Research Square

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Alkaline Phosphatase to Albumin Ratio: A Novel Prognostic Biomarker for Hepatocellular Carcinoma after Microwave Ablation as the Initial Treatment

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Research Article

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Abstract

Background

As a new serum-based biomarker, albumin to alkaline phosphatase ratio (AAPR) has been studied among several cancers. However, alkaline phosphatase to albumin ratio (APAR) has not been investigated among hepatocellular carcinoma (HCC) patients undergoing microwave ablation (MWA) as the initial therapy.

Methods

228 HCC patients undergoing MWA as the initial treatment were included in this study. Firstly, receiver operating curve (ROC) analysis was performed to identify the optimal cutoff values for APAR and other biomarkers. Then, the associations between APAR and clinicopathological variables were assessed. Additionally, Kaplan-Meier analysis was accomplished to evaluate the impacts of APAR on prognosis of HCC patients. Ultimately, Cox regression analysis was performed to identify independent prognostic factors for HCC patients.

Results

It was initially revealed that the optimal cutoff value for APAR was 2.44 ($P < 0.001$). Then it was demonstrated that high APAR was significantly associated with tumor size ($P = 0.043$). Subsequently, through Kaplan-Meier analysis, it was revealed that high APAR was significantly associated with worse overall survival (OS, $P < 0.001$) and disease-free survival (DFS, $P < 0.001$). Ultimately, along with tumor size ($P = 0.018$, HR = 2.292, 95%CI: 1.152–4.561), high APAR ($P < 0.001$, HR = 5.881, 95%CI: 3.093–11.185) was demonstrated to be an independent predictive factor for overall survival (OS). Similarly, along with Child-Pugh grade ($P = 0.001$, HR = 3.467, 95%CI: 1.705–7.050), GAR ($P = 0.004$, HR = 2.152, 95%CI: 1.281–3.613), and number of tumors ($P = 0.015$, HR = 2.678, 95%CI: 1.213–5.917), high APAR ($P = 0.032$, HR = 1.572, 95%CI: 1.040–2.377) was demonstrated to be an independent predictive factor for disease-free survival (DFS).

Conclusion

APAR was a reliable biomarker predicting survival of HCC patients.

Background

As the sixth most commonly diagnosed malignant tumor, hepatocellular carcinoma (HCC) causes the third most cancer-related deaths[1, 2]. Doctors should consider multiple factors when managing HCC patients, such as cancer characteristics, liver function reserve, and physical status. For HCC at an early

stage, curative hepatectomy, liver transplantation, and radiofrequency or microwave ablation are curative choices[3]. However, for most HCC patients, liver transplantation is not the preferred choice due the lack of donor organs, high medical cost and long-term use of immunosuppressive medications, whereas curative hepatectomy is only feasible for patients with sufficient liver function reserve[3]. Like curative hepatectomy and liver transplantation, image-guided locoregional therapy such as radiofrequency or microwave ablation (RFA or MWA) has been reported to yield favorable long-term outcomes to patients with early-stage HCC[4–6]. Thus, RFA and MWA have been approved to treat patients with early stage HCC with or without compromised liver function (Child-Pugh A or B liver function).

However, MWA has also been compared to RFA in terms of local recurrence and overall survival (OS). For HCC smaller than 3cm, MWA is not significantly different from RFA in terms of complication rate, local recurrence, overall survival and mortality rate[7–9]. Thus, for HCC smaller than 3cm, both methods can be safely and effectively applied. However, the cutoff diameter distinguishing MWA from RFA in terms of complication rate, local recurrence and overall survival is controversial. In most studies, this diameter is 3cm. Whereas, in a study by Gaia S et al, it was reported that for HCC between 15–20 mm MWA was not significantly different in terms of complete response rate and overall survival, while MWA was superior to RFA for HCC between 21 and 35mm[10]. Additionally, the anatomical location of HCC may also affect the efficiency of locoregional ablation. In a study published by Chen J et al, it was reported that a perivascular location might lead to a high tumor recurrence rate[11]. In a newly published study, An C et al reported that periportal HCC was related with high local tumor progression rate after RFA and MWA instead of RFA should be applied to these patients[12]. For HCC larger than 3cm, it has been widely accepted that MWA is associated with better tumor control despite the other controversial aspects such as overall survival. Liu W et al reported that RFA was inferior to MWA for treating HCC within the Milan criteria, but had comparable efficacy to MWA for solitary HCC ≤ 3 cm[13]. Facciorusso A et al reported that MWA and RFA were similar to each other in terms of survival efficiency while for larger neoplasms, MWA was significantly superior to RFA[14]. Thus, considering all these studies, we could conclude that for HCC ≤ 3cm, both RFA and MWA can be applied while for HCC between 3 and 5cm or perivascular HCC, MWA is the preferred method. Given these findings from the aforementioned studies, at our center, most HCC patients qualified for locoregional therapy underwent MWA instead of RFA.

Over the past few years, several clinical and biochemical factors have been reported to be predictive indicators for HCC patients after MWA or RFA, such as size, number, α-fetoprotein (AFP), albumin, γ-glutamyl transpeptidase (GGT), and alkaline phosphatase (AKP). However, no satisfactory predictive capability has been observed among these factors. Thus, it is necessary for us to identify accurate biomarkers that may accurately predict prognosis of HCC patients after a curative MWA. Obtained from dividing the serum AKP level by the albumin level, alkaline phosphatase to albumin ratio (APAR) has been reported to predict prognosis of several malignancies. Zhou W et al reported that APAR was useful in predicting synchronous metastasis and recurrences among patients with well-differentiated pancreatic neuroendocrine neoplasms[15]. Pu N et al demonstrated that APAR was a prognostic factor for patients with pancreatic ductal adenocarcinoma after curative surgery[16]. However, APAR has not been studied in other cancers such as gastric cancer, HCC, colorectal cancer, lung cancer, and breast cancer. Whereas, the

reverse of APAR, AAPR has been widely investigated in many malignant tumors. Li X et al reported that the integration of pre-operative and post-operative AAPR can accurately predict survival of patients with limited small-cell lung cancer[17]. Long ZQ et al demonstrated that AAPR was an independent predictive factor for OS of patients with non-metastatic breast cancer[18]. Zhang F et al reported that AAPR was an independent prognostic factor for patients with combined hepatocellular and cholangiocarcinoma[19]. Zhang F et al demonstrated that AAPR was a predictor of recurrence and OS of patients with early-stage HCC undergoing radiofrequency ablation as the initial treatment[20]. However, neither AAPR nor APAR has been assessed for its prognostic significance among HCC patients after curative MWA.

In the current study, we evaluated the prognostic significance of pre-treatment APAR among HCC patients undergoing MWA as the initial treatment.

Materials And Methods

Patients

Between January 2010 and December 2017, there were 228 HCC patients undergoing curative MWA as the initial treatment at The Department of Radiology, The Affiliated Zhujiang Hospital, Southern Medical University and The Department of Interventional Radiology, Shenzhen Traditional Chinese Medicine Hospital. Diagnosis and treatment of HCC was in compliance with guidelines on HCC[21–24]. Chinese guidelines on HCC were the ultimate reference when discrepancy occurred. The inclusion criteria of the present study were as follows: diagnosed with HCC; conforming to the Milan criteria (single nodule smaller than 5cm; 2 to 3 lesions and each lesion not larger than 3cm); without vascular invasion; without involvement of lymph node or extrahepatic metastasis; with complete clinicopathological and follow-up information data; with Child-Pugh A or B liver function; and undergoing curative MWA as the initial treatment. And the exclusion criteria adopted in this study were as follows: incomplete clinicopathological and follow-up information; undergoing other treatments before MWA; incomplete ablation that is confirmed by contrast-enhanced MRI or CT performed 4 weeks after MWA; concurrently diagnosed with other malignant tumors; and dysfunction of other organs such as kidney failure, liver failure, heart failure and respiratory failure.

Demographic, clinicopathological and follow-up data were obtained from the medical records: age, gender, Child-Pugh liver function grade, pre-treatment laboratory tests, and tumor characteristics and follow-up information. Hematological and biochemical tests were accomplished 3 days prior to MWA. APAR was calculated via dividing the serum AKP level (U/L) by serum albumin level (g/L). ALBI was calculated according to the following formula: ALBI = 0.660 × log10 [TBil (μmol/L)] − 0.085 × (ALB [g/L]).

Ethics approval

The present study was retrospective in nature. The Ethics Committee of The Affiliated Zhujiang Hospital, Southern Medical University approved this study and this study was in compliance with Declaration of Helsinki[25]. Before the beginning of this study, each patient gave his or her informed consent.

MWA procedures and follow-ups

MWA procedures in this study were accomplished as previously described[26, 27]. The ECO microwave system (ECO-100A1, ECO Medical Systems Corps, Nanjing, China) was used to accomplish MWA. MWA procedures were performed with the assistance of real-time CT under local anesthesia. Ablations were repeated several times to make sure a sufficiently large margin of 1cm.

Four weeks after MWA, contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) was performed to assess the range of MWA therapy. MWA would be considered curative if neither contrast enhancement nor abnormal washout phenomenon was detected within or around the ablation area[28, 29].

After MWA, all the patients were instructed to undergo follow-ups at the outpatient department. The first follow-up took place 1 month after MWA and two to three months thereafter. The follow-ups included the following aspects: physical examination, routine blood examination, liver function assessment, AFP test, and contrast-enhanced ultrasonography. Contrast-enhanced MRI or CT would be performed if recurrence was suspected.

Statistical analysis

Quantitative variables were presented as means ± standard deviations and further compared through Student's t test (normally distributed variables) or Mann–Whitney U test (abnormally distributed variables), while categorical variables were presented as counts with percentages and further compared by the $\chi 2$ test and Fisher's exact test. The time length between initial curative MWA and death or the last follow-up was defined as overall survival (OS) while disease-free survival (DFS) recorded as the duration from the initial MWA and death or cancer recurrence, no matter which one occurred first. Notably, "recurrence" within the primary tumor occurring within four weeks after MWA was considered as incomplete ablation rather than true cancer recurrence. Receiver operating curve (ROC) analysis was initially performed to identify the optimal cutoff values. Then the associations between APAR and clinicopathological variables were evaluated. Kaplan-Meier analysis curves were plotted to assess the impacts of APAR and other biomarkers on OS and DFS of HCC patients after MWA as the initial treatment. Ultimately, Cox regression proportional hazard model analysis was accomplished to identify independent prognostic factors. All the statistical analyses in this study were accomplished by SPSS (Version 24.0, Armonk, New York, IBM Corp). The statistical analyses involved in the present study were two-tailed in nature and P values < 0.05 were deemed as statistically significant.

Results

The associations between APAR and clinicopathological variables

There was a total of 228 HCC patients receiving MWA as the initial treatment qualified for this study and the detailed screening process was demonstrated in Fig. 1. Representative MRI confirming the diagnosis of HCC, CT guiding MWA procedure and MRI confirming complete ablation were presented in Fig. 2. By ROC analysis, we first identified the optimal cutoff values for APAR, GAR, and TAR as 2.44, 0.71, and 0.36 (shown in Fig. 3). Then patients were divided into high APAR group or low APAR group. The associations between APAR and clinicopathological variables were demonstrated in Fig. 4, from which we could see that high APAR was significantly associated with tumor size (P = 0.043, OR = 1.919, 95%CI: 1.020–3.611).

Survival analysis

Baseline characteristics of the 228 HCC patients were summarized in Table 1. The media survival of these 228 patients was 60 months and 1-year, 3-year and 5-year survival rates were 90.78%, 74.12%, and 53.50%, respectively. The median disease-free survival of these 228 patients were 33 months and 1-year, 3-year, and 5-year disease-free rates were 73.24%, 46.93%, and 28.51% respectively. According to Kaplan-Meier analysis, high APAR was significantly with worse OS (92.5% VS 62%) (P < 0.001) (Fig. 5A) and DFS (51.9% VS 29.6%) (P < 0.001) (Fig. 5D). Similarly, high GAR was significantly associated with worse OS (96.1% VS 79.8%) (P = 0.002) (Fig. 5B) and DFS (65.7% VS 38%) (P < 0.001) (Fig. 5E) and high TAR significantly with worse OS (91.1% VS 75.4%) (P = 0.001) (Fig. 5C) and DFS (51.2% VS 40%) (P = 0.009) (Fig. 5F).

Table 1
Baseline characteristics of HCC Patients

Variable		Total patients	Percentage of patients
Gender	Male	195	85.5%
	Female	33	14.5%
Age (years)	≤ 60	161	70.6%
	> 60	67	29.4%
Child-Pugh	A	217	95.2%
	B	11	4.8%
AFP (ng/ml)	≤ 400	168	73.7%
	> 400	60	26.3%
ALP/ALB*	-	-	13.88 ± 1.19
GGT/ALB*	-	-	1.98 ± 3.10
TBIL/ALB*	-	-	0.41 ± 0.26
ALBI*	-	-	-2.75 ± 0.41
Tumor size (cm)	≤ 3	109	47.8%
	> 3	119	52.2%
No. of tumor	Single	220	96.5%
	Multiple	8	3.5%
* Continuous variables were displayed as mean ± standard deviation (SD)			
ALBI = ($\log_{10}$ bilirubin μmol/L × 0.66) + (albumin g/L × -0.085)			

It was revealed through univariate Cox regression analysis that high APAR (P = 0.003, HR = 3.050, 95%CI: 1.462–6.363), high TAR (P = 0.012, HR = 2.247, 95%CI: 1.199–4.210), high GAR (P = 0.055, HR = 1.812, 95%CI: 0.989–3.323), ALBI (P = 0.016, 0.004, HR = 2.426, 95%CI: 1.327–4.436) and tumor size (P = 0.005, HR = 2.682, 95%CI: 1.351–3.323) were significantly associated with OS (shown in Table 2). Then these variables significant associated with OS proven by univariate Cox regression analysis and GAR were included in multivariate Cox regression analysis to identify independent predictive factors for OS, revealing that high APAR (P < 0.001, HR = 5.881, 95%CI: 3.093–11.185) and larger tumor size (> 3cm) (P = 0.018, HR = 2.292, 95%CI: 1.152–4.561) were independent predictive factors for OS (shown in Table 2).

Table 2
Univariate and multivariate analysis for overall survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender Male	Reference	0.388	-	-
Female	1.432 (0.633–3.239)			
Child-Pugh A	Reference	0.089	Reference	0.942
B	2.453 (0.872–6.899)		1.040 (0.355–3.050)	
AFP ≤ 400	Reference	0.230	-	-
(ng/ml) > 400	1.469 (0.784–2.751)			
APAR ≤ 2.44	Reference	0.003	Reference	< 0.001
> 2.44	3.050 (1.462–6.363)		5.881(3.093–11.185)	
TAR ≤ 0.36	Reference	0.012	Reference	0.139
> 0.36	2.247 (1.199–4.210)		1.662 (0.848–3.254)	
GAR ≤ 0.71	Reference	0.055	Reference	0.196
> 0.71	1.812 (0.989–3.323)		2.279 (0.654–7.947)	
ALBI < -2.60	Reference	0.016	Reference	0.982
-2.60 to -1.39	2.426 (1.327–4.436)	0.004	0.931 (0.446–1.946)	0.849
≥ -1.39	-	-	-	-
Tumor size ≤ 3	Reference	0.005	Reference	0.018
(cm) > 3	2.682 (1.351–3.323)		2.292 (1.152–4.561)	
No. of Single	Reference	0.766	-	-
tumor Multiple	0.740 (0.102–5.388)			

Similarly, univariate Cox regression analysis was initially performed, demonstrating that Child-Pugh liver function grade (P < 0.001, HR = 3.512, 95%CI: 1.757–7.021), APAR (P < 0.001, HR = 2.176, 95%CI: 1.479–3.203), GAR (P < 0.001, HR = 2.536, 95%CI: 1.547–4.159), TAR (P = 0.010, HR = 1.625, 95%CI: 1.121–2.357) and number of tumors (P = 0.004, HR = 3.174, 95%CI: 1.460–6.899) were significantly associated with DFS (Table 3). Then these variables significant associated with DFS proven by univariate Cox regression analysis were included in multivariate Cox regression analysis to identify independent predictive factors for DFS, revealing that Child-Pugh liver function grade (P = 0.001, HR = 3.467, 95%CI:1.705–7.050), GAR (P = 0.004, HR = 2.152, 95%CI: 1.281–3.613), number of tumors (P = 0.015, HR

= 2.678, 95%CI: 1.213–5.917) and high APAR (P = 0.032, HR = 1.572, 95%CI: 1.040–2.377) were independent predictive factors for DFS (Table 3).

Table 3
Univariate and multivariate analysis for disease free survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender Male	Reference	0.277	-	-
Female	0.717 (0.394–1.306)			
Age (years) > 60	Reference	0.460	-	-
≤ 60	0.862 (0.581–1.278)			
Child-Pugh A	Reference	< 0.001	Reference	0.001
B	3.512 (1.757–7.021)		3.467 (1.705–7.050)	
AFP ≤ 400 (ng/ml) > 400	Reference	0.219	-	-
	1.293 (0.858–1.949)			
APAR ≤ 2.44	Reference	< 0.001	Reference	0.032
> 2.44	2.176 (1.479–3.203)		1.572 (1.040–2.377)	
TAR ≤ 0.36	Reference	0.010	Reference	0.550
> 0.36	1.625 (1.121–2.357)		1.134 (0.750–1.716)	
GAR ≤ 0.71	Reference	< 0.001	Reference	0.004
> 0.71	2.536 (1.547–4.159)		2.152 (1.281–3.613)	
ALBI < -2.60	Reference	< 0.001	Reference	0.144
-2.60 to -1.39	2.053 (1.392–3.030)	< 0.001	1.540 (0.975–2.435)	0.064
≥ -1.39	5.492 (1.326–22.746)	0.019	0.953 (0.167–5.427)	0.957
Tumor size ≤ 3	Reference	0.249		
(cm) >3	1.245 (0.858–1.808)			
No. of Single	Reference	0.004	Reference	0.015
tumor Multiple	3.174 (1.460–6.899)		2.678 (1.213–5.917)	

Discussion

In the current study, the prognostic value of APAR among HCC patients undergoing curative MWA as the initial treatment was evaluated, revealing that high APAR was significantly associated with worse OS and DFS. Additionally, high APAR was also proven to be an independent predictor for OS and DFS. Thus, considering all these results, we could draw the conclusion that APAR is a useful biomarker in helping us formulate personalized treatment strategies.

In clinical practice, liver function reserve is a major concern in patient management and predicting survival of HCC patients[30, 31]. Stratification of cancer recurrence and mortality is a crucial task since patients with different risks might be managed with distinct strategies. Child-Pugh liver function grade is the most commonly adopted method to assess liver function reserve of HCC patients[32]. Besides its role in assessing liver function reserve, Child-Pugh liver function could also be used to evaluate recurrence and survival of HCC patients[33]. However, it has been reported in several studies that Child-Pugh liver function grade has a poor discriminatory capability in stratifying HCC patients, especially among patients with early HCC[33, 34]. Thus, it is necessary to develop novel methods to help us more efficiently predict survival of HCC patients.

Obtained from AKP/ALB, APAR is a novel parameter predicting survival of patients with malignant tumors. As a matter of fact, both AKP and ALB have been reported to be related with malignant phenotype of HCC. According to Yamamoto K et al, high level of ALPase located in the nucleus might promote proliferation and aggressiveness of HCC cells[35]. And as a matter of fact, Rao SR et al reported that tumor-derived AKP regulated tumor growth, epithelial- mesenchymal plasticity and disease-free survival in metastatic prostate cancer[36]. It has been universally accepted that epithelial-mesenchymal transition (EMT) is a milestone event in progression and metastasis of HCC cells[37–39]. Thus, it is no surprise at all that AKP-based biomarker such as APAR is an independent prognostic factor for HCC patients. And albumin is usually considered as a parameter for nutritional status and low albumin level is indicative of abnormal protein synthesis within the liver, which would further lead to impaired immunity[40]. Apart from its role as an indicator of nutritional status, albumin has also been reported to stabilize cell proliferation, antagonize the oxidant effects of carcinogens and inhibit proliferation of cancer cells through decreasing the phosphorylation level of Rb proteins[41, 42]. Thus, according to these studies, it is a normal phenomenon that, the biomarker based on AKP and ALB, high APAR is significantly associated with worse prognosis of HCC patients and can independently predict survival of HCC patients.

However, some limitations of the current study should not be neglected. Firstly, the study is a retrospective one, meaning that potential selection bias is not absolutely avoidable and further prospective studies are needed to verify the findings of our study. Secondly, most of HCC patients in this study are HBV-related and therefore, the findings of this study should not be directly put into clinical practice in the United States and most European countries where most HCC patients are caused by HCV infection or alcohol abuse. Additionally, according to some published studies different etiologies of HCC are associated with remarkably different molecular mutations[43]. Jin YJ et al reported that HCC caused by different risk factors were related with different splicing regulation[44]. Song MA et al reported that HBV-related HCC was significantly different from HCV-related HCC in terms of DNA methylation

profiles[45]. Seshachalam VP et al identified functionally distinct candidate upstream regulators for HCC arising from different etiologic risk factors[46]. Thus, APAR should be re-assessed by studies performed in western countries before its application in clinical practice. Thirdly, high AKP could be detected in other diseases such as extrahepatic cholangiocarcinoma, pancreatic cancer located in the “head”, and cholangiolithiasis, suggesting that HCC patients should not simultaneously suffer from these diseases when APAR is used to stratify HCC patients. Fourthly, patients receiving other treatments besides MWA were excluded in this study and thus, the prognostic significance of APAR among these patients should be evaluated by other studies. Fifthly, the number of patients included in the current study is relatively small and this study is performed by one institution, meaning that larger-scaled and multi-institution studies are needed to verify the conclusions of our study. Sixthly, the molecular mechanisms through which high APAR contributes to aggressive phenotype of HCC have not been explored. However, some other studies have investigated these aspects. Despite these aforementioned drawbacks, our study still could provide some clues for clinical practice and future studies given the fact that as far as we know, our study is the first to investigate the prognostic significance of APAR among patients undergoing MWA as the initial therapy.

Conclusions

High APAR is significantly associated with worse prognosis of HCC patients undergoing MWA as the initial treatment and is an independent predictive factor for OS and DFS.

List Of Abbreviations

AAPR
albumin to alkaline phosphatase ratio
APAR
alkaline phosphatase to albumin ratio
HCC
hepatocellular carcinoma
MWA
microwave ablation
ROC
receiver operating curve
OS
overall survival
DFS
disease-free survival
95%CI
95% confidential interval
GAR

GGT to albumin ratio
RFA
radiofrequency ablation
GGT
γ-glutamyl transpeptidase
AFP
-fetoprotein
AKP
alkaline phosphatase
TAR
total bilirubin to albumin ratio
ALBI
albumin-bilirubin grade
SPSS
Statistical Product and Service Solutions
EMT
epithelial-mesenchymal transition

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee, Zhujiang Hospital, Southern Medical University and each individual patient in this study had given his or her informed consent in the written form.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

B. C., T.A. and X.Q. conceived and designed this study. B.C., X.L, Z.X, X.S, and Y.W collected the data. B.C., T.A and Y.W performed the statistical analysis. B.C. and T.A. drafted the manuscript. Y.W and X.Q revised the manuscript. X.Q supervised this study. All the authors read and approved the final manuscript.

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Figures

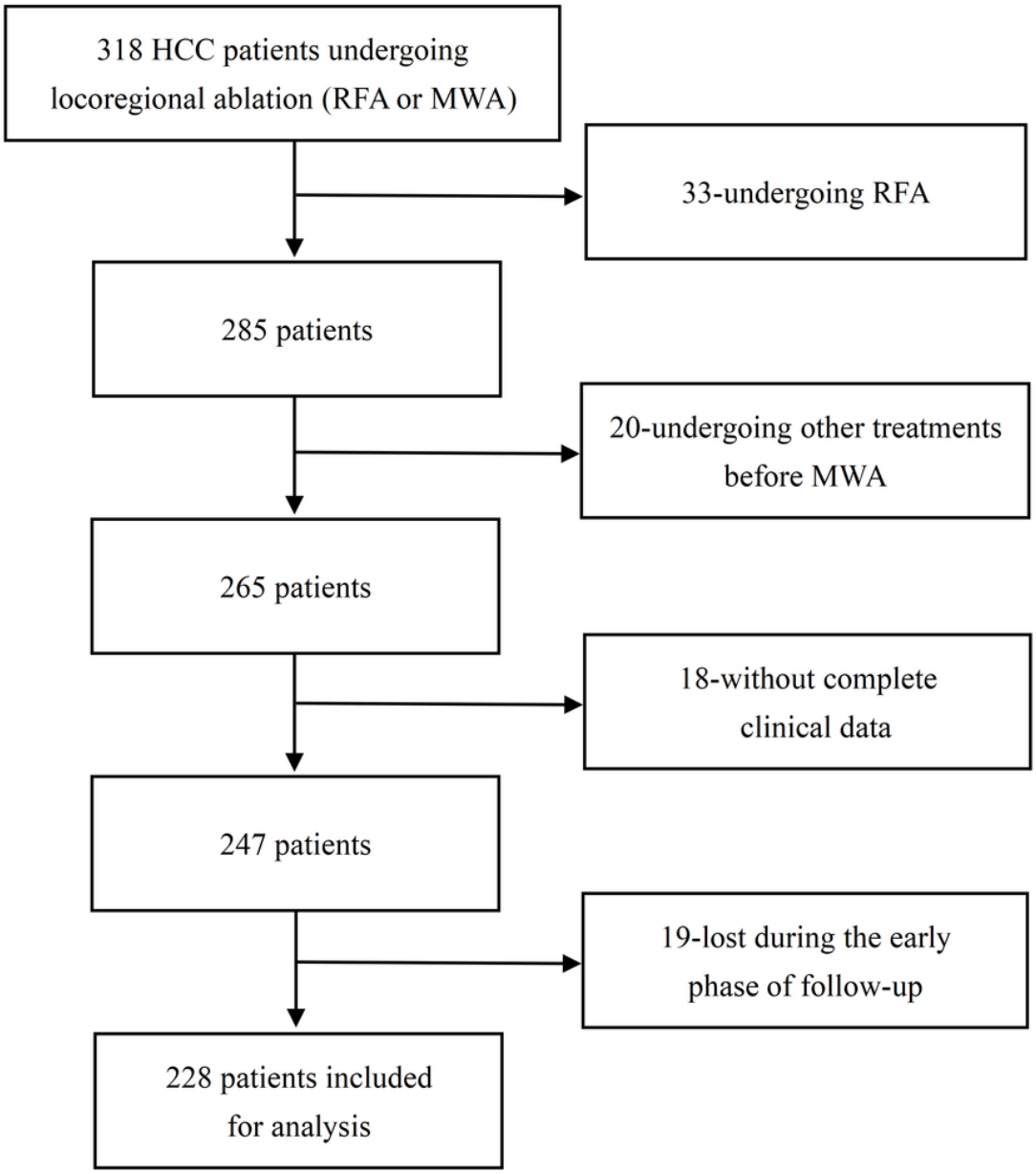

Figure 1

The flowchart illustrating the detailed process of this study.

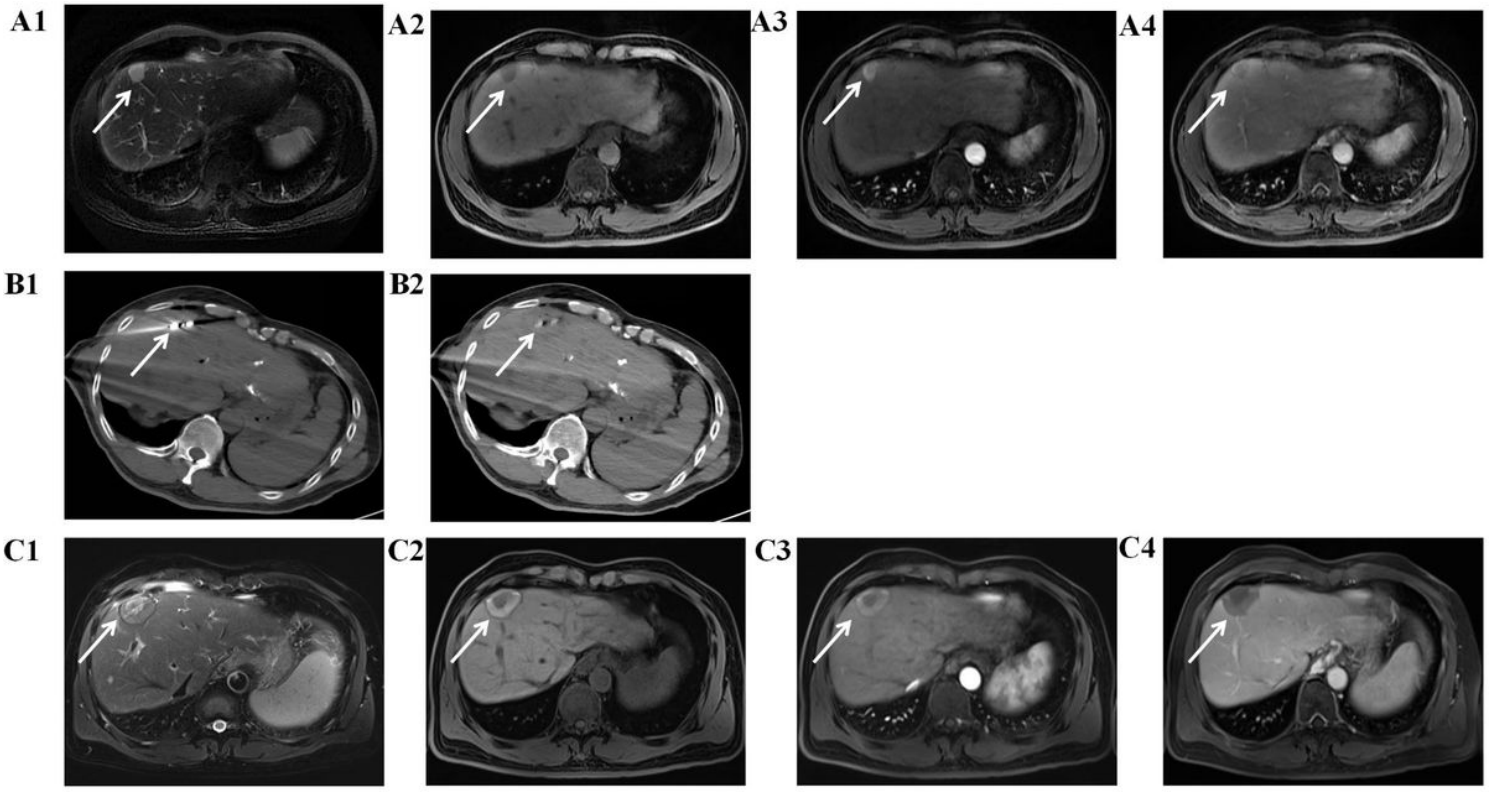

Figure 2

Representative images confirming the diagnosis of HCC, guiding MWA, and excluding incomplete ablation. **A1 to A4:** MRI performed before MWA to confirm the diagnosis of HCC. **A1:** T2-weighted MRI. **A2:** T1-weighted MRI. **A3:** Arterial phase of contrast-enhanced T1-weighted MRI. **A4:** Portal venous phase of contrast-enhanced T1-weighted MRI. **B1 to B2:** CT-guided MWA procedure. **B1:** CT performed to guide MWA procedure. **B2:** CT performed after MWA procedure. **C1 to C4:** Four weeks after MWA procedure, MRI was performed to exclude incomplete ablation. **C1:** T2-weighted MRI. **C2:** T1-weighted MRI. **C3:** Arterial phase of contrast-enhanced T1-weighted MRI. **C4:** Portal venous phase of contrast-enhanced T1-weighted MRI.

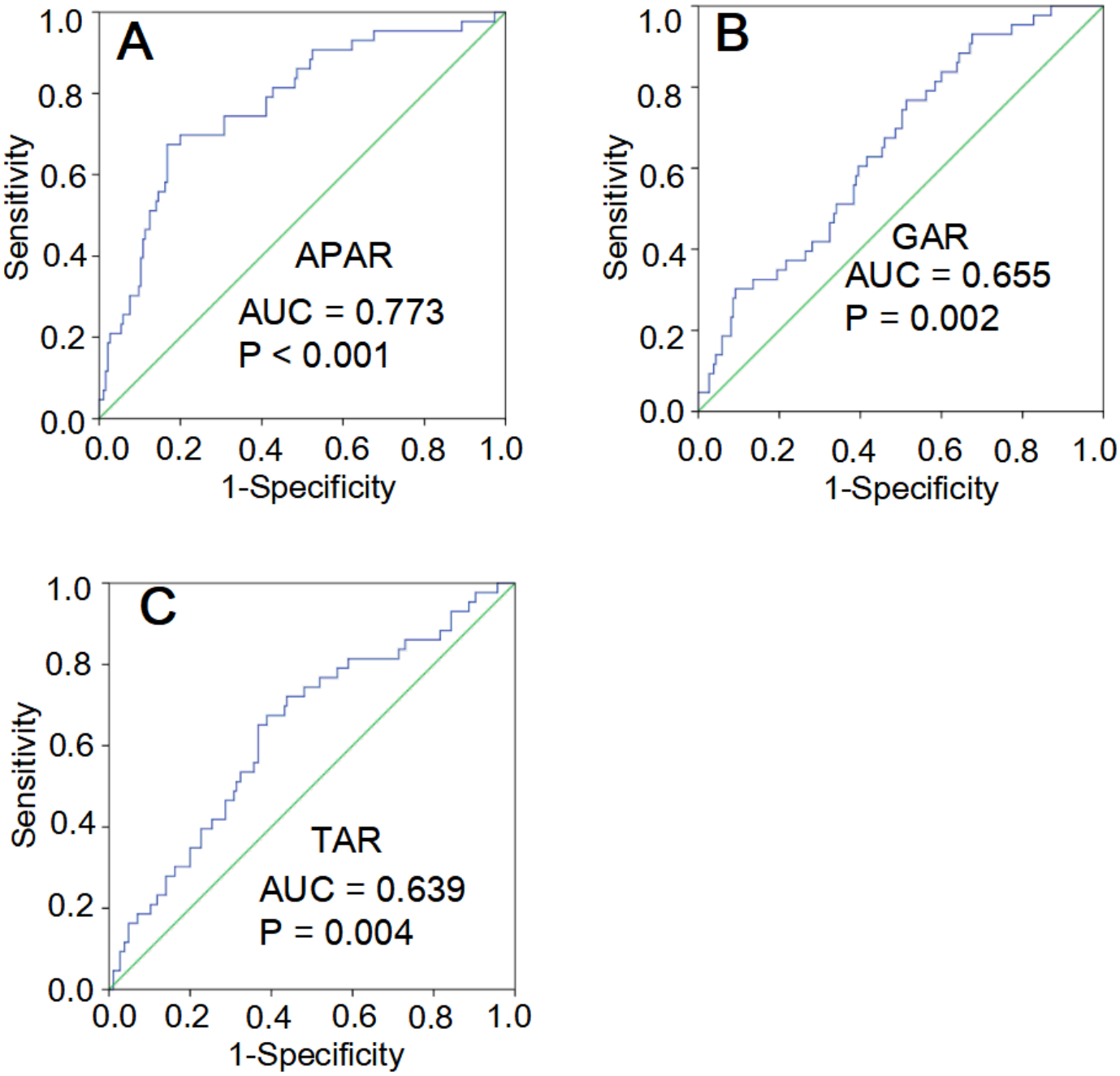

Figure 3

ROC analysis to identify the optimal cutoff values for APAR, GAR and TAR. **A:** ROC analysis identifying the optimal cutoff value for APAR. **B:** ROC analysis identifying the optimal cutoff value for GAR. **C:** ROC analysis identifying the optimal cutoff value for TAR.

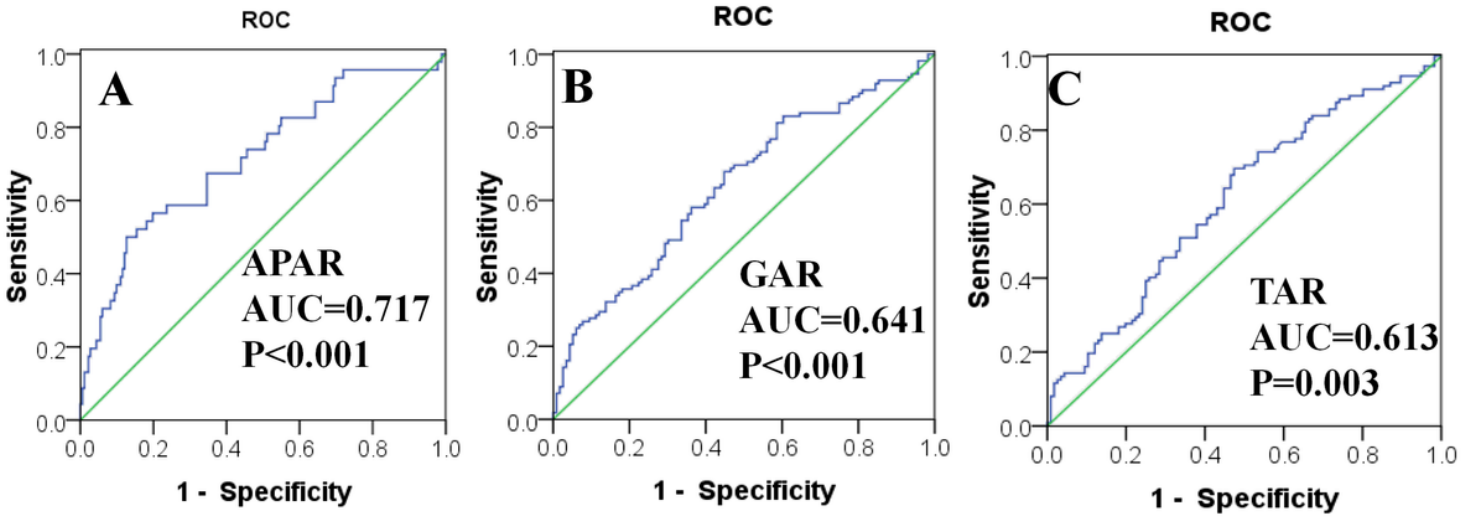

Figure 4

Forest plots illustrating the associations between APAR and clinicopathological variables.

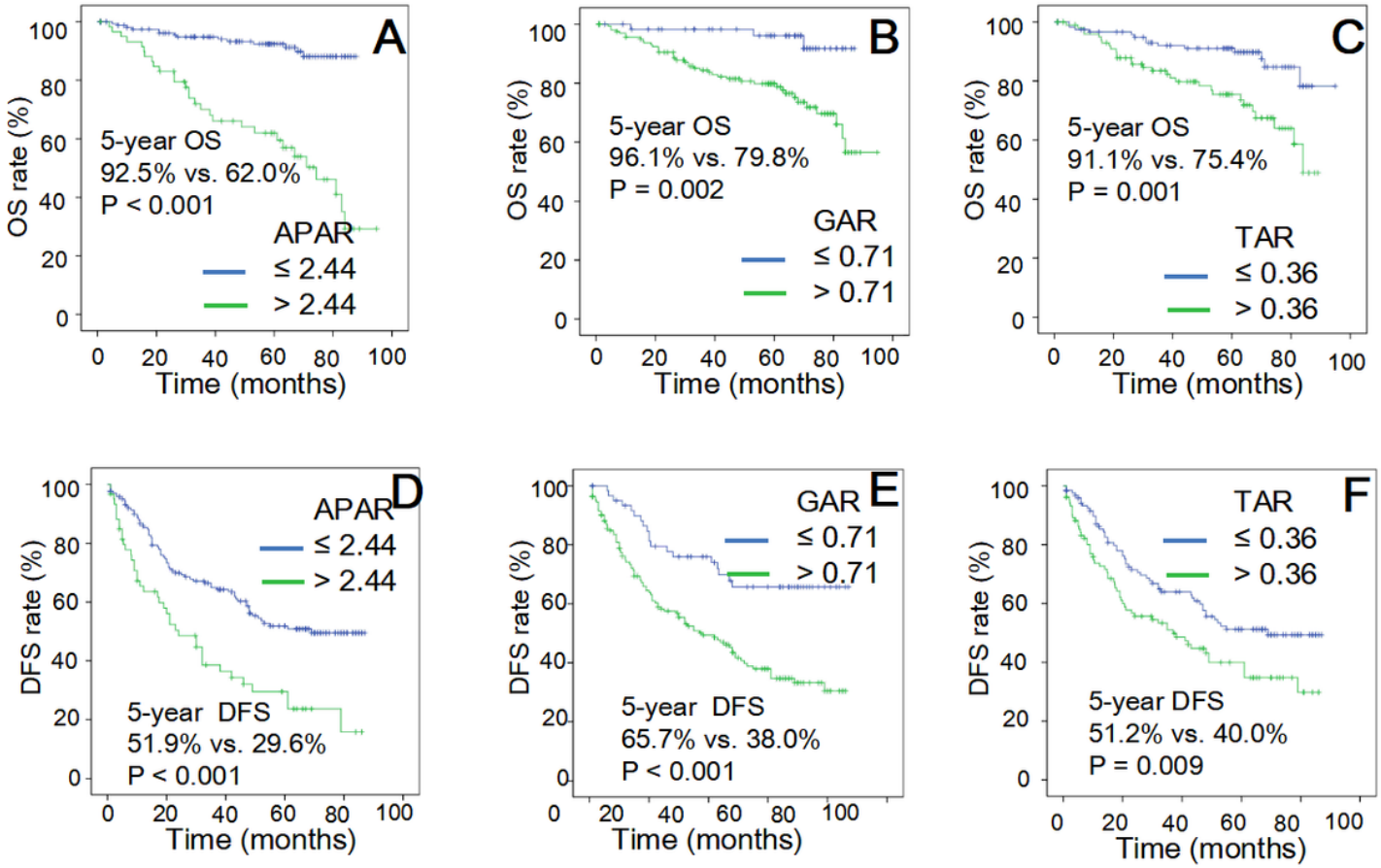

Figure 5

Kaplan-Meier analyses assessing the prognostic impacts of APAR, GAR and TAR on HCC patients undergoing curative MWA as the initial treatment. **A:** The impacts of APAR on OS of HCC patients. **B:** The impacts of GAR on OS of HCC patients. **C:** The impacts of TAR on OS of HCC patients. **D:** The impacts of APAR on DFS of HCC patients. **E:** The impacts of GAR on DFS of HCC patients. **F:** The impacts of TAR on DFS of HCC patients.