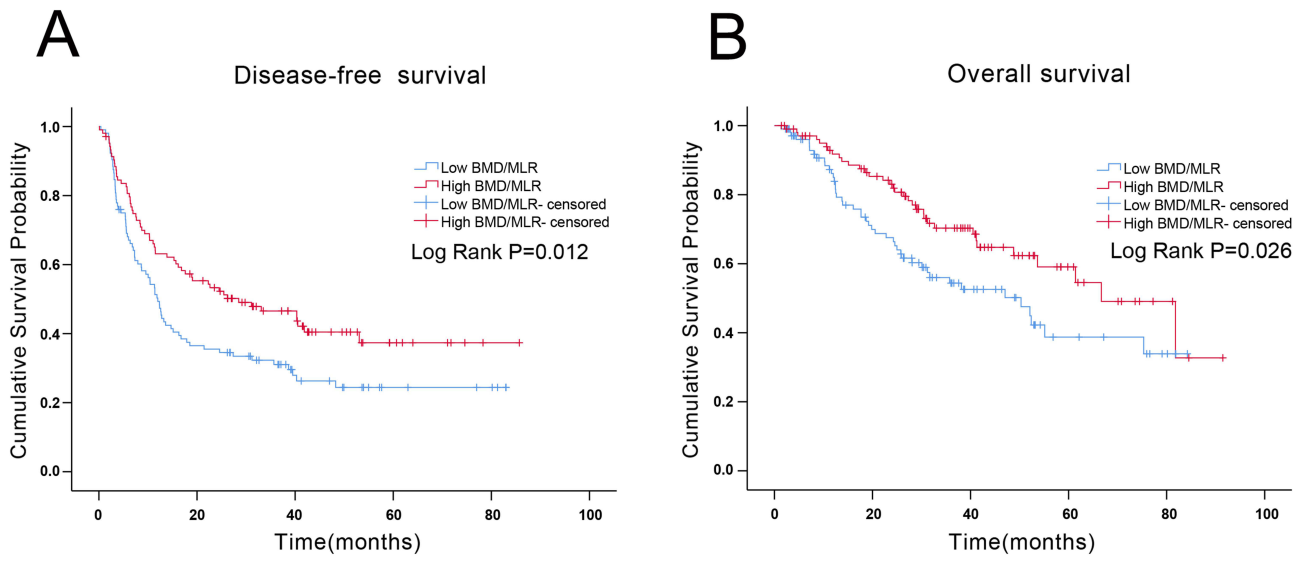

Figure 5 Log rank tests were used to compare DFS (**A**) and OS (**B**) between high BMD/MLR and low BMD/MLR groups after PSM.

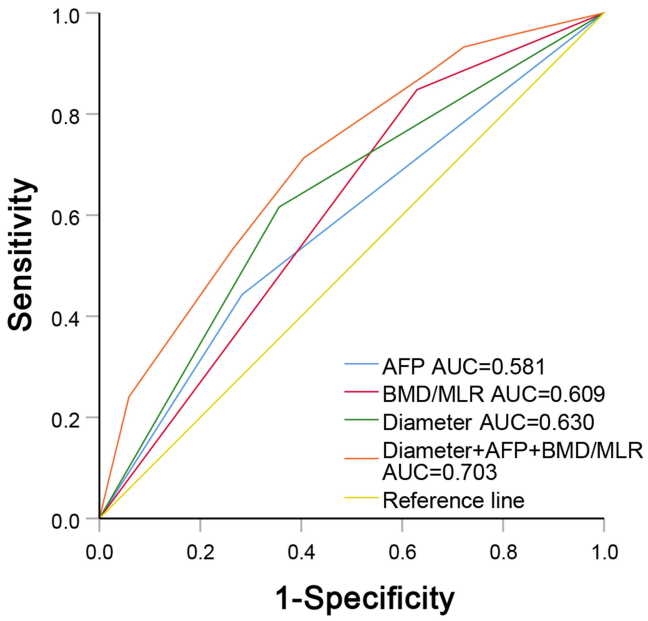

Figure 6 Comparison of the AUCs for AFP, BMD/MLR, diameter and the combination of diameter, AFP level and BMD/MLD in predicting early recurrence of HCC after liver resection.

Discussion

HCC is the predominant form of liver cancer in adults, and liver resection is widely regarded as the primary curative treatment for patients with HCC.[3,4] Nevertheless, despite significant therapeutic progress, HCC exhibits a nearly universal recurrence and fatality rate following liver resection.[8,26] The therapeutic approaches for HCC predominantly rely on factors such as tumor burden, liver function, and performance status, however, the inclusion of patients' inflammation and immune status in the clinical guidelines is lacking. To date, research has documented the potential role of systemic inflammatory biomarkers and nutrient indexes in prognosticating the outcomes of various malignancies.[17,21] Several studies have provided evidence for the predictive value of MLR in patients with HCC. Mao et al found that a high baseline MLR reliably predicts the recurrence of AFP-negative HCC.[27] Silva et al demonstrated that a high pre-treatment MLR is associated with shorter OS in patients with early HCC.[28] Meanwhile, recent studies have identified a novel immunonutrition index BMD as a potential prognostic predictor for patients with HCC. Muller et al showed that BMD is an independent predictive factor for survival in elderly patients with HCC who underwent TACE.[21] Miyachi et al demonstrated that BMD is a highly predictive factor for patients with HCC who underwent liver resection.[29] Moreover, reduced BMD is significantly correlated with sarcopenia, which is a severe condition common to various chronic diseases and it is reckoned as a biomarker of poor prognosis for HCC.[23,24,30] However, these variables have limitations, as MLR solely reflects the inflammatory state of the body, while BMD solely reflects nutritional status. Consequently, a novel composite indicator which combines these two metrics, namely BMD/MLR, was developed in our study. The findings from both univariate and multivariate analyses demonstrate a significant association between early HCC recurrence and elevated BMD/MLR, as well as larger tumor size and higher AFP level. Moreover, Kaplan-Meier survival analysis demonstrated that a high BMD/MLR remained an unfavorable biomarker for both OS and PFS before and after PSM.

The literature reports a close association between inflammation, nutrition, and the progression of malignancies.[15,16] Within the tumor microenvironment, tumor and immune cells can produce various cytokines such as pro-inflammatory mediators, growth factors, and chemokines during the inflammatory process, all of which play a role in tumor progression.[31,32] Peripheral blood monocytes can be mobilized towards the tumor stroma and differentiate into tumor-associated macrophages. These macrophages can facilitate tumor progression and confer resistance to therapeutic interventions via several mechanisms. Primarily, this involves the upregulation of CXCL6, CCL2, CCL17, and CCL24, which in turn attract chemokines, myeloid-derived inhibitory cells, and regulatory T cells, thereby inducing

immunosuppressive effects.[31] Peripheral blood lymphocytes can migrate to the tumor microenvironment and differentiate into different subtypes. For example, CD8+ cytotoxic lymphocytes can identify tumor antigens and induce apoptosis in cancer cells through the production of cytotoxins like perforin and granzyme,[33,34] while γδ T cells exhibit the capacity to promptly recognize and respond to a wide range of tumor antigens.[35] Meanwhile, BMD serves as an indicator of the body's nutritional status, which influences the completeness of the immune surveillance and subsequently affecting the efficacy of the timely detection of recurrent tumor cells.[21,29] In general, both MLR and BMD exhibit associations with the prognosis of HCC and a combination of these two indicators may offer enhanced predictive efficacy. Given that an elevated inflammatory index signifies a robust inflammatory response, while a diminished bone mineral density indicates suboptimal nutritional status, we devised a novel indicator, BMD/MLR, which amalgamates these two measures. This amalgamation enables us to obtain a more robust predictor for HCC prognosis.

The clinical significance of this study resides in the provision of a relatively convenient and non-invasive biomarker which combines inflammation and nutrition status to predict early recurrence and long-term survival in patients with HCC who have undergone liver resection. Furthermore, previous research has indicated that models incorporating multiple factors exhibit improved predictive abilities. Likewise, the incorporation of BMD/MLR with other clinical markers was found to enhance their predictive efficacy in this study. This information can assist clinicians in identifying patients who have an increased risk of recurrence after liver resection.

Considering these notable findings, it is imperative to acknowledge the limitations inherent in the current study. Firstly, it is crucial to recognize that this study adopted a retrospective design, rendering it inherently vulnerable to potential biases, particularly selection bias. Secondly, it should be noted that our study was conducted in a region with a high prevalence of hepatitis B, which is not the predominant etiology of HCC in Europe or America. Consequently, caution should be exercised when generalizing our findings to the global population. It is imperative to conduct further validation studies encompassing larger and more diverse patient cohorts to substantiate the clinical applicability of this biomarker.

Conclusion

In summary, our findings indicate that a heightened preoperative BMD/MLR level serves as a distinct risk factor for early tumor recurrence and unfavorable prognosis among patients with HCC who undergo liver resection. Consequently, incorporating BMD/MLR as a biomarker may be practical in a clinical setting, enabling clinicians to develop more rational and personalized treatment strategies.

Data Sharing Statement

The data sets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

This retrospective study was approved by the institutional review boards of the Second Xiangya Hospital of Central South University, in accordance with the principles outlined in the Declaration of Helsinki. Given the retrospective nature of the study and the anonymization and de-identification of patient data prior to analysis, the need for written consent was waived.

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Disclosure

The authors report no conflicts of interest in this work.

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