

The Age-Male-Albumin-Bilirubin-Platelets (aMAP) Risk Score Predicts Liver Metastasis Following Surgery for Breast Cancer in Chinese Population: A Retrospective Study

Li Chen^{1,2,*}, Qiang Liu^{2,*}, Chunlei Tan^{3,*}, Tiangen Wu^{4,*}, Meng Wu⁵, Xiaosheng Tan⁵, Jinwen Liu¹, Jing Wang²

¹Department of Thyroid and Breast Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, 430030, People's Republic of China; ²Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, People's Republic of China; ³Department of Breast Surgery, Harbin Medical University Cancer Hospital, Harbin, Heilongjiang, 150081, People's Republic of China; ⁴Department of Hepatobiliary&Pancreatic Surgery, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, 430071, People's Republic of China; ⁵Institute of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology; Key Laboratory of Organ Transplantation, Ministry of Education; NHC Key Laboratory of Organ Transplantation; Key Laboratory of Organ Transplantation, Chinese Academy of Medical Sciences, Wuhan, Hubei, 430030, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jing Wang, Department of Breast Surgical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, People's Republic of China, Email wangjing@cicams.ac.cn; Jinwen Liu, Department of Thyroid and Breast Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, 430030, People's Republic of China, Email Liujiunwen@tjh.tjmu.edu.cn

Objective: The current study is conducted to investigate the potential prognostic value of the age-male-albumin-bilirubin-platelets (aMAP) score in breast cancer patients with liver metastasis after surgery.

Methods: This is a retrospective study of 178 breast cancer patients who developed liver metastasis after surgery. These patients were treated and followed up from 2000 to 2018 at our hospital. The aMAP risk score was estimated in accordance with the following formula: $\{0.06 \times \text{age} + 0.48 \times [(\log_{10}\text{bilirubin} \times 0.66) - (\text{albumin} \times 0.085)] - 0.01 \times \text{platelet} + 7.4\} / 14.77 \times 100$. The optimal cutoff value of the aMAP was evaluated via X-tile. Kaplan-Meier, Log-rank and Cox proportional hazards regression models were applied to determine the clinical influence of the aMAP score on the survival outcomes. The nomogram models were established by multivariate analyses. The calibration curves and decision curve analysis were applied to evaluate the estimated performance of the nomogram models.

Results: A total of 178 breast cancer patients were divided into low aMAP score group (<47.6) and high aMAP score group (≥ 47.6) via X-tile plots. The aMAP score was a potential prognostic factor in multivariate analysis. The median disease free survival ($p=0.0013$) and overall survival ($p=0.0003$) in low aMAP score group were longer than in high aMAP score group. The nomograms were constructed to predict the DFS with a C-index of 0.722 (95% CI, 0.673–0.771), and the OS with a C-index of 0.708 (95% CI, 0.661–0.755). The aMAP-based nomograms had good predictive performance.

Conclusion: The aMAP score is a potential prognostic factor in breast cancer with liver metastasis after surgery. The aMAP score-based nomograms were conducive to discriminate patients at high risks of liver metastasis and develop adjuvant treatment and prevention strategies.

Keywords: breast cancer, aMAP score, liver metastasis, albumin, prognosis

Introduction

In the era of widespread application of early detection and diagnosis of tumors, breast cancer is the main cause of cancer-related deaths in females in the scope of world.¹ The treatment choice for cancer is decided by the stage of the disease.²

For breast cancer, surgical resection and chemotherapy are first-line curative therapies.³ Nevertheless, the two treatments also have a few restrictions.^{4–6} After this treatment, more than half of breast cancer mortality give rise to distant metastasis.⁷ Previous research reports have demonstrated that metastasis and recurrence might take its rise from primary tumors as a result of their invasive biological behavior and it was usually related to a variety of factors, such as tumor stage, pathological type, and biomarkers.^{8–10} Hence, the key to materialize the aspiring global orientation is to diminish the metastasis, recurrence, and mortality of breast cancer.

A sensitive and efficient breast cancer monitoring plan can provide early diagnosis and improve prognosis. We go a step further by establishing an accurate and simple tool to discriminate breast cancer patients with different risks. In the past several years, some biomarkers and risk scores had been tested and verified to assess the risks of cancer progression, such as molecular classification,¹¹ C-reactive protein,¹² Naples prognostic score,¹³ circulating tumor cells,¹⁴ PAM50 risk of recurrence (ROR) score.¹⁵ Although these indicators were favored by researchers in terms of the prognosis of breast cancer, there were few studies on breast cancer metastasis. For breast cancer, common metastatic sites include liver, lung, brain, and bone.¹⁶ It is reported that liver metastasis causes about 20% to 35% of patients with metastatic breast cancer to die.¹⁷ Studies have reported that breast cancer patients with liver metastasis had survived less than 9 months under no treatment.¹⁸

In recent years, researchers have become more and more interested in creating predictive biomarkers for different cancers based on serological and hematology characteristics. Fan et al reported the age-male-ALBI-platelets (aMAP) score, which based on age, sex, ALBI, and platelets, acted as a novel model for evaluating 5-year liver cancer risk in patients with chronic hepatitis.¹⁹ Moreover, albumin-bilirubin (ALBI) grade, based on serum bilirubin and albumin levels, acted as a novel model for objective measure of liver function.²⁰ For aMAP score, it can effectively predict the 5-year liver cancer risk regardless of aetiology or ethnicity. Furthermore, recent studies have performed that aMAP score had prognostic value in other diseases, such as HBV-related acute-on-chronic liver failure.²¹ Another study performed that aMAP score was a model that predicts risk of hepatocellular carcinoma (HCC) development in patients with chronic hepatitis, and aMAP discrimination was greater for younger individuals.²² As far as we know, the potential prognosis value of aMAP score in evaluating breast cancer, especially for liver metastasis from breast cancer, has not been reported. We presume that the aMAP score may furnish a well-prognostic value for breast cancer patients with liver metastasis after surgery. As a consequence, the current study will go deeply into the potential prognostic value of aMAP score, then, aMAP-based nomograms will apply to predict the probability of breast cancer patients with liver metastasis after surgery.

Patients and Methods

Ethics Approval and Consent to Participate

The Institutional Review Board of Cancer Hospital Chinese Academy of Medical Sciences approved the retrospective study. This retrospective single-center study was conducted in line with the amended Declaration of Helsinki. The enrolled patients provided written informed consent for treatment. The personal information of these patients was kept confidential.

Patients

In the current study, breast cancer with liver metastasis after surgery was treated at our hospital from 2000 to 2018. A total of 178 breast cancer patients with liver metastasis were included in the current study, and the clinical and pathological data of these patients were gained from the electronic medical records. Inclusion requirements were that 1) breast cancer patients with liver metastasis after surgery were confirmed by CT and/or MR when followed up; 2) complete clinical and pathological data and follow-up information. Exclusion requirements were that 1) more than one region; 2) postoperative metastasis of breast cancer to more than one site, such as bone and lungs; 3) missing data and lost to follow up.

Calculation of aMAP Risk Score

aMAP, also known as the age-male-ALBI-platelets (aMAP), were calculated using age, sex, bilirubin, albumin and platelets. In our study, the aMAP risk score was estimated in accordance with the following formula: $(0.06 \times \text{age} + 0.48 \times \text{ALBI} - 0.01 \times \text{platelet} + 7.4) / 14.77 \times 100$, referred Fan R' study.¹⁹ The albumin-bilirubin

(ALBI) score was estimated in accordance with the following formula: $(\log_{10} \text{bilirubin} \times 0.66) - (\text{albumin} \times 0.085)$, where bilirubin is in $\mu\text{mol/L}$ and albumin in g/L . The optimal cutoff value of aMAP was evaluated via X-tile. In this research, these patients were divided into low aMAP score group (<47.6) vs high aMAP score group (≥ 47.6).

Follow-Up

All enrolled patients were followed up regularly. The patients had routine checkups with a physical examination, hematology examination, breast and abdominal ultrasound, or CT every 3 months. The treatment and protocol were the same as described previously. Disease free survival (DFS) was defined as the time from surgery to progression with liver metastasis. Overall survival (OS) was defined as the time from surgery to the date of death from any cause or last follow-up.

Statistical Analysis

In this study, the categorical variables were compared using Chi-square test and Fisher's exact test. X-tile software was applied to assess the optimal cut-off value for the variables. The cumulative DFS and OS were appraised using Kaplan-Meier and Log rank tests. The potential factors were examined using Cox proportional hazards models. Nomograms were constructed by multivariate analysis. The time-dependent receiver operating characteristic curve, concordance index, calibration curve, and decision curve analysis were used to graphically evaluate the accuracy of predictive performance of these models. Statistical analysis was performed using the R (<http://www.R-project.org/>). The P-value of <0.05 indicated statistical significance.

Results

Clinical Characteristics of the Patients

During this study, a total of 178 breast cancer patients with liver metastasis after surgery were included in the analysis. Patients were grouped into two groups by aMAP score. Then, 138 cases were divided into the low aMAP group, and 40 cases were divided into the high aMAP group. The expression of Ki67 was lower than 14%, divided into negative group. The expression of AR, CK5/6, E-cad, EGFR, P53, and TOP2A was evaluated by immunohistochemistry, and negative expression of these parameters was divided into negative group. As shown in Table 1, the demographic data were compared. Age, BMI, menopause, pathological tumor size, pathological TNM stage, and E-cad showed significant differences between the groups.

Comparison of Serological and Hematological Characteristics According to aMAP Score

During this study, these serological and hematological indicators were tested before surgery. The median value served as a grouping indicator for these characteristics' markers. As shown in Table 2, the serological and hematological characteristic data of low aMAP group ($n=138$) and high aMAP group ($n=40$) were compared. The carcinoembryonic antigen (CEA) and platelet showed significant differences between the groups.

The Potential Prognostic Factors for Breast Cancer Patients with Liver Metastasis After Surgery

In the univariate and multivariate Cox regression analysis, the aMAP, menarche age, C-reactive protein (CRP), monocyte, positive lymph nodes (PLN), PR, lymph vessel invasion were the potential prognostic factors for DFS (Table 3); the aMAP, menarche age, albumin (ALB), monocyte, postoperative endocrine therapy were the potential prognostic factors for OS (Table 4)

Clinical Impact of the aMAP Score on Survival

In accordance with the optimal cut-off value of aMAP score, there were 138 patients in low aMAP score group, and 40 patients in high aMAP score group. First, to probe into the effects of the aMAP score on survival. The median DFS and

Table I Clinical Characteristics of the Breast Cancer Patients with Liver Metastasis After Surgery Based on aMAP Score

Characteristics n	Level	Low aMAP 138	High aMAP 40	p
Age	<49	92 (66.7)	6 (15.0)	<0.001
	≥49	46 (33.3)	34 (85.0)	
BMI	<23.51	75 (54.3)	14 (35.0)	0.048
	≥23.51	63 (45.7)	26 (65.0)	
Family history	No	109 (79.0)	31 (77.5)	1.000
	Yes	29 (21.0)	9 (22.5)	
Menarche age	<14	40 (29.0)	10 (25.0)	0.769
	≥14	98 (71.0)	30 (75.0)	
Menopause	No	92 (66.7)	13 (32.5)	<0.001
	Yes	46 (33.3)	27 (67.5)	
Type of surgery	Mastectomy	131 (94.9)	38 (95.0)	1.000
	Breast-conserving surgery	7 (5.1)	2 (5.0)	
Pathological tumor size	≤2cm	41 (29.7)	19 (47.5)	0.026
	>2 and ≤5cm	85 (61.6)	15 (37.5)	
	>5cm	12 (8.7)	6 (15.0)	
Histologic grade	I	6 (4.3)	5 (12.5)	0.052
	II	87 (63.0)	18 (45.0)	
	III	45 (32.6)	17 (42.5)	
Pathological TNM stage	I	5 (3.6)	6 (15.0)	0.009
	II	47 (34.1)	7 (17.5)	
	III	86 (62.3)	27 (67.5)	
TLN	<19	63 (45.7)	23 (57.5)	0.254
	≥19	75 (54.3)	17 (42.5)	
PLN	<5	66 (47.8)	20 (50.0)	0.950
	≥5	72 (52.2)	20 (50.0)	
ER	Negative	43 (31.2)	17 (42.5)	0.252
	Positive	95 (68.8)	23 (57.5)	
PR	Negative	47 (34.1)	13 (32.5)	1.000
	Positive	91 (65.9)	27 (67.5)	
HER2	Negative	89 (64.5)	24 (60.0)	0.739
	Positive	49 (35.5)	16 (40.0)	
Ki67	Negative	44 (31.9)	14 (35.0)	0.858
	Positive	94 (68.1)	26 (65.0)	
AR	Negative	133 (96.4)	39 (97.5)	1.000
	Positive	5 (3.6)	1 (2.5)	
CK5/6	Negative	120 (87.0)	36 (90.0)	0.809
	Positive	18 (13.0)	4 (10.0)	
E-cad	Negative	70 (50.7)	28 (70.0)	0.048
	Positive	68 (49.3)	12 (30.0)	
EGFR	Negative	124 (89.9)	38 (95.0)	0.492
	Positive	14 (10.1)	2 (5.0)	
P53	Negative	73 (52.9)	26 (65.0)	0.240
	Positive	65 (47.1)	14 (35.0)	
TOP2A	Negative	92 (66.7)	33 (82.5)	0.083
	Positive	46 (33.3)	7 (17.5)	
Lymph vessel invasion	Negative	91 (65.9)	27 (67.5)	1.000
	Positive	47 (34.1)	13 (32.5)	
Neural invasion	Negative	127 (92.0)	36 (90.0)	0.933
	Positive	11 (8.0)	4 (10.0)	

(Continued)

Table 1 (Continued).

Characteristics n	Level	Low aMAP 138	High aMAP 40	p
Postoperative chemotherapy	No	28 (20.3)	13 (32.5)	0.161
	Yes	110 (79.7)	27 (67.5)	
Postoperative radiotherapy	No	33 (23.9)	14 (35.0)	0.231
	Yes	105 (76.1)	26 (65.0)	
Postoperative endocrine therapy	No	52 (37.7)	17 (42.5)	0.714
	Yes	86 (62.3)	23 (57.5)	
Postoperative targeted therapy	No	110 (79.7)	30 (75.0)	0.674
	Yes	28 (20.3)	10 (25.0)	

Abbreviations: BMI, body mass index; TLN, Total lymph nodes; PLN, Positive lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, Human Epidermal Growth Factor Receptor 2; AR, androgen receptor; CK5/6, Cytokeratin 5/6; E-cad, E-cadherin; EGFR, Epidermal Growth Factor Receptor; TOP2A, topoisomerase 2A.

Table 2 Comparison of Serological and Hematological Characteristics According to aMAP Score in Breast Cancer Patients with Liver Metastasis After Surgery

Characteristics n	Level	Low aMAP 138	High aMAP 40	p
ALT (U/L)	<17	70 (50.7)	17 (42.5)	0.461
	≥17	68 (49.3)	23 (57.5)	
AST (U/L)	<20	68 (49.3)	20 (50.0)	1.000
	≥20	70 (50.7)	20 (50.0)	
ALB (g/L)	<44.1	61 (44.2)	22 (55.0)	0.305
	≥44.1	77 (55.8)	18 (45.0)	
CRP (mg/dl)	<0.07	73 (52.9)	16 (40.0)	0.209
	≥0.07	65 (47.1)	24 (60.0)	
TBIL (umol/L)	<8.60	67 (48.6)	20 (50.0)	1.000
	≥8.60	71 (51.4)	20 (50.0)	
DBIL (umol/L)	<2.75	69 (50.0)	20 (50.0)	1.000
	≥2.75	69 (50.0)	20 (50.0)	
IBIL (umol/L)	<5.85	69 (50.0)	20 (50.0)	1.000
	≥5.85	69 (50.0)	20 (50.0)	
CHOL (mmol/L)	<3.80	72 (52.2)	17 (42.5)	0.369
	≥3.80	66 (47.8)	23 (57.5)	
TG (mmol/L)	<1.16	67 (48.6)	20 (50.0)	1.000
	≥1.16	71 (51.4)	20 (50.0)	
TP (g/L)	<73.0	67 (48.6)	21 (52.5)	0.795
	≥73.0	71 (51.4)	19 (47.5)	
G (g/L)	<29.0	68 (49.3)	19 (47.5)	0.986
	≥29.0	70 (50.7)	21 (52.5)	
PAB (mg/dl)	<27.0	66 (47.8)	19 (47.5)	1.000
	≥27.0	72 (52.2)	21 (52.5)	
CA125 (U/mL)	<10.57	70 (50.7)	19 (47.5)	0.857
	≥10.57	68 (49.3)	21 (52.5)	
CA153 (U/mL)	<13.01	70 (50.7)	19 (47.5)	0.857
	≥13.01	68 (49.3)	21 (52.5)	
CEA (ng/mL)	<1.95	78 (56.5)	11 (27.5)	0.002
	≥1.95	60 (43.5)	29 (72.5)	
DD (mg/L)	<0.21	68 (49.3)	20 (50.0)	1.000
	≥0.21	70 (50.7)	20 (50.0)	

(Continued)

Table 2 (Continued).

Characteristics n	Level	Low aMAP 138	High aMAP 40	p
FIB (g/L)	<2.75	69 (50.0)	20 (50.0)	1.000
	≥2.75	69 (50.0)	20 (50.0)	
White blood cell (×10 ⁹ /L)	<5.45	68 (49.3)	21 (52.5)	0.857
	≥5.45	70 (50.7)	19 (47.5)	
Neutrophils (×10 ⁹ /L)	<3.23	65 (47.1)	23 (57.5)	0.328
	≥3.23	73 (52.9)	17 (42.5)	
Lymphocyte (×10 ⁹ /L)	<1.70	71 (51.4)	17 (42.5)	0.414
	≥1.70	67 (48.6)	23 (57.5)	
Monocyte (×10 ⁹ /L)	<0.35	67 (48.6)	22 (55.0)	0.590
	≥0.35	71 (51.4)	18 (45.0)	
Platelet (×10 ⁹ /L)	<233	59 (42.8)	30 (75.0)	0.001
	≥233	79 (57.2)	10 (25.0)	

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALB, Albumin; CRP, C-reactive protein; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; CHOL, Cholesterol; TG, Triglyceride; TP, Total protein; G, Globulin; PAB, Prealbumin; CA125, Carbohydrate antigen 125; CA153, Carbohydrate antigen 153; CEA, Carcinoembryonic antigen; DD, D-Dimer; FIB, Fibrinogen.

Table 3 The Potential Prognostic Indicators of Disease Free Survival for Breast Cancer Patients with Liver Metastasis After Surgery

Characteristics	Group	Univariate		95% CI		Multivariate		95% CI	
		P	HR	Low	High	P	HR	Low	High
aMAP	Low	1 (Ref.)				1 (Ref.)			
	High	0.000	4.787	2.257	10.153	0.000	2.333	1.497	3.636
Age	<49	1 (Ref.)							
	≥49	0.476	1.329	0.607	2.911				
BMI	<23.51	1 (Ref.)							
	≥23.51	0.187	1.462	0.832	2.571				
Family history	No	1 (Ref.)							
	Yes	0.352	1.348	0.719	2.526				
Menarche age	<14	1 (Ref.)				1 (Ref.)			
	≥14	0.010	2.236	1.214	4.117	0.004	1.909	1.229	2.965
Menopause	No	1 (Ref.)							
	Yes	0.214	0.567	0.232	1.388				
ALT	<17	1 (Ref.)							
	≥17	0.212	0.632	0.307	1.300				
AST	<20	1 (Ref.)							
	≥20	0.155	1.763	0.808	3.848				
ALB	<44.1	1 (Ref.)				1 (Ref.)			
	≥44.1	0.004	0.355	0.176	0.714	0.378	0.832	0.552	1.253
CRP	<0.07	1 (Ref.)				1 (Ref.)			
	≥0.07	0.013	0.614	0.418	0.904	0.002	0.521	0.341	0.794
DBIL	<2.75	1 (Ref.)							
	≥2.75	0.137	0.607	0.314	1.172				
CHOL	<3.80	1 (Ref.)							
	≥3.80	0.610	1.180	0.625	2.229				
TG	<1.16	1 (Ref.)							
	≥1.16	0.201	0.677	0.372	1.232				

(Continued)

Table 3 (Continued).

Characteristics	Group	Univariate		95% CI		Multivariate		95% CI	
		P	HR	Low	High	P	HR	Low	High
TP	<73.0	I(Ref.)							
	≥73.0	0.535	1.245	0.623	2.486				
G	<29.0	I(Ref.)							
	≥29.0	0.199	0.666	0.359	1.238				
PAB	<27.0	I(Ref.)							
	≥27.0	0.155	1.564	0.844	2.897				
CA125	<10.57	I(Ref.)							
	≥10.57	0.797	1.097	0.541	2.226				
CA153	<13.01	I(Ref.)							
	≥13.01	0.158	1.530	0.848	2.759				
CEA	<1.95	I(Ref.)							
	≥1.95	0.583	1.112	0.762	1.623				
D-D	<0.21	I(Ref.)							
	≥0.21	0.311	0.731	0.399	1.340				
FIB	<2.75	I(Ref.)							
	≥2.75	0.929	1.027	0.565	1.869				
White blood cell	<5.45	I(Ref.)							
	≥5.45	0.376	1.187	0.812	1.733				
Neutrophils	<3.23	I(Ref.)							
	≥3.23	0.062	1.437	2.249	12.223				
Lymphocyte	<1.70	I(Ref.)							
	≥1.70	0.693	1.134	0.607	2.120				
Monocyte	<0.35	I(Ref.)				I(Ref.)			
	≥0.35	0.032	1.521	1.036	2.233	0.026	1.572	1.056	2.338
Platelet	<233	I(Ref.)							
	≥233	0.359	0.749	0.404	1.389				
Type of surgery	Mastectomy	I(Ref.)							
	Breast-conserving surgery	0.831	1.166	0.284	4.793				
Pathological tumor size	≤2cm	I(Ref.)							
	>2 and ≤5cm	0.458	1.262	0.682	2.336				
	>5cm	0.218	1.848	0.695	4.915				
Histologic grade	I	I(Ref.)							
	II	0.442	1.597	0.484	5.266				
	III	0.744	1.241	0.340	4.533				
Pathological TNM stage	I	I(Ref.)							
	II	0.551	1.422	0.447	4.528				
	III	0.750	0.790	0.186	3.359				
TLN	<19	I(Ref.)							
	≥19	0.846	1.054	0.621	1.788				
PLN	<5	I(Ref.)				I(Ref.)			
	≥5	0.048	1.467	1.003	2.145	0.038	1.542	1.025	2.321
ER	Negative	I(Ref.)							
	Positive	0.086	0.370	0.118	1.153				
PR	Negative	I(Ref.)				I(Ref.)			
	Positive	0.000	0.412	0.279	0.609	0.000	0.380	0.251	0.574
HER2	Negative	I(Ref.)							
	Positive	0.940	0.977	0.528	1.805				
Ki67	Negative	I(Ref.)							
	Positive	0.677	1.150	0.596	2.221				

(Continued)

Table 3 (Continued).

Characteristics	Group	Univariate		95% CI		Multivariate		95% CI	
		P	HR	Low	High	P	HR	Low	High
AR	Negative	1 (Ref.)							
	Positive	0.608	0.546	0.054	5.498				
CK5/6	Negative	1 (Ref.)							
	Positive	0.306	1.394	0.738	2.633				
E-cad	Negative	1 (Ref.)							
	Positive	0.068	1.458	0.973	2.184				
EGFR	Negative	1 (Ref.)							
	Positive	0.825	0.868	0.249	3.029				
P53	Negative	1 (Ref.)							
	Positive	0.789	1.084	0.600	1.960				
TOP2A	Negative	1 (Ref.)				1 (Ref.)			
	Positive	0.045	0.391	0.156	0.979	0.584	0.858	0.497	1.482
Lymph vessel invasion	Negative	1 (Ref.)				1 (Ref.)			
	Positive	0.035	1.938	1.049	3.580	0.008	1.787	1.167	2.737
Neural invasion	Negative	1 (Ref.)							
	Positive	0.455	1.299	0.654	2.581				
Postoperative chemotherapy	No	1 (Ref.)							
	Yes	0.758	0.929	0.580	1.488				
Postoperative radiotherapy	No	1 (Ref.)							
	Yes	0.848	1.067	0.549	2.074				
Postoperative endocrine therapy	No	1 (Ref.)							
	Yes	0.452	1.372	0.602	3.127				
Postoperative targeted therapy	No	1 (Ref.)							
	Yes	0.524	1.283	0.596	2.762				

Abbreviations: BMI, body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALB, Albumin; CRP, C-reactive protein; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; CHOL, Cholesterol; TG, Triglyceride; TP, Total protein; G, Globulin; PAB, Prealbumin; CA125, Carbohydrate antigen 125; CA153, Carbohydrate antigen 153; CEA, Carcinoembryonic antigen; DD, D-Dimer; FIB, Fibrinogen; TLN, Total lymph nodes; PLN, Positive lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, Human Epidermal Growth Factor Receptor 2; AR, androgen receptor; CK5/6, Cytokeratin 5/6; E-cad, E-cadherin; EGFR, Epidermal Growth Factor Receptor; TOP2A, topoisomerase 2A.

Table 4 The Potential Prognostic Indicators of Overall Survival for Breast Cancer Patients with Liver Metastasis After Surgery

Characteristics	Group	Univariate		95% CI		Multivariate		95% CI	
		P	HR	Low	High	P	HR	Low	High
aMAP	Low	1 (Ref.)				1 (Ref.)			
	High	0.001	3.745	1.727	8.120	0.000	2.312	1.495	3.573
Age	<49	1 (Ref.)							
	≥49	0.955	1.023	0.465	2.252				
BMI	<23.51	1 (Ref.)							
	≥23.51	0.142	1.494	0.875	2.551				
Family history	No	1 (Ref.)							
	Yes	0.911	1.035	0.562	1.905				
Menarche age	<14	1 (Ref.)				1 (Ref.)			
	≥14	0.004	2.562	1.360	4.826	0.001	2.236	1.416	3.532
Menopause	No	1 (Ref.)							
	Yes	0.566	1.296	0.535	3.141				
ALT	<17	1 (Ref.)							
	≥17	0.353	0.728	0.372	1.424				

(Continued)

Table 4 (Continued).

Characteristics	Group	Univariate		95% CI		Multivariate		95% CI	
		P	HR	Low	High	P	HR	Low	High
AST	<20	I(Ref.)							
	≥20	0.442	1.331	0.642	2.757				
ALB	<44.1	I(Ref.)				I(Ref.)			
	≥44.1	0.002	0.339	0.170	0.677	0.037	0.648	0.432	0.974
CRP	<0.07	I(Ref.)							
	≥0.07	0.935	0.975	0.526	1.805				
DBIL	<2.75	I(Ref.)							
	≥2.75	0.593	0.844	0.453	1.572				
CHOL	<3.80	I(Ref.)							
	≥3.80	0.634	1.173	0.608	2.260				
TG	<1.16	I(Ref.)							
	≥1.16	0.197	0.680	0.379	1.221				
TP	<73.0	I(Ref.)							
	≥73.0	0.593	1.211	0.599	2.448				
G	<29.0	I(Ref.)							
	≥29.0	0.087	0.578	0.309	1.083				
PAB	<27.0	I(Ref.)							
	≥27.0	0.210	1.453	0.811	2.604				
CA125	<10.57	I(Ref.)							
	≥10.57	0.909	0.961	0.487	1.896				
CA153	<13.01	I(Ref.)							
	≥13.01	0.080	1.608	0.944	2.739				
CEA	<1.95	I(Ref.)							
	≥1.95	0.173	0.683	0.394	1.182				
D-D	<0.21	I(Ref.)							
	≥0.21	0.357	0.757	0.419	1.368				
FIB	<2.75	I(Ref.)							
	≥2.75	0.567	0.848	0.483	1.490				
White blood cell	<5.45	I(Ref.)							
	≥5.45	0.119	1.356	0.925	1.989				
Neutrophils	<3.23	I(Ref.)				I(Ref.)			
	≥3.23	0.002	3.845	1.645	8.989	0.494	1.159	0.759	1.771
Lymphocyte	<1.70	I(Ref.)							
	≥1.70	0.102	1.702	0.900	3.217				
Monocyte	<0.35	I(Ref.)				I(Ref.)			
	≥0.35	0.015	2.139	1.156	3.959	0.005	1.769	1.183	2.646
Platelet	<233	I(Ref.)							
	≥233	0.782	0.916	0.491	1.707				
Type of surgery	Mastectomy	I(Ref.)							
	Breast-conserving surgery	0.935	0.945	0.237	3.760				
Pathological tumor size	≤2cm	I(Ref.)							
	>2 and ≤5cm	0.759	0.910	0.499	1.660				
	>5cm	0.178	1.923	0.743	4.974				
Histologic grade	I	I(Ref.)							
	II	0.098	2.923	0.821	10.415				
	III	0.380	1.841	0.472	7.180				
Pathological TNM stage	I	I(Ref.)							
	II	0.384	1.661	0.530	5.205				
	III	0.701	0.766	0.196	2.988				

(Continued)

Table 4 (Continued).

Characteristics	Group	Univariate		95% CI		Multivariate		95% CI	
		P	HR	Low	High	P	HR	Low	High
TLN	<19	1 (Ref.)							
	≥19	0.433	0.859	0.588	1.255				
PLN	<5	1 (Ref.)							
	≥5	0.109	2.072	0.850	5.051				
ER	Negative	1 (Ref.)				1 (Ref.)			
	Positive	0.007	0.196	0.060	0.641	0.309	0.606	0.231	1.589
PR	Negative	1 (Ref.)							
	Positive	0.425	0.699	0.290	1.685				
HER2	Negative	1 (Ref.)							
	Positive	0.576	0.839	0.454	1.550				
Ki67	Negative	1 (Ref.)							
	Positive	0.435	0.764	0.389	1.500				
AR	Negative	1 (Ref.)							
	Positive	0.679	0.630	0.070	5.632				
CK5/6	Negative	1 (Ref.)							
	Positive	0.538	1.325	0.540	3.253				
E-cad	Negative	1 (Ref.)							
	Positive	0.178	1.328	0.879	2.006				
EGFR	Negative	1 (Ref.)							
	Positive	0.474	0.622	0.170	2.279				
P53	Negative	1 (Ref.)							
	Positive	0.282	1.410	0.755	2.633				
TOP2A	Negative	1 (Ref.)							
	Positive	0.316	0.615	0.238	1.590				
Lymph vessel invasion	Negative	1 (Ref.)							
	Positive	0.088	1.633	0.929	2.871				
Neural invasion	Negative	1 (Ref.)							
	Positive	0.686	1.152	0.581	2.285				
Postoperative chemotherapy	No	1 (Ref.)							
	Yes	0.741	0.923	0.572	1.487				
Postoperative radiotherapy	No	1 (Ref.)							
	Yes	0.146	0.613	0.316	1.186				
Postoperative endocrine therapy	No	1 (Ref.)				1 (Ref.)			
	Yes	0.000	0.377	0.251	0.567	0.006	0.466	0.269	0.807
Postoperative targeted therapy	No	1 (Ref.)							
	Yes	0.975	1.012	0.486	2.105				

Abbreviations: BMI, body mass index; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALB, Albumin; CRP, C-reactive protein; TBIL, Total bilirubin; DBIL, Direct bilirubin; IBIL, Indirect bilirubin; CHOL, Cholesterol; TG, Triglyceride; TP, Total protein; G, Globulin; PAB, Prealbumin; CA125, Carbohydrate antigen 125; CA153, Carbohydrate antigen 153; CEA, Carcinoembryonic antigen; DD, D-Dimer; FIB, Fibrinogen; TLN, Total lymph nodes; PLN, Positive lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, Human Epidermal Growth Factor Receptor 2; AR, androgen receptor; CK5/6, Cytokeratin 5/6; E-cad, E-cadherin; EGFR, Epidermal Growth Factor Receptor; TOP2A, topoisomerase 2A.

OS were 47.40 months and 94.60 months in low aMAP score group; 26.43 months and 55.43 months in high aMAP score group (DFS Log rank: $p=0.0013$, OS Log rank: $p=0.0003$) (Figure 1A and B). On the basis of DFS, 1-year survival rate was 0.881 (95% CI, 0.827–0.937), 3-year survival rate was 0.565 (95% CI, 0.482–0.661), 5-year survival rate was 0.408 (95% CI, 0.322–0.518), 10-year survival rate was 0.181 (95% CI, 0.095–0.346), 15-year survival rate was 0.136 (95% CI, 0.058–0.321) in low aMAP score group; and 1-year survival rate was 0.822 (95% CI, 0.710–0.951), 3-year survival rate was 0.418 (95% CI, 0.282–0.620), 5-year survival rate was 0.168 (95% CI, 0.075–0.380), 10-year survival rate was 0.042 (95% CI, 0.006–0.277) in high aMAP score group. In light of OS, 1-year survival rate was 0.986 (95% CI,

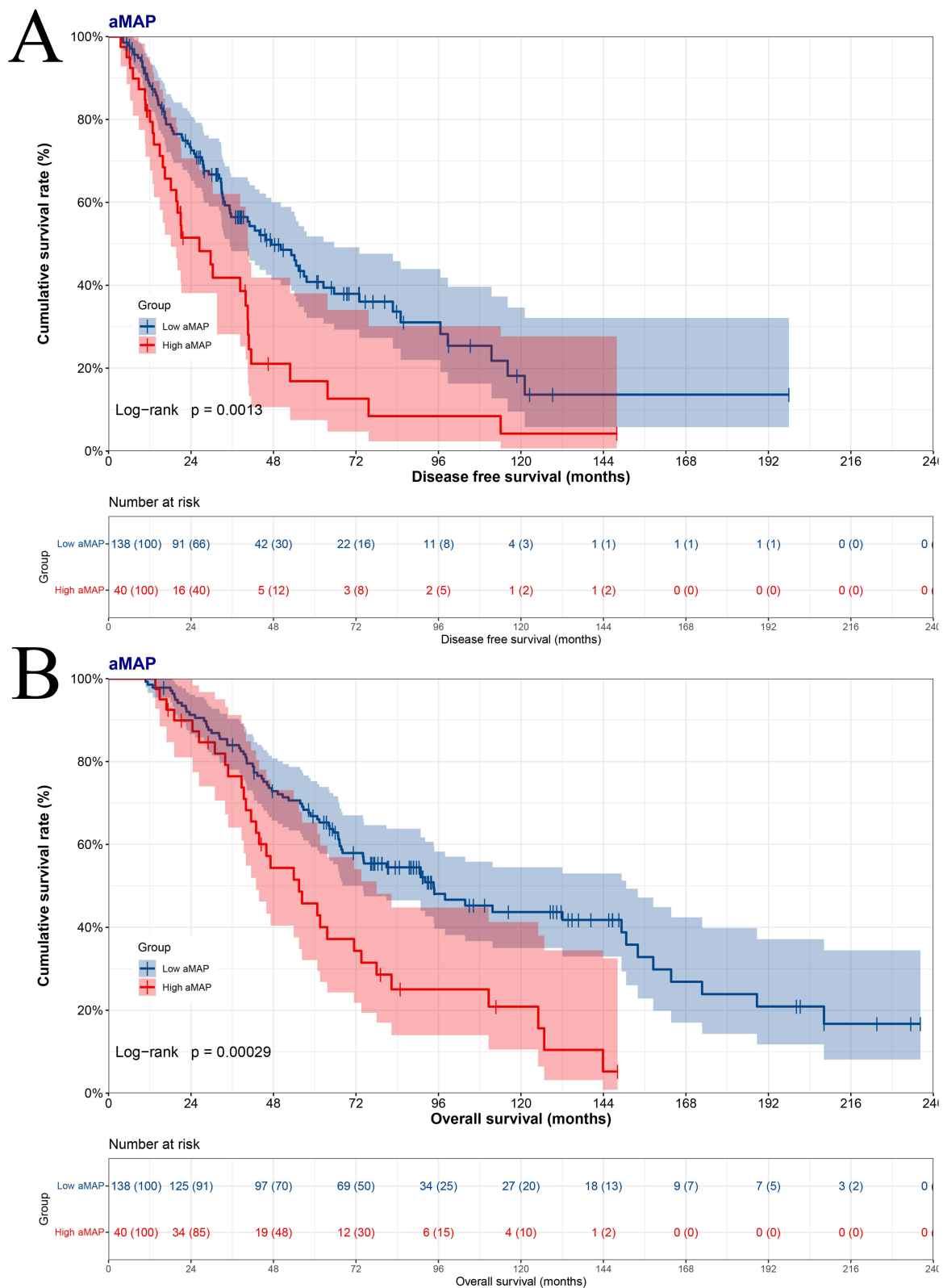


Figure 1 Kaplan-Meier survival plots comparing disease free survival (DFS) and overall survival (OS) in breast cancer patients with liver metastasis after surgery ((**A**) for DFS, (**B**) for OS).

0.966–1.000), 3-year survival rate was 0.840 (95% CI, 0.780–0.903), 5-year survival rate was 0.668 (95% CI, 0.594–0.753), 10-year survival rate was 0.437 (95% CI, 0.350–0.545), 15-year survival rate was 0.239 (95% CI, 0.143–0.398) in low aMAP score group; and 1-year survival rate was 1.000 (95% CI, 1.000–1.000), 3-year survival rate was 0.764 (95% CI, 0.641–0.912), 5-year survival rate was 0.458 (95% CI, 0.321–0.652), 10-year survival rate was 0.209 (95% CI, 0.105–0.413) in high aMAP score group.

Model Performance and Validation of the Nomograms

Nomograms were established to determine the DFS and OS probabilities for breast cancer patients with liver metastasis after surgery (Figure 2A and B). In these nomograms, the potential risk factors for DFS that were determined through Cox multivariate analysis (aMAP, menarche age, C-reactive protein, monocyte, positive lymph nodes, PR, lymph vessel invasion); and for OS that were determined through Cox multivariate analysis (aMAP, menarche age, albumin, monocyte, postoperative endocrine therapy). Every enrolled factor was distributed a score, and the sum of these scores was located on the total score axis to achieve the DFS and OS probability. The C-index for a nomogram-based model based on DFS was 0.722 (95% CI, 0.673–0.771) (Figure S1A). The C-index for a nomogram-based model based on OS was 0.708 (95% CI, 0.661–0.755) (Figure S1B). In addition, the calibration curves of DFS at 1-year, 3-year, and 5-year after operation indicated that the best consistency between the actual and predicted observations (Figure 3A–C). The calibration curves of OS at 1-year, 3-year, 5-year, and 10-year after operation showed that the best agreement between the actual and predicted observations (Figure 3D–G). Moreover, the decision curve analysis of DFS at 1-year and 3-year after operation proved that the constructed nomograms had better predictive value than aMAP score (Figure 4A–D). The decision curve analysis of OS at 3-year and 5-year after operation performed that the established nomograms had better predictive value than aMAP score (Figure 4E–H). Besides, TDROC analysis showed that areas under the receiver operating characteristic curves (AUROCs) at 1-year, 3-year, 5-year, and 10-year of DFS after operation of follow-up were 0.549, 0.547, 0.587, and 0.538 for the aMAP score and at 1-year, 3-year, 5-year, 10-year, and 15-year of OS after operation of follow-up were 0.614, 0.547, 0.576, 0.577, and 0.633 for the aMAP score. Furthermore, the aMAP score showed that the AUROCs for survival time had the highest value at 5-year point (95% CI: 51.67–65.69%) for DFS (Figure 5A and B), at 15-year point (95% CI, 58.84–67.74%) for OS (Figure 5C and D).

Subgroup Analyses to Assess the Effects of the aMAP Score on Survival

Age and platelets constituted part of aMAP score. Whereupon, we conducted a subgroup analysis to assess the impact of aMAP score on survival based on age and platelet. Kaplan–Meier curves indicated that the aMAP score was related to DFS (Log rank: $p=0.015$) and OS (Log rank: $p=0.0022$) in age condition (Figure S2A and B). Older patients with breast cancer with high aMAP score had poor prognosis and survival time. Higher age was also correlated with higher aMAP score. Kaplan–Meier curves showed that the aMAP score was connected with DFS (Log rank: $p=0.014$) and OS (Log rank: $p=0.0022$) in platelet condition (Figure S3A and B). Patients with high-level platelet and high aMAP score had poor prognosis and survival time. Higher level platelet was also correlated with higher aMAP score. Additionally, we also analyzed the effects of aMAP score on survival based on BMI and menopause. Kaplan–Meier curves showed that the aMAP score was significantly associated with DFS (Log rank: $p=0.0016$) and OS (Log rank: $p=0.0011$) in BMI status (Figure S4A and B). Obese breast cancer patients with high aMAP score had poor prognosis and survival time. Kaplan–Meier curves also indicated that the aMAP score was significantly related to DFS (Log rank: $p=0.0022$) and OS (Log rank: $p=0.0011$) in BMI status (Figure S5A and B). Premenopausal patients with breast cancer with high aMAP score had poor prognosis and survival time. Moreover, the pathological tumor size and pathological TNM stage were analyzed to evaluate the effects of aMAP score. Kaplan–Meier curves also indicated that the aMAP score was significantly related to DFS (Log rank: $p=0.0063$) and OS (Log rank: $p=0.0028$) in different pathological tumor size (Figure S6A and B). Patients with larger tumor sizes and higher aMAP scores had poor prognosis and survival time. Kaplan–Meier curves also showed that the aMAP score was significantly related to DFS (Log rank: $p=0.045$) and OS (Log rank: $p=0.0037$) in different pathological TNM stage (Figure S7A and B). Patients with higher TNM stage and high aMAP score had poor prognosis and survival time. Higher TNM stage was also correlated with higher aMAP score. Furthermore, we analyzed the effects of aMAP score on survival based on the E-cad and CEA. Kaplan–Meier curves also indicated that the aMAP score was significantly related to DFS (Log rank: $p=0.0011$) and OS (Log rank: $p=0.00074$) in E-cad status (Figure S8A and B). Patients with positive expression of E-cad and

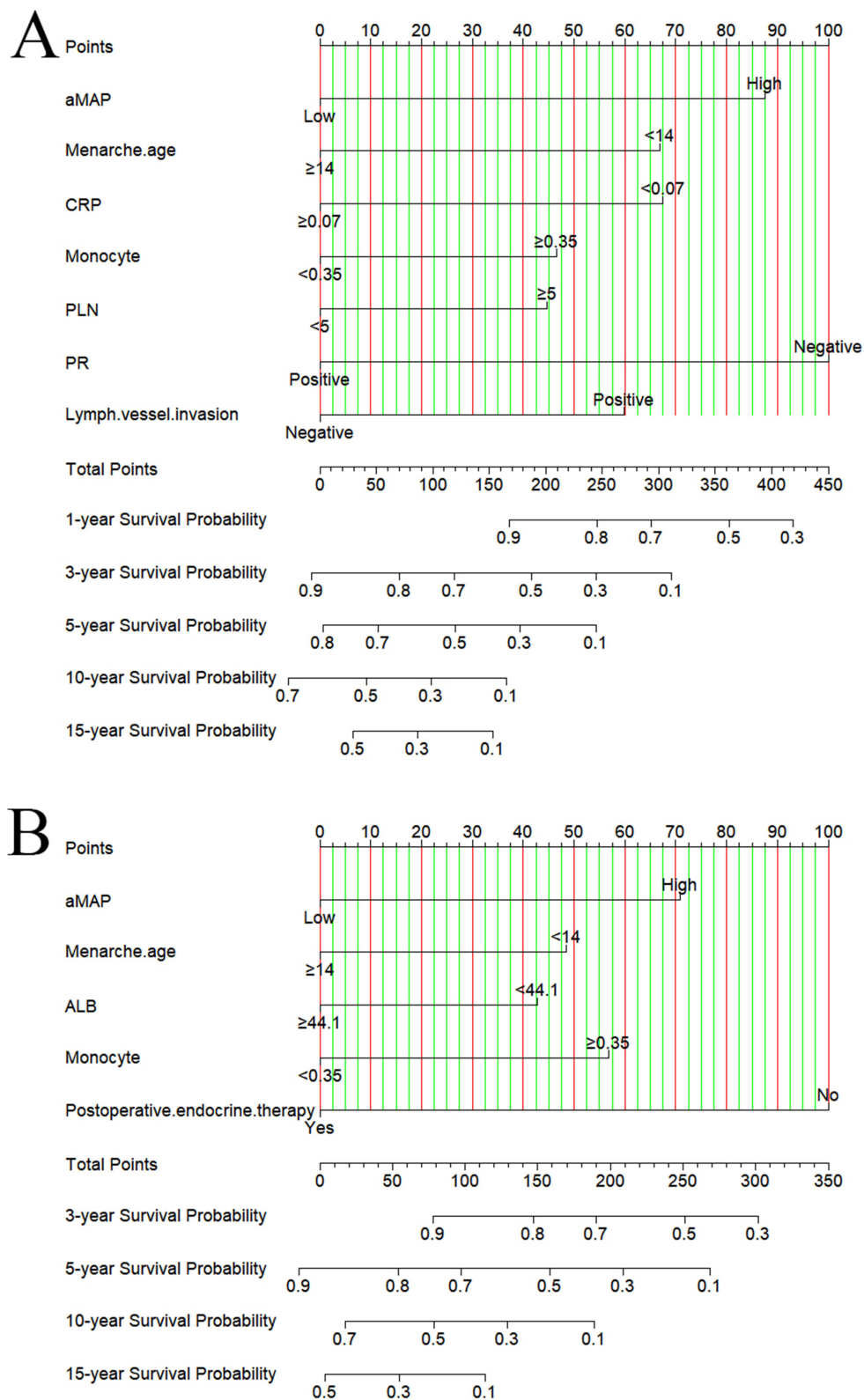


Figure 2 The constructed of aMAP-based nomograms in breast cancer patients with liver metastasis after surgery ((**A**) nomogram of disease free survival; (**B**) nomogram of overall survival).

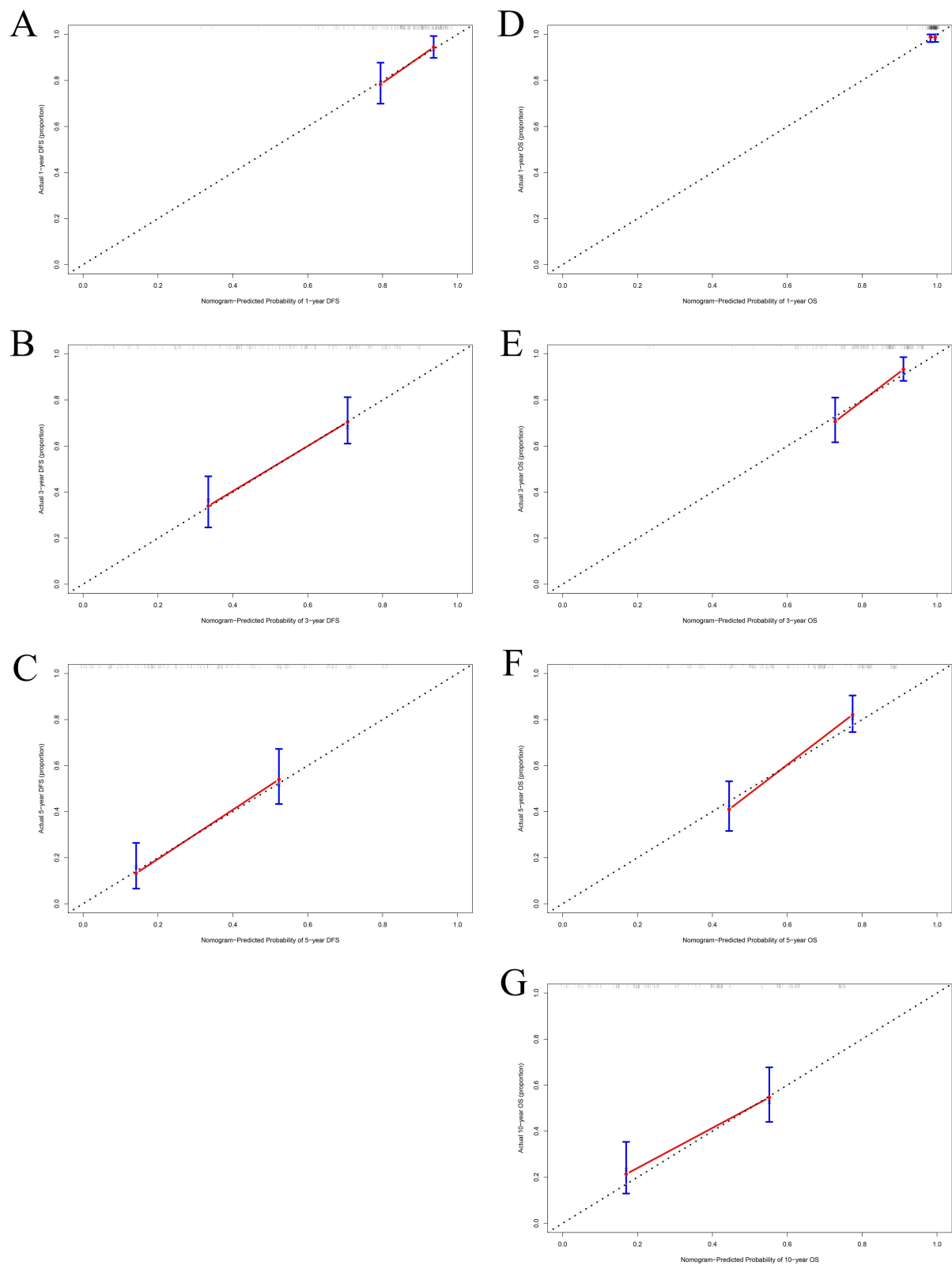


Figure 3 The calibration curves for aMAP-nomogram model in predicting different survival time. **(A)** 1-year DFS, **(B)** 3-year DFS, **(C)** 5-year DFS, **(D)** 1-year OS, **(E)** 3-year OS, **(F)** 5-year OS, **(G)** 10-year OS.

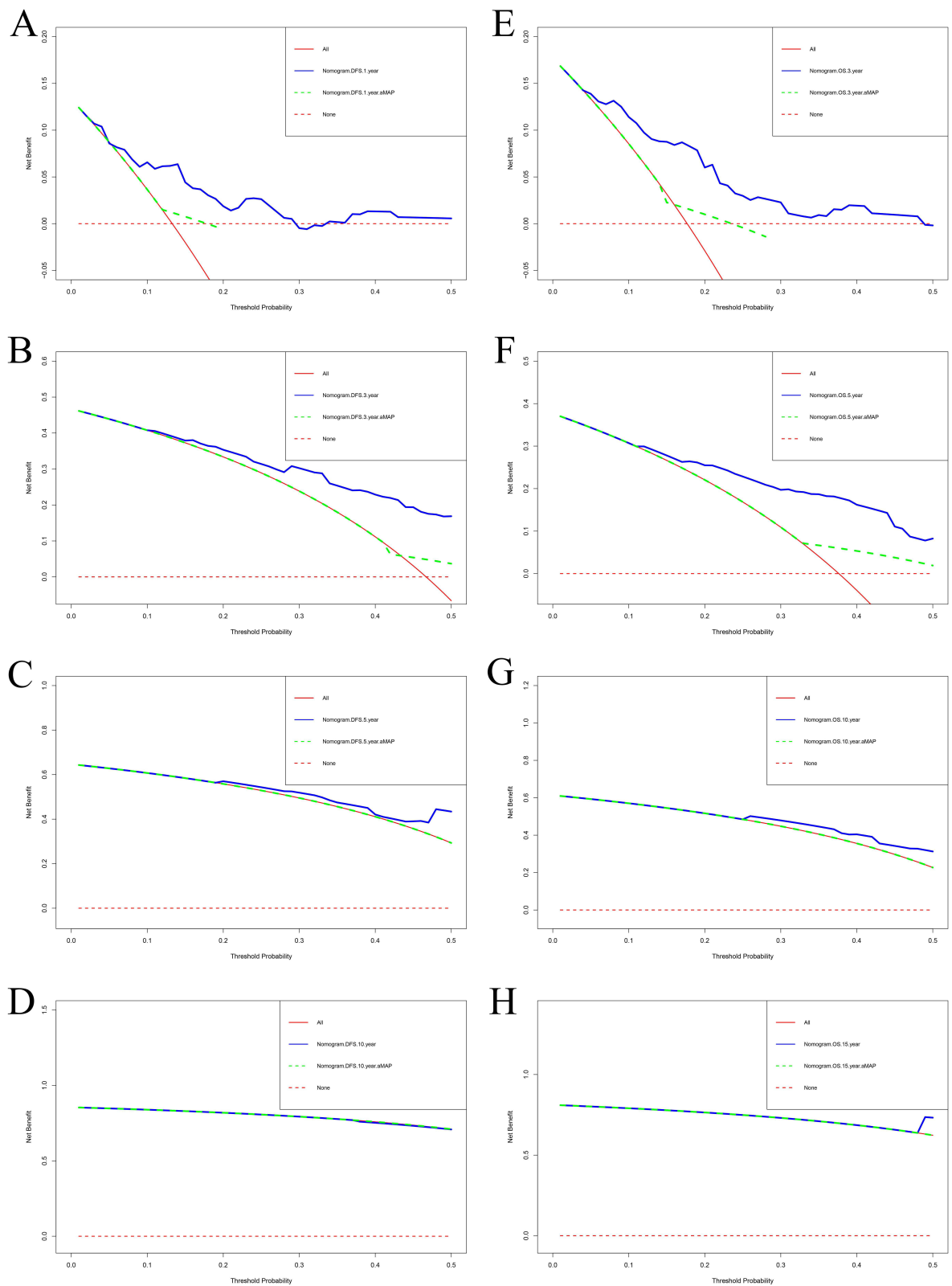


Figure 4 The decision curve analysis for the aMAP-nomogram and aMAP score model in evaluating the benefits for different survival time. (A) 1-year DFS, (B) 3-year DFS, (C) 5-year DFS, (D) 10-year DFS, (E) 3-year OS, (F) 5-year OS, (G) 10-year OS, (H) 15-year OS.

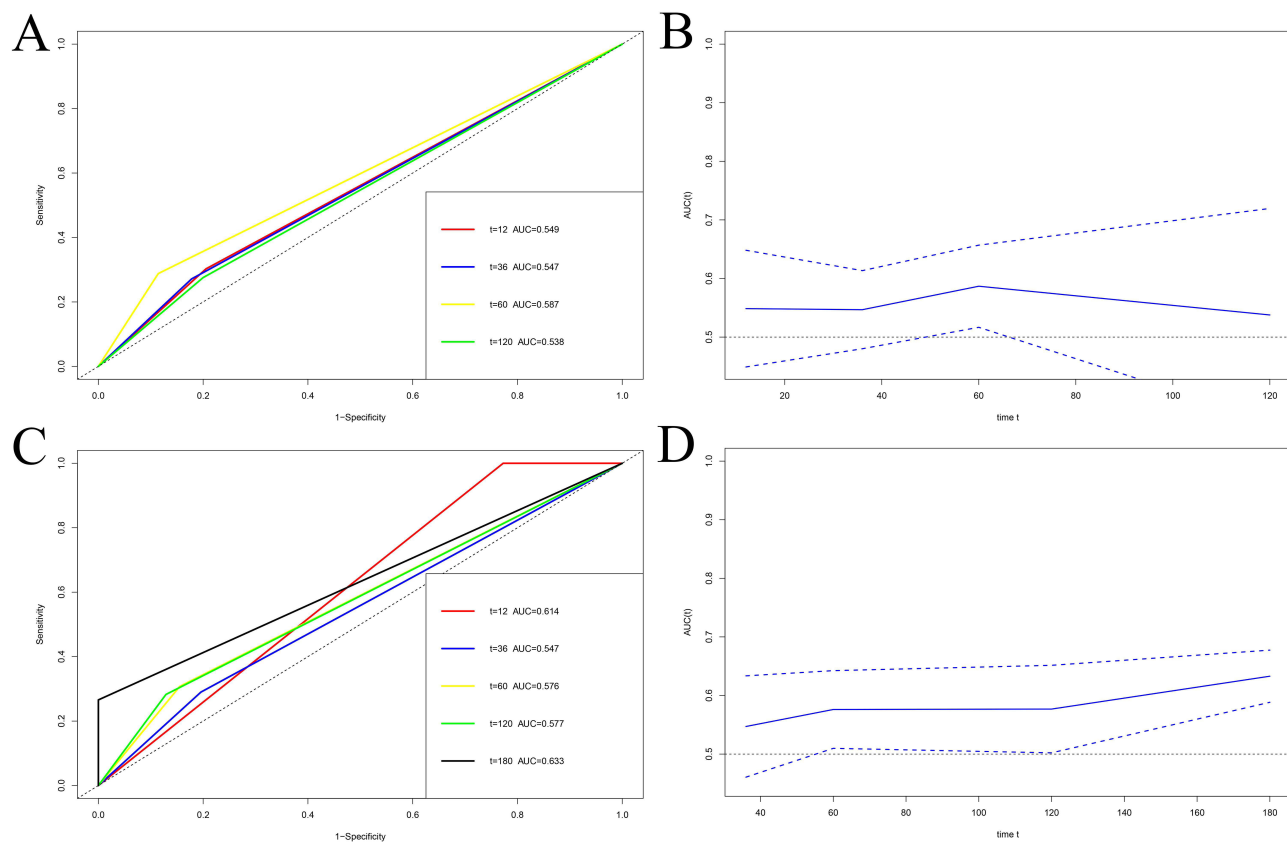


Figure 5 Time-dependent receiver operating characteristic (TDROC) analyzed the plots of area under the receiver operating characteristic curves (AUROCs) for aMAP score in breast cancer patients with liver metastasis after surgery of followup. **(A)** Time-dependent AUROCs for DFS, **(B)** 95% CI changes of AUROCs for DFS, **(C)** Time-dependent AUROCs for OS, **(D)** 95% CI changes of AUROCs for OS.

high aMAP score had poor prognosis and survival time. Kaplan–Meier curves also showed that the aMAP score was significantly related to DFS (Log rank: $p=0.014$) and OS (Log rank: $p=0.0039$) in CEA level ([Figure S9A](#) and [B](#)). Patients with high level of CEA and high aMAP score had poor prognosis and survival time.

Discussion

High incidence of tumor recurrence and metastasis to critical organs is a critical factor affecting long-term survival of breast cancer patients after surgery.^{23,24} In the past few years, many studies have shown that breast cancer exhibited different heterogeneity in metastasis and the priority of metastasis varies among different organs, leading to different prognosis and treatment responses in breast cancer patients.^{16,23,25} For instance, ductal carcinoma in situ (DCIS) is a heterogeneous disease and only some patients will progress to invasive breast cancer. However, patients with DCIS after breast-conserving surgery had clinically significant recurrence rates, and approximately half of these cases will be life-threatening invasive recurrences.²⁶ Histological subtype has emerged as an important tool in predicting prognosis for breast cancer and has been shown to correlate with differences in survival with invasive micropapillary carcinoma groups having poor outcomes.^{27,28} The bony skeleton, lung, liver, and brain are the primary targets of breast cancer metastasis.^{29,30} For breast cancer, the liver is the third most common metastatic site for solid cancer followed by lung and bony skeleton metastases, and accounts for 20% to 35% of the deaths of metastatic breast cancer patients.³¹ Research also indicated that adipokines were related to proliferation, invasion, and metastasis of breast cancer cells, and were also associated with the prognosis of breast cancer.³² Moreover, it is important to note that breast cancer patients with liver metastasis exhibited drug resistance and eventually develop resistance to systemic chemotherapy, endocrine therapy, and targeted therapy.^{33–36} Nevertheless, study had performed that the survival time for breast cancer patients with liver metastasis is only 4–8 months without treatment.^{37,38} Recently, it is difficult to accurately predict the occurrence of liver

metastasis from tumors. Some markers or scores are connected with the prognosis of breast cancer patients; however, it is not clear whether these indicators reflect prognosis in survival time.^{39–41}

Fan et al developed an objective and accurate hepatocellular carcinoma (HCC) surveillance programme tool (called the aMAP score) could predict the risk of HCC development and offer early diagnosis.¹⁹ The aMAP score involves five factors, including age, sex, albumin, bilirubin, and platelets.¹⁹ Gui et al also performed that the aMAP score accurately predicted the risk of HCC in at-risk patients with compensated cirrhosis undergoing antiviral therapy.⁴² Although the aMAP score has been confirmed in some studies and proven to be the best performing liver cancer forecasting model, its role has not been determined in other tumors, such as breast cancer.^{42,43}

In this study, we are attempting to explore the application of aMAP score on breast cancer patients with liver metastasis after surgery. The results showed that aMAP score was a potential prognostic factor for DFS and OS in breast cancer patients with liver metastasis after surgery. The results indicated that the aMAP score could furnish a well-discriminated risk stratification for liver metastasis after surgery as the low aMAP score group (median DFS time: 47.40 months, median OS time: 94.60 months) and high aMAP score group (median DFS time: 26.43 months, median OS time: 55.43 months). Chen et al found that the median OS time in the low-risk aMAP group was 26.2 months, in the medium-risk aMAP group was 23.3 months, and in the high-risk group was 10.4 months for HCC; and the Kaplan–Meier curve showed that aMAP score had a remarkable effect on OS ($p < 0.0001$).⁴⁴ Other study also indicated that the aMAP score was a detached risk factor for HBV-related hepatocellular carcinoma, and the high-risk group was related to the worst RFS and OS compared with medium-risk and low-risk groups.⁴⁵ Our findings were consistent with previous reports, and we also explored the clinical impact of aMAP score on patients with liver metastasis after breast cancer surgery.

In the current study, the aMAP score was noticeably associated with age, BMI, menopause, pathological tumor size, pathological TNM stage, E-cad, CEA, and platelet (Table 1 and Table 2). In Wang R's study, the multivariable analyses indicated that age was a detached prognostic factor for stage IV breast cancer patients with different metastatic sites, and the patients with liver metastasis were the lowest than those with other metastasis sites.⁴⁶ Our study also indicated that age was a potential prognostic factor for breast cancer with liver metastasis after surgery, and the older patients with high aMAP score had poor prognosis and survival time. A study had shown that obese breast patients tended to have large tumor size compared with normal weight breast cancer patients, whereas there was no significant difference of DFS between overweight and obese and normal weight premenopausal patients.⁴⁷ Obese breast cancer patients with high aMAP score had poor prognosis and survival time in our study. For menopause, postmenopausal estrogen activates EMT gene to stimulate breast cancer metastasis.⁴⁸ Our results also showed that premenopausal breast cancer patients with high aMAP score had poor prognosis and survival time. Furthermore, patients with larger tumor size and higher tumor staging had worse prognosis. Many studies indicated that TNM stage and tumor size were associated with the prognosis of survival time.^{49–51} In various cancers, increased levels of E-cad have been found, and E-cad correlated dramatically with TNM stage, tumor grade, and lymph node metastasis; furthermore, E-cad level was a potential prognostic factor in Asian breast cancer patients.^{52–54} In our study, patients with positive expression of E-cad and high aMAP score had poor prognosis and survival time. One study has shown that CEA can be used in the diagnosis of metastatic breast cancer, and different combinations of tumor markers had different diagnostic values.⁵⁵ In the current study, patients with high level of CEA and high aMAP score had poor prognosis and survival time. Garmi et al performed the study to show that platelets might be a prognostic marker for breast cancer and that patients who died in 1 year had low platelet counts before treatment.⁵⁶ Patients with high-level platelet and high aMAP score had poor prognosis and survival time in our study.

At the same moment, we also constructed aMAP-based nomograms to evaluate breast cancer patients with liver metastasis after surgery. The discriminated and calibrated nomograms based on potential prognostic factors of breast cancer liver metastasis with a C-index of 0.722 (95% CI, 0.673–0.771) to predict the probability of DFS, and 0.708 (95% CI, 0.661–0.755) to predict the probability of OS. Moreover, the calibration curves at 1-year, 3-year, and 5-year after surgery showed the best consistency between the actual and predicted observations. Decision curve analysis at 1-year and 3-year after surgery indicated that the constructed nomograms had better predictive value than aMAP score. Furthermore, the TDROC analysis performed showed that the AUROCs for aMAP score had the highest value at 5-year point for DFS and 15-year point for OS. These models may contribute to individualized risk stratification.

Notwithstanding, our study also has a few limitations. Firstly, this research was a retrospective study with small sample size, which may be potentially subject to selection bias. Secondly, our study requires prospective cohort studies to evaluate the prognostic accuracy of aMAP score in breast cancer. Finally, the established nomogram models should be performed for further validation.

Conclusion

In conclusion, aMAP score has a high prognostic ability for DFS and OS in breast cancer with liver metastasis after surgery. The aMAP score is a risk score that helps simple, particularity, dependable prediction of the risk of breast cancer with liver metastasis after surgery. The constructed nomogram models are conducive to discriminate breast cancer patients at high risks of liver metastasis.

Institutional Review Board Statement

This retrospective single-center study was conducted in accordance with the amended Declaration of Helsinki and was approved by the ethics committee of Cancer Hospital Chinese Academy of Medical Sciences (No.82173328).

Data Sharing Statement

The material supporting the conclusion of this article has been included within the article.

Informed Consent Statement

The enrolled patients provided written informed consent for using their data in this retrospective study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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