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ORIGINAL RESEARCH

Prognostic value of aspartate aminotransferase to platelet ratio index as a noninvasive biomarker in patients with hepatocellular carcinoma: a meta-analysis

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Yi Zhang, Xu Zhang

Department of General Surgery, the First People's Hospital of Neijiang, Neijiang, Sichuan Province, China

Background: The aspartate aminotransferase-to-platelet ratio index (APRI) has been correlated with clinical outcome in patients with hepatocellular carcinoma (HCC), but controversial results were obtained with previous studies. This study was aimed to evaluate the prognostic value of the APRI in patients with HCC.

Materials and methods: A literature survey was conducted by searching PubMed, Web of Science, Cochrane library, Embase, Wanfang, and National Knowledge Infrastructure for publications released prior to March 1, 2018. Pooled hazard ratios (HRs) with 95% CIs were calculated to assess the association between the APRI and HCC prognosis using Stata SE 12.0 software.

Results: Analysis was performed on a total of 15 articles that included 5,051 patients. The pooled results showed that APRI was significantly associated with overall survival for patients with HCC (HR =1.62, 95% CI: 1.23–2.01). Furthermore, HCC patients with higher APRI were at significantly greater risk of short recurrence-free survival (HR =1.83, 95% CI: 1.48–2.18) and poor disease-free survival (HR =1.46, 95% CI: 1.26–1.66).

Conclusions: APRI could serve as a promising and noninvasive marker for predicting HCC prognosis.

Keywords: aspartate aminotransferase-to-platelet ratio index, hepatocellular carcinoma, prognosis, meta-analysis

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death globally.[1,2] Despite great advances in early diagnosis and treatments, the prognosis, especially the long-term survival, remains dissatisfactory in patients with HCC.[3–6] Additionally, the prognostic markers of HCC have not been completely elucidated. Established prognostic factors can contribute to predicting the survival and relapse for HCC patients as well as guiding their clinical management.

Recently, several serum markers that can be used as noninvasive tools have been identified in human cancers, including HCC.[7–10] Among them, there has been great interest in the aspartate aminotransferase-to-platelet ratio index (APRI) because it is an inexpensive and feasible test that can be used for daily oncologic practice.

It has been reported that APRI might be a candidate as a prognostic biomarker in HCC.[11–20] However, there were shortcomings in the current clinical studies because they were of limited sample sizes, and some results regarding the clinical value of

Correspondence: Xu Zhang
Department of General Surgery, the First People's Hospital of Neijiang, Neijiang 641000, Sichuan Province, China
Email 1990486976@qq.com

APRI in HCC were inconsistent and debatable.[14,21,22] Therefore, we conducted this systematic review and meta-analysis based on all relevant studies for a better understanding of the relationship between APRI and prognosis of HCC patients.

Materials and methods

Search strategy and study selection

A comprehensive literature search was performed in several electronic databases to retrieve the eligible studies before March 1, 2018. The online databases included PubMed, Web of Science, Cochrane library, Embase, Wanfang, and National Knowledge Infrastructure. The combined key words and search terms were as follows: (aspartate aminotransferase-to-platelet ratio index OR aspartate aminotransferase/platelet count ratio index OR AST-to-platelet ratio index OR AST/PLT ratio index OR APRI) AND (liver cancer OR HCC OR hepatocellular carcinoma OR liver neoplasms OR hepatic tumor). We also manually reviewed the references in retrieved papers for potential studies.

Publications with full text that met the following criteria were considered to be eligible and were included in this meta-analysis: 1) studies concerned with the prognostic impact of APRI in primary HCC, 2) a definite cutoff value of APRI was given, 3) the hazard ratio (HR) with 95% CI for prognosis was available, and 4) patients with HCC were divided into two groups according to the APRI value.

Data extraction and quality assessment

The collected information from all studies included name of the first author, study country, year of publication, included time, sample size, number of male and female patients, age distribution, survival type, follow-up period, cutoff value for APRI, cutoff selection, treatment methods, tumor stage, HR, and the corresponding 95% CI. HRs and the corresponding 95% CIs were directly extracted from the original article if a study reported the HRs and 95% CIs in univariate and/or multivariate analysis. Otherwise, Engauge Digitizer software (version 4.1) was used to estimate the HR from the Kaplan–Meier curve.

All included studies were assessed by the Newcastle–Ottawa quality assessment scale (NOS). In this method, NOS scores ranged from 0 (lowest) to 9 (highest) points. A study with an NOS score ≥6 was considered to be of high quality.

Statistical analysis

In this meta-analysis, statistical analyses for pooled HRs were executed using Stata 12.0 software (Stata, College Station, TX, USA).

For measuring the heterogeneity among research studies, Cochran's Q test and Higgins I-squared statistic were applied. A probability value of $P_Q<0.05$ or $I^2>50\%$indicated that heterogeneity existed. If heterogeneity was present, the random-effects model was used to calculate the integrated HRs. If there was no significant heterogeneity across studies, the fixed-effects model was adopted.

Funnel plot and Begg's test were used to judge the potential publication bias. Sensitivity analysis was applied to evaluate the robustness of the pooled results. All P-values <0.05 were regarded as statistically significant.

Results

The detailed steps of the potential literature search are shown in Figure 1. Based on the selection criteria for the eligible studies, high-quality articles (including 17 studies) written in English were identified in this meta-analysis.[11–25] A total of 5,051 patients with HCC were enrolled. All included studies were retrospective and reported the relationship between the APRI value and HCC prognosis. The detailed characteristics of all included studies are summarized in Table 1.

Relationship between APRI and overall survival in HCC

A total of 12 articles (including 14 studies) with 4,558 subjects reported the relationship between APRI and overall survival (OS) in patients with HCC. Considering the significant heterogeneity among these articles (I^2=62.9%, P_Q=0.001), a random-effects model was applied. As shown in Figure 2, the overall results indicated that elevated APRI predicted a poor outcome for OS of HCC (HR =1.62, 95% CI: 1.23–2.01).

Exploratory subgroup analyses were performed according to analysis type (multivariate analysis and univariate analysis), cutoff value selection (receiver operating characteristic curve and Others), and treatments (With surgery, No surgery, and Mixed). Table 2 shows that the calculated pooled HR values were significantly >1.0 in those subgroup analyses. Interestingly, the APRI could be an independent predictor of OS in patients with HCC (HR =1.41, 95% CI: 1.08–1.73, $P<0.001$).

Nine studies with a total of 2,965 HCC patients reported the prognostic value of APRI for recurrence-free survival (RFS). No significant heterogeneity was observed among studies (I^2=0.0%, P_Q =0.930), and the fixed-effects model was adopted. The pooled HR was 1.83 (95% CI: 1.48–2.18, $P<0.001$; Figure 3), indicating that high APRI was an unfavorable factor for RFS in HCC. In addition, we found that the analysis types, cutoff value selections, and treatments did not affect the prognostic predictor of RFS in HCC patients from the subgroup analyses (Table 3).

Table 1 Main characteristics of all included studies

Study/Year	Country	Included time	No. (M/F)	Age (Years)	Survival type	Follow-up (Months)	Cutoff value	Cutoff selection	Treatment methods	Stage	MVA	NOS score
Huang HH, et al 2010[11]	China	1990–2002	76 (64/12)	Median 57	OS;RFS	Median 77.0±50.7	0.47	ROC analysis	With surgery	Child-Pugh A/B	OS-Yes, RFS-No	6
Kao W, et al 2011[12]	China	2002–2007	190 (121/69)	Mean 67.4	OS;RFS	Median 30.7±17.5	1	NA	No surgery	Child-Puge A/B	Yes	7
Shen SL, et al 2014[13]	China	2006–2009	332 (292/40)	Mean 49.82	OS;DFS	1-80	0.62	ROC analysis	With surgery	Edmonson stage: I–II–III–IV	Yes	8
Pang Q-1, et al 2015[14]	China	2002–2012	172 (139/33)	Mean 53.52	OS;DFS	Median 46	1.23	ROC analysis	With surgery	No extrahepatic spread	Yes	7
Pang Q-2, et al 2015[14]	China	2002–2012	191 (159/32)	Mean 54.12	OS;DFS	Median 40	1.79	ROC analysis	No surgery	No extrahepatic spread	Yes	7
Pang Q, et al 2015[15]	China	2002–2012	172 (139/33)	Mean 53.5	RFS	Median 52	1.94	ROC analysis	With surgery	No extrahepatic spread	Yes	6
Okamura Y, et al 2016[16]	Japan	2002–2014	140 (115/25)	Median 71	OS;RFS	Median 38.9	0.544	ROC analysis	With surgery	UICC: I–II–III	No	7
Chuang HA, et al 2016[17]	Korea	2005–2013	98 (70/28)	Mean 60.5	RFS	Median 40	1.38	ROC analysis	No surgery	Modified UICC: I–II–III	Yes	6
Ji F, et al 2016[18]	China	2006–2009	321 (285/36)	Mean 51	OS;DFS	1-96	1.68	ROC analysis	With surgery	TNM stage: I–II–III	Yes	8
Liu Y, et al 2016[19]	China	2004–2011	223 (189/34)	Median 54	RFS	Median 26.1	0.23	ROC analysis	With surgery	TNM stage: I–II–III–IV	Yes	7
Peng W, et al 2016[20]	China	2007–2013	244 (213/31)	Mean 50	OS;RFS	1-80	1	ROC analysis	With surgery	No extrahepatic metastasis	Yes	8
Teng W, et al 2017[21]	China	2010–2013	153 (82/71)	Median 64.1	OS;RFS	NA	2	NA	No surgery	BCLC stage:0/A/B/C	Yes	7
Toyoda H, et al 2017[22]	Japan	1997–2016	1669 (1181/488)	Mean 68.7	OS;RFS	1-240	1.2	ROC analysis	With surgery	BCLC stage:0/A/B/C/D	OS-Yes, RFS-No	8
Sarkar J, et al 2017[23]	USA	1993–2014	94 (71/23)	Mean 62	OS	>60	0.5	NA	Mixed	NA	No	6
Yang HJ, et al 2017[24]	China	2004–2010	661 (574/87)	NA	OS;DFS	1-60	0.25	ROC analysis	With surgery	BCLC stage:0/A/B/C	Yes	8
Tang T-1, et al 2018[25]	China	2005–2013	158 (136/22)	NA	OS	1-40	0.4	X-tile plots	No surgery	BCLC stage:B	No	7
Tang T-2, et al 2018[25]	China	2005–2014	157 (135/22)	NA	OS	1-35	0.4	X-tile plots	No surgery	BCLC stage:B	No	7

Note: All the studies were retrospective.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; DFS, disease-free survival; MVA, multivariate analysis; NA, not available; NOS, Newcastle–Ottawa quality assessment scale; OS, overall survival; RFS, recurrence-free survival; ROC, receiver operating characteristic curve; TNM, tumor-node-metastasis; UICC, Union for International Cancer Control.

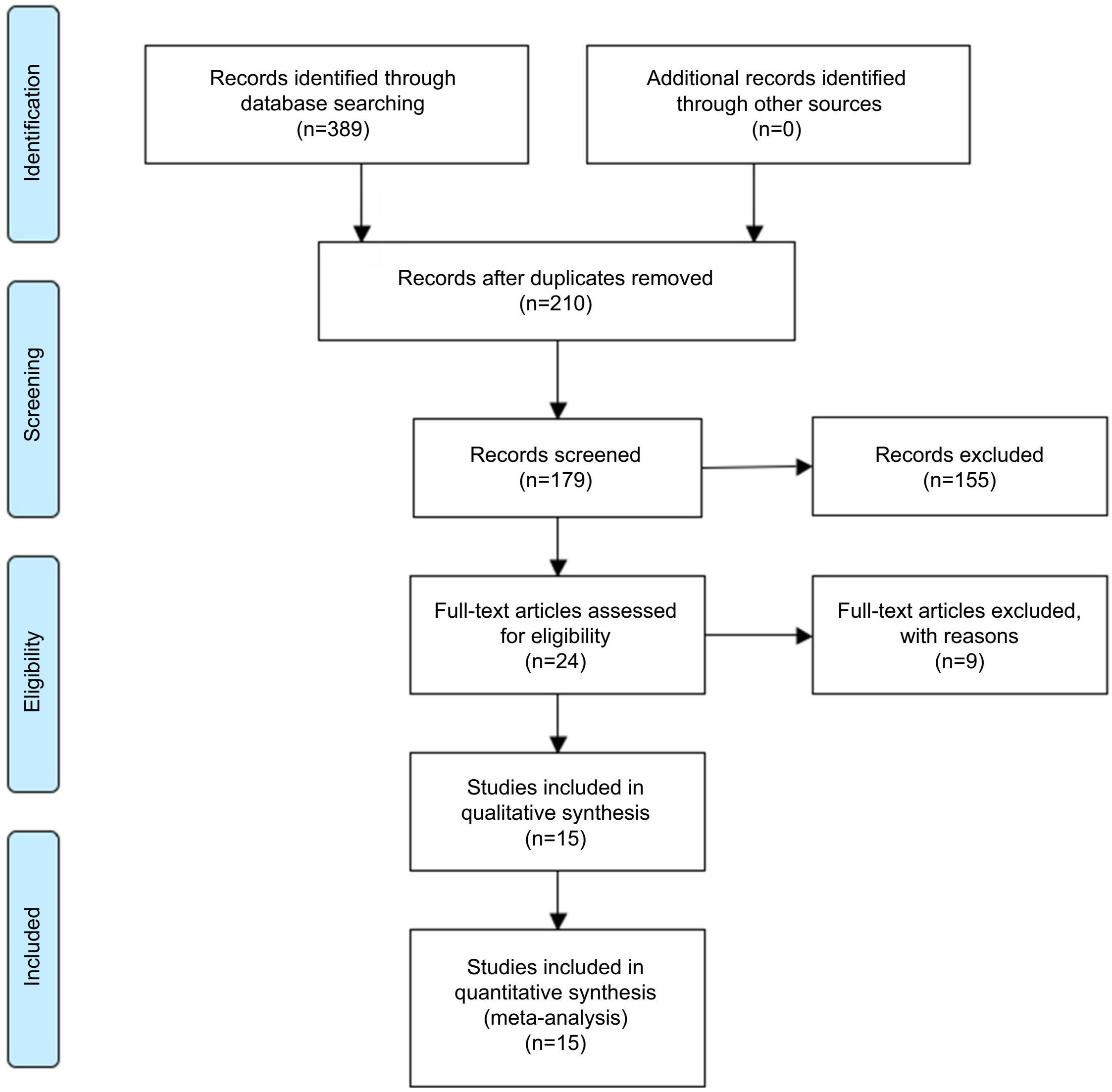

Figure 1 The flowchart of literature selection.

Table 2 Results of subgroup analysis of pooled HRs of OS of HCC patients with high APRI

Stratified analysis	No. of studies	No. of patients	Pooled HR (95% CI)	*P*-value	I^2(%)	P_Q
Analysis type						
MVA	10	4,009	1.41 (1.08–1.73)	<0.001	55.1	0.018
UVA	4	549	3.59 (2.32–4.87)	<0.001	5.2	0.367
Cutoff value selection						
ROC analysis	9	3,806	1.46 (1.10–1.81)	<0.001	58.1	0.014
Others	5	752	3.08 (1.23–4.92)	0.001	73.9	0.004
Treatments						
No surgery	5	849	2.24 (1.14–3.33)	<0.001	72.5	0.006
With surgery	8	3,615	1.48 (1.07–1.90)	<0.001	63.3	0.008
Mixed	1	94	4.09 (1.59–10.50)	<0.001	NA	NA

Note: Relationship between APRI and RFS in HCC.
Abbreviations: APRI, aminotransferase-to-platelet ratio index; HCC, hepatocellular carcinoma; HR, hazard ratio; MVA, multivariate analysis; NA, not available; OS, overall survival; RFS, recurrence-free survival; ROC, receiver operating characteristic curve; UVA, univariate analysis.

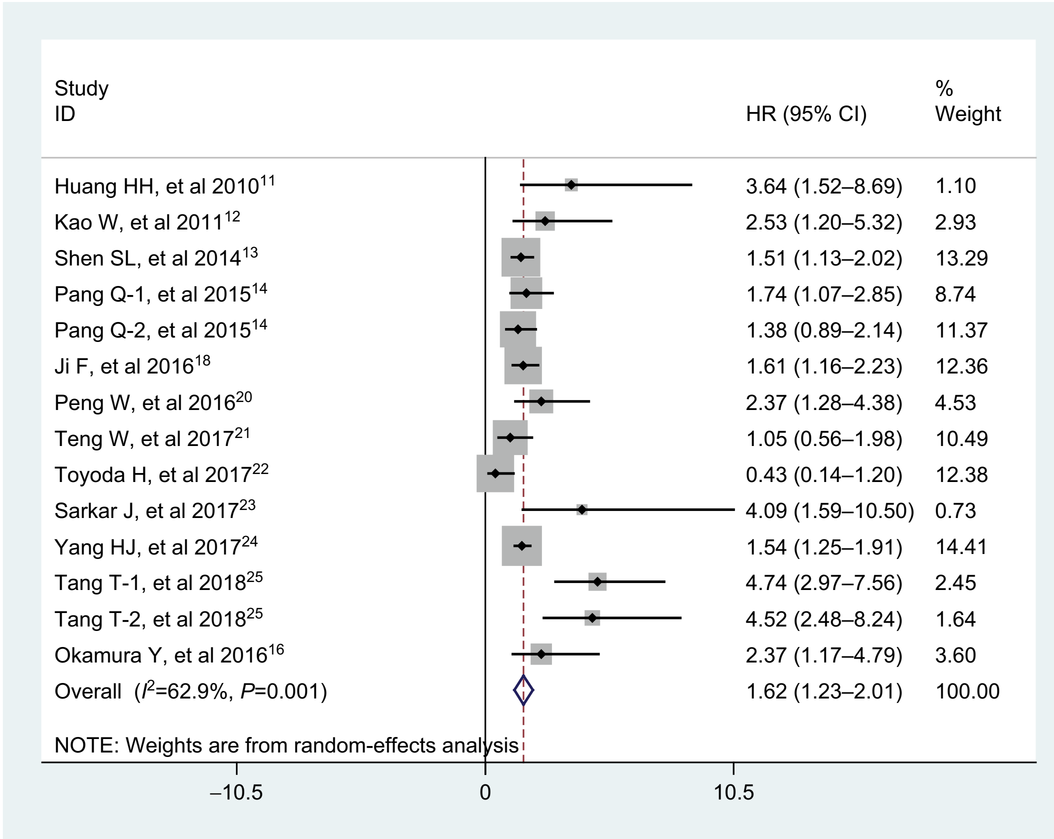

Figure 2 Forest plot for the relationship between APRI and OS.
Abbreviations: APRI, aminotransferase-to-platelet ratio index; HR, hazard ratio; OS, overall survival.

Five studies, consisting of 1,677 patients, explored the association between APRI and disease-free survival (DFS) in multivariate analysis. There was no obvious heterogeneity across studies (I^2=0.0%, P_Q=0.814), and therefore, the fixed-effects model was used. Analysis revealed the pooled HR of 1.46 with 95% CI: 1.26–1.66 (P<0.001), which showed that APRI was an independent predictive factor of DFS in patients with HCC (Figure 4).

Publication bias

Funnel plot and Begg's test both suggested no evidence of publication bias for OS, RFS, and DFS ($Pr_{\text{Begg's test}}$>|z|=0.228 for OS; $Pr_{\text{Begg's test}}$>|z|=0.118 for RFS; $Pr_{\text{Begg's test}}$>|z|=1.000 for DFS; Figure 5).

Sensitivity analysis

Sensitivity analysis was performed to assess the potential impact of each individual study on the overall results. The results showed that any single study had little influence on the pooled results (Figure 6), thus indicating that our results were relatively stable and credible.

Discussion

As a noninvasive scoring marker, APRI consists of two routinely available clinical and laboratory variables, aspartate aminotransferase (AST) and platelets (PLT), and can be calculated using the following formula: (AST / the upper limit of normal value)×100: PLT (10^9/L).[26] It was firstly proposed as a simple, straightforward test to assess liver fibrosis stage and liver function reserve.[27–29] In-depth studies determined that APRI also had potential prognostic value and could be used as a stable marker to predict the outcome of patients with HCC.[11–13] It has been known that AST and PLT play an important role in tumor progression and are associated with prognosis in several human cancers, including HCC.[15,30,31] APRI is a combination of the above two predictors, and it is low in cost and more easily detectable. Its clinical predictive value could be enhanced due to its stability and reliability.

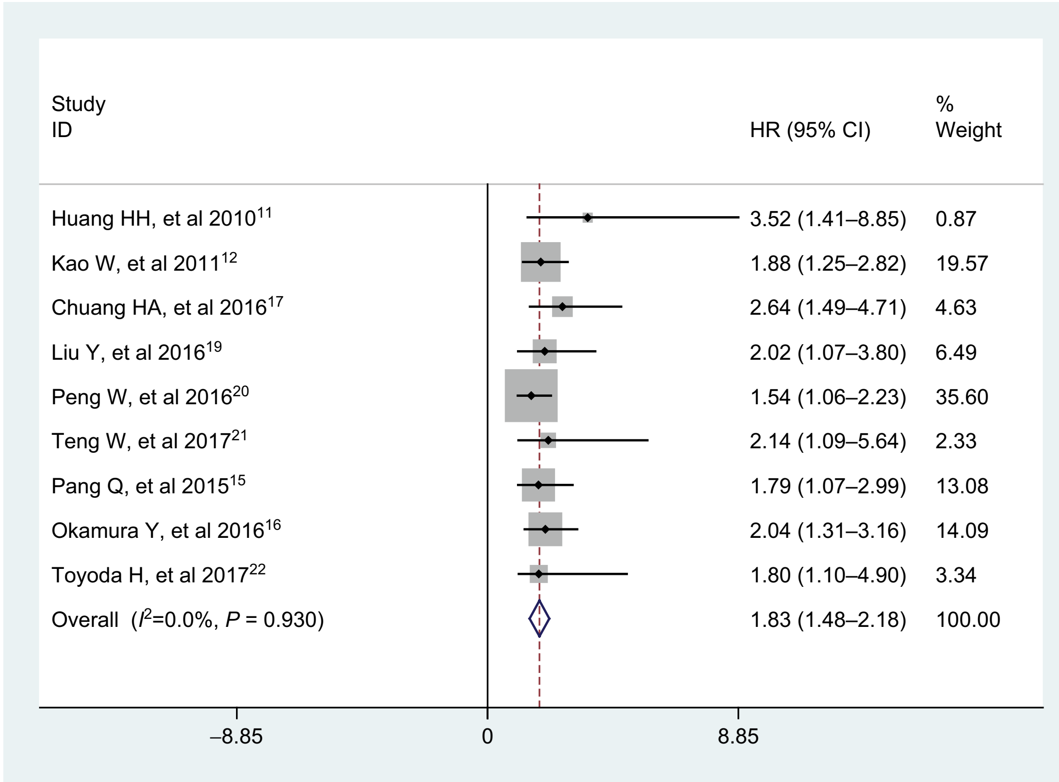

Figure 3 Forest plot for the relationship between APRI and RFS.
Abbreviations: APRI, aminotransferase-to-platelet ratio index; HR, hazard ratio; RFS, recurrence-free survival.

Table 3 Results of subgroup analysis of pooled HRs of RFS of HCC patients with high APRI

Stratified analysis	No. of studies	No. of patients	Pooled HR (95% CI)	*P*-value	I^2(%)	P_Q
Analysis type						
MVA	6	1,080	1.78 (1.39–2.16)	<0.001	0.0	0.848
UVA	3	1,885	2.07 (1.26–2.88)	<0.001	0.0	0.716
Cutoff value selection						
ROC analysis	7	2,622	1.81 (1.42–2.20)	<0.001	0.0	0.811
Others	2	343	1.90 (1.16–2.65)	0.001	0.0	0.832
Treatments						
No surgery	3	441	2.03 (1.36–2.71)	<0.001	0.0	0.703
With surgery	6	2,524	1.76 (1.35–2.16)	<0.001	0.0	0.862

Note: Relationship between APRI and DFS in HCC.
Abbreviations: APRI, aminotransferase-to-platelet ratio index; DFS, disease-free survival; HCC, hepatocellular carcinoma; HR, hazard ratio; MVA, multivariate analysis; RFS, recurrence-free survival; ROC, receiver operating characteristic curve; UVA, univariate analysis.

The exact mechanisms governing the prognostic values of APRI still remain unclear; however, there are some possible explanations.[24,25] HCC patients with a high APRI value frequently have elevated AST levels, and the level of AST could represent the cirrhosis level or the injury to the hepatocytes, and could also reflect liver stress or damage arising from progressive liver fibrosis or reactivation of hepatitis virus replication. All of these are major contributors to liver carcinogenesis.[32–34] In contrast, many patients with HCC and elevated APRI often have a low PLT level. Progressive destruction of an enlarged spleen and progressive liver fibrosis can often lead to low preoperative PLT,[35–37] and there were also close relationships between low preoperative PLT and great risk of major liver-related complications.[37,38] All of these factors and events are closely linked to poor clinical outcomes in HCC patients.

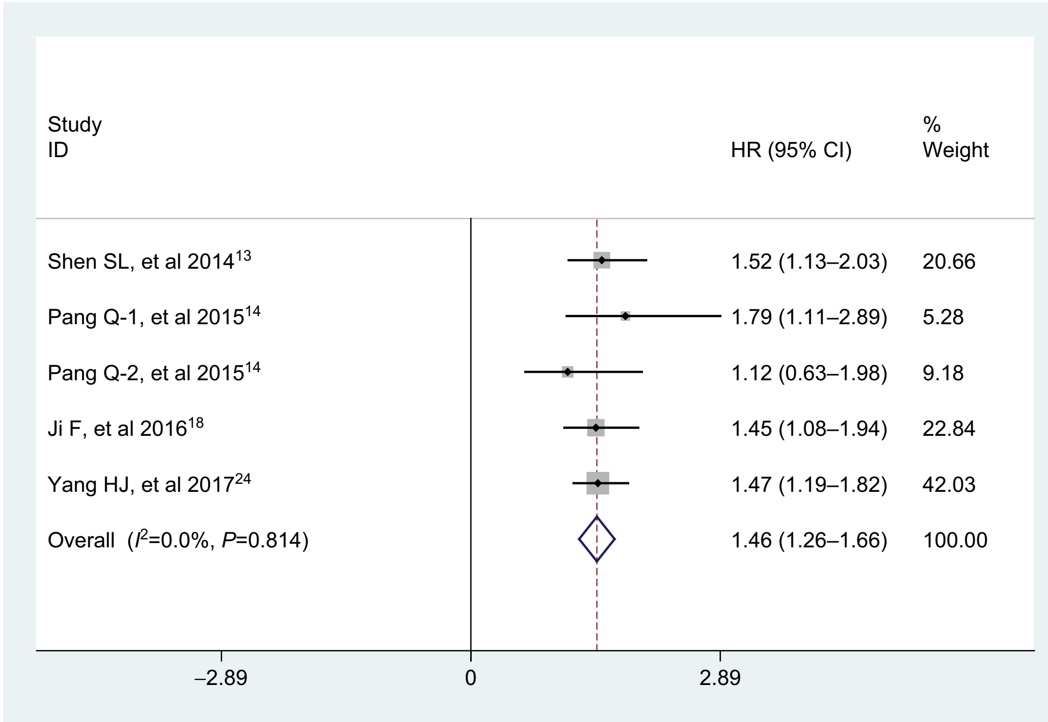

Figure 4 Forest plot for the relationship between APRI and DFS.
Abbreviations: APRI, aminotransferase-to-platelet ratio index; DFS, disease-free survival; HR, hazard ratio.

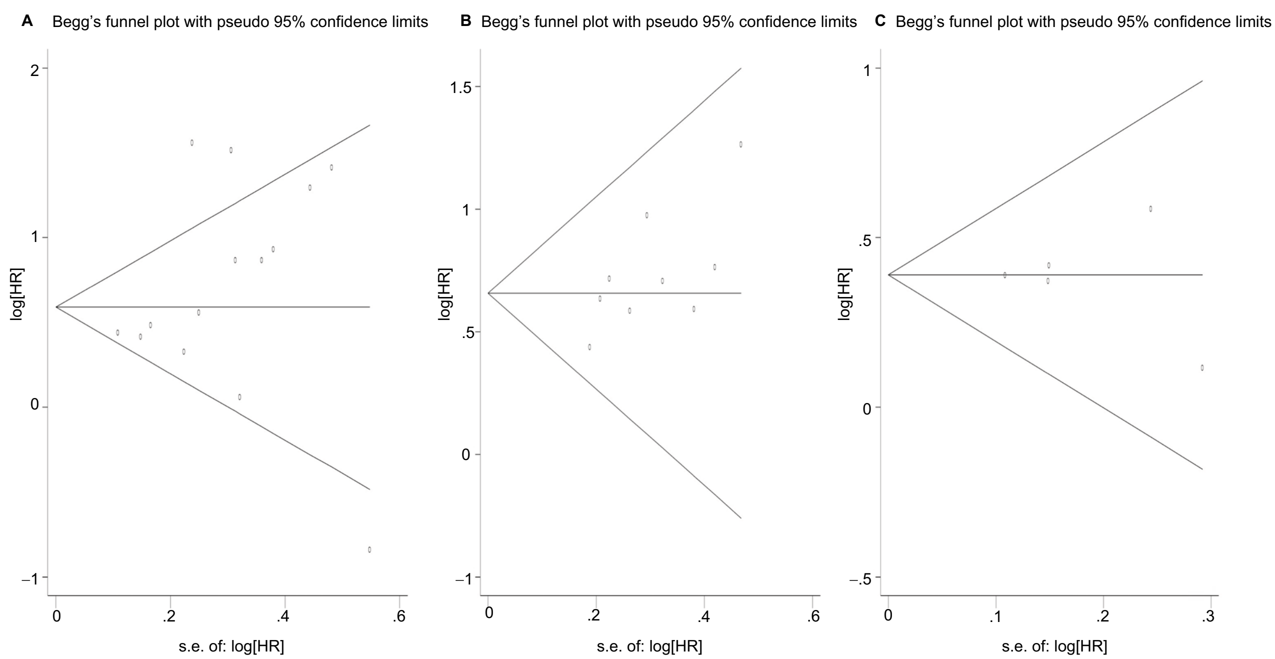

Figure 5 Funnel plots for publication bias test.
Note: (**A**) For OS; (**B**) for RFS; (**C**) for DFS.
Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival.

To the best of our knowledge, this is the first meta-analysis that comprehensively assesses the prognostic value of APRI in HCC. In the present meta-analysis, a total of 15 published articles with 5,051 HCC patients were collected. When the outcomes from all available studies were combined and pooled, we found that an elevated APRI was significantly associated with poor OS (HR =1.62, 95% CI: 1.23–2.01) in HCC, although there was heterogeneity. Furthermore, the subgroup analyses

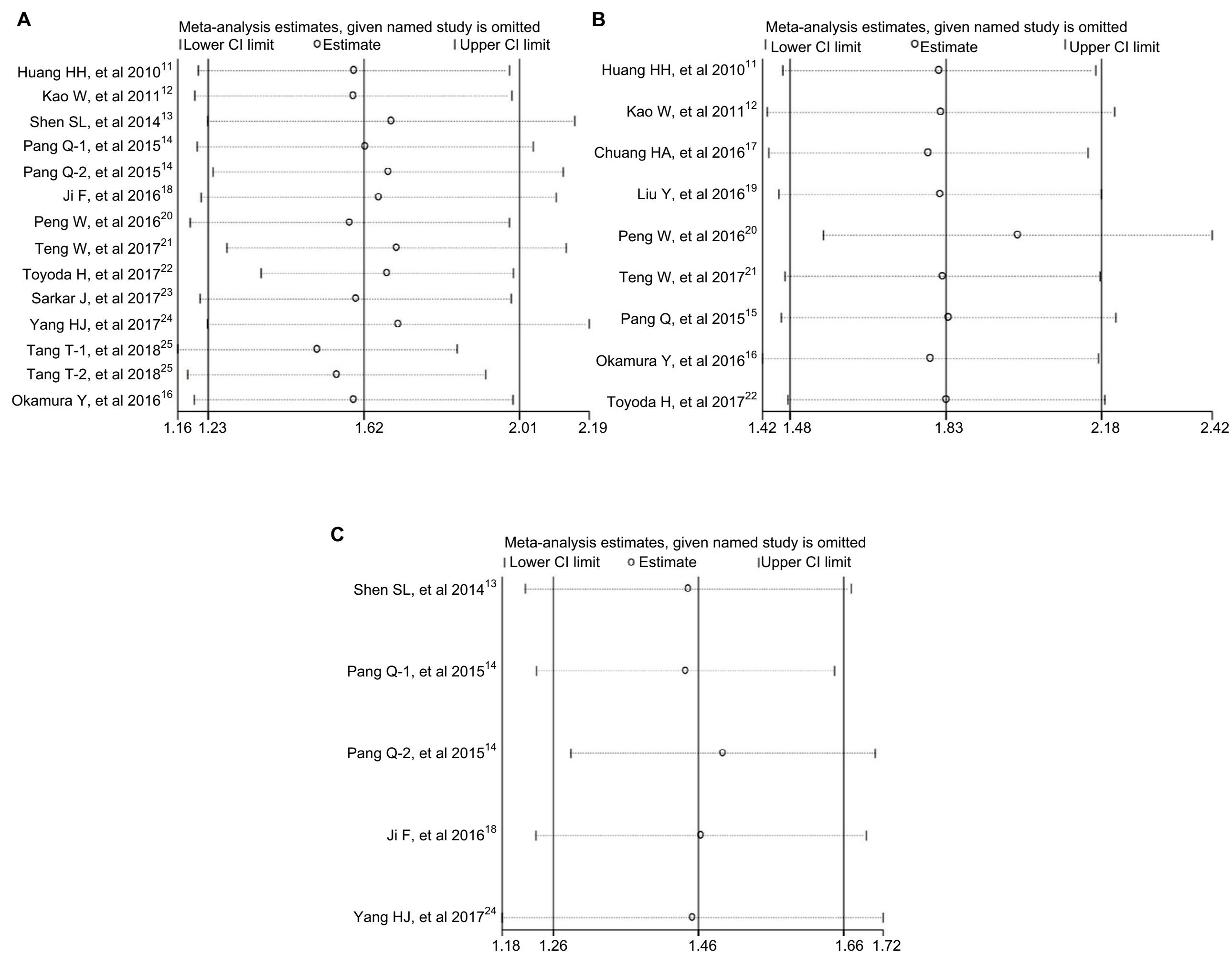

Figure 6 Sensitivity analysis of the relationship between APRI and HCC prognosis.
Note: (**A**) For OS; (**B**) for RFS; (**C**) for DFS.
Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; DFS, disease-free survival; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival.

revealed that APRI could be an independent prognostic factor of OS in patients with HCC. For the relationship between APRI and secondary endpoints, the combined results showed that APRI might act as a prognostic indicator for RFS in HCC (HR =1.83, 95% CI: 1.48–2.18), and the subgroup analyses also confirmed the prognostic value of APRI for RFS in HCC. Furthermore, HCC patients with high APRI had a worse DFS when compared with that of patients with low APRI (HR =1.46, 95% CI: 1.26–1.66). Thus, the APRI might represent a predictive biomarker with great clinical utility in HCC patients.

Nevertheless, there are some limitations existing in the meta-analysis that should be carefully interpreted. Firstly, all studies enrolled were retrospective, and the number of published studies included was not sufficiently large for a more detailed subgroup analysis. Secondly, because the majority of studies included were from Asian countries (China, Japan, and Korea), additional clinical studies from other countries are required. Thirdly, four of 14 studies for OS only reported HRs in the univariate analysis, which might cause a bias toward overestimation of the prognostic role of APRI. In addition, some heterogeneity was observed among studies for OS, which was probably due to factors such as the adjusted multivariate analysis of studies with different factors or different start time to follow-up or diverse therapies applied. In addition, there are some other factors that could influence AST and PLT, such as antiviral drugs and other accompanying diseases of the patients, and this should also be noted. Finally, the cutoff value for defining high or low APRI differed in studies, and it is essential that they be unified before APRI can be utilized in clinical prognostication for HCC.

In summary, the results of our study suggest that high APRI indicated poor prognosis in HCC patients, and APRI could serve as a cost-effective, significant biomarker for predicting HCC survival outcome. Considering the limitations mentioned above, larger well-designed clinical studies with more diverse populations are warranted in the future to validate our findings.

Disclosure

The authors report no conflicts of interest in this work.

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