Systematic Review / Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

Prognosis of hepatocellular carcinoma using the albumin to alkaline phosphatase ratio, literature review, and meta-analysis

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Background: Data about the impact of albumin-to-alkaline phosphatase ratio (AAPR) on prognosis in hepatocellular cancer (HCC) patients are inconclusive and conflicting.

Methods: The authors systematically searched literatures from seven databases (PubMed, Medline, Web of Science, Cochrane Library, Embase, Google Scholar, and CINAHL), updated to September 2023. Hazard ratios (HRs) and 95% CIs were pooled and synthesized using Comprehensive Meta-Analysis version 3 in order to assess the overall impact of AAPR on patient's prognosis.

Results: In total, 8 studies involving 13 cohorts with 3774 cases were included. Pooled results from both univariate and multivariate analyses revealed that higher AAPR was an independent prognostic factor for overall survival (HR = 0.429, 95% CI: 0.361–0.509, $P = 0.001$; HR = 0.476, 95% CI: 0.421–0.538, $P = 0.001$; respectively). Similarly, pooled multivariate results showed that higher AAPR was associated with better disease-free survival (HR = 0.558, 95% CI: 0.452–0.688, $P = 0.001$). Moreover, pooled results from both univariate and multivariate analyses revealed that higher AAPR was an independent prognostic factor for recurrence-free survival (HR = 0.540, 95% CI: 0.420–0.694, $P = 0.001$; HR = 0.647, 95% CI: 0.494–0.848, $P = 0.002$; respectively). Subgroups analysis showed that elevated AAPR still significantly correlated with better overall survival across the confounding factors. Moreover, sensitivity analysis suggested the robustness of these findings and no publication bias was detected.

Conclusions: In summary, higher AAPR could be considered as a reliable prognostic factor in patients with HCC, which could be used as a routine inspection of HCC patients to individualized prognosis prediction and clinical decision making.

Keywords: Albumin-to-alkaline phosphatase ratio [AAPR], cancers, disease-free survival, overall survival, prognosis

Introduction

Hepatocellular cancer (HCC), the most common form of liver cancer, is nowadays one of the most frequent cancer-related cause of death worldwide[1]. It accounts for 70–85% of the total liver cancer burden and is the second leading cause of cancer death in East Asia and sub-Saharan Africa and the sixth most common in western countries[2]. The majority of HCC cases occur in patients with chronic liver disease, with cirrhosis being the main risk factor. Hepatitis B virus is the leading cause of incident cases of HCC and deaths in the world [33%], followed by alcohol [30%], hepatitis C virus [21%], and other causes [16%][3]. Several therapies have been suggested for HCC. These therapies include the surgical resection, various locoregional treatments including percutaneous ethanol injection, trans-arterial chemoembolization, radiofrequency ablation, and radioembolization[4,5].

HIGHLIGHTS

- Database search and study selection: a total of 678 studies were screened, and 8 articles meeting eligibility criteria were included, representing 13 cohorts.
- Disease-free survival (DFS): pooled multivariate analysis results showed that elevated AAPR was significantly associated with better DFS (HR = 0.558, 95% CI: 0.452–0.688, $P = 0.001$).
- Recurrence-free survival (RFS): higher AAPR was significantly associated with better RFS in both univariate and multivariate analytic results.
- Publication Bias: Egger's test did not show evidence of publication bias in the included studies.
- Subgroup analysis: subgroup analysis based on sample size, cutoff value of AAPR, and treatment method showed variations in HRs for overall survival, indicating potential sources of heterogeneity.
- Sensitivity analysis: omission of single studies did not substantially alter the combined HRs, indicating the robustness of the results.
- Elevated AAPR was consistently associated with better survival outcomes in HCC patients. AAPR, derived from ALB and ALP levels, was proposed as a practical and promising prognostic biomarker due to its simplicity and availability in routine clinical practice.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:6062–6070

Received 22 April 2024; Accepted 6 July 2024

Published online 24 July 2024

http://dx.doi.org/10.1097/MS9.0000000000002375

The prognosis of HCC is evaluated depending on several factors, such as liver function, hepatitis virus type and tumor load. Albumin (ALB), an indicator of liver function test, is the most abundant protein in plasma, and its levels in the blood reflects the function of internal organs. Moreover, ALB is also a significant indicator of diverse diseases such as liver disorders[6]. Alkaline phosphatase (ALP) is also an important biomarker of liver function test, whose elevation is correlated with poor outcomes and is an indicator of hepatobiliary diseases[7].

Interestingly, several studies have investigated the value of ALB to alkaline phosphatase ratio (AAPR) as a marker to predict the survival outcomes of patients with diverse cancer, including breast cancer[8], cholangiocarcinoma[9], renal cell carcinoma[10], and hepatocellular carcinoma[11]. However, findings are discordant due to the inevitable heterogeneity in study design and sample size of these studies. Indeed, some studies suggested that elevated AAPR was closely correlated with better survival outcomes[12,13], but others showed that AAPR was not associated with survival outcomes[12,14]. The prognostic value of AAPR in HCC has rarely been systematically investigated and little is known about their relationships.

Therefore, it is interesting to evaluate the association between AAPR and HCC outcomes based on available evidence. We conducted a systematic review and meta-analysis to assess the prognostic value of AAPR in HCC patients.

Methods

This systematic review and meta-analysis study was prospectively registered at Research Registry CRD 42022364316 and was carried out in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines[15]. The level of compliance with AMSTAR 2 was of medium level[16].

Search strategy

A systematic search was conducted on PubMed, Medline, Web of Science, Cochrane Library, Embase, Google Scholar, and CINAHL from database inception until March 2023 to look for potentially eligible articles. The search strategy was based on the following key search terms: 'albumin-to-alkaline phosphatase ratio' OR 'albumin to alkaline phosphatase ratio' OR 'AAPR' AND 'overall survival' OR 'disease-free survival' OR 'recurrence-free survival' AND 'Hepatocellular carcinoma' OR 'HCC'. All retrieval processes were performed independently by two researchers.

Selection criteria

Relevant articles were screened by title and abstract after removing duplicates. Studies were eligible for inclusion if they addressed the prognostic prediction of AAPR in HCC patients. The remaining studies were then examined in full text to confirm eligibility. Inclusion criteria for articles were [1]: cohort studies (retrospective or prospective) reporting the prognostic prediction of AAPR in HCC patients in terms of overall survival (OS), disease-free survival (DFS), or recurrence-free survival (RFS) [2]; the survival outcomes were measured by hazard ratio (HRs) with 95% CI, Kaplan–Meier curve, or data for calculating HR with its corresponding 95% CI; and [3] studies were full text and published in English. Exclusion criteria were [1]: no full text electronically available [2]; publication in a language other than

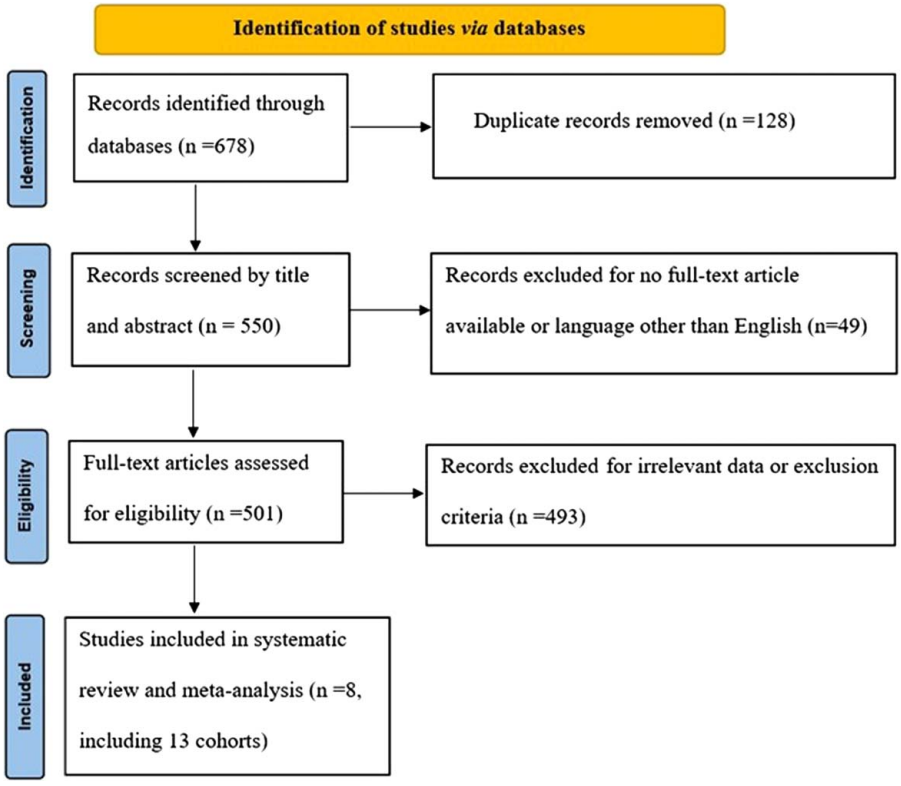

Figure 1. PRISMA flow diagram.

Table 1

Characteristics of included studies in this meta-analysis

Study ID	Study design	Country	Study duration	Sample size	Age, years [range]	Treatment method	Cutoff value of AAPR	Survival outcomes	Analytic method	Median follow-up period [months]
Cai *et al.* 2018[11]	Retrospective	China	2006–2010	237	56 [45–66]	Any treatment	0.38	OS	Multivariate	Not defined
Chan *et al.* 2015- Training cohort[20]	Retrospective	Hong Kong	2001–2006	217	54.0 ± 11.4	Curative surgical resection	0.23	OS DFS	Univariate and Multivariate	44.5 [0.1–160.7]
Chan *et al.* 2015- Validation cohort I[20]	Retrospective	Hong Kong	2006–2011	256	57.8 ± 10.1	Curative surgical resection	0.23	OS DFS	Multivariate	38.9 [0.1–95.4]
Chan *et al.* 2015- Validation cohort II[20]	Retrospective	Hong Kong	2007–2011	425	60.4 ± 12.1	Palliative treatment resection	0.23	OS	Multivariate	5.3 [0.1–62.6]
Chen *et al.* 2018-Training cohort[19]	Retrospective	China	2009–2013	372	52 [44–61]	Trans-catheter arterial chemoembolization therapy	0.439	OS	Multivariate	Not defined
Chen *et al.* 2018- Validation cohort I[19]	Retrospective	China	2009–2013	202	56 [45–65]	Supportive care	0.439	OS	Multivariate	Not defined
Chen *et al.* 2018- Validation cohort II[19]	Retrospective	China	2009–2013	82	55 [45–66]	Trans-catheter arterial chemoembolization therapy	0.439	OS	Multivariate	Not defined
Huang *et al.* 2023[22]	Retrospective	China	2013–2022	656	53 [44–62]	Radical resection	0.52	OS RFS	Univariate and Multivariate	Not defined
Li H *et al.* 2020[23]	Retrospective	China	2003–2014	149	51.26 ± 9.96	Liver transplantation	0.38	OS	Univariate and Multivariate	Not defined
Li Q *et al.* 2020[24]	Retrospective	China	2010–2015	188	Mean not defined	Curative hepatectomy	0.4	OS RFS	Univariate and Multivariate	46.5 months
Li *et al.* 2023[25]	Retrospective	China	2015–2019	545	Mean not defined	Transcatheter Chemoembolization therapy	0.26	OS	Univariate and Multivariate	27 months
Zhang *et al.* 2021- Training cohort[21]	Retrospective	China	2007–2016	297	58.7 ± 10.9	Radiofrequency ablation	0.4	OS	Multivariate	Median 28.5 months
Zhang *et al.* 2021- Validation cohort[21]	Retrospective	China	2007–2016	148	59.0 ± 12.1	Radiofrequency ablation	0.4	OS	Multivariate	Median 28.5 months

Table 2

Modified Newcastle–Ottawa quality assessment scale for retrospectives studies included in this meta-analysis

	Selection				Comparability	Outcome			
Study	Representativeness of the sample	Selection of the non-exposed group	Ascertainment of exposure	Outcome not present at the start of study	Cohort statistical analysis	Evaluation of the outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up	Quality score
Cai *et al.* 2018[11]	★	★	★	0	★★	★	★	★	8 [Good]
Chan *et al.* 2015[20]	★	★	★	0	★★	★	★	★	8 [Good]
Chen *et al.* 2018[19]	★	★	★	0	★	★	★	★	7 [Good]
Huang *et al.* 2023[22]	★	★	★	0	★★	★	★	★	8 [Good]
Li H *et al.* 2020[23]	★	★	★	0	★★	★	★	★	8 [Good]
Li Q *et al.* 2020[24]	★	★	★	0	★	★	★	★	7 [Good]
Li *et al.* 2023[25]	★	★	★	0	★★	★	★	★★	8 [Good]
Zhang *et al.* 2021[21]	★	★	★	0	★★	★	★	★★	8 [Good]

English [3]; comments, letters, editorials, protocols, guidelines, and review papers [4]; studies with insufficient data to calculate the HR with 95% CI [5]; animal studies.

Data extraction

Two independent authors retrieved information from the eligible articles following the inclusion and exclusion criteria, and information were collected on a standardized data sheet that included [1]: Study ID [name of first author, year of publication] [2], study design [3], country [4], sample size [5], age [6], cancer stage [7], treatment method [8], survival outcomes [9], analytic method [univariate/multivariate] and [10] median follow-up period [months]. The inconsistencies between reviewers were resolved by a third investigator through discussion. In this study, we extracted prognostic data as much as possible both from univariate and multivariate analyses.

Quality assessment of the studies

Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included literature, which evaluates selection bias, comparability and outcome evaluation. Each criterion was assessed as 1 star or 0 stars. The total stars of the NOS checklist ranged from 0 to 9 stars. A study with score from 7 to 9, has good quality, 4 to 6, fair quality, and 0–3 poor quality[16]. Two independent authors assessed quality independently and discordances were solved by discussion.

Statistical analysis

The statistical analyses were performed using Comprehensive Meta-Analysis version 3 (Biostat Inc. USA). HRs with corresponding 95% CI were used to assess the prognostic value of AAPR on survival outcomes in patients with HCC, using the Mantel–Haenszel method[17]. A value of $P<0.05$ was considered as the level of significance. The heterogeneity between studies was tested by Cochran's Q and Higgins I^2 statistics. I^2 values $\geq 50\%$ and $P<0.05$ indicated a moderate to high degree of heterogeneity among pooled studies. A fixed-effects design was used when I^2 <50% and $P>0.05$; otherwise, a random-effects model was adopted[18]. We also performed subgroup analysis to assess the possible sources of heterogeneity. For evaluating the stability of the results, a sensitivity analysis was performed through precluding individual studies sequentially. Only publication bias was evaluated in this meta-analysis. Egger's test was conducted to evaluate publication bias. The result was defined as statistically significant if $P<0.05$. Publication bias was further assessed by the visual inspection of the symmetry in funnel plots.

Results

Identification of studies

The database search identified 678 studies to be screened, of which 501 abstracts were identified as potentially eligible and retrieved for full text review. Eligibility criteria were met by 8 articles, which were represented by 13 cohorts. The PRISMA flowchart is shown in Figure 1.

Characteristics of included studies

All the included studies were retrospective cohorts published from 2015 to 2023. Two special studies were conducted based on three cohorts[19,20] and one special study was conducted based on two cohorts[21]. Eight studies were from China and one study was performed in Hong Kong. The sample size of the included articles varied from 82 to 656 patients. The cutoff value of AAPR varied between 0.23 and 0.52. The survival outcomes investigated were: OS [10 studies], DFS [3 studies], and RFS [2 studies]. All other basic information relevant to these studies are displayed in Table 1.

Quality assessment

Following the NOS criteria, all of the included studies achieved a score ≥ 7, with scores ranging from 7 to 8 [Table 2].

Selection

All included studies scored 3 stars in the selection section. The reason for not receiving a full quality score was that there is no demonstration that outcome of interest was not present at start of study.

Comparability

Among the included studies, six studies controlled for the outcomes and for additional factors [e.g. age] and scored two stars. However, two studies controlled for only the outcomes and scored one star.

Outcome

All studies received a full quality score in outcome section. Indeed, all studies described the tools used for the assessment of the outcomes and scored a star. Similarly, they scored a supplementary star as they were followed-up after an adequate time. The follow-up period was adequate in all studies, and they scored the third star.

Meta-analysis with OS

Regarding OS, five studies, involving five cohorts by univariate analytic results, and eight studies, involving 13 cohorts by multivariate analytic results, were collected in total.

The Cochran's Q test and I^2 statistic revealed a significant heterogeneity in both univariate (Q-value = 15 569, $P = 0.004$, $I^2 = 74\%$) and multivariate (Q-value = 24 145, $P = 0.019$, $I^2 = 50\%$] analytic results, so a random model was used.

It was showed that higher AAPR was significantly associated with better OS from pooled univariate (HR = 0.429, 95% CI: 0.361–0.509, $P = 0.001$) [Fig. 2A] and multivariate analytic results (HR = 0.476, 95% CI: 0.421–0.538, $P = 0.001$] [Fig. 2B].

Meta-analysis with DFS

Regarding DFS, one study involving two cohorts by multivariate analytic results was collected in total. The Cochran's Q test and I^2 statistic revealed a low heterogeneity (Q-value = 0.019, $P = 0.891$, $I^2 = 0\%$), so a fixed model was used.

Pooled multivariate analytic results showed that elevated AAPR was significantly associated with better DFS (HR = 0.558, 95% CI: 0.452–0.688, $P = 0.001$) [Fig. 3B].

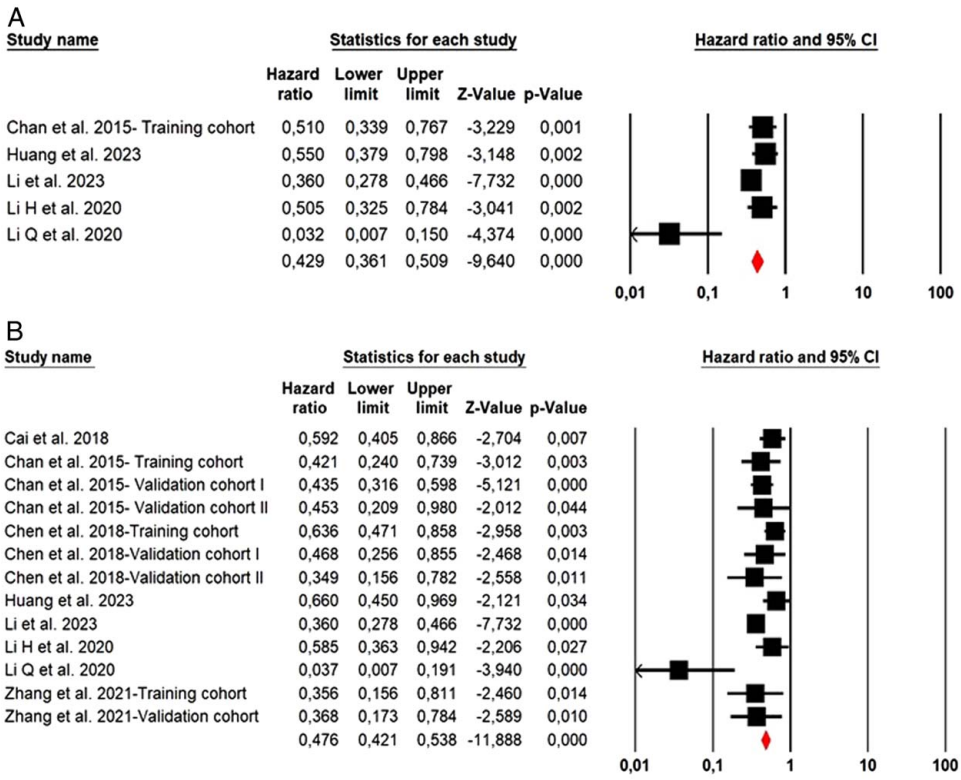

Figure 2. Forest plots of HR for OS via univariate analysis [A] and multivariate analysis [B].

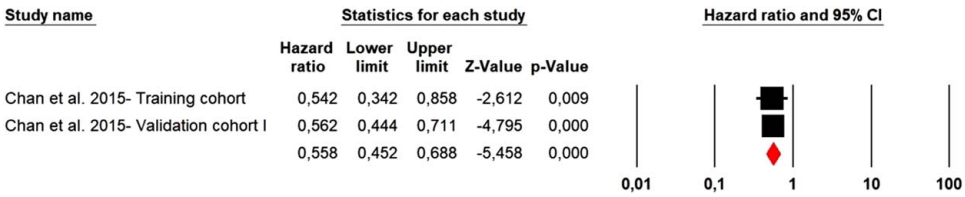

Figure 3. Forest plots of HR for DFS via multivariate analysis.

Meta-analysis with RFS

Regarding RFS, only two studies were collected for both univariate and multivariate analytic results.

The Cochran's Q test and I^2 statistic revealed a significant heterogeneity in both univariate (Q-value = 9.161, $P = 0.002$, $I^2 = 89\%$) and multivariate (Q-value = 8.587, $P = 0.003$, $I^2 = 88\%$) analytic results, so a random model was used.

It was showed that higher AAPR was significantly associated with better RFS from pooled univariate (HR = 0.540, 95% CI: 0.420–0.694, $P = 0.001$) [Fig. 4A] and multivariate analytic results (HR = 0.647, 95% CI: 0.494–0.848, $P = 0.002$) [Fig. 4B].

Publication bias

Funnel plot appeared asymmetric in meta-analysis with HR for OS via multivariate analytic results (Fig. 5), but Egger's test failed to show evidence of publication bias ($P = 0.091$). Because the numbers of cohorts were <10 in the remaining outcomes, the publication bias was not performed.

Subgroup analysis

We performed subgroup analysis in OS multivariate analysis group to assess the source of heterogeneity. The OS multivariate analysis group was stratified into three parameters, including sample size, cutoff value of AAPR, and treatment method [Table 3].

According to the sample size, the HR for OS was not significantly different between studies with a sample size <250 and those with a sample size ≥250 ($P = 0.953$). Moreover, a high heterogeneity was revealed among studies with a sample size ≥250 ($I^2 = 57\%$, $P = 0.040$).

When the cutoff value of AAPR was adopted as a moderator, there was no significant difference between studies with a cutoff value <0.4 and those with a cutoff value ≥0.4 ($P = 0.127$). Moreover, a high heterogeneity was revealed among studies with a cutoff value ≥0.4 ($I^2 > 61\%$, $P = 0.015$).

According to the treatment methods, there was no significant difference between studies using surgery and those using others treatment methods ($P = 0.979$). However, a high heterogeneity was revealed among studies in both subgroups ($I^2 > 50\%$, $P < 0.05$).

Sensitivity analysis

Sensitivity analysis was further performed to investigate whether the pooled results would be affected by any single study. At each step, one single study was omitted; the combined HRs for the multivariate analysis of OS was not changed substantially, suggesting the robustness of the results. Indeed, the HR values ranged from 0.449 (95% CI: 0.393–0.514) to 0.516 (95% CI: 0.449–0.593] [Figure 5].

Discussion

AAPR, calculated from ALB and ALP, was an inexpensive and quickly acquired biomarker in routine clinical practice. AAPR

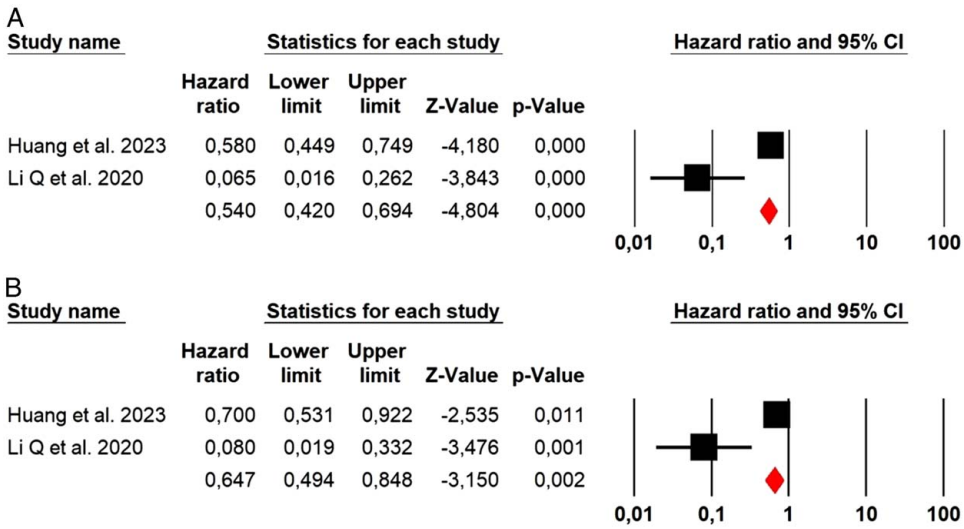

Figure 4. Forest plots of HR for RFS via univariate analysis [A] and multivariate analysis [B].

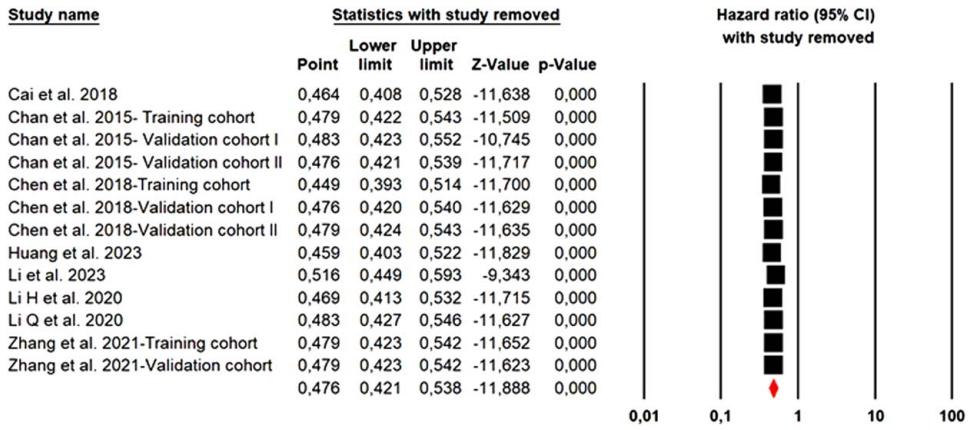

Figure 5. Sensitivity analysis.

was firstly investigated to be a novel biomarker of prognosis in HCC patients in 2015[20]. In the years following, many studies have evaluated the prognosis value of AAPR in several cancers[9,10,12,13,26,27]. However, findings about the association between AAPR and survival outcomes in patients with cancers were inconclusive. Recently, a meta-analysis about the prognostic role of AAPR among HCC patients was performed. However, the authors did not investigate DFS outcome[28].

Here, we conducted an updated systematic review and meta-analysis on studies investigating the prognostic role of AAPR on OS, DFS, and RFS outcomes in patients with HCC, using both univariate and multivariate analytic results. We noticed that all studies demonstrated that elevated AAPR was associated with better survival outcomes. In summary, the pooled results from all included studies showed that elevated AAPR significantly correlated with better OS, DFS, and RFS in HCC patients. Our findings were consistent with those of previous studies. Indeed, Zeng *et al*., and Zhou *et al*., demonstrated that patients with higher serum AAPR level were probable to sustain better survival outcomes in patients with nasopharyngeal carcinoma and lung cancer, respectively[12,13]. In the same context, the results obtained from a recent meta-analysis revealed that lower AAPR in patients with HCC predicted inferior survival outcomes, and AAPR might be a promising indicator for the prognosis of HCC.

Table 3
Subgroup analysis

Stratified analysis	Number of cohorts	HR [95% CI], p	Heterogeneity I^2	Heterogeneity *P*
Sample size				
< 250	7	0.478 [0.384–0.596], *P* = 0.000	52%	0.052
≥ 250	6	0.475 [0.410–0.550], *P* = 0.000	57%	0.040
Cutoff value of AAPR				
< 0.4	6	0.441 [0.377–0.516], *P* = 0.000	17%	0.301
≥ 0.4	7	0.537 [0.441–0.653], *P* = 0.000	61%	0.015
Treatment method				
Surgery	8	0.475 [0.395–0.571], *P* = 0.000	51%	0.047
Others	5	0.477 [0.405–0.561], *P* = 0.000	59%	0.042

There were various theories for the probable prognostic values of AAPR in cancer, despite the fact that they were not fully understood. One of the best techniques for evaluating nutritional status was to measure ALB. Indeed, ALB concentration reflects the protein status of the blood and function of internal organs and had a close association with immunity and inflammation[6]. There was growing evidence that ALB might control immunological responses, encourage cell division, and sustain DNA replication[29]. ALB could exert antioxidant effects against carcinogens. Hence, hypoALBemia is often detected in human cancers, which often correlates with poor outcomes and deterioration in immune response among cancer patients[28]. Moreover, ALB is associated with elevated inflammatory status, which usually causes poor outcomes[29]. Previous research has shown that ALB is a useful prognostic and predictive factor for a number of cancers, including prostate cancer, renal carcinoma, and HCC[30–34].

ALP comprising diverse enzymes, which are expressed in different tissues. Similarly, ALP is considered as a tumor marker. Indeed, hyperphosphatasia has been proposed as prognostic indicator in various cancers, including HCC[35], prostate cancer[36], gastric cancer[30], and renal cell carcinoma[31]. It has been previously demonstrated that hyperphosphatasia could increase liver isoenzyme leakage and cause local biliary obstruction in metastatic cancers[32]. According to Mori *et al*., increased ALP may indicate micrometastases that are invisible on traditional imaging. This partially clarified the association between poor prognosis and increased ALP in cancer patients. On the other hand, intensive therapy would be more beneficial for cancer patients with increased ALP than would routine therapy[37].

Both ALB and ALP are common serum biochemical indicators used during routine clinical practice and AAPR is a simple and less invasive approach that can be obtained from peripheral blood samples and dynamically monitored. It was demonstrated that numerous factors affecting single ALB and ALP would not affect AAPR[38,39]. Consequently, the predictive value of AAPR was clearly superior to that of ALB or ALP alone and thus, we suggested that AAPR can be a more practical biomarker of

prognosis in HCC. The pathological characteristics of hypoalbuminemia and hyperphosphatasia could be the underlining mechanism behind AAPR becoming a prognostic biomarker of human cancers. Indeed, the low level of AAPR could be caused by either one or both of the two abnormalities, both of which significantly associated with poor survival outcomes in human cancers. AAPR might identify more patients with poor outcomes in comparison with hypoalbuminemia or hyperphosphatasia, because some patients might present with normal serum ALP concentration but hypoalbuminemia, or normal serum ALB concentration but hyperphosphatasia. It should be taken into account that neither hypoalbuminemia nor hyperphosphatasia is HCC-specific. Hyperphosphatasia is also associated with a variety of pathological processes including liver dysfunction, bone diseases and endocrine diseases[33]. Therefore, it is necessary to pay attention to these confounding factors when using AAPR as prognostic indicator in patients with HCC.

The findings of our study are consistent with those of Zhang *et al*.[34] who conducted a similar systematic review and meta-analysis, which was identified during the follow-up on new studies on the prognostic effect of albumin-to-alkaline phosphatase ratio on patients with hepatocellular carcinoma. However, our study had included more recent data, which may have contributed to the differences in effect sizes observed between the two studies. Our study also included and investigated the DFS which was not evaluated in aforementioned study.

Our systematic review has some limitations that should be acknowledged. First, heterogeneity was significant in survival outcomes via both univariate and multivariate analytic results, which might be due to the diverse clinicopathological factors, including patient's characteristics, tumor classification, tumor stage, treatment method, as well as follow-up interval. A subgroups analysis was further conducted according to three factors. Heterogeneity still existed in the different subgroups and consequently, the interaction between AAPR and OS did not remain stable. Considerable heterogeneity, which is expected in meta-analysis studies, can alter the interpretability of results[40]. Consequently, the findings of this meta-analysis have to be analyzed with attentiveness. Second, our meta-analysis including researches from Asian countries, while the prognostic value of AAPR in HCC also needs to be assessed by further research in western countries, especially research conducted in the greater HCC community. Third, there were limited studies included in this meta-analysis and the sample size was low. Fourth, the included studies were from two countries. The limited geographic area of the studies does not allow the applicability of our results at a global level. Hence, further studies conducted in different countries are required to confirm our findings.

Despite these limitations, the major strength of our meta-analysis is the methodological quality of the included studies, which presented a good or fair quality score. Additionally, the sensitivity analysis showed that the estimated HRs were reliable and not effected when a single study was omitted. In summary, this study provides the most up-to-date and comprehensive data about the prognostic role of AAPR in patients with HCC.

Conclusion

In summary, higher AAPR levels had better survival outcomes in patients with HCC. As a low-cost routine clinical test, it should be considered as a promising biomarker in the clinical management of HCC. However, well-designed clinical diagnostic research based on large scale, comparing the accuracy of AAPR, ALB, and ALP, is still required to clarify this issue and confirm our findings.[41]

Ethical approval

No ethical approval was done, as it a systemic review and meta-analysis.

Consent

Informed consent was not required for this systematic review.

Source of funding

No Funding for this article.

Author contribution

All authors contributed to the conception and design of the study. A.I.A. and K.A.: conducted the literature search and data extraction; S.F. [Outside analyst]: performed the statistical analysis and synthesis of the data; A.I.A. and A.A.: contributed to the interpretation of the results and the drafting of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: https://www.crd.york.ac.uk/prospero/
2. Unique identifying number or registration ID: CRD420 22364316.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=364316.

Guarantor

Abdulrahman Ibn Awadh.

Data availability statement

All data analyzed during this meta-analysis are included in the reference section of this article and its supplementary information files.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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