Monocyte-to-High-Density Lipoprotein-Cholesterol Ratio Predicts Prognosis of Hepatocellular Carcinoma in Patients with Metabolic-Associated Fatty Liver Disease

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Purpose: The incidence of non-B and non-C hepatocellular carcinoma (NBNC-HCC) is increasing globally. Metabolically associated fatty liver disease (MAFLD) has been a contributing factor to this rising trend in NBNC-HCC incidence. The monocyte-to-high-density lipoprotein-cholesterol ratio (MHR) is a new prognostic marker that connects systemic inflammation with disorders of lipid metabolism. Therefore, MHR may be a potential prognostic predictor of patients with MAFLD-related HCC (MAFLD-HCC). This study aims to investigate the relationship between the MHR and prognosis of patients with MAFLD-HCC and construct a novel prognostic prediction tool for MAFLD-HCC.

Patients and Methods: This retrospective study of patients with MAFLD-HCC included training (n = 112) and internal validation (n = 37) cohorts. Univariate and multivariate Cox proportional hazard regression analysis was conducted to identify independent risk factors of survival. A visual nomogram was constructed to assess the performance of the two groups. Furthermore, receiver operating characteristic (ROC) curves and calibration curves were used to verify the prognostic discriminative ability of this nomogram, even in the MHR, ALBI grade, and MHR–ALBI model.

Results: Univariate and multivariate analyses revealed that extrahepatic metastases, Vascular invasion, Barcelona staging B, C, D, elevated ALBI Grade 3, C-reactive protein (CRP), and MHR were independent risk factors for the prognosis of MAFLD-HCC. Moreover, calibration plots showed good discrimination and consistency when the significant factors were entered into the nomogram. Meanwhile, the MHR strongly correlated with the prognosis of cancer under a background of MAFLD-HCC, with a sensitivity of 88.89% and a specificity of 79.61%. Importantly, the performance of the MHR alone (AUC = 86.2) was not only superior to the ALBI grade (AUC = 63.8) but was comparable to the combination of MHR and ALBI (AUC = 88.5).

Conclusion: The novel nomogram demonstrated good value in predicting the overall survival of patients with MAFLD-HCC. The MHR may be a potential predictor of prognosis.

Keywords: lipid metabolism, MAFLD-HCC, prognostic prediction, nomogram, MHR

Introduction

Hepatocellular carcinoma (HCC) has a high morbidity and mortality. Worldwide, 906,000 new cases of HCC are recorded annually.[1] Although chronic infections with hepatitis B (HBV) and C viruses (HCV), chronic alcohol consumption, and diabetes or obesity-related non-alcoholic steatohepatitis (NASH) mainly contribute to HCC, the incidence of virus-related HCC has decreased in recent years with HBV vaccination programs, control of HCV transmission, and changes in lifestyle. Notably, there is an increase in the number of patients with non-virus HCC (non-B, non-C HCC [NBNC-HCC]) associated with metabolic syndrome.[2] Metabolically associated fatty liver disease (MAFLD) has been a contributing factor to this rising trend in NBNC-HCC incidence. MAFLD, which is the proposed new term instead of NAFLD as it better reflects the metabolic nature, is closely related to metabolic syndrome.[3,4] Moreover, multiple complications, such as diabetes, hypertension, and hypertriglyceridemia, result in the limitation of treatment options that lead to poor prognosis of patients with HCC in the context of MAFLD. Additionally, levels of related indices, including C-reactive protein (CRP) or serum high-density lipoprotein (HDL)-cholesterol (HDL-C) are altered,[5–7] which may also play an important role in MAFLD-HCC. However, the relationship between MAFLD and CRP or HDL-C remains unclear. Thus, understanding the risk factors associated with MAFLD-HCC and accurately assessing its prognosis are crucial for prognostic counseling, follow-up and surveillance, and treatment decisions.

Currently, there is no consensus regarding the optimal tool for prognosticating MAFLD-HCC, which may partially contribute to failure of clinical therapy. Prognostic prediction models, including the China liver cancer staging, Japan integrated staging score and Barcelona Clinic Liver Cancer (BCLC) system, utilize various clinical and pathological factors to stratify patients into different risk groups based on their likelihood of disease progression, recurrence, or survival, further enabling prognostic assessments. Meanwhile, the ALBI grading system, which relies on serum bilirubin and albumin levels as crucial indicators for assessing liver function, is frequently employed to assess the recurrence and prognosis of patients with HCC.[8] Nevertheless, each prognostic prediction model has specific limitations, and may not be applicable to all clinical scenarios encountered. Additionally, the monocyte-to-HDL-C ratio (MHR), which is the ratio of the monocyte count to HDL-C level, has been proposed as a potential marker of systemic inflammation and oxidative stress.[9–11] Several studies have suggested that an elevated MHR is associated with a higher risk for MAFLD and cardiometabolic diseases;[12,13] the MHR may be a potential predictor of prognosis of MAFLD-HCC. However, using the MHR in the assessment and management of MAFLD-HCC has not been validated.

Therefore, in this study, we aimed to determine the following: 1) characterize MAFLD-HCC and reveal the related factors; 2) investigate the relationship between the MHR and prognosis of patients with MAFLD-HCC; and 3) construct a novel prognostic prediction tool for MAFLD-HCC.

Patients and Methods
Subjects

All patients with HCC (n=2311) were recruited from Hebei Medical University Third Hospital from January 2011 to December 2020. HCC was diagnosed according to the practice guidelines recommended by the American Association for the Study of Liver Diseases.[14] The patients who were seronegative for hepatitis B surface antigen, HBV-DNA, hepatitis C antibody, and HCV-RNA test were considered patients with NBNC-HCC (n=321).[15] The inclusion criteria were as follows: 1) pathological/clinical diagnosis of NBNC-HCC, 2) age≥18 years, 3) more than 48h of hospitalization, 4) MAFLD was defined by either MRI imaging findings or liver biopsy where the presence of >5% liver steatosis.[5] After 172 patients were excluded including non-MAFLD, a history of other cancers, or incomplete clinical data, a total of 149 patients with MAFLD-HCC were included in this study. Additionally, we developed an internal validation dataset came from these patients through 30% selection randomly (shown in Figure 1). Written informed consent was obtained from all the participants of this study. This study was approved by the institutional ethics committee of the Third Hospital of Hebei Medical University (Approve Number: K2019-014-2), and it conformed to the ethical guidelines of the Declaration of Helsinki.

Data Collection

All patients underwent routine examinations, which included hepatitis B and C immunology, HBV-DNA load, alpha-fetoprotein (AFP) levels, liver and kidney function examinations, ultrasonography, dynamic contrast-enhanced computed
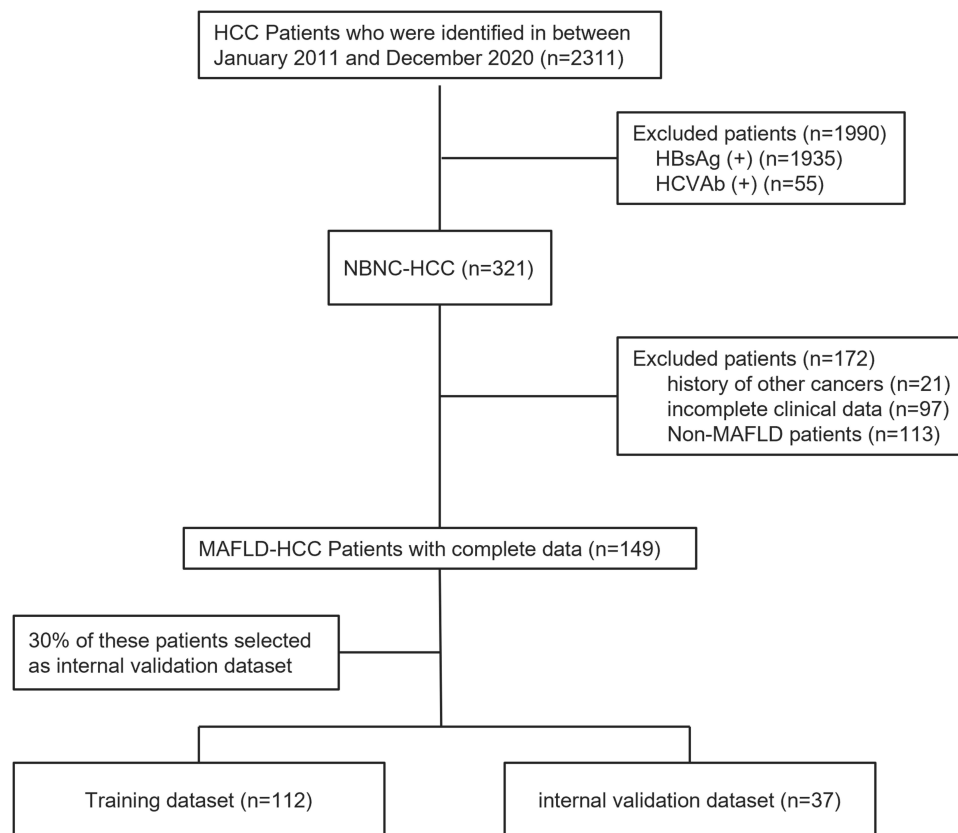
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Figure 1 Patients selection flow diagram.
Abbreviations: HCC, hepatocellular carcinoma; NBNC-HCC, non-B and non-C hepatocellular carcinoma; MAFLD, metabolically associated fatty liver disease.

tomography (CT) and magnetic resonance imaging (MRI). Clinical information and laboratory data of patients was collected from electronic medical records system. Patients' information was involved in demographic characteristic (age, sex, smoking status, alcohol consumption), comorbidity (liver cirrhosis, hypertension, diabetes), and family history of cancers.

Clinical Variables

For hematological investigations, we utilized the initial results from the hospitalization upon admission. The formulas for calculating the indices (MHR, NLR, and NγLR) have been previously described in studies.[11,12,16–18] The imaging data, including macrovascular invasion, extrahepatic metastases, was obtained from contrast-enhanced computed tomography or contrast-enhanced magnetic resonance imaging. Tumor diameter was the diameter of the largest tumor. ALBI scores were calculated using the following formula: -0.085 (albumin g/l) + 0.66 log (bilirubin μmol/l). ALBI grades 1, 2, and 3 are defined as ALBI scores of ≤-2.60, >-2.60 to ≤-1.39, and >-1.39, respectively.[8] Macrovascular invasion was defined as vascular invasion of large vessels detectable radiologically.

Survival Outcome

Patient follow-up data were carried out through outpatient visits, hospitalization records, and regular telephone follow-ups. The primary survival outcomes observed in this study was the overall survival (OS) of patients with HCC, defined as the time from the initial cancer diagnosis to either death or the last censored data point.

Statistical Methods

The 149 patients were randomly divided into either a training cohort for creating a new prognostic model or a validation cohort for evaluating the resulting prognostic index, roughly in a 3:1 ratio. Categorical variables were presented as percentages and

continuous variables were expressed as the mean ± standard deviation [SD] or median with interquartile range [IQR], the latter for variables with highly skewed. Categorical data were compared by the Pearson χ2 test or the Fisher exact test, while continuous variables were assessed by Student's *t* test. OS was calculated using the Kaplan-Meier method and compared with the Log rank test. Univariate analysis was performed to identify significant prognostic factors by using the Cox regression model. The multivariate Cox proportional hazards regression model was performed to identify independent predictors by including all the variables demonstrated to be significant in the univariate analyses. All statistical analyses were performed with SPSS18.0 (SPSS Inc., Chicago, IL). Statistical significance was defined as P<0.05.

Results

Clinical Characteristics

Overall, 149 patients with MAFLD-HCC were randomly divided into training (n = 112) and validation (n = 37) cohorts in a 3:1 ratio. There was no statistical difference in clinical characteristics between the two cohorts (P > 0.05). The average ages in the training and validation cohorts were 61.88 ± 10.3 and 62.59 ± 9.89 years, respectively. Most of the patients with MAFLD-HCC were men (60.7–62.2%) and had cirrhosis (69.6%–81.1%). In the training cohort, 20 patients (17.9%) were classified as BCLC-A, 27 (24.1%) were BCLC-B, 51 (45.5%) were BCLC-C, and 14 (12.5%) were BCLC-D. Meanwhile, 21 patients (18.8%) were classified as ALBI-1, 73 (65.2%) were ALBI-2, and 18 (16.1%) were ALBI-3. In the validation cohort, 5 patients (13.5%) were classified as BCLC-A, 12 (32.4%) were BCLC-B, 17 (45.9%) were BCLC-C, and 3 (8.1%) were BCLC-D. Additionally, 9 patients (24.3%) were classified as ALBI-1, 14 (37.8%) were ALBI-2, and 14 (37.8%) were ALBI-3. In the training and validation cohorts, there were 89 (79.5%) and 29 (78.4%) patients with diabetes, as well as 24 (21.4%) and 10 (27%) patients with hypertension, respectively. In both cohorts, cirrhosis was present in 69.6% and 81.1% of MAFLD-HCC patients. (Table 1).

Table 1 Baseline Characteristics of Patients with MAFLD-HCC

Baseline Characteristic	Training Cohort (N=112)	Internal Validation Cohort (N=37)	P value
Age, years	61.88±10.30	62.59±9.89	0.710
Gender			0.876
Male, n (%)	68 (60.7)	23 (62.2)	
Female, n (%)	44 (39.3)	14 (37.8)	
Cigarette smoking, n (%)	13 (11.6)	2 (5.4)	0.277
Alcohol consumption, n (%)	12 (10.7)	4 (10.8)	0.987
Diabetes, n (%)	89 (79.5)	29 (78.4)	0.889
Hypertension, n (%)	24 (21.4)	10 (27.0)	0.482
Cirrhosis, n (%)	78 (69.6)	30 (81.1)	0.177
Ascites, n (%)	54 (48.2)	24 (64.9)	0.079
Macrovascular invasion*, n (%)	23 (20.5)	9 (24.3)	0.627
Extrahepatic metastases*, n (%)	27 (24.1)	8 (21.6)	0.757
AFP, ng/mL (%)			0.382
≤20	69 (61.6)	18 (48.6)	
20–400	7 (6.3)	3 (8.1)	
≥400	36 (32.1)	16 (43.2)	
BCLC staging system, n (%)			
A	20 (17.9)	5 (13.5)	
B	27 (24.1)	12 (32.4)	
C	51 (45.5)	17 (45.9)	
D	14 (12.5)	3 (8.1)	

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Table 1 (Continued).

Baseline Characteristic	Training Cohort (N=112)	Internal Validation Cohort (N=37)	P value
ALBI grade, n (%)			
1	21 (18.8)	9 (24.3)	
2	73 (65.2)	14 (37.8)	
3	18 (16.1)	14 (37.8)	
ALBI grade	−1.99±0.74	−1.87±0.94	0.457
BMI (kg/m^2)	24.19±3.97	23.92±4.21	0.720
ALT (U/L)	66.09±71.87	61.15±71.41	0.717
AST (U/L)	106.24±137.43	102.78±106.33	0.889
ALB (g/L)	36.07±6.54	35.10±8.83	0.479
TB (umol/L)	84.69±118.89	89.74±105.73	0.818
DB (umol/L)	60.03±91.84	65.06±83.87	0.768
LDH (U/L)	387.43±327.96	373.30±333.19	0.821
γ-GT (U/L)	198.50±168.66	256.52±279.35	0.131
CRP (mg/L)	27.81±22.82	28.30±17.98	0.906
UREA (mmol/L)	8.33±6.20	9.01±5.53	0.555
CRE (umol/L)	86.20±48.46	87.51±51.30	0.889
TG (mmol/L)	1.37±0.75	1.38±0.76	0.932
HDL-C (mmol/L)	0.78±0.36	0.69±0.40	0.172
LDL-C (mmol/L)	3.07±1.23	3.06±1.73	0.971
WBC (10^9/L)	8.07±6.04	7.78±5.03	0.795
RBC (10^{12}/L)	3.67±0.64	3.60±0.60	0.546
HGB (g/L)	113.31±22.86	114.7±19.94	0.742
PLT (10^9/L)	174.49±109.96	159.74±93.30	0.465
Monocyte Count (10^9/L)	0.44±0.26	0.39±0.25	0.382
Neutrophil Count (10^9/L)	5.64±4.37	5.64±5.00	0.996
Lymphocyte Count (10^9/L)	1.33±1.00	1.23±0.79	0.558
NLR	5.60±4.14	5.70±4.71	0.900
MHR	1.30±2.03	1.89±2.89	0.176
NγLR	1327.65±1931.06	1388.63±1703.99	0.864
OS (months)	17.61±10.75	18.76±17.61	0.635

Notes: Data are presented as mean ± standard deviation. * Images were obtained from contrast-enhanced Computed Tomography or contrast-enhanced magnetic resonance imaging.
Abbreviations: AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ALBI, albumin-bilirubin; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; TB, total bilirubin; DB, direct bilirubin; LDH, lactate dehydrogenase; γ-GT, gamma-glutamyl transpeptidase; CRP, C-reactive protein; CRE, creatinine; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet; NLR, neutrophil to lymphocyte ratio; MHR, monocyte -to-HDL ratio; NγLR, neutrophil times g-glutamyl transpeptidase to lymphocyte ratio; OS, Overall Survival.

Development of Prognostic Nomogram for Prediction of Survival

Univariate Cox proportional hazard regression analyses showed that there was a significant relationship between the MHR, ALBI, and survival, and that the monocyte count, neutrophil count, ALT, AST, TP, ALB, TB, CRP, LDH, γ-GT, WBC, PLT, AFP, UREA, and CRE levels, BCLC stage, extrahepatic metastases, and macrovascular invasion were optimal indicators (Table 2). Moreover, multivariate analyses revealed that extrahepatic metastases (hazard ratio with 95% confidence interval [CI] = 2.014 [1.077–3.766], P = 0.028), macrovascular invasion (2.075 [1.068–4.03], P = 0.031), BCLC-B (2.369 [1.091–5.144], P = 0.029), BCLC-C (4.449 [1.957–10.114], P < 0.001), BCLC-D (26.473 [7.978–87.843], P < 0.001), ALBI grade 3 (11.687 [1.625–84.029], P = 0.015), CRP level (1.018 [1.006–1.03], P = 0.003), LDH level (0.998 [0.997–1.004], P = 0.003), and MHR (1.491 [1.24–1.791], P < 0.001) were independent risk factors (Table 3). A prognostic nomogram model of patients with MAFLD-HCC was also constructed by integrating statistically significant variables (Figure 2).

Table 2 Univariate Cox Regression Analysis of Risk Factors of Survival in Training Cohort

Variable	HR	95% CI	P value
Diabetes	2.365	1.411–3.966	0.001
Extrahepatic metastases	2.655	1.676–4.205	<0.001
Macrovascular invasion	2.829	1.744–4.588	<0.001
BCLC Staging			
A	REF		
B	2.629	1.350–5.120	0.004
C	7.519	3.908–14.464	<0.001
D	28.938	12.342–67.853	<0.001
ALT	1.005	1.002–1.008	0.001
AST	1.003	1.002–1.005	<0.001
TP	0.949	0.909–0.990	0.016
ALB	0.968	0.938–0.999	0.046
ALBI Grade	1.541	1.168–2.032	0.002
ALBI Grade			
1	REF		
2	1.563	0.927–2.636	0.094
3	3.252	1.676–6.039	<0.001
TB	1.003	1.002–1005	<0.001
CRP	1.017	1.009–1.025	<0.001
LDH	1.001	1.000–1.001	0.006
γ-GT	1.002	1.001–1.003	0.001
UREA	1.096	1.049–1.146	<0.001
CRE	1.007	1.002–1.012	0.008
MHR	1.368	1.244–1.503	<0.001
WBC	1.061	1.030–1.092	<0.001
PLT	1.002	1.000–1.004	0.028
Monocyte Count	4.110	1.885–8.957	<0.001
Neutrophil Count	1.090	1.042–1.139	<0.001
AFP			
≤20	REF		
20–400	1.931	0.871–4.280	0.105
≥400	1.559	1.020–2.381	0.040

Abbreviations: HR, hazard ratio; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; REF, reference; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TP, total protein; ALB, albumin; ALBI, albumin-bilirubin; TB, total bilirubin; CRP, C-reactive protein; LDH, lactate dehydrogenase; γ-GT, gamma-glutamyl transpeptidase; CRE, creatinine; MHR, monocyte -to-HDL ratio; WBC, white blood cell; PLT, platelet; AFP, alpha fetoprotein.

Performance of Nomogram in Prognostic Prediction

Calibration plots revealed 1-, 2-, and 3-year survival in patients with MAFLD-HCC (Figure 3). Additionally, receiver operating characteristic (ROC) curves also showed the survival of patients with MAFLD-HCC with high accuracy in the training (1-year, area under the curve [AUC] = 90.6 [95% CI: 0.854–0.959]; 2-year, AUC = 92.4 [95% CI: 0.91–0.997]; 3-year, AUC = 91.6 [95% CI: 0.899–0.988]), and validation (1-year, AUC = 92.4 [95% CI: 0.832–1.00]; 2-year, AUC = 92.4 [95% CI: 0.836–1.00], 3-year, AUC = 89.2 [95% CI: 0.786–0.999]) cohorts (Figure 4).

## Analyses of the Prognostic Value of MHR, ALBI Grade, and MHR–ALBI

Next, we used the MHR to predict the survival of patients with MAFLD-HCC. As shown in Figure 5, the AUCs of MHR at different time points (1-, 2-, and 3-year) were 0.734 (95% CI: 0.636–0.832), 0.749 (95% CI: 0.657–0.842), and 0.862 (95% CI: 0.773–0.955), respectively. Meanwhile, the sensitivity and specificity for 3-year survival was 88.89% and

Table 3 Multivariate Cox Regression Analyses of Risk Factors of Survival in Training Cohort

Variable	HR	95% CI	P value
Extrahepatic metastases	2.014	1.077–3.766	0.028
Macrovascular invasion	2.075	1.068–4.03	0.031
BCLC staging system			
A	REF		
B	2.369	1.091–5.144	0.029
C	4.449	1.957–10.114	<0.001
D	26.473	7.978–87.843	<0.001
ALBI Grade			
1	REF		
2	4.807	1.498–15.427	
3	11.687	1.625–84.029	0.015
CRP	1.018	1.006–1.030	0.003
LDH	0.998	0.997–1.004	0.003
MHR	1.491	1.240–1.791	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; REF, reference; ALBI, albumin-bilirubin; CRP, C-reactive protein; LDH, lactate dehydrogenase; MHR, monocyte -to-HDL ratio.

79.61%, respectively. Similarity, according to the quartile of MHR (Q1–Q4), Kaplan–Meier survival curves at 12-, 24-, 36-month were the following: Q1, <0.32; Q2, ≥0.32, <0.56; Q3: ≥0.56, <1.35; Q4: ≥1.35. Kaplan–Meier analysis also showed a significant relationship between MHR and overall survival (OS). Additionally, the MHR was significantly associated with poor OS in patients with MAFLD-HCC (Log rank test; HR, 1.491, 95% CI: 1.24–1.791, P < 0.05) (Figure 6). Based on the ALBI grade, we plotted the ROC curves at 1-year (0.644 [95% CI: 0.540–0.749]), 2-year (0.647 [95% CI: 0.530–0.763], and 3-year (0.638 [95% CI: 0.464–0.811]) and the KM curve, which showed that patients with ALBI grade 3 had the lowest survival rate (Figures 7–8).
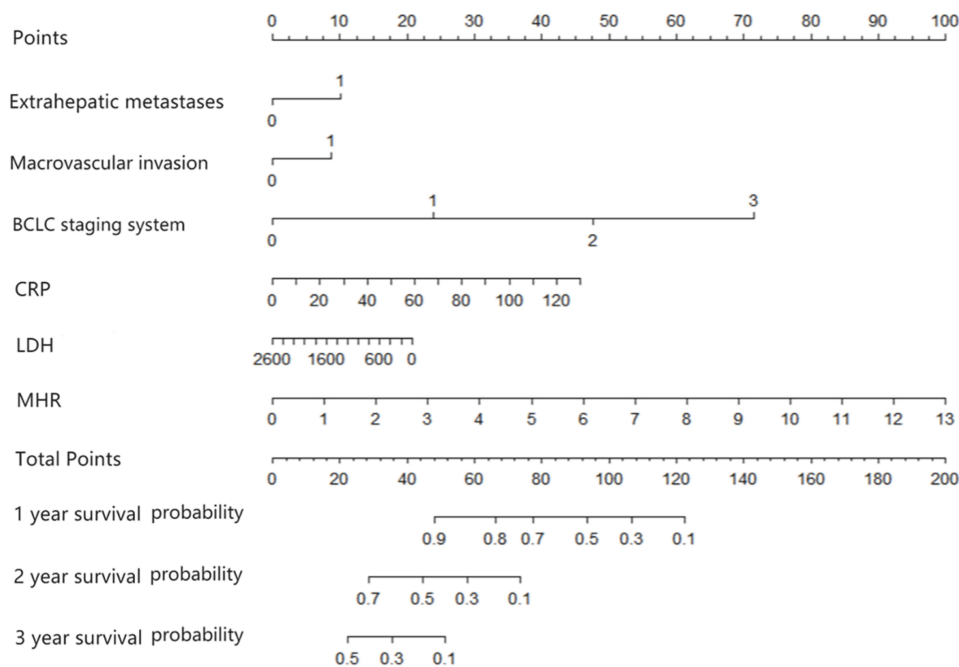
Figure 2 Nomogram predicting OS in patients with MAFLD-HCC.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CRP, C-reactive protein; LDH, lactate dehydrogenase; MHR, monocyte -to-HDL ratio.
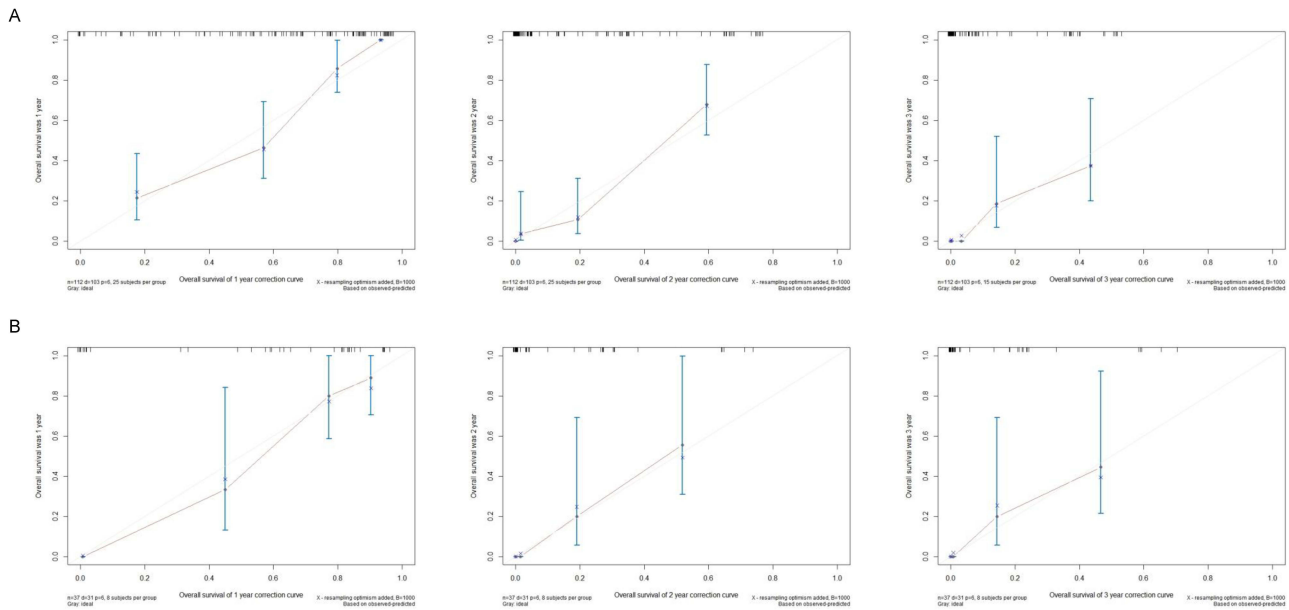
Figure 3 The calibration curves for predicting the 1-, 2-, and 3-year nomogram in the training cohort(**A**) and validation cohort(**B**).
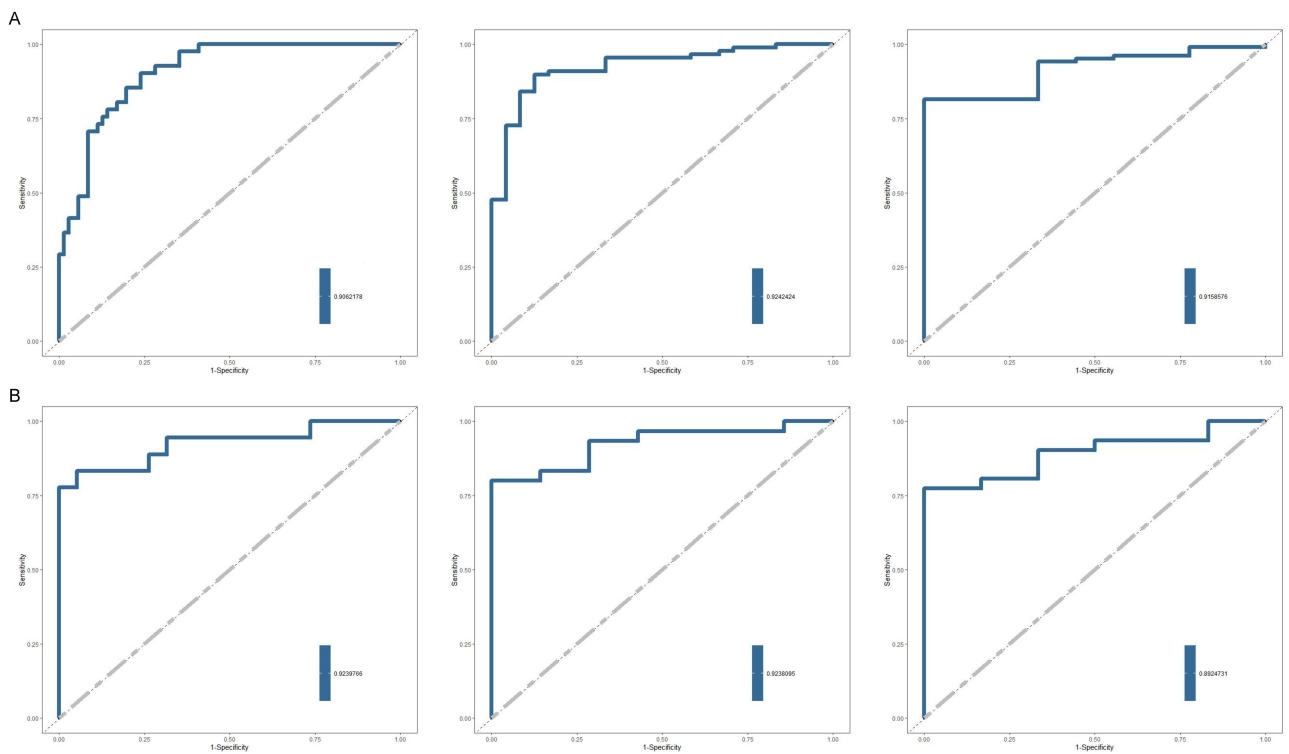

Figure 4 ROC curve analysis for 1-, 2-, and 3-year in the training cohort(**A**) and validation cohort(**B**).

We also found that the predictive ability of the MHR in patients with MAFLD-HCC may be enhanced by integrating the ALBI grade. We compared the predictive values of the MHR, ALBI grade, and MHR–ALBI for survival in 3-year periods, revealing that the AUCs were 0.862, 0.638, and 0.885, respectively (Figure 9). In terms of predictive value, although the MHR–ALBI was not superior over the MHR, the MHR–ALBI model had a higher specificity (88.9%) than the MHR-only model (79.61%).
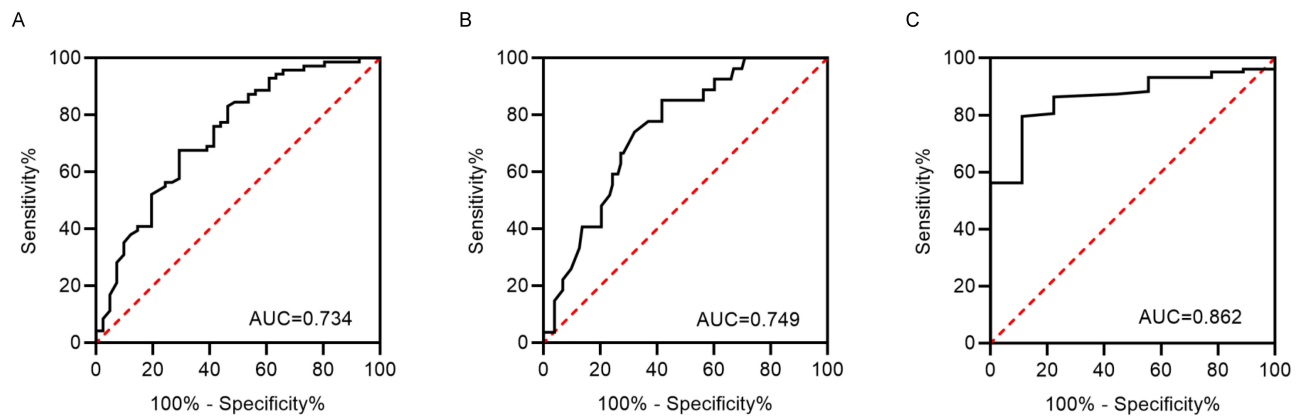
Figure 5 ROC curve analysis of MHR for 1-year (**A**), 2-year (**B**), and 3-year (**C**).
Abbreviations: MHR, monocyte -to-HDL ratio; ROC, receiver operating characteristic; AUC, area under ROC curve.
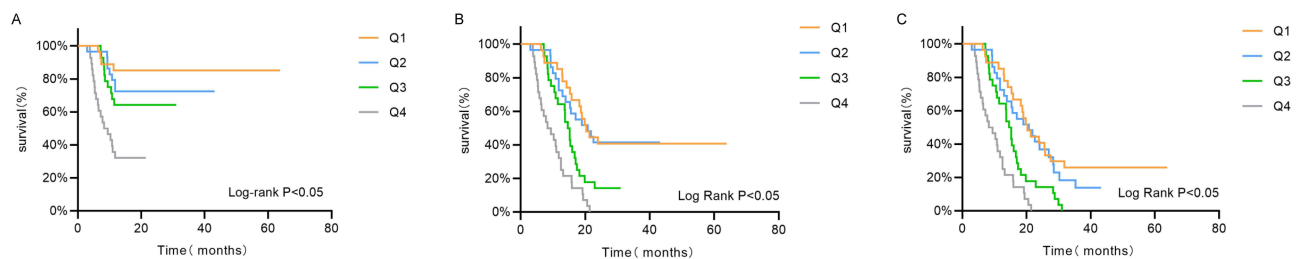
Figure 6 Kaplan-Meier curve analysis of MHR for 12-month (**A**), 24-month (**B**), and 36-month (**C**).
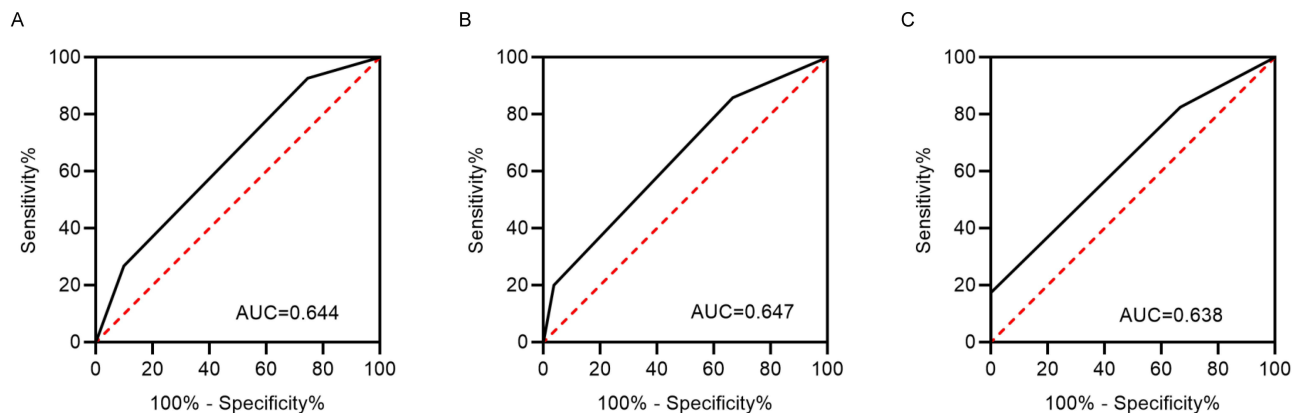**Abbreviation**: MHR, monocyte -to-HDL ratio.

Figure 7 ROC curve analysis of ALBI Grade for 1-year (**A**), 2-year (**B**), and 3-year (**C**).
Abbreviations: ALBI, albumin-bilirubin; ROC, receiver operating characteristic; AUC, area under ROC curve.

Kaplan–Meier curves for MHR and MHR–ALBI effectively stratified the survival outcomes of patients with MAFLD-HCC. According to the cutoff value of the 36-month ROC curve for MHR, patients were divided into high and low expression groups. Survival curves were subsequently plotted for 12-, 24-,36-month in conjunction with the ALBI grade. In the MHR–ALBI model, the median OS was longest in patients with an ALBI grade of 1 and low MHR (MHR < 0.325), whereas it was shortest in patients with an ALBI grade of 2 and 3 and high MHR (MHR > 0.325); the differences were statistically significant (p < 0.05) (Figure 9).
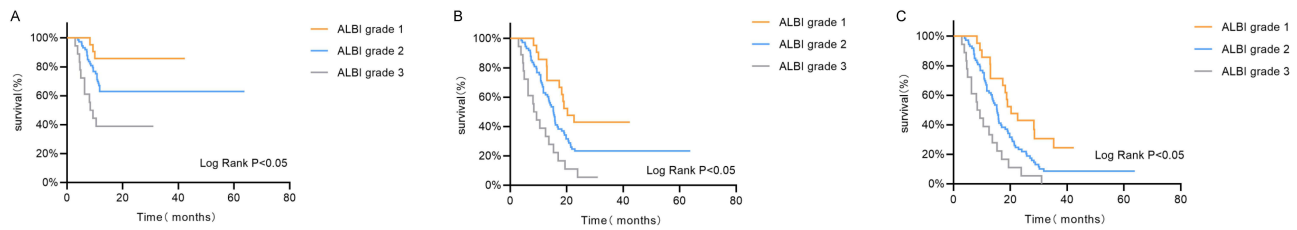
Figure 8 Kaplan-Meier curve analysis of ALBI Grade for 12-month (**A**), 24-month (**B**), and 36-month (**C**).
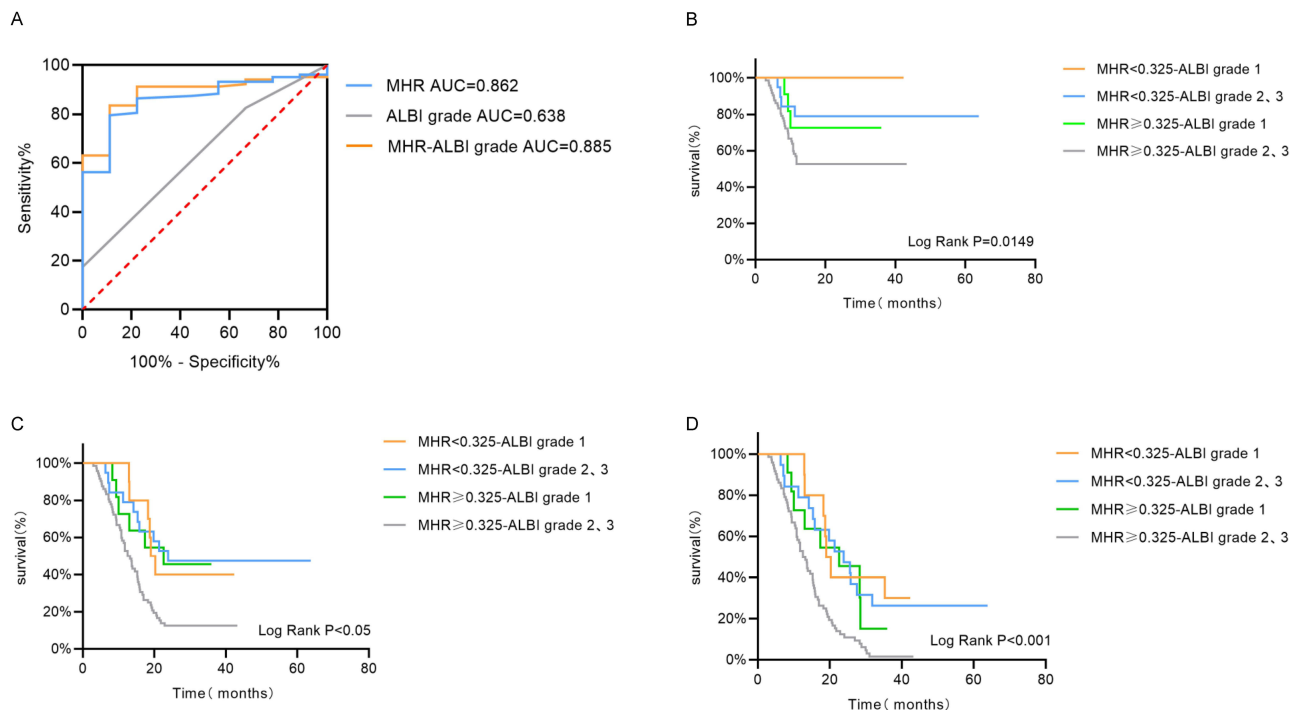**Abbreviation**: ALBI, albumin-bilirubin.

Figure 9 ROC curve analysis of MHR-ALBI for 3-year (**A**); Kaplan-Meier curve analysis of MHR-ALBI for 12-month (**B**), 24-month (**C**), and 36-month (**D**).
Abbreviations: MHR, monocyte -to-HDL ratio; ALBI, albumin-bilirubin; ROC, receiver operating characteristic; AUC, area under ROC curve.

Discussion

It is necessary to accurately predict the prognosis of patients with NBNC-HCC as the disease has an insidious onset with a poor prognosis when compared with HCC associated with viral hepatitis.[18] Among patients in this study, 82.1% had intermediate to advanced HCC, but only 17.9% received curative treatment. Metabolic syndrome is regarded as a risk factor for HCC, particularly for NBNC-HCC. NBNC-HCC caused by metabolic syndrome and MAFLD, which is characterized by abnormal lipid accumulation, may be associated with each other.[19–21] The incidence rate of MAFLD in China has significantly increased. In this study, MAFLD-HCC comprised 46.4% of the NBNC-HCC cases. Several studies have shown that the prevalence of MAFLD is greater in individuals with type 2 diabetes (T2D), ranging from 60% to 75%.[22,23] MAFLD-HCC and T2D are becoming increasingly clinically significant, with 79.5% of MAFLD-HCC patients also having T2D in this study. Moreover, 69.6% of patients with MAFLD-HCC had liver cirrhosis, similar to that in other studies on HCC in the background of metabolic syndrome or MAFLD.[24–26]

Due to the complicated nature of this disease, the prognosis and treatment decisions for patients with MAFLD-HCC can be challenging. Presently, the most used staging system for HCC is the BCLC;[27] however, it may not fully capture the unique characteristics and prognosis of patients with MAFLD-HCC. Developing staging systems specifically customized for MAFLD-HCC could significantly improve the precision of prognosis prediction and treatment decisions. Additionally,

metabolic dysregulation stands as a defining feature of MAFLD-HCC. Factors such as obesity, diabetes, and dyslipidemia can impact the progression of the disease and response to treatment. Hence, to better predict the prognosis and guide therapeutic choices for MAFLD-HCC, it is essential to construct a suitable model combining representative factors of metabolic syndrome and inflammation. Nomogram, a valuable and convenient tool for individualized cancer prognoses, represents an application direction from transforming complex regression equations into visual graphics.[28] By generating an intuitive graph for a statistical predictive model, nomograms are utilized not only for predicting the risk of tumor occurrence but are also widely employed in the assessment of various cancer prognoses, such as lung cancer,[29] liver cancer,[30–32] and other malignancies, serving as valuable references for clinicians in devising tailored preventive and treatment strategies for patients. Hence, we developed and validated a novel nomogram that can provide individual prediction of OS for patients with MAFLD-HCC. This practical prognostic model incorporates BCLC staging and lipid metabolism parameters as well as extrahepatic metastases, macrovascular invasion, and CRP and LDH levels.

Extrahepatic metastases and macrovascular invasion are known independent prognostic factors correlated with advanced tumor stage and poor clinical outcomes. The incidence of HCC accompanied by portal vein tumor thrombus ranged from 44% to 62.2%. Moreover, the median survival period in the absence of any interventions was 2.7 months.[33] In this study, in both training and validation cohorts, patients with macrovascular invasion comprised 20.5% and 24.3%, respectively. CRP is not only an inflammatory marker but is also a prognostic indicator in MAFLD-HCC. Studies have shown that elevated CRP levels are associated with poorer outcomes and an increased risk for disease progression in patients with MAFLD-HCC,[34–37] suggesting that monitoring CRP levels in patients with MAFLD-HCC may provide valuable insights into the presence and severity of inflammation as well as more severe liver injury and disease state and a high risk for complications or unfavorable prognosis.[38] Monocytes play a significant role in the initial immune response and inflammation in HCC, recruiting cells to the tumor microenvironment and differentiating into tumor-associated macrophages, which contribute to increased tumor progression, metastasis, and reduced patient survival.[39–41] HDL-C removes cholesterol from peripheral tissues, including the liver, through reverse cholesterol transport, thereby attenuating inflammation and oxidative stress properties, positively impacting the prognosis of patients with NAFLD-HCC.[42,43] The role of HDL should be further researched in patients with MAFLD-HCC.

The MHR has been proposed as being representative of both systemic inflammation and abnormal lipid metabolism.[44–46] While the specific influence of MHR on the prognosis of MAFLD-HCC remains unknown, it has been studied as a potential prognostic marker in various diseases, especially cardiovascular diseases.[47,48] Moreover, an elevated MHR represents high levels of systemic inflammation linked to a worse prognosis in various cancers.[49] Furthermore, dysregulated lipid metabolism is a hallmark of MAFLD and has the potential to contribute to tumor growth, angiogenesis, and metastasis.[50–52] Therefore, the MHR may provide insights into the interaction between inflammation and lipid metabolism in MAFLD-HCC. Our study revealed that the constructed nomogram was a valuable prognostic tool for patients with MAFLD-HCC that performed well, and the time-dependent ROC curves also demonstrated that the nomogram possessed superior discrimination, prognostic prediction ability, and clinical benefit. Moreover, we integrated the MHR and ALBI grade into a new model to enhance survival prediction for patients with MAFLD-HCC. Interestingly, combining the MHR and ALBI grade did not result in a better predictive power than the MHR alone. The MHR model needs to be validated in prospective cohorts of diverse populations to confirm its applicability.

In summary, we developed an effective nomogram with a novel lipid/inflammation index through the MHR to predict the prognosis of patients with MAFLD-HCC. Adopting the MHR would be beneficial for facilitating the timely management of patients with MAFLD-HCC in clinical practice by using simple demographic and clinical variables.

Conclusion

The novel nomogram demonstrated good value in predicting the overall survival of patients with MAFLD-HCC. The MHR may be a potential predictor of prognosis.

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Disclosure

The authors have no conflicts of interest to declare.

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