Prognostic value of aldo-keto reductase family 1 member B10 in solid tumors: a systematic review and meta-analysis

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Abstract

Background: It has been reported that the expression of aldo-keto reductase family 1 member B10 (AKR1B10) is abnormal in various types of cancer, and could be used as a prognostic biomarker. However, the results are controversial. Therefore, the aim of this study was to comprehensively evaluate the prognostic value of AKR1B10 expression in solid tumors by conducting a meta-analysis.

Methods: The pooled hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival and disease-free survival/relapse-free survival were calculated to estimate the prognostic significance of AKR1B10 using the random effects model. Subgroup, meta-regression, and sensitivity analyses were used to investigate sources of heterogeneity. Begg's test and Egger's test were used to evaluate publication bias.

Results: Eleven studies involving 1,389 patients were included in this meta-analysis. The pooled analysis displayed that high expression of AKR1B10 was not associated with OS(HR=1.22; 95% CI: 0.73–2.04) and DFS/PFS (HR=1.23, 95% CI 0.75–2.01) in solid tumors. Sensitivity analysis indicated that the results of the meta-analysis were stable. Begg's test and Egger's test also confirmed the absence of publication bias.

Conclusions: We demonstrated that high expression of AKR1B10 was not associated with survival outcomes in patients with solid tumors. Further large-sample, prospective, multi-centric, and well-designed studies are warranted to investigate the prognostic role of AKR1B10 in various cancers.

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 plays an important role in tumorigenesis and the development of cancer, and can be used for clinical purposes such as tumor diagnosis and prognosis [2]. Among them, Aldo-keto reductase family 1 member B10 (AKR1B10) is one of the most attractive members of the aldehyde ketone reductase family.

The AKR1B10 gene is located on chromosome 7q33 and encodes a protein 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 showed that abnormal expression of AKR1B10 is significantly correlated with the prognosis of certain solid tumors [5-15]. However, the currently available results are inconsistent, and the prognostic value of AKR1B10 remains unclear. Therefore, we performed a meta-analysis to further confirm the prognostic role of AKR1B10 in various types of cancer. In this article, we also discuss the suitability of AKR1B10 as a prognostic marker for cancer.

Material And Methods

Search strategy

We synthetically searched the literature available on PubMed, Embase, and Web of Science until November 31, 2019. 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 tumour OR tumor). We earnestly screened the titles,

abstracts, full texts, and reference lists to identify objective studies. Two authors independently performed the search.

Selection criteria

The inclusion criteria were as follows: (1) investigated the patients with any type of cancer; (2) determined the expression of AKR1B10 in tumor tissue or blood; (3) explored the relationship between the expression of AKR1B10 and survival outcome; and (4) provided sufficient data to calculate the hazard ratio (HR) and 95% confidence interval (CI). The exclusion criteria were as follows: (1) provided insufficient data to calculate the HR and 95% CI; and (2) case reports, abstracts, animal studies, reviews, letters, non-English language publications and data from public databases.

Data extraction and quality assessment

Two authors independently extracted the data. The relevant information included the first author's name, publication year, country, tumor type, sample size, tumor stage, follow-up time, methods for the assessment of AKR1B10 expression, and HRs with the corresponding 95% CIs. Multivariate analysis was preferred because it considers the confounding factors and exhibits high accuracy. Kaplan–Meier curves were used to extract the HR value. The quality of each study was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) [16].

Statistical analysis

We used HRs and the corresponding 95% CIs to calculate the pooled data. If the statistical variables were described in the study, we then directly used them in our analysis. Otherwise, the data were extracted from graphical survival plots according to the methods described by Tierney [17]. Data from the Kaplan–Meier survival curves were analyzed using the Engauge Digitizer version 4.1 software. A fixed effects model was used when I^2 was <50%. A random effects model was used when I^2 was >50%. Subgroup, meta-regression, and sensitivity analyses were used to investigate sources of heterogeneity. Begg's test and Egger's test were used to evaluate publication bias. All the analyses were performed using the STATA version 12.0 software (Stata Corporation, College Station, TX, USA). P-values <0.05 denoted statistically significant differences.

Results

Study selection

A total of 909 articles were initially collected from specified database. After removing 474 duplicates, 435 articles were screened for further information. 412 articles were excluded according to the selection criteria, and 23 articles were further screened. After full-text review, 12 articles were excluded. Eventually, we identified 11 articles published between 2014 and 2019, which were included in the final analysis [5-15]. The flow diagram of the literature search is shown in Fig1.

Study characteristics

The included articles involved a total of 1389 patients, ranging from 53 to 255. In all studies, the expression of AKR1B10 was detected in tumor tissue. Nine studies detected the AKR1B10 by immunohistochemistry and two

study by quantitative reverse-transcription polymerase chain reaction (qRT-PCR). Ten studies were all conducted in Asian and one in Caucasian. The tumors involved included non-small-cell lung cancer (NSCLC), oral squamous cell carcinomas (OSCC), gastric cancer (GC), hepatocellular carcinoma (HCC). Nine HRs were reported in the included studies and two HRs were assessed by analyzing K-M curves. Basic information is shown in Table 1.

Association of AKR1B10 expression with OS

Eleven studies focused on OS analysis (Table 2, Fig 2). The random effects model was adopted due to the obvious heterogeneity ($I^2=85\%$). The pooled results revealed that high expression of AKR1B10 was not associated with OS in solid tumors (HR=1.22; 95% CI: 0.73–2.04).

Considering the heterogeneity among the studies, subgroup and meta-regression analyses were performed based on the tumor type, publication year, sample size, region, analysis type, detection methods (Table 3). In the subgroups based on publication year (>2015) and detection method (qRT-PCR), we found that high expression of AKR1B10 displayed worse OS (HR=2.08, 95% CI: 1.18–3.64; HR=2.29, CI: 1.42–3.7). Moreover, the subgroup with publication year (≤ 2015), the high expression of AKR1B10 predicted the favorable OS (HR=0.61, 95% CI: 0.46–0.81). The results of the analysis for the other subgroups were consistent with the overall analysis. Meta-regression showed that the heterogeneity was caused by publication year ($P=0.01$) instead of tumor type ($P=0.2$), sample size ($P=0.92$), region ($p=0.61$), analysis type ($P=0.41$) or detection methods ($P=0.25$).

Association of AKR1B10 expression with DFS/RFS

Seven studies that reported DFS/RFS showed obvious heterogeneity ($I^2=81.2\%$) (Table 2, Fig 3). We also calculated the pooled HR using a random effects model. Comprehensive analysis indicated that there was no significant relationship between the expression of AKR1B10 and DFS/RFS (HR=1.23, 95% CI: 0.75–2.01). In addition, data were analyzed based on DFS and RFS. We found that high expression of AKR1B10 was not associated with DFS (HR=1.43; 95% CI: 0.61–3.33, $I^2=88.7\%$) and RFS (HR=1.10; 95% CI: 0.53–2.28, $I^2=78.5\%$).

Subgroup analyses and meta-regression were performed based on tumor type, publication year, sample size, analysis type, detection methods (Table 4). In the subgroups based on tumor type (other type), analysis type (multivariate) and detection method (qRT-PCR), we found that high expression of AKR1B10 was associated with poor DFS/RFS. In addition, we did not note the existence of heterogeneity in subgroup studies with tumor type (other type), publication year (≤ 2015) and detection method (qRT-PCR) ($I^2=0\%$). Therefore, these three factors may contribute to the heterogeneity.

Sensitivity analysis

Sensitivity analysis was performed by sequentially removing each of the included studies. The results were not significantly different from the complete analysis, indicating that the outcome was stable for OS (Fig 4) and DFS/PFS (Fig 5).

Publication bias

We used funnel plots to evaluate the publication bias for the total OS or DFS/RFS analyses. Begg's test and Egger's test were used to provide statistical evidence for funnel plot symmetry. P-values of the Begg's test and

Egger's test were 1 and 0.526 for OS and 0.133 and 0.114 for DFS/RFS, respectively. There was no significant publication bias for OS (Fig 6) and DFS/RFS (Fig7).

Discussion

The present study was the first meta-analysis to comprehensively assess the prognostic role of AKR1B10 in various types of cancer. A total of eleven studies involving 1389 patients were included. Eleven studies assessed the prognostic role of AKR1B10 in OS and seven studies evaluated the prognostic role of AKR1B10 in DFS/PFS/RFS. The results of the meta-analysis demonstrated that high expression of AKR1B10 was not associated with worse OS (HR=1.22; 95% CI: 0.73–2.04) and DFS/RFS (HR=1.23, 95% CI: 0.75–2.01) in solid tumors. Meta-regression showed that publication year may be the sources of heterogeneity in OS. Moreover, Tumor type, publication year, detection method may contribute to the heterogeneity in DFS/PFS/RFS. Sensitivity analysis indicated that the results of the meta-analysis were stable. Begg's test and Egger's test also confirmed the absence of publication bias.

In general, AKR1B10 is normally expressed in the gastrointestinal tract, and exhibits low levels in the liver and prostate. However, it is not expressed in other human tissues. AKR1B10 is highly expressed in a variety of non-gastrointestinal solid tumors, while it is low expressed in gastrointestinal tumors such as gastric cancer and colorectal cancer. AKR1B10 protects the body from carbonyl damage by reducing the levels of carbonyl compounds to prevent canceration. In addition, it inhibits tumor formation, and promotes tumorigenesis and the development of cancer by regulating fatty acid metabolism and retinoic acid signaling pathways, respectively [18].

AKR1B10 regulates tumors through various mechanisms. P53 is an important tumor suppressor gene. Ohashi et al. found that silencing of AKR1B10 significantly inhibited p53-induced apoptosis of colorectal cancer cells. In contrast, overexpression of AKR1B10 enhanced p53-induced apoptosis of tumor cells and inhibited tumor proliferation. The results showed that AKR1B10 was the transcriptional target of p53, and the decreased expression of AKR1B10 may impair the tumor inhibitory function of p53 [19]. A study on lung cancer demonstrated that AKR1B10 may regulate the proliferation, adhesion, and invasion of lung cancer cells through the extracellular-signal-regulated kinase (ERK)/mitogen activated protein kinase signal pathway [20]. Huang et al. displayed that overexpression of AKR1B10 can promote the invasion and metastasis of breast cancer through the regulation of the ERK and FAK/Src/Rac1 signaling pathways [21]. In addition, AKR1B10 increases the expression of matrix metalloproteinase 2 (MMP2) and vimentin by activating the ERK signaling pathway, thus promoting the migration and invasion of breast cancer cells [22]. Wang et al. revealed that deletion or inhibition of the AKR1B10 gene affects mitochondrial function and induces oxidative stress to promote apoptosis of tumor cells [23]. Silencing the expression of AKR1B10 in pancreatic cancer cells increases Kras activity and the phosphorylation of C-raf and ERK. Moreover, E-cadherin is significantly upregulated, leading to a significant decrease in the proliferation, invasion, and metastasis of pancreatic cancer cells [24]. Sphingosine-1-phosphate (S1P) is a bioactive phospholipid closely related to tumor progression [25]. A previous study has shown that AKR1B10 promotes the proliferation of liver cancer cells by increasing the secretion of S1P. Following the silencing of AKR1B10, tumor cells undergo obvious apoptosis, and the secretion of S1P is significantly decreased [11]. Furthermore, the epidermal growth factor activates the activator protein-1(AP-1) signaling pathway to upregulate the expression of AKR1B10 and promote the proliferation of liver cancer cells [26]. The mechanism involved in the regulation of tumors by AKR1B10 is complex and warrants further investigation.

This meta-analysis was characterized by several limitations. Firstly, all included studies had small sample sizes, increasing the likelihood of inaccurate results. Secondly, some of the HR and CI values extracted from the survival curve may not be equal to the true value. Thirdly, the research methods of different studies and cut-off values are inconsistent. Fourthly, most studies included in the meta-analysis were conducted in Asia. Future studies involving patients of different races and from various regions are warranted. Finally, we did not investigate the relationship between AKR1B10 and other pathological parameters due to insufficient data, such as tumor stage and metastasis.

Conclusion

We demonstrated that high expression of AKR1B10 was not associated with survival outcomes in solid tumor. However, the majority of included studies were single-center, small sample and retrospective studies. Therefore, further large-sample prospective, multi-centric, and well-designed studies are warranted to confirm the present results and investigate the prognostic role of AKR1B10 in various cancers.

Abbreviations

AKR1B10: aldo-keto reductase family 1 member B10; NOS: Newcastle-Ottawa Quality Assessment Scale; HR: hazard ratio; CI: confidence interval; qRT-PCR: quantitative reverse-transcription polymerase chain reaction; NSCLC: non-small-cell lung cancer; OSCC: oral squamous cell carcinomas; GC: gastric cancer; HCC: hepatocellular carcinoma. ERK: extracellular signal regulated kinase; MMP2 : metalloproteinase 2; S1P :sphingosine-1-phosphate; AP-1:activator protein-1;

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing Interests

No competing interests.

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Authors' contributions

Rongqiang Liu, Shiyang Zheng and Shengjia Peng was in charge of writing the main article, data collection and data analysis. Qianmin Ge, Qi Lin, Rongbing Liang, Wenqing Shi contributed to the investigation and supervision of the article. Yi Shao was in charge of conceptualization, data curation and writing – review and editing of the article.

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Not applicable.

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Tables

Table1. Basic characteristics of included articles in meta-analysis										
Study	Country	Study design	Cancer type	Recruitment period	Mean follow-up time(Months)	Case Number	Age (years)	Sex (M/F)	Stage	Survival analysis
Hung et al. (2018)	China	R	NSCLC	2011-2012	29.9	96	64.7	42/54	I-III	OS, RFS
Jin et al. (2016)	China	R	HCC	2001-2007	36.0	144	NR	122/22	I-IV	OS, DFS
Fang et al. (2019)	China	R	OSCC	1997-2010	300	107	54.9	97/10	I-IV	OS, DFS
Ko et al. (2017)	China	R	OSCC	2010-2014	NR	77	53	61/16	I-IV	OS
Schmitz et al. (2011)	Germany	R	HCC	NR	20	168	NR	124/44	NR	DSS
Sonohara et al. (2016)	Japan	R	HCC	1998-2011	48.5	158	65	84/16	I-IV	OS, RFS
Liu et al. (2015)	China	R	HCC	1999-2001	NR	109	NR	82/27	NR	OS, RFS
Wang, et al. (2017)	China	R	HCC	2013-2014	20	110	44	96/14	NR	OS, RFS
Yao et al. (2014)	China	R	GC	2004-2006	NR	112	60	80/32	I-IV	OS
Ha et al. (2014)	Korea	R	HCC	2000-2006	119.8	255	52.3	208/47	NR	DFS, DSS
Ahmed et al(2019)	China	R	GC	2006-2015	NR	53	58	40/13	I-IV	OS
Abbreviation: R=Retrospective; NSCLC=Non-small-cell lung cancer; NPC: Nasopharyngeal carcinoma; BC=Breast cancer; OSCC=Oral squamous cell carcinomas; GC=Gastric cancer; HCC=Hepatocellular carcinoma; OS=Overall survival; DFS= Disease-free survival; RFS=Recurrence-free survival; MFS=Metastasis-free survival; DSS=Disease specific survival.										

Table 2. The effect of AKR1B10 on OS and DFS/RFS in enrolled studies.									
Study	Detection method	Case number(n)		OS			DFS/RFS		
		High expression	Low expression	HR(95%CI)	p value	Source of HR	HR(95%CI)	p value	Source of HR
Hung et al.(2018)	IHC	22	74	2.574(0.43-15.422)	0.301	Reported	3.222(1.284-8.086)*	0.013	Reported
Jin .et al(2016)	qPCR	99	45	1.866 (1.127-3.091)*	0.015	Reported	1.965 (1.187-3.256)*	0.009	Reported
Fang. (2019)	IHC	35	77	2.09 (1.03-4.27)*	0.042	Reported	2.41(1.16-5.05)	0.019	Reported
Ko et al. (2017)	IHC	NR	NR	3.647 (1.710-5.443)*	0.001	Reported	NR	NR	-
Schmitz et al. (2011)	IHC	81	87	0.78(0.50-1.21)	NR	SC	NR	NR	-
Sonohara et al. (2016)	qPCR	132	26	3.06(1.58-5.71)*	0.0011	Reported	1.59(0.78-3.04)*	0.1884	Reported
Liu. et al. (2015)	IHC	69	40	0.376(0.171-0.827)*	0.015	Reported	0.646(0.340-1.227)*	0.182	Reported
Wang et al. (2017)	IHC	67	43	0.429(0.193-0.951)*	0.037	Reported	0.572(0.34-0.963)*	0.036	Reported
Yao et al. (2014)	IHC	35	77	0.46(0.25-0.87)	0.017	Reported	NR	NR	
Ha et al. (2014)	IHC	125	130	0.65(0.42-0.99)*	0.046	Reported	0.70 (0.52-0.95)*	0.024	Reported
Ahmed et al(2019)	IHC	31	22	5.23(1.133-24.131)*	0.034	Reported	NR	NR	NR
Abbreviation: IHC=Immunohistochemistry; OS=Overall survival; DFS= Disease-free survival; RFS=Recurrence-free survival; SC=Survival curve.									
*Data of multivariate analysis									

analysis and meta-regression of the studies reporting the effect of AKR1B10 on OS.

No. of studies	Pooled HR(95% CI)	Meta-regression			Heterogeneity	
		Tau2	Adj R ² (%)	p-value	I ² (%)	p-value
		0.65	5.47	0.2		
6	0.9(0.5-1.63)				84.6	<0.01
2	1.03(0.97-1.09)				0	0.345
2	1.13(0.89-1.44)				100	-
1	2.57(0.43-15.42)					
		0.25	63.65	<0.01		
7	2.08(1.18-3.64)				72.3	<0.01
4	0.61(0.46-0.81)				14.4	0.32
		0.79	-14.49	0.92		
7	1.23(0.52-2.88)				86.5	<0.01
4	1.27(0.65-2.48)				86.4	<0.01
		0.77	-11.87	0.61		
10	1.3(0.72-2.33)				85.8	<0.01
1	0.78(0.5-1.21)				-	-
		0.68	0.48	0.41		
3	0.71(0.39-1.29)				49.9	0.136
8	1.42(0.75-2.69)				90.7	<0.01
		0.62	9.88	0.25		
9	1.03(0.58-1.83)				83.8	<0.01
2	2.29(1.42-3.7)				29	0.24

roup analysis and meta-regression of the studies reporting the effect of AKR1B10 on DFS/RFS.

udy	No. of studies	Pooled HR(95% CI)	Meta-regression			Heterogeneity	
			Tau ²	Adj R ² (%)	p-value	I ² (%)	p-value
			0.2	45.67	0.08		
	5	0.94(0.58-1.53)				78.2	<0.01
e	2	2.7(1.52-4.79)				0	0.63
ear		(-)	0.25	32.32	0.13		
	5	1.62(0.87-3.01)				78.3	0.01
	2	0.69(0.53-0.91)				0	0.82
		(-)	0.47	-26.52	0.95		
	3	1.24(0.54-2.85)				83.2	<0.01
	4	1.26(0.6-2.62)				85.8	<0.01
		(-)	0.36	3.71	0.36		
e	1	1.11(0.67-1.83)				-	-
te	6	2.41(1.16-5.03)				80.6	<0.01
		(-)	0.36	2.41	0.42		
	5	1.05(0.59-1.87)				80.2	<0.01
	2	1.82(1.22-2.73)				0	0.62

Figures

Figure 1

Flow diagram of the literature search

Figure 2

Forest plot of association of AKR1B10 expression with OS

Figure 3

Forest plot of association of AKR1B10 expression with DFS/RFS

Figure 4

Sensitivity analysis for OS

Figure 5

Sensitivity analysis for DFS/PFS

Figure 6

Funnel plots for publication bias to evaluate OS

Figure 7

Funnel plots for publication bias to evaluate DFS/PFS