Effect of ARID1A mutation and expression on prognosis of hepatocellular carcinoma and cholangiocarcinoma: a meta-analysis

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Abstract

Background: Hepatocellular carcinoma (HCC) and cholangiocarcinoma are the most common liver malignant tumors worldwide. Investigating the molecular basis of these malignancies is vital to the development of new treatments. Recent studies have found that mutation and abnormal expression of ARID1A, are frequently shown in HCC and cholangiocarcinoma. Herein, we aimed to estimate the effects of ARID1A mutation and expression on prognosis of HCC and cholangiocarcinoma.

Methods: We searched PubMed, EMBASE, Web of Science, the Cochrane Library for studies evaluating the relationship between ARID1A mutations or expression and the survival of HCC or cholangiocarcinoma patients. Meta-analysis was performed to generate a combined *HR* with a 95% confidence interval (*CI*) for overall survival (OS).

Results: We identified 12 articles that evaluated the impact of ARID1A mutation or expression on the prognosis of patients with HCC or cholangiocarcinoma. Six studies provided data on HCC survival and 6 studies examined cholangiocarcinoma survival. For HCC, ARID1A mutation carriers or patients with low ARID1A expression had worse OS (*HR* = 1.75; 95% *CI* = 1.22–2.51) than non-carriers or patients with high ARID1A expression. For cholangiocarcinoma, ARID1A mutation carriers or patients with low ARID1A expression also had significantly shorter OS (*HR* = 3.70, 95% *CI* = 2.88–4.76).

Conclusions: Our study suggests that ARID1A mutation or low expression is strongly associated with poor prognosis of patients with HCC or cholangiocarcinoma, and may be considered as a potential prognostic biomarker for these patients.

Background

Liver cancer is one of the most common malignancies in the world and the fourth leading cause of cancer death[1, 2]. Cholangiocarcinoma, also known as bile duct cancer, originating from the biliary epithelium, is a group of heterogeneous malignant tumors with poor prognosis which ranked the second most common cancer of the liver and gallbladder worldwide[3].

ATP-dependent chromatin remodelers utilize the energy of ATP to regulate DNA transcription[4]. Next-generation gene sequencing shows that subunits of the SWI/SNF complex, encoding the ATP-dependent chromatin remodelers, are frequently mutated in a wide variety of cancers, such as lung cancer[5], rhabdoid tumors, gastric adenocarcinoma, malignant melanoma[6]. ARID1A mutations are frequently shown in SWI/SNF genes. Previous study had demonstrated that repeated mutation of ARID1A related to the development of many types of cancer. Most ARID1A mutations are inactivated mutations that lead to loss of ARID1A expression[7]. Thus, ARID1A was considered as a broad tumor suppressor[8]. Mutations and abnormal expression of ARID1A have been found in a variety of cancers, such as urothelial bladder tumors[9], colorectal cancer[10], nonfunctional pancreatic neuroendocrine tumors[11], invasive micropapillary carcinomas of the breast[12], endometriosis and uterine endometrioid carcinoma[13, 14].

ARID1A has a relatively high mutation frequency in both HCC (6.9%-17%)[15–17] and biliary tract cancers(12.1%-33%)[18–20]. *Hu, Chaobo et al.* reported that ARID1A deficiency occurred in advanced human HCC and promoted HCC progression[21]. A large amount of studies have manifested that patients of HCC or cholangiocarcinoma with ARID1A mutation or low expression had shorter OS than those of noncarriers or patients with high ARID1A expression[17, 22–25]. However, inconsistent conclusions were demonstrated that ARID1A mutation or expression has no significant influence on OS[26–28]. In HCC, *Zhao, Jie et al.* reported that 87.8% tumors ARID1A mRNA and BAF250a protein expression levels were increased compared with adjacent noncancerous tissues[27]. Animal experiment showed that ARID1A had both oncogenic and tumor suppressor functions in liver cancer[29]. Therefore, to further understand the association between ARID1A and liver cancer, we perform a meta-analysis to assess the effectiveness of ARID1A mutation and expression on the prognosis of HCC and cholangiocarcinoma.

Methods

This meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement[30].

1. Literature search

All relevant studies were selected from PubMed, Embase, Web of Science and Cochrane Library from the inception of the databases through July 15, 2020. Searching terms included subject terms("ARID1A") AND ("hepatocellular carcinoma" OR "cholangiocarcinoma") and their related entry terms. We also retrieved the references of the included publications and related reviews manually.

2. Eligibility Criteria

The selection criteria of this study were: (a) patients recruited with proven HCC or cholangiocarcinoma according to histological results; (b) investigated the association between ARID1A mutation or expression and prognosis of HCC or cholangiocarcinoma; (c) reported the hazard ratio or 95% confidence interval or provided data for calculation. We excluded the studies as follow: (a) non-English paper; (b) animal or in vitro experiments; (c) review articles, case reports, editorials, letters, commentaries; (d) not HCC or cholangiocarcinoma; (e) studies without liver cancer overall survival data or without sufficient data or Kaplan-Meier plots to calculate risk.

3. Study Selection And Data Extraction

Two investigators (G.-X. M. and L.-J. Y.) performed a preliminary screening on titles and abstracts of all retrieved literatures independently. Then, full texts were reviewed for eligibility. When two investigators had different opinions, disagreements were resolved by thorough discussion with another reviewer (Z.-R.D.). We extracted the following information from each article: authors' information, year of publication, country, test methods, number of patients (altered and non-

altered), follow-up period, endpoints (OS) and clinical features of HCC patients included sex, cirrhosis, tumor size, histological differentiation, HBV infection. If *HR* and 95%*CI* were not provided, *Get Data* software was used to extract the survival information from the Kaplan-Meier curve.

4. Quality Assessment

The quality of each article was independently assessed by two investigators (G.-X. M. and L.-J. Y.) according to the Newcastle-Ottawa Scale (NOS). Each article can be rated with a maximum of 9 points: selection has 4, comparability has 2 and outcome has 3.

5. Statistical analysis

We extracted any reported relative risks (*RRs*), hazard ratios (*HRs*), odds ratios (*ORs*) with 95% confidence interval (*CI*) for *OS*. When adjusted and unadjusted effect sizes were both available, priority was given to the former one. The heterogeneity between the groups was examined by Q test. $I^2 > 50\%$ accompanied with p value < 0.1 was considered as a cutoff for statistically significant heterogeneity. The fixed-effects model was initially used to obtain the aggregated *HRs* and 95% *CI*, and if substantial heterogeneity existed, the aggregated *HRs* were estimated using random-effects models. The publication bias was assessed through visually inspecting the symmetry of the funnel plot and evaluated with Begg’s funnel plot and Egger’s test. Sensitivity analysis is used to detect the stability of the results. This meta-analysis was performed using the STATA 12.0 software (Stata Corporation, College Station, TX, USA).

Results

1. Study selection

We retrieved 563 papers according to search strategy. There left 384 articles after the exclusion of duplicates. Finally, 12 articles meeting the eligibility criteria were included in this study. One of them was a meeting abstract. Figure 1 summarizes the process of literature screening. The average NOS score of these studies was 8.5(Additional file 1: Supplementary Table 1), which indicated that included studies were of relatively high quality.

2.Study characteristics

The meta-analysis for HCC included six studies. The characteristics of the patient cohort are shown in Table 1. The relationship between the clinical characteristics of HCC patients and the expression level of ARID1A is shown in Table 2. The studies published between 2015 and 2020. A total of 950 patients were assimilated into our study including 195 patients with ARID1A mutation or low expression, and 755 patients with no ARID1A mutation or high expression. Two studies focused on ARID1A gene mutations[16, 17], and four focused on ARID1A expression[22, 26, 27, 31]. In these studies, the most used methods to detect mutations and expression of ARID1A were PCR, next-generation sequencing, and immunohistochemistry.

Table 1
Baseline characteristics of hepatocellular carcinoma included in the studies.

Author(ref.) year	Country	Methods	ARID1A(number)				Median/range Of follow-up, m	Hazard ratio	95% CI	p- value	Altered
			ALL	Altered	Normal						
Abe, Hiroyuki[26]2015	Japan	immunohistochemistry	290	63	227	NA		1.08	0.80–1.45	0.99	expression
He, Fei[22]2015	China	PCRwestern blottingimmunohistochemistry	64	41	23	NA		2.12	1.14–3.94	0.042	expression
Kelly, L[16]2020	US	institutional multigene assay	64	11	53	NA		2.12	1.01–4.43	0.046	gene
Li, Li[17]2020	China	Next-generation sequencing	362	25	337	NA		2.577	1.42–4.675	0.0372	gene
Zhao, Jie[27]2016	China	PCR immunohistochemistry	115	14	101	38(3–72)		1.19	0.58–2.43	0.612	expression
Zhou, Dingzhong[32]2019	China	immunohistochemistry	60	41	19	NA		2.31	1.36–3.92	0.021	expression

Table 2
The relationship between the clinical characteristics of HCC patients and the expression level of ARID1A.

Author(ref.) year	Sex	Cirrhosis				Tumor size				Histological differentiation						
		ARID1A expression			ARID1A expression			ARID1A expression			ARID1A expression					
		high	low	P value			high	low	P value			high	low	P value		
Abe, Hiroyuki [26]2015	Male	180	49	0.79	Present	127	38	0.54	≤ 5 cm	168	38	0.034	Well	69	23	0.035
	Female	47	14		Absent	100	25		5-10 cm	59	25		Mod	123	38	
													Poor	35	2	
He, Fei [22]2015	Male	10	6	0.554	Present	14	9	0.396	≤ 5 cm	20	14	0.252	Well-	33	19	0.557
	Female	31	17		Absent	27	14		5-10 cm	21	9		Mod	8	4	
													Poor			
Zhao, Jie [27]2016	Male	81	13	0.460	Present	66	8	0.563	≤ 5 cm	81	6	0.005	NA	NA	NA	NA
	Female	20	1		Absent	35	6		5-10 cm	20	8					
Zhou, Dingzhong[32]2019	Male	17	26	0.907	Present	18	23	0.365	≤ 5 cm	18	16	0.019	Well-	12	11	0.688
	Female	7	10		Absent	6	13		5-10 cm	6	20		Mod	8	9	
													Poor	4	7	

The meta-analysis for cholangiocarcinoma included six studies. The characteristics of the patient cohort are shown in Table 3. The studies published between 2016 and 2020. We included 620 patients composed of 70 patients with ARID1A mutation or low expression and 550 patients with no ARID1A mutation or high expression. Four studies focused on ARID1A gene mutations[23, 24, 28, 32], and two focused on ARID1A expression[25, 33]. In these studies, the most used methods to detect mutations and expression of ARID1A were generation sequencing, PCR, western blotting, and immunohistochemistry.

Table 3
Baseline characteristics of cholangiocarcinoma included in the studies.

Author(ref.) year	Country	Methods	ARID1A(number)							
			ALL	Altered	Normal	Median/range Of follow-up, m	Hazard ratio	95% CI	p-value	Altered
Ruzzenente, A [23]2016	NA	generation sequencing	18	2	16	28.3 ± 25.8	5.337	1.325–21.489	0.018	gene
Sasaki, Motoko [28]2016	Japan	generation sequencing	53	6	47	21	1.15	0.46–2.88	0.98	gene
Simbolo, Michele [33]2018	Italy	generation sequencing	66	6	60	40.7 (2.0–152.7)	6.9059	2.271–21.008	0.0007	gene
Wardell, Christopher P [24] 2018	Japan Italy	generation sequencing	357	22	335	24	4.13	3.05–5.60	0.025	gene
Yang, S. Z [34]2016	China	PCR+western blotting	57	19	38	NA	3.967	1.299–12.118	0.016	expression
Yoshino, J[25]2020	Japan	Immunohistochemistry western blotting+PCR	69	15	54	NA	2.73	1.29–5.78	0.008	expression

3. Prognostic value of ARID1A mutations and expression for HCC and cholangiocarcinoma

3.1. HCC prognosis

Six studies were conducted on the effect of ARID1A mutations and expression on the OS of HCC. In this OS meta-analysis, patients with ARID1A mutation or low expression had worse OS, with a combined *HR* of 1.75 (95% *CI*, 1.12–2.51, Fig. 2). Because of the substantial heterogeneity ($I^2 = 61\%$, $p = 0.025$), the random-effects model was used. Due to different states of altered ARID1A, six articles were divided into two groups. Two articles focused on the effect of ARID1A gene mutation on OS of HCC, combined *HR* was 2.39 (95% *CI*, 1.50–3.79). Heterogeneity was not found in two studies ($I^2 = 0\%$, $p = 0.687$). Four articles focused on the effect of ARID1A expression on OS of HCC, combined *HR* was 1.51 (95% *CI*, 1.01–2.37). Significant heterogeneity was found in four

studies ($I^2 = 63.6\%$, $p = 0.041$). Besides, the results showed that the expression of ARID1A in HCC was not related to sex, cirrhosis, histological differentiation, or HBV infection, but was negatively correlated with tumor size ($RR = 1.53$, 95% CI , 1.18–1.99; **Additional file 2: Supplementary Fig. 1**).

3.2. Cholangiocarcinoma prognosis

Six studies were conducted on the effect of ARID1A mutations and expression on the OS of cholangiocarcinoma. Patients with ARID1A mutation or low expression had a significantly shorter OS, with a combined HR of 3.70 (95% CI , 2.88–4.76; Fig. 2). On account of slight heterogeneity without statistical significance ($I^2 = 43.6\%$, $p = 0.115$), the fixed effect model was used for analysis. Due to different states of altered ARID1A, six articles were divided into two groups. Four articles focused on the effect of ARID1A gene mutation on OS of cholangiocarcinoma, combined HR was 3.84 (95% CI , 2.92–5.05). Significant heterogeneity was found ($I^2 = 63.2\%$, $p = 0.043$). Two articles focused on the effect of ARID1A expression on OS of cholangiocarcinoma and combined HR was 3.07 (95% CI , 1.65–5.71). Heterogeneity was not found ($I^2 = 0\%$, $p = 0.586$).

4. Publication bias analysis

Slight publication bias was detected by the Egger's test in HCC studies, but there was no publication bias according to Begg's test in this meta-analysis (Fig. 3).

5. Sensitivity analysis

To understand how each study on the influence of this meta-analysis, we conducted a sensitivity analysis. The result showed that no studies that have an impact on the pooled HR (Fig. 4). This confirmed the robustness of the meta-analysis.

Discussion

In our study, we estimated the effects of ARID1A mutation and expression on the prognosis of HCC and cholangiocarcinoma. The results showed that both HCC and cholangiocarcinoma patients with ARID1A mutation or low expression had significantly shorter OS. Our findings suggest that ARID1A may be considered as a potential prognostic biomarker for HCC and cholangiocarcinoma patients.

Genome sequencing finds there are many common mutated genes in HCC and cholangiocarcinoma, such as TP53, CTNNB1, ARID1A[15, 17–19]. ARID1A is considered to be a broad tumor suppressor. However, the exact mechanism by which ARID1A abnormality leads to increased risk of HCC and cholangiocarcinoma and decreases overall survival remains largely unknown. Existing studies suggest that subunits of the SWI/SNF complex, encoding the ATP-dependent chromatin remodelers, are frequently mutated in a wide variety of cancers and ARID1A mutations are frequently shown in SWI/SNF genes. Most ARID1A mutations are inactivated mutations, resulting in the loss of ARID1A expression[7]. Because of the absence of ARID1A, abnormal SWI/SNF complex leads to a defect in enhancer activity, which impairs differentiation programs and causes widespread dysregulation of gene expression, thus promoting tumor formation[34]. Furthermore, mutations and deletions of ARID1A contribute to the proliferation and migration of HCC[29, 35], and this situation also exists in the cholangiocarcinoma[25], which may lead to poor prognosis of patients suffering from HCC and cholangiocarcinoma. It is worth noting that the inactivation of ARID1A is significantly correlated with the activation of the PI3K/mTOR pathway, which is considered as a carcinogenic pathway by virtue of its role in cell proliferation and cell cycle control [36, 37]. This is consistent with our findings.

Our meta-analysis also integrated the clinicopathologic features of HCC patients. The results showed that expression of ARID1A was not related to sex, cirrhosis, histological differentiation, or HBV infection. However, low ARID1A expression in HCC was associated with tumor size. This further indicated that the low expression of ARID1A promoted cancer proliferation. Since only four studies included these clinical features, it is necessary to conduct more accurate detection of ARID1A expression and clinicopathological features in the future.

This study also has some limitations that cannot be neglected. Firstly, due to the number of included studies, there are not enough cases to adequately evaluate the relationship between ARID1A changes and OS with HCC and cholangiocarcinoma. Secondly, the included studies are retrospective cohort studies rather than randomized controlled studies (RCT), inevitable recall bias and selection bias still exist, which may lead to a less convincing conclusion. Owing to limited OS data, we only conducted a group of subgroup analyses. Finally, slight publication bias was detected by the egger's test in HCC studies, but there was no publication bias according to Begg's test, this may be caused by the low number of studies.

Conclusions

In summary, this meta-analysis provides evidence for the hypothesis that ARID1A mutation or low expression is associated with poor prognosis in patients with HCC or cholangiocarcinoma. Thus, ARID1A may be considered as a potential prognostic biomarker for HCC and cholangiocarcinoma patients. However, more detailed studies with more dependable data and larger sample sizes are needed to further clarify the prognostic role of ARID1A mutation and expression.

List Of Abbreviations

Hepatocellular carcinoma, HCC; AT-rich interactive domain 1A, ARID1A; Confidence interval, CI; Overall survival, OS; Newcastle-Ottawa Scale, NOS.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Study concept and design: TL, GXM, LJY; Search strategy: GXM, LJY; Selection criteria: ZQC, YFY, ZND; Study selection: GXM, LJY, ZRD; Data extraction: GXM, LJY, ZRD, SYY; Analyze the data: GXM, LJY, HCL, KXL; Quality Assessment: YCY, CCY. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow chart of literature selection.

Figure 2

A, Forest plots of associations between ARID1A mutation or low expression and OS in cholangiocarcinoma; B, Forest plots of associations between ARID1A mutation or low expression and OS in HCC.

Figure 3

A, B: Publication bias analysis of HCC; C, D: Publication bias analysis of cholangiocarcinoma.

Figure 4

Sensitivity analysis of HCC studies and cholangiocarcinoma studies.

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