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Prognostic value of aldo-keto reductase family 1 member B10 (AKR1B10) in digestive system cancers

A meta-analysis

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Abstract

Background: Numbers of studies have reported that the expression of aldo-keto reductase family 1 member B10 (AKR1B10) is abnormal in digestive system cancers, and could be used as a prognostic biomarker. However, the results are argued. Therefore, we conduct a meta-analysis to comprehensively evaluate the prognostic value of high AKR1B10 expression for overall survival (OS), disease specific survival (DSS), and disease-free survival/recurrence-free survival (DFS/PFS) in digestive system cancers.

Methods: Hazard ratios (HRs) with its 95% confidence intervals (CIs) were calculated to assess the prognostic value of AKR1B10 by using the random effects model. The STATA version 12.0 software were used to perform all the analyses.

Results: Eleven articles including 1428 patients involved in this meta-analysis. The pooled analysis suggested that high AKR1B10 expression was not associated with OS (HR: 1.18; 95% CI: 0.69–2.00) and DFS/PFS (HR: 1.08, 95% CI: 0.67–1.76) in digestive system cancers. However, Further analysis revealed that high AKR1B10 expression indicated poor OS in oral squamous cell carcinomas (OSCC) (HR: 2.92, 95% CI: 1.86–4.58) and favorable DSS in hepatocellular carcinoma (HCC) (HR: 0.71, 95% CI: 0.52–0.97).

Conclusions: The prognostic value of high AKR1B10 expression varied in different types of digestive system cancers. Further studies exploring the prognostic role of AKR1B10 in digestive system cancers are needed.

Abbreviations: AKR1B10 = aldo-keto reductase family 1 member B10, CI = confidence interval, CRC = colorectal cancer, DFS/PFS = disease-free survival/recurrence-free survival, DSS = disease specific survival, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, NOS = Newcastle-Ottawa Quality Assessment Scale, OS = overall survival, OSCC = oral squamous cell carcinomas.

Keywords: aldo-keto reductase family 1 member B10, digestive system cancers, meta-analysis, prognosis

1. Introduction

The aldosterone reductase family is a small class of monomer-soluble proteins that perform redox reactions with nicotinamide adenine dinucleotide phosphate as a coenzyme. It plays an indispensable role in the detoxification, metabolism, and lipid synthesis of the human body, as well as the complications of diabetes.[1,2] It also has an important effect on tumorigenesis, and can be severed as useful biomarkers for tumor diagnosis and

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RL, SZ, and CY contributed equally to this work.

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The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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prognosis.[2] Aldo-keto reductase family 1 member B10 (AKR1B10), as one of the aldehyde-ketone reductase family members, has received more and more attention from researchers in recent years.

The location of AKR1B10 gene is on chromosome 7q33, and the AKR1B10 protein is composed of 316 amino acids.[3] AKR1B10 is involved in various pathophysiological activities of the body, such as detoxification, retinoic acid metabolism, and lipid synthesis. Studies have shown that AKR1B10 is characterized by obvious carcinogenicity and can be used as a tumor marker.[4] Recently, an increasing number of studies have explored the association between AKR1B10 expression and prognostic value in digestive system cancers.[5–15] For example, Yao et al, confirmed that low AKR1B10 expression indicated poor prognosis for gastric cancer (GC) and colorectal cancer (CRC).[14,15] Wang et al, also found that high AKR1B10 expression revealed a lower risk of recurrence in patients with hepatocellular carcinoma (HCC).[13] However, Fang et al, demonstrated that AKR1B10 was significantly correlated with tumor size, perineural invasion and recurrence, and was a risk factor for poor prognosis in oral squamous cell carcinomas (OSCC).[5] Moreover, Jin et al, also showed that high AKR1B10 expression was related to a shorter disease free survival (DFS) and overall survival (OS).[10] The conclusions of the above researches are controversial.

The prognostic significance of AKR1B10 in digestive system cancers remains unclear. Therefore, we implemented a meta-analysis to further evaluate the prognostic role of AKR1B10 in digestive system cancers. In addition, we also discussed the suitability of AKR1B10 as a prognostic marker for cancers.

2. Material and methods

2.1. Search strategy

We synthetically searched the literature available on PubMed, EMBASE, and Web of Science until August 31, 2020. The following key words were used: "AKR1B10" OR "aldo-keto reductase family 1 member B10" OR "Aldo-keto reductase 1B10" AND "cancer" OR "carcinoma" OR "neoplasm" OR "tumor" OR "tumor" AND "prognosis" OR "prognostic" OR "survival" OR "outcome". We earnestly screened the titles, abstracts, full texts, and reference lists to select objective studies. Two authors (RQ.L and SHY.ZH) independently performed the search. This study does not require the approval of the ethics committee because it is a meta-analysis.

2.2. Selection criteria

The inclusion criteria were listed:

1. investigated patients with digestive system cancers;
2. determined the expression of AKR1B10 in blood or tumor tissue;
3. explored the relationship between the expression level of AKR1B10 and survival outcome; and
4. provided ample data to compute the hazard ratio (HR) and its 95% confidence interval (CI).

The exclusion criteria were listed:

1. provided insufficient data to calculate the HR and 95% CI;
2. case reports, abstracts, reviews, letters and non-English language publications;
3. animal or cell experiments; and
4. data from public databases.

2.3. Data extraction and quality assessment

Basic information was independently collected by 2 authors (RQ. L and CY.Y). The relevant information were listed including the first author name, publication year, country, study type, tumor type, sample size, detected method, analysis type and HRs with the corresponding 95% CIs. Multivariate analysis which considered the confounding factors and exhibited high accuracy was preferred. The HR value was extracted by Kaplan–Meier curves. The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of each included study.[16]

2.4. Statistical analysis

HRs and the corresponding 95% CIs were applied to calculated comprehensive results. We directly used statistical variables in our analysis if they were displayed in the study. Otherwise, we adopted the methods described by Tierney to extract the data from graphical survival plots.[17] A fixed effects model was applied to synthesized HRs when I^2 was $<50\%$; Otherwise, a random effects model was used. The sources of heterogeneity were by subgroup and regression analysis. Publication bias was investigated by Begg test and Egger test. All the analyses were performed by the STATA version 12.0 software (Stata Corporation, College Station, TX, USA). P values $<.05$ denoted statistically differences.

3. Results

3.1. Study selection

Three hundred fifty seven articles were initially collected from specified database. After removing 134 duplicates, 223 articles were screened for further information. Two hundred two articles were excluded according to the title and abstracts, and 21 articles were further evaluated. After full-text review, thirteen articles were excluded. Eventually, we identified eleven articles published between 2014 and 2020.[5–15] The flow diagram of the selection is displayed in Figure 1.

3.2. Study characteristics

The included articles involved a total of 1428 patients, ranging from 53 to 255. In all studies, the expression of AKR1B10 was detected in tumor tissue. Eight studies detected the AKR1B10 by immunohistochemistry and 3 studies by quantitative reverse-transcription polymerase chain reaction (qRT-PCR). Ten studies were conducted in Asian and one in Caucasian. Four different cancers were assessed, including OSCC, GC, HCC, and CRC. Ten HRs were reported in the included studies and 1 HRs was assessed by analyzing K-M curves. Basic information is displayed in Table 1.

3.3. Association of AKR1B10 expression with OS

Nine studies focused on OS analysis. Due to the apparent heterogeneity ($I^2 = 88.9\%$), the random effects model was applied. The pooled results displayed that high AKR1B10 expression was not associated with OS in digestive system cancers (HR: 1.18, 95% CI: 0.60–2.32) (Fig. 2).

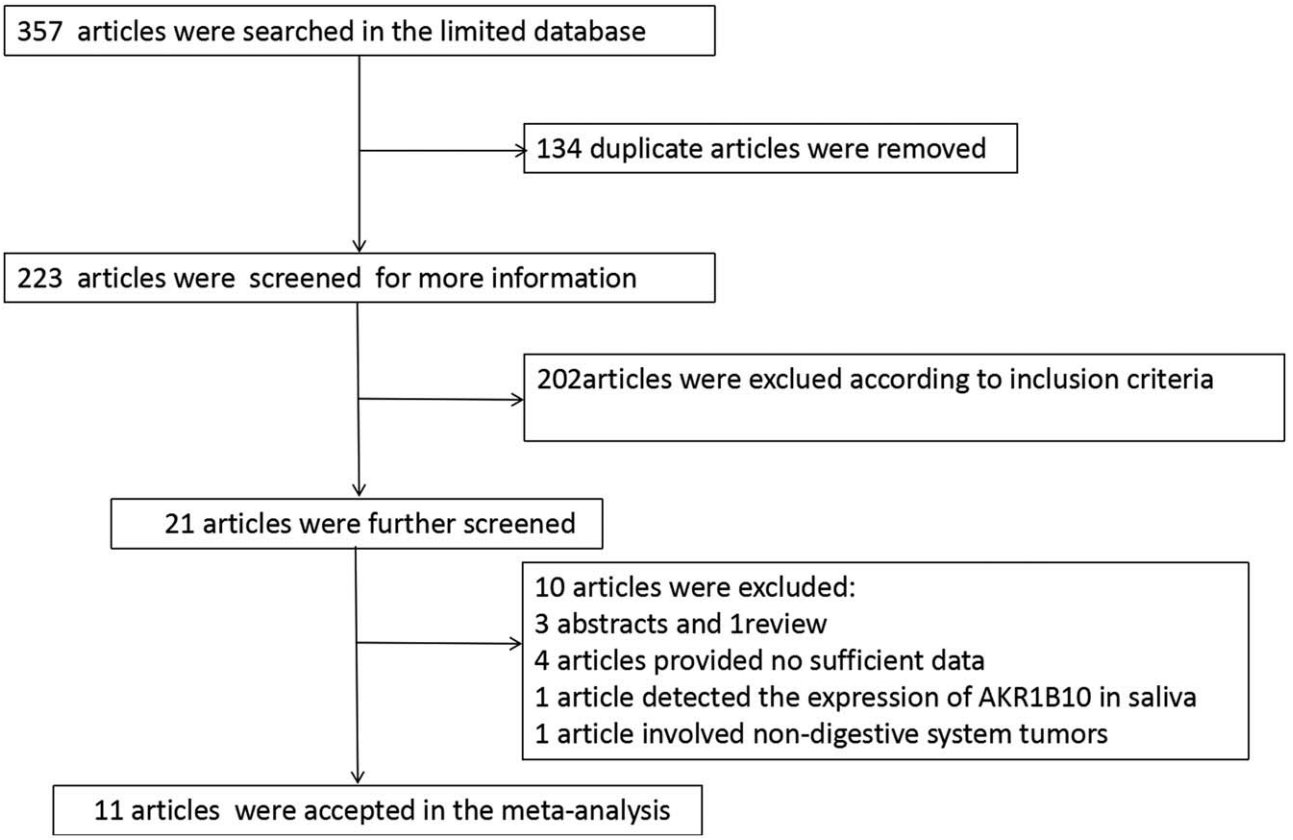

Figure 1. Flow diagram of the literature search.

3.4. Subgroup analysis

Subgroup analyses were implemented based on the cancer type, analysis type, country, detected methods, NOS score (Table 2). We found that high AKR1B10 expression displayed no correction with OS in HCC (HR: 1.01, 95% CI: 0.38–2.69) and GC (HR: 1.40, 95% CI: 0.13–14.99). However, high AKR1B10 expression indicated obvious worse OS in OSCC (HR: 2.92, 95% CI: 1.86–4.58).Furthermore, in the subgroup NOS = 6, we noticed high AKR1B10 expression suggested unfavourable OS (HR: 2.60, 95% CI: 1.80–3.76). All other subgroups containing more than 2 studies revealed that there were no significant association between elevated AKR1B10 expression and OS. In addition, we also used GEPIA Database to assess the prognostic role of AKR1B10 in a single tumor. We found that high AKR1B10 expression was associated with unfavorable OS in HCC, but not in GC and CRC (Fig. 3).

3.5. Association of AKR1B10 expression with DFS/RFS, DSS

Six studies that reported DFS/RFS showed obvious heterogeneity ($I^2 = 80.2\%$). A random effects model was conducted to

Table 1

Basic characteristics of included articles.

Study	e	Country	Study type	Tumor type	Sample size	Detected sample	Detected method	Analysis type	Survival analysis	Source of HR	NOS score
Jin	2016	China	Retrospective	HCC	144	Tissue	qPCR	Multivariate	OS, DFS	Reported	6
Fang	2019	China	Retrospective	OSCC	107	Tissue	IHC	Multivariate	OS, DFS	Reported	7
Ko	2017	China	Retrospective	OSCC	77	Tissue	IHC	Multivariate	OS	Reported	6
Schmitz	2011	Germany	Retrospective	HCC	168	Tissue	IHC	Univariate	DSS	SC	7
Sonohara	2016	Japan	Retrospective	HCC	158	Tissue	qPCR	Multivariate	OS, RFS	Reported	7
Liu	2015	China	Retrospective	HCC	109	Tissue	IHC	Multivariate	OS, RFS	Reported	7
Wang	2017	China	Retrospective	HCC	110	Tissue	IHC	Multivariate	OS, RFS	Reported	7
Yao	2014	China	Retrospective	GC	112	Tissue	IHC	Univariate	OS	Reported	7
Ha	2014	China	Retrospective	HCC	255	Tissue	IHC	Multivariate	DSS, DFS	Reported	7
Ahmed	2019	Korea	Retrospective	GC	53	Tissue	IHC	Multivariate	OS	Reported	6
Yao	2020	China	Retrospective	CRC	135	Tissue	qPCR	Multivariate	OS	Reported	7

CRC = colorectal cancer, DFS = disease-free survival, DSS = disease specific survival, GC = gastric cancer, HCC = hepatocellular carcinoma, OS = overall survival, OSCC = oral squamous cell carcinomas, RFS = recurrence-free survival.

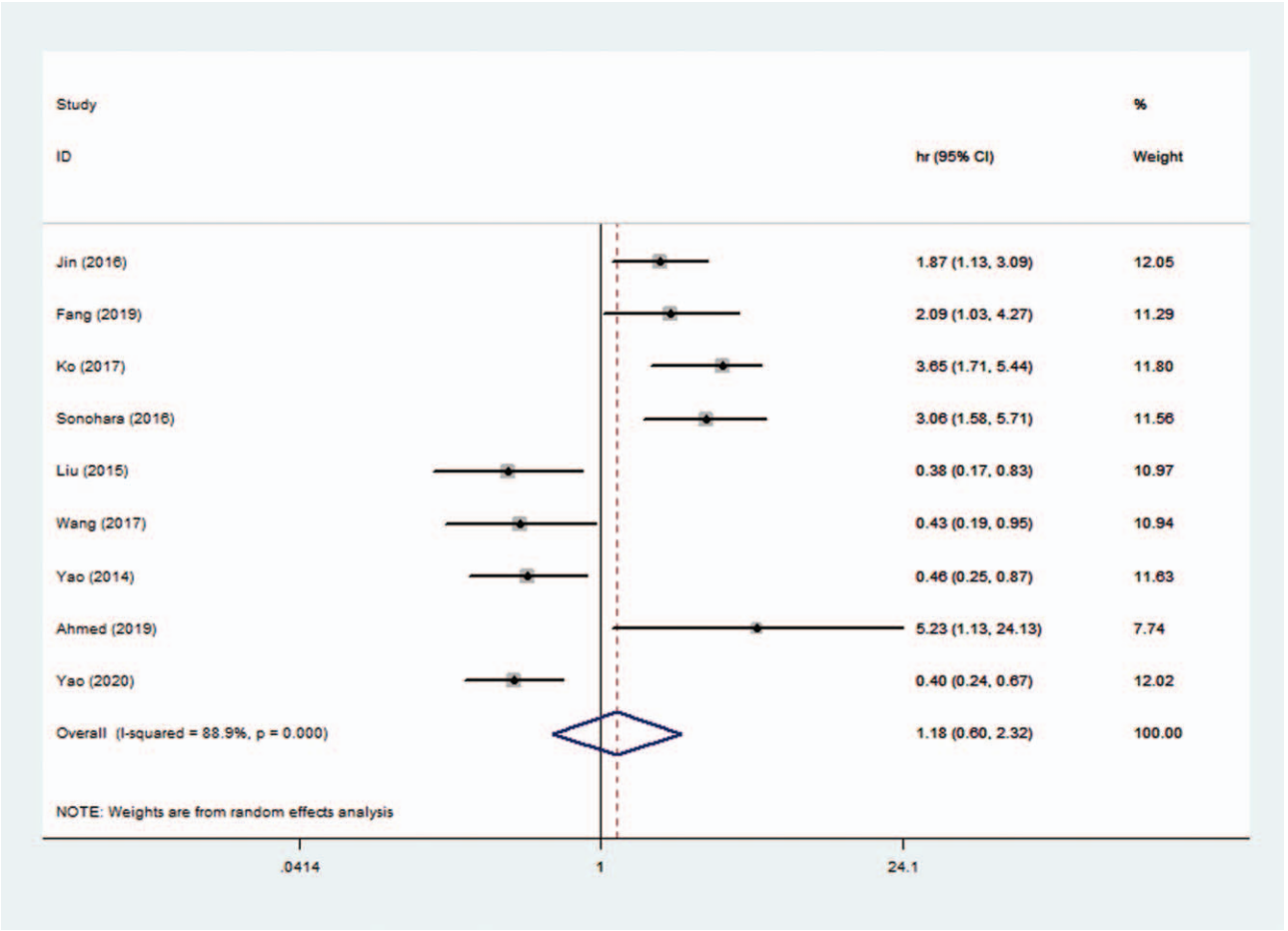

Figure 2. Forest plot of association of highAKR1B10 expression with OS.

Table 2

Subgroup analysis for OS in patients with high AKR1B10 expression.

Stratified analysis	No. of studies	HR (95% CI)	*P* value	Heterogeneity		
				I^2 (%)	*P* value	Model
Cancer type						
HCC	4	1.01 (0.38–2.69)	.982	88.3		Random
OSCC	2	2.92 (1.86–4.58)		29.4	.234	Fixed
GC	2	1.40 (0.13–14.99)	.782	88	.004	Random
CRC	1	0.40 (0.24–0.67)				
Analysis type						
Univariate analysis	1	0.46 (0.25–0.87)				
Multivariate analysis	8	1.34 (0.65–2.75)	.425	88.9		Random
Country						
China	7	0.90 (0.43–1.86)	.768	89.6		Random
Japan	1	3.06 (1.58–5.71)				
Korea	1	5.23 (1.13–24.13)				
Detected method						
IHC	6	1.13 (0.45–2.83)	.794	88.5		Random
qPCR	3	1.30 (0.39–4.34)	.664	93		Random
NOS score						
NOS = 6	3	2.60 (1.80–3.76)		47	.15	Fixed
NOS = 7	6	0.76 (0.35–1.63)		87.3	.48	Random

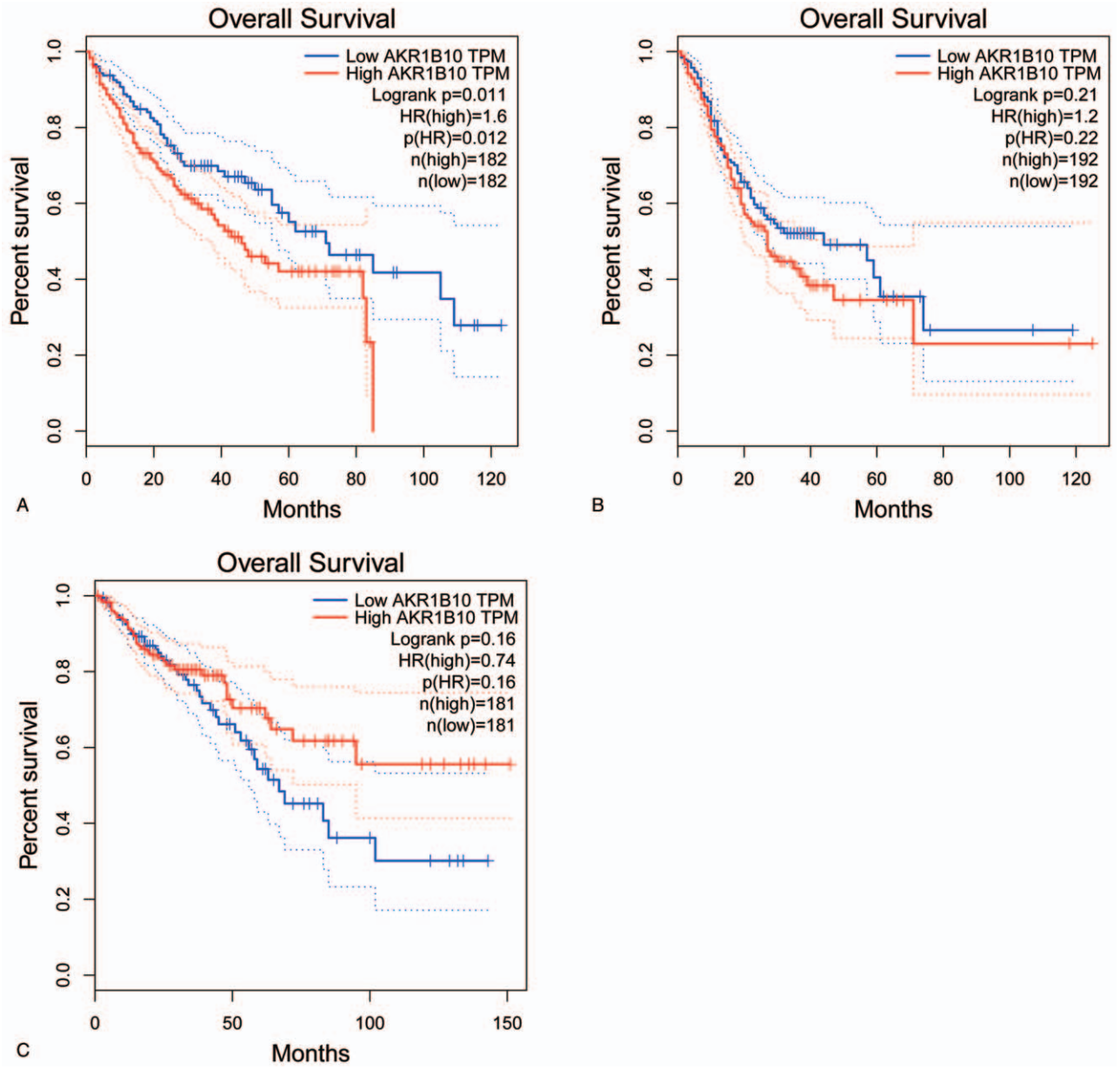

Figure 3. Kaplan–Meier survival analysis for cancer patients in TCGA. (A) hepatocellular carcinoma.(B)gastric cancer.(C)colorectal cancer.

perform the pooled HR. Comprehensive analysis revealed that there was no significant relationship between high AKR1B10 expression and DFS/RFS (HR: 1.08, 95% CI: 0.67–1.76) (Fig. 4). DFS and RFS also were used to analyze the data. The results indicated that high AKR1B10 expression was not connected with DFS (HR: 1.43; 95% CI: 0.61–3.33) and RFS (HR: 0.82; 95% CI: 0.45–1.50). In addition, 2 studies about HCC reported DSS. The results suggested that high AKR1B10 expression displayed the favorable DSS (HR: 0.71, 95% CI: 0.52–0.97) (Fig. 5).

3.6. Sensitivity analysis

Sensitivity analysis was displayed by sequentially omitting 1 study in turn. The results were not significantly changed from the above results, suggesting that the outcomes were robust for OS (Fig. 6A) and DFS/PFS (Fig. 6B).

3.7. Publication bias

The publication bias for the total OS or DFS/RFS analyses were performed by funnel plots. Begg test and Egger test were applied to display the statistical evidence of funnel plot symmetry. *P* values of Begg test and Egger test were 1.00 and 0.856 for OS (Fig. 7A) and 0.260 and 0.267 for DFS/RFS (Fig. 7B), respectively. No significant publication bias was observed.

4. Discussion

This study was the first meta-analysis to comprehensively assess the prognostic role of AKR1B10 in digestive system cancers.

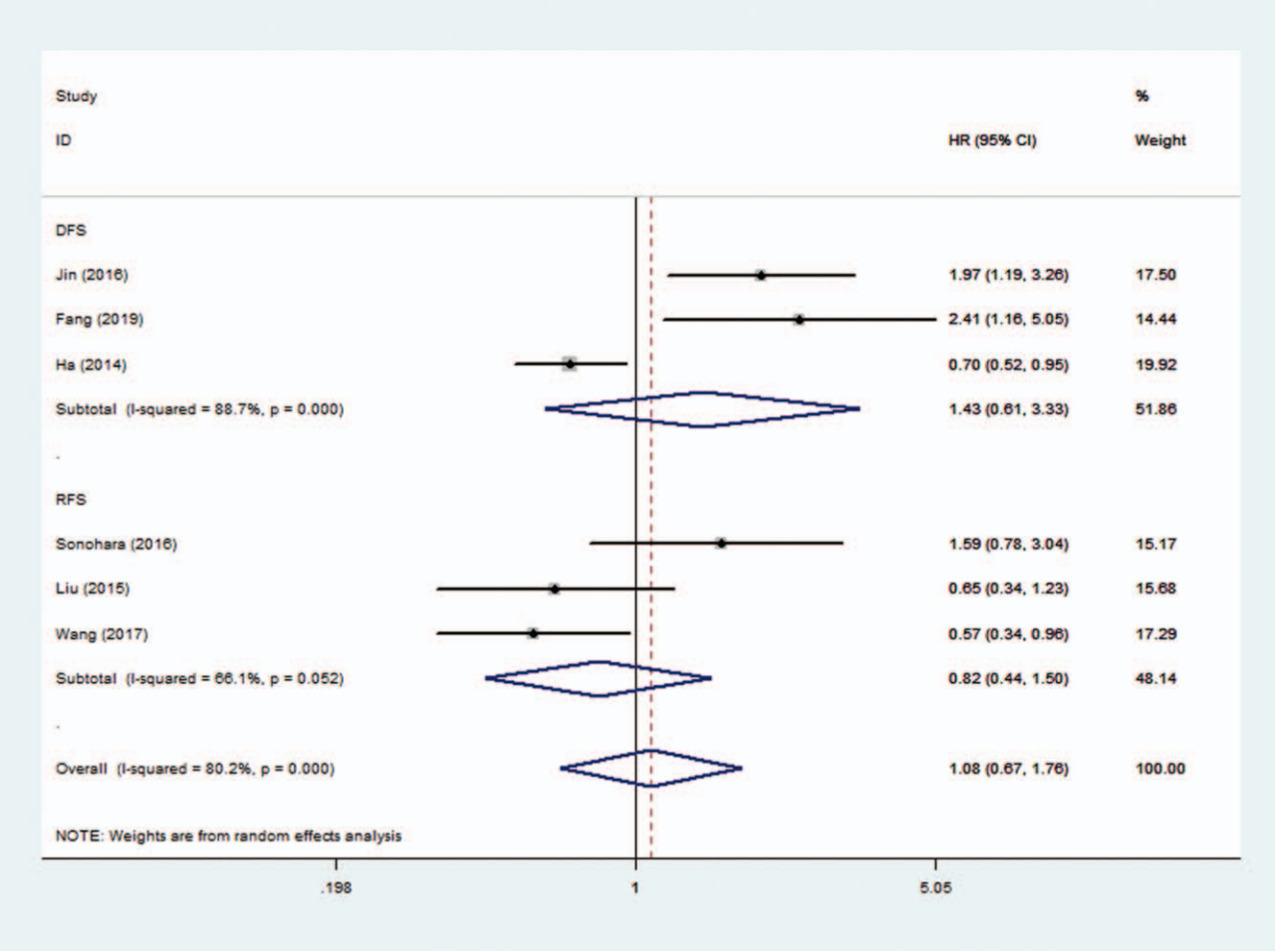

Figure 4. Forest plot of association of high AKR1B10 expression with DFS/RFS.

Eleven studies involving 1428 patients were included. Nine studies assessed OS data, 6 studies evaluated DFS/RFS data and 2 studies about HCC reported the DSS data. The results demonstrated that high AKR1B10 expression was not correlated with worse OS (HR: 1.18; 95% CI: 0.60–2.32) and DFS/RFS (HR: 1.08, 95% CI: 0.67–1.76) in digestive system cancers. However, there was obvious association between high AKR1B10 expression and DSS (HR: 0.71, 95% CI: 0.52–0.97) in HCC. Based on subgroup analysis, we found that high AKR1B10 expression indicated worse OS in OSCC, but not in HCC and GC. Shi et al., showed that high AKR1B10 expression indicated poor OS in HCC patients according to the TCGA database.[26] This is consistent with our database analysis based on TCGA, but different from our meta-analysis. We speculated that this was due to the fact that we included fewer literatures about HCC, while the TCGA database had abundant data resources. In addition, it may be caused by the differences in research methods, statistical methods, detection methods, sample sizes and the clinical experience of researchers in the included literatures.

AKR1B10 regulates tumors through various mechanisms. Ohashi et al, found that low AKR1B10 expression could inhibit p53-induced apoptosis of colorectal cancer cells and promote tumor development.[18] In lung cancer, AKR1B10 may regulate the proliferation, adhesion, and invasion of cancer cells via ERK/MAPK signaling pathway.[19] In breast cancer, AKR1B10 could enhance the invasion and metastasis of cancer by regulating the extracellular signal regulated kinase (ERK) and FAK/Src/Rac1 signaling pathways.[20,21] Wang et al, revealed that deletion or inhibition of the AKR1B10 gene affected mitochondrial function and induced oxidative stress to promote apoptosis of tumor cells.[22] Moreover, silencing the expression of AKR1B10 could inhibit the proliferation, invasion and metastasis of pancreatic cancer cells by modulating the Kras-E-cadherin pathway.[23] Sphingosine-1-phosphate (S1P) is a bioactive phospholipid and closely related to tumor progression.[24] Jin et al, reported that AKR1B10 promoted the proliferation of liver cancer cells by increasing the secretion of S1P.[10] Furthermore, epidermal growth factor induced tumor marker AKR1B10 expression through activator protein-1 signaling to promote the proliferation of liver cancer cells.[25] The mechanism involved in the regulation of tumors by AKR1B10 is complex and warrants further investigation.

This study was characterized by several limitations. Firstly, all included studies had small sample sizes, which increased the likelihood of inaccurate results. Secondly, there was significant

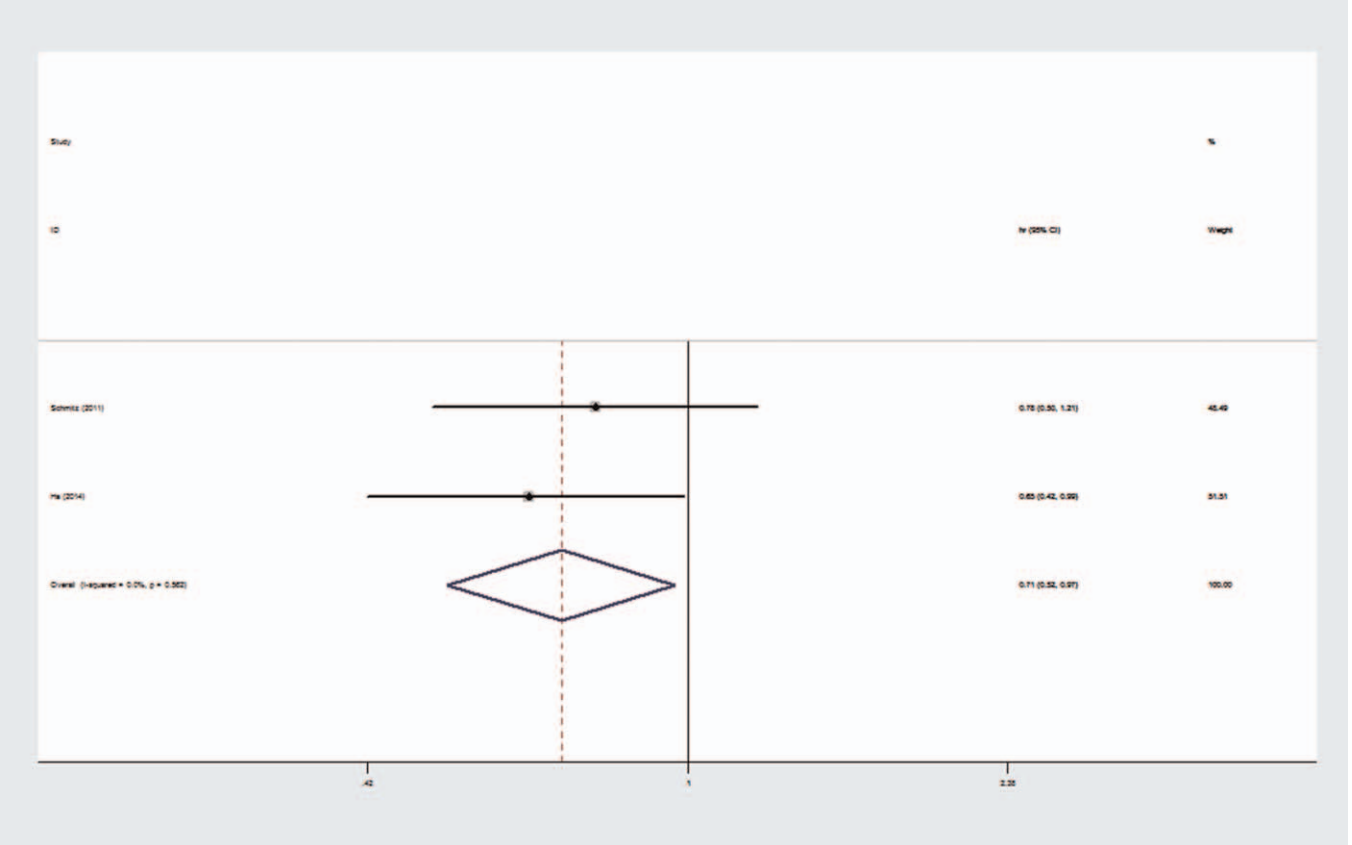

Figure 5. Forest plot of association of high AKR1B10 expression with DSS in HCC.

heterogeneity and the results needed to be treated with caution. Thirdly, the research methods of different studies and cut-off values were inconsistent, which may affect the evaluation of AKR1B10 as a prognostic biomarker. Fourthly, most studies involved in the study were implemented in Asia. Finally, we did not investigate the relationship between AKR1B10 and other pathological parameters due to insufficient data, such as tumor stage and metastasis.

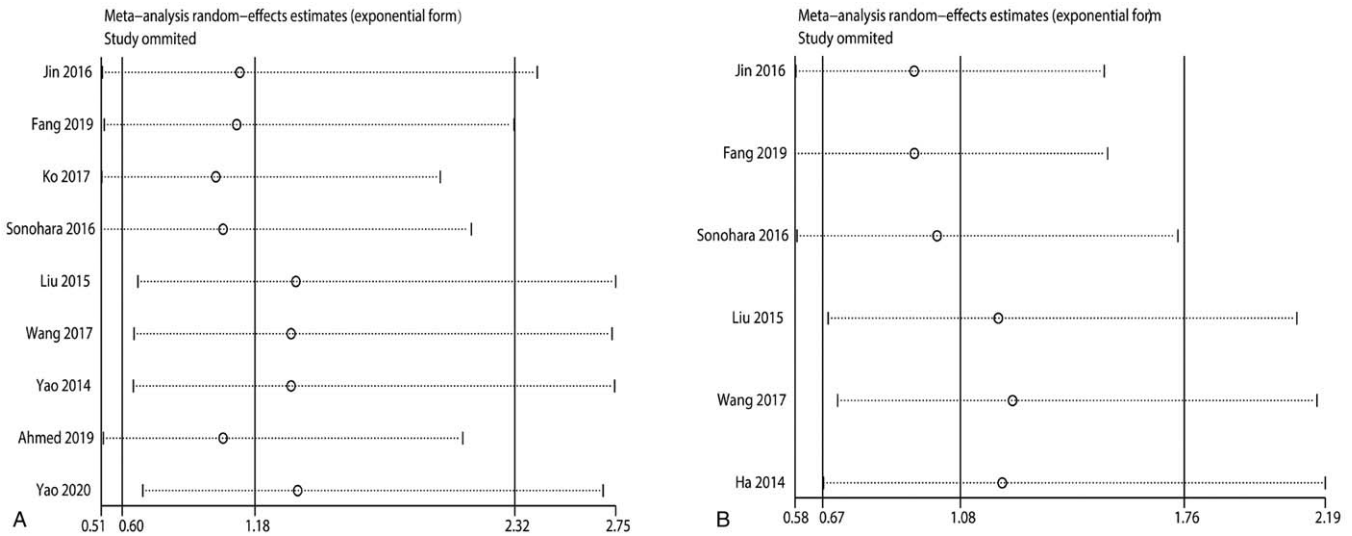

Figure 6. Sensitivity analysis. (A) Sensitivity analysis for OS. (B)Sensitivity analysis for DFS/PFS.

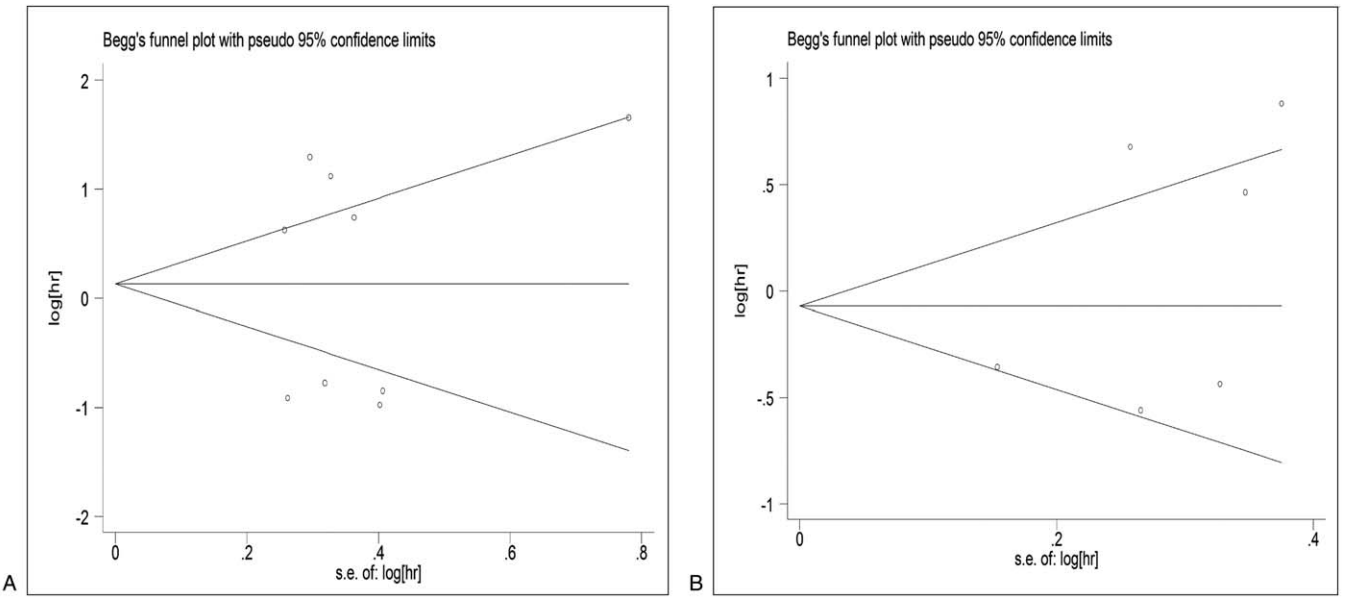

Figure 7. (A) Funnel plots for publication bias to evaluate OS. (B)Funnel plots for publication bias to evaluate DFS/PFS.

In conclusion, we demonstrated that the prognostic value of high AKR1B10 expression varied in different types of digestive system cancers. Further studies exploring the prognostic role of AKR1B10 in digestive system cancers are needed.

Author contributions

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Writing – original draft: Rongqiang Liu.
Writing – review & editing: Rongqiang Liu, Yi Shao.

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