Systematic Review and Meta-Analysis

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Prognostic value of ATPase family, AAA+ domain containing 2 expression in human cancers

A systematic review and meta-analysis

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Abstract

Background: ATPase family, AAA+ domain containing 2 (ATAD2) is also known as AAA+ nuclear coregulator cancer-associated protein or PRO2000. ATAD2 has been reported as a prognostic factor in different cancer types, but the association between ATAD2 high expression and survival is still unclear. Thereby, this meta-analysis was performed to evaluate the prognostic value of ATAD2 high expression in human cancers.

Methods: All of the studies included were retrieved from PubMed, EMBASE, and Cochrane Library electronic databases. The clinical outcomes were evaluated by calculating hazard ratio (HR) with their 95% confidence interval (CI).

Results: Thirteen studies including 2689 patients were eligible for this analysis. The pooled results showed that ATAD2 over-expression was significantly associated with shorter overall survival (OS) (HR = 2.32, 95% CI = 1.77–3.02), as well as shorter recurrence-free survival (RFS), disease-free survival (DFS), and disease-specific survival (DSS) (HR = 1.83, 95% CI = 1.51–2.23) among human cancers. Subgroup analyses for OS were implemented in terms of region, tumor type, and sample size and the results were coincident with overall pooled results. Begg funnel plot and Egger test showed the presence of publication bias for OS. Sensitivity analysis indicated that both results were not affected for removing any study.

Conclusion: ATAD2 would be likely to act as a prognostic biomarker for the patients of different cancer types and provide a guide on clinical treatment. Prospective clinical studies are needed to support these findings.

Abbreviations: 95% CI = 95% confidence interval, AR = androgen receptor, BC = breast cancer, CC = cervical cancer, CRC = colorectal cancer, DFS = disease-free survival, DSS = disease-specific survival, EC = endometrial cancer, ER = estrogen receptor, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, IHC = immunohistochemistry, LAC = lung adenocarcinoma, NOS = Newcastle–Ottawa Quality Assessment Scale, OC = ovarian cancer, OS = overall survival, RFS = recurrence-free survival, SCLC = squamous cell lung carcinoma.

Keywords: AAA+ domain containing 2, ANCCA, ATPase family, meta-analysis, PRO2000, prognostic value, survival

1. Introduction

AAA+ (ATPases associated with various cellular activities) proteins, an evolutionarily conserved family of enzymes, can change conformation of their substrate protein complexes.[1] ATPase family, AAA+ domain containing 2 (ATAD2) is a member of the AAA+ ATPase family.[2] In the Gene database, the ATAD2 is also known as AAA+ nuclear coregulator cancer-associated protein (ANCCA) or PRO2000. ATAD2 gene contains 2 AAA+ ATPase domains, which mediate protein multimerization and a bromodomain which is responsible for its binding to histones.[3–5] Because of the special function of the structure, ATAD2, as a coactivator of estrogen receptor (ER) and androgen receptor (AR), mediates the expression of E2 (ER-α and ER-β) and AR target gene in human breast and prostate cancer cells, respectively.[2,6,7] MYC is a oncogene that contributes to the malignancy of many aggressive cancers. In addition to participating in the regulation of the estrogen and androgen receptors pathways, ATAD2 has also been confirmed to be a MYC cofactor and high expression in several different human cancers.[8] Subsequently, it was reported that ATAD2 was over-expressed in various hormone-dependent or non-hormone-dependent cancers and played an important role in cancer cells proliferation, invasion, migration, and differentiation, such as estrogen-dependent tumors,[9–13] digestive system tumors,[14–16] lung adenocarcinoma,[17,21] and hepatocellular carcinoma.[18–20] Hence, the high expression of ATAD2 was possibly associated with poor prognosis in different cancer types.

In recent years, more and more investigators are devoted to the studies of prognostic significance of ATAD2 expression in human cancers, but the view is still unclear. So far, no systematic review has been reported in this field. Therefore, based on the existing reports, we first compiled this meta-analysis to systematically evaluate the prognostic impact of ATAD2 expression in human cancers.

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2. Materials and methods

2.1. Literature search

Using the electronic databases, PubMed, EMBASE, and Cochrane Library, 2 authors (H-JH and Q-YH) independently completed a comprehensive search for the articles relevant with this topic, ending on March 2, 2019. The inconsistencies on findings were resolved through discussing with a third reviewer. We performed the literature search by the listed keywords.

"ATAD2" or "ANCCA" or "PRO2000"; and "cancer" or "neoplasm" or "carcinoma" or "tumor". The reference of relative articles was manually screened to ensure that all were enrolled.

2.2. Literature selection

Inclusion studies needed to meet the following criteria: studies based on cancer patients; ATAD2 expression was detected from tumor tissue with immunohistochemistry (IHC) staining; clinical studies regarding prognostic impact of ATAD2 expression; Kaplan–Meier curve or the survival data including hazard ratio (HR) and 95% confidence interval (95% CI) were available; publication with a full paper in English. Studies were excluded according to the following criteria: conference abstracts, reviews, case reports, and comments; the samples of studies derived from cells lines or animals. All articles were screened independently by the 2 authors based on inclusion and exclusion criteria. When the studies were published by a same group, only the latest articles with the largest sample size were included. The inconsistencies on findings were resolved through discussing with a third reviewer.

2.3. Data extraction and quality assessment

Two authors (H-JH and Q-YH) independently extracted data from qualified studies that we screened and evaluated quality according to Newcastle-Ottawa Quality Assessment Scale (NOS). The scoring projects include the selection of the research population, comparability, and measurement of the outcome and the score range is 0 to 9 points. Scores equal to or higher than 6 out of 9 are regarded as qualified. The relevant details were extracted from each article as follows: name of First author, year of publication, cancer types, country, number of patients, detection method and staining site, cut-off value for high ATAD2 expression, percentage of ATAD2 expression, follow-up period, survival outcomes, methods of data extraction, and quality assessment score. The inconsistencies on findings were resolved through discussing with a third reviewer. Prognostic value of high ATAD2 expression were assessed by several different clinical outcomes, including overall survival (OS), recurrence-free survival (RFS), disease-free survival (DFS), and disease-specific survival (DSS). HR and 95% CIs were obtained directly from reported studies. For the articles containing only Kaplan–Meier curves, survival data were estimated by using Engauge Digitizer V 10.8 and spreadsheets that were provided by Tierney et al.[22] HR and 95% CIs were collected from multivariate analysis, besides 1 study,[9] of which the method of survival analysis was not reported.

2.4. Statistical analysis

The prognostic value of ATAD2 expression in human cancers was measured through meta-analysis. Pooled HR with 95% CIs was used to evaluate the correlation between ATAD2 expression, and OS, DFS, RFS, and DSS by using STATA 12.0 (StataCorp LP, College Station, TX). Subgroup analyses were implemented in terms of region, tumor type, and sample size. The chi-square test and I^2 metric were used to determine statistical heterogeneity. $I^2 > 50\%$ or $P < .1$ were regarded as significant heterogeneity and random effect model was used. If the results reversed, fixed-effect model was applied. The effect of single study on the pooled outcomes was assessed via sensitivity analysis which was used to analyze possible causes of heterogeneity. By using Begg funnel plot and Egger linear regression test, potential publication bias of the studies was evaluated. P value $< .05$ was regarded as statistically significant.

2.5. Ethics approval

All patients are not directly involved in the study, so ethical approval is not required.

3. Results

3.1. Eligible studies

A total of 170 articles were found from PubMed, Embase, and Cochrane Library. The process of selection was illustrated in Fig. 1. One hundred ten articles were retained after removing the duplicate records. We excluded 89 articles including some conference abstracts, reviews, case reports, comments, non-English studies, and studies related to animals or cells lines by reviewing the titles and abstracts, and some of them were unrelated to our study. The remaining 21 articles were reviewed in detail, and 8 articles were excluded due to publication reported by a same research group or insufficient data. Finally, 13 articles were identified as qualified in the meta-analysis.

3.2. Study characteristics

The main characteristics of all qualified studies were summarized in Table 1. These studies were reported since 2010. In our study, 9 different cancer types with 2689 patients were included[9–21] and the studies were completed in 4 different countries (including China, USA, Korea, and Norway). All ATAD2 expression levels in tumor tissue were detected by IHC staining and each study defined definite cut-off value to assess low or high ATAD2 expression. Unexpectedly, the ATAD2 expression of all of inclusion studies was more than 50%. Among 13 studies, OS, as a primary outcome of survival analysis, was applied in 11 studies[9–19] and was not described in the rest 2. The secondary outcomes including RFS, DFS, and DSS were applied in 6 studies with 7 effect sizes: RFS was evaluated in 3 studies; DFS was in 2 studies; DFS was in 2 studies. For the studies involving both multivariate and univariate analyses, HR with 95% CIs were obtained from multivariate analysis. The survival data from 12 studies were reported and only 1 was estimated from survival curve, which greatly ensured the reliability of the results. Since the NOS scores were equal to or more than 6, all of the studies included were of high quality.

3.3. ATAD2 as a prognostic factor for human cancers

The meta-analysis about the association between ATAD2 over-expression and prognostic value in human cancers is involved in 11 articles. High ATAD2 expression was significantly associated with shorter OS in human tumors (HR = 2.32, 95% CI = 1.77–3.02, P value $< .001$). Since heterogeneity test for the pooled

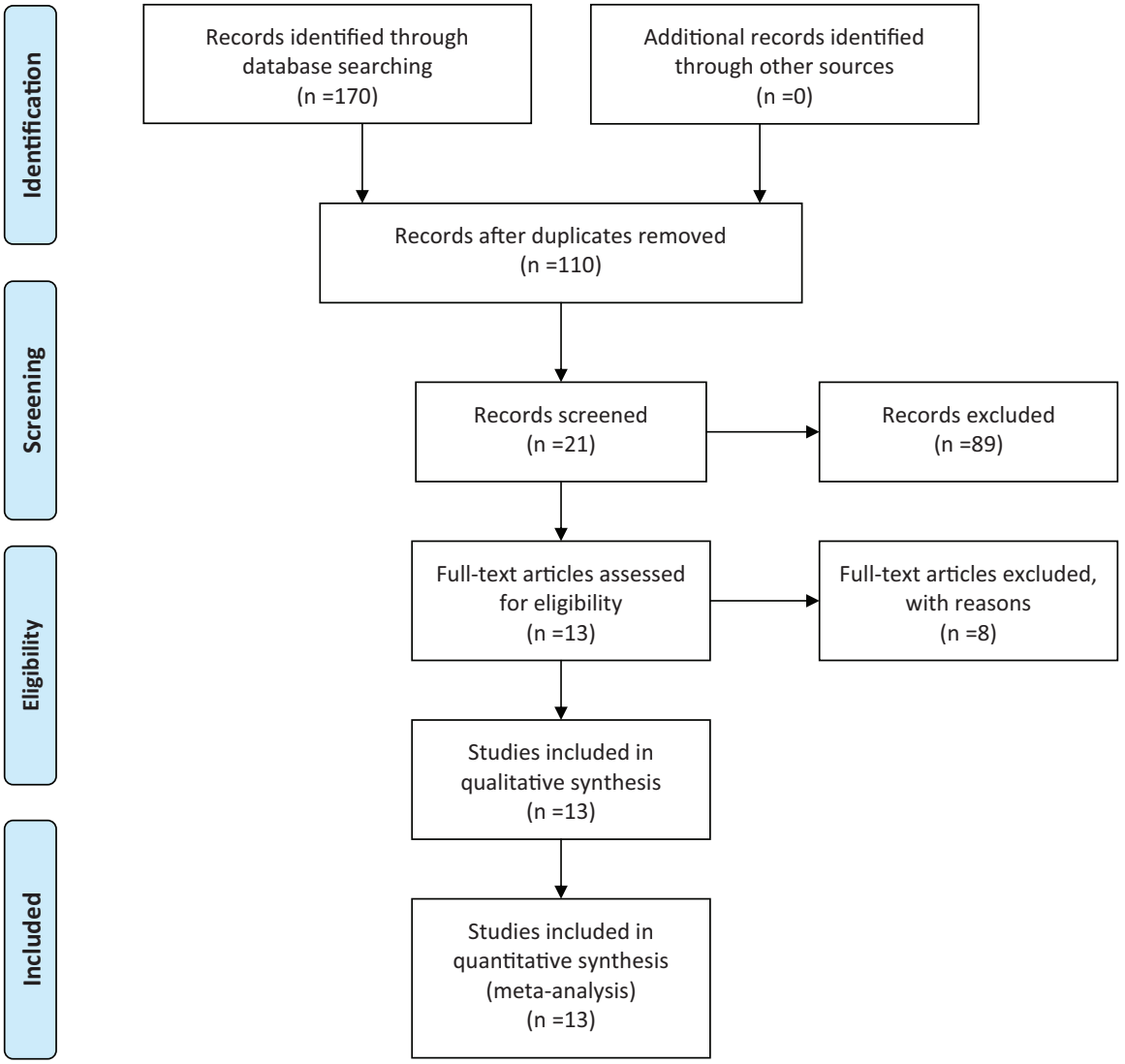

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Figure 1. Flowchart of screening relevant studies.

Table 1

Characteristics of studies included in this meta-analysis.

First author	Year	Cancer	Country	No of patients	Method staining	Cut-off	ATAD2 expression (%)	Median/follow-up time (mouth)	Survival analysis	Data extract	Score
Kalashnikova[9]	2010	BC	USA	225	IHC,N	≥26%	176/225 (78.0)	132	OS,RFS	Curve	8
Wan WN[10]	2014	OC	China	110	IHC,N	Index≥3	72/110 (65.5)	NR	OS (M)	Reported	7
Krakstad C[11]	2015	EC	Norway	564	IHC,N	Index≥3	283/564 (50.2)	NR	OS (M)	Reported	7
Shang P[12]	2015	EC	China	207	IHC,N	Index≥3	159/207 (76.8)	70 (9–78)	OS (M),DFS (M)	Reported	8
Zheng L[13]	2015	CC	China	135	IHC,N/C	Index≥5	96/135 (71.1)	NR	OS (M)	Reported	7
Luo Y[14]	2015	CRC	China	300	IHC	Index≥6	176/300 (58.7)	NR	OS (M)	Reported	6
Hou M[15]	2016	CRC	China	155	IHC,N	Index≥3	90/155 (58.1)	72	OS (M),DFS (M)	Reported	8
Zhang M[16]	2016	GC	China	166	IHC,N	Index>3	86/166 (51.8)	96	OS (M)	Reported	8
Zhang Y[17]	2013	LAC	China	143	IHC,N	H-score≥15	74/143 (51.7)	NR	OS (M,RFS (M)	Reported	7
Wu G[18]	2014	HCC	China	129	IHC,N/C	Index≥5	83/129 (64.3)	60	OS (M)	Reported	8
Huang J[19]	2016	HCC	China	221	IHC,N/C	≥0%	142/221 (64.3)	NR	OS (M)	Reported	6
Hwang HW[20]	2015	HCC	Korea	182	IHC,N	≥5%	119/182 (65.4)	120 (14–151.4)	RFS (M),DSS (M)	Reported	8
Wang D[21]	2016	SCLC	China	152	IHC,N	Index≥4	82/152 (54.0)	NR	DSS (M)	Reported	7

BC = breast cancer, C = cytoplasm, CC = cervical cancer, CRC = colorectal cancer, DFS = disease-free survival, DSS = disease-specific survival, EC = endometrial cancer, GC = gastric cancer, HCC = hepatocellular carcinoma, IHC = immunohistochemistry, LAC = lung adenocarcinoma, M = multivariate, N = nuclear, NR = not reported, OC = ovarian cancer, OS = overall survival, RFS = recurrence- free survival, SCLC = squamous cell lung carcinoma, semiquantitative H-score = staining intensities× staining distributions, staining index = staining intensity× proportion of positively stained tumor cells.

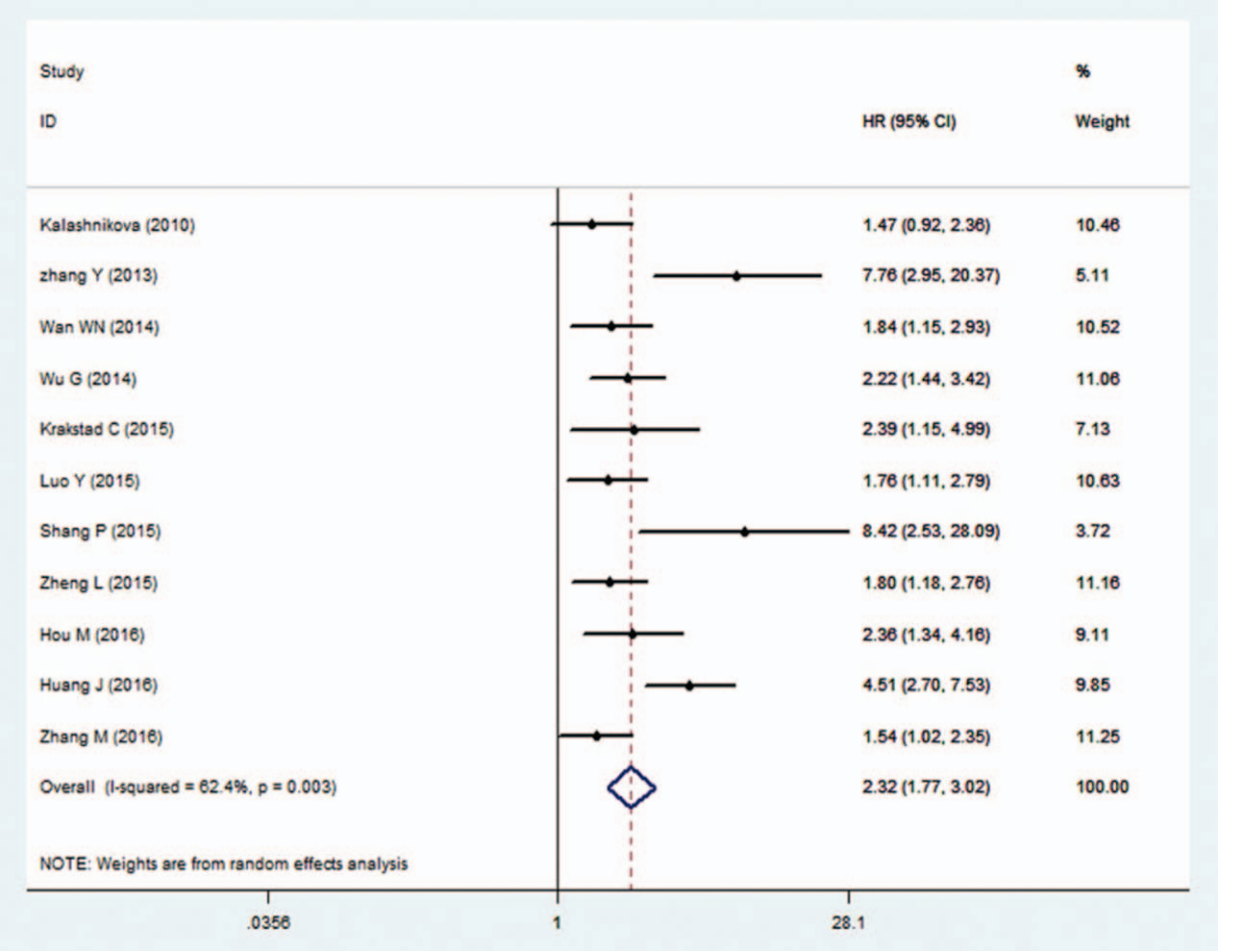

Figure 2. Forest plot of studies evaluating the association of ATAD2 expression and OS in different cancer types. ATAD2 = ATPase family, AAA+ domain containing 2, OS = overall survival.

results showed significant heterogeneity with $I^2 = 62.4\%$ and P value = .003, a random effect model was applied in our study (Fig. 2). Subgroup analyses were implemented in terms of region, tumor type, and sample size, and the results were illustrated in Table 2. The analysis results of region suggested the high ATAD2 expression was associated with shorter OS of cancer patients in both Asian and non-Asian countries (HR = 2.47, 95% CI = 1.81–3.36 and HR = 1.72, 95% CI = 1.10–2.69, respectively). However, compared with Asian countries, the heterogeneity of non-Asian subgroup significantly declined ($I^2 = 66.6\%$, $P = .002$ vs $I^2 = 16.2\%$, $P = .275$). The subgroup analysis by the tumor type indicated that ATAD2 over-expression was correlated with

Table 2

Subgroup analysis of studies included in the outcome of overall survival.

Analysis	No. of studies	No. of patients	HR (95% CI)	Heterogeneity	*P* value
Overall survival	11	2355	2.32 (1.77,3.02)	$I^2 = 62.4\%$, $P = .003$	<.001
Region					
Asian	9	1566	2.47 (1.81,3.36)	$I^2 = 66.6\%$, $P = .002$	<.001
Non-Asian	2	789	1.72 (1.10,2.69)	$I^2 = 16.2\%$, $P = .275$	.017
Tumors type					
Estrogen-dependent tumors	5	1241	2.01 (1.41,2.85)	$I^2 = 46.4\%$, $P = .113$	<.001
Hepatocellular carcinoma	2	350	3.12 (1.56,6.24)	$I^2 = 76.7\%$, $P = .038$	.001
Gastrointestinal tumors	3	621	1.78 (1.36,2.34)	$I^2 = 0.0\%$, $P = .501$	<.001
Lung adenocarcinoma	1	143	7.76 (2.96,20.37)	NA	<.001
Sample size					
≥200	5	1517	2.66 (1.55,4.55)	$I^2 = 74.7\%$, $P = .003$	<.001
<200	6	838	2.32 (1.77,3.02)	$I^2 = 49.8\%$, $P = .077$	<.001

95% CI = 95% confidence interval, HR = hazard ratio, NA = not applicable.

shorter OS in 4 different types of tumors: estrogen-dependent tumors (HR = 2.01, 95% CI = 1.41–2.85, and I^2 = 46.4%, P = .113), hepatocellular carcinoma (HR = 3.12, 95% CI = 1.56–6.24, and I^2 = 76.7%, P = .038), gastrointestinal tumors (HR = 1.78, 95% CI = 1.36–2.34, and I^2 = 0.0%, P = .501), lung adenocarcinoma (HR = 7.76, 95% CI = 2.96–20.37). The heterogeneity of the both subgroups including estrogen-dependent and gastrointestinal tumors was greatly lower than that of hepatocellular carcinoma. Likewise, no matter how many samples, the high ATAD2 expression was correlated with shorter OS of cancer patients (sample size ≥ 200: HR = 2.66, 95% CI = 1.55–4.55 and sample size < 200: HR = 2.32, 95% CI = 1.77–3.02) and the heterogeneity of the subgroup with few samples decreased (I^2 = 49.8%, P = .077).

Six studies with 7 effect sizes evaluated the correlation between ATAD2 over-expression and the secondary outcomes including RFS, DFS and DSS by using a fixed effect model (I^2 = 0.0%, P = .582). The results indicated that ATAD2 over-expression was greatly associated with poor RFS, DFS, and DSS in human tumors (HR = 1.83, 95% CI = 1.51–2.23). The pooled results were shown in Fig. 3.

3.4. Publication bias and sensitivity analysis

Begg funnel plot and Egger test were used to assess potential publication bias (Fig. 4). The results indicated the presence of publication bias for OS (Begg P value = .043, Egger P value = .010), yet no publication bias was found for the secondary outcomes including RFS, DFS, and DSS (Begg P value = .764, Egger P value = .182). As shown in Fig. 5, sensitivity analysis regarding removing any single study from all included studies indicated that had no significant effect on both the primary and secondary outcomes, confirming the pooled results of this study were robust.

4. Discussion

ATAD2 was reported to be involved in the occurrence and development of tumors in 2007.[2] Since then, a lot of relevant studies have been published, highlighting the expanding interest in the prognostic influence of high ATAD2 expression in different tumor types. To our knowledge, this is the first meta-analysis to assess the relationship between ATAD2 high expression and clinical outcomes. We included 2689 patients from 13 studies

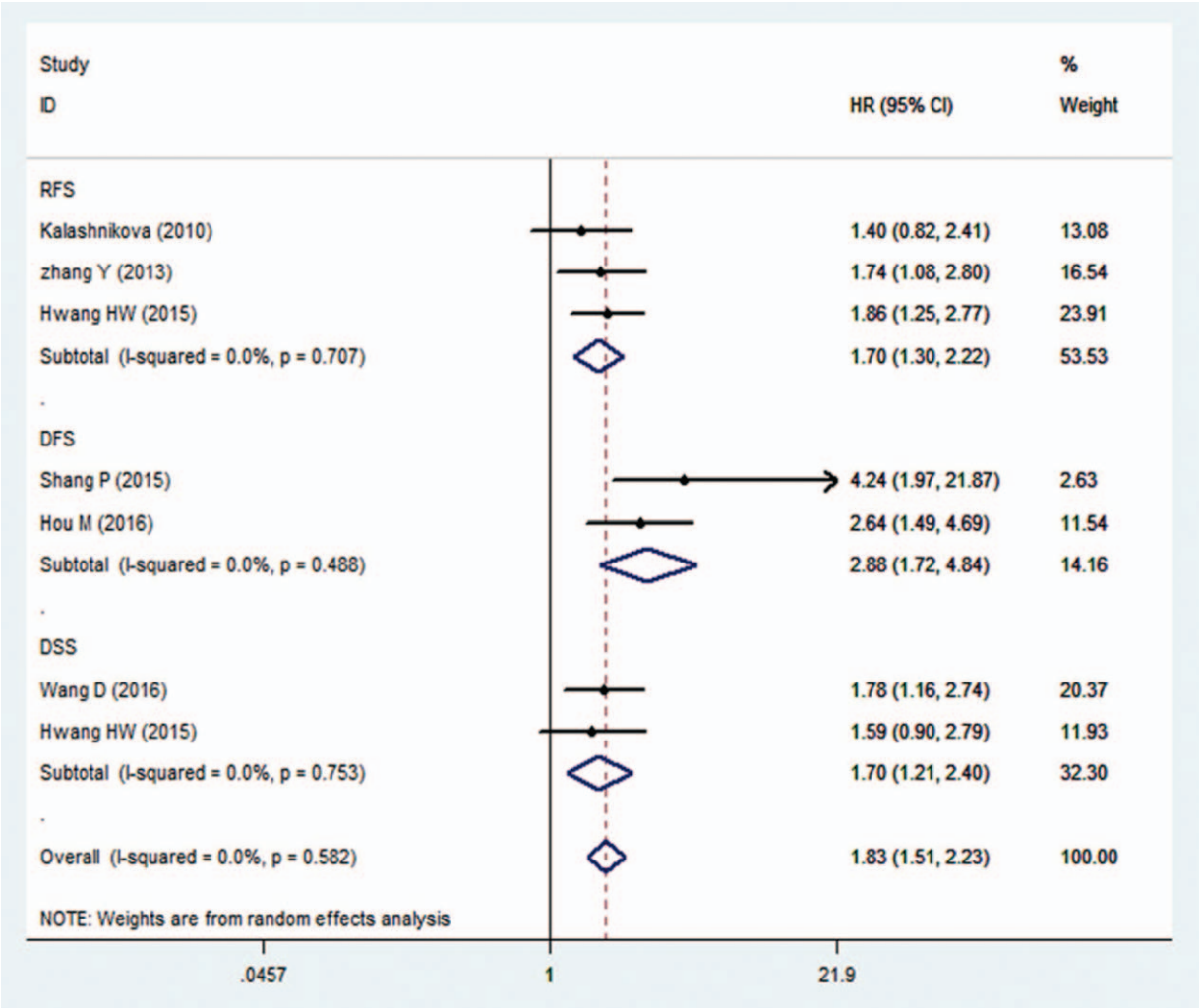

Figure 3. Forest plot of studies evaluating the association between ATAD2 expression and RFS, DFS, and DSS in different cancer types. ATAD2 = ATPase family, AAA+ domain containing 2, DFS = disease-free survival, DSS = disease-specific survival, OS = overall survival, RFS = recurrence-free survival.

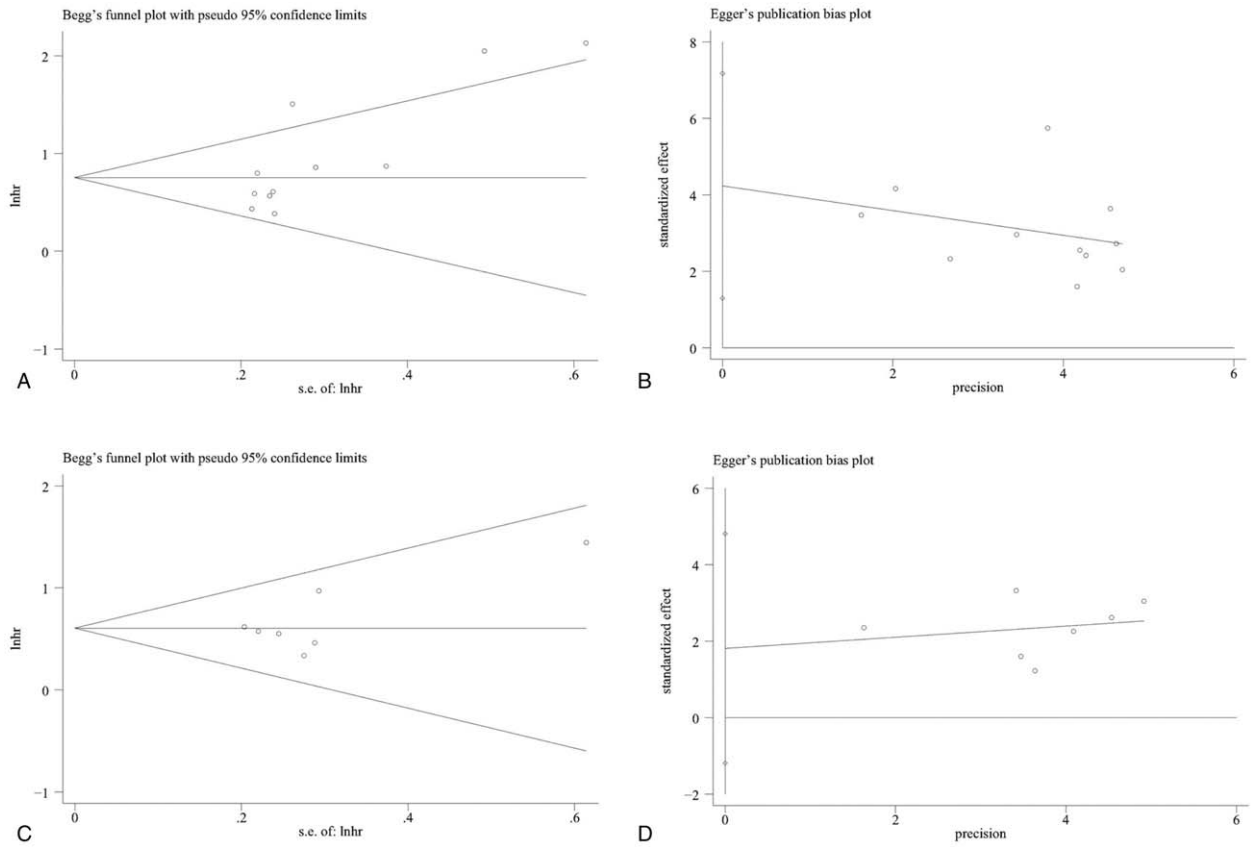

Figure 4. Begg funnel plot and Egger linear regression test for evaluating potential publication bias in the meta-analysis. Begg funnel plot for the effect of ATAD2 expression in OS (A). Egger linear regression test in OS (B). Begg funnel plot in RFS, DFS, and DSS (C). Egger linear regression test in PFS, DFS, and DSS (D). ATAD2 = ATPase family, AAA+ domain containing 2, DFS = disease-free survival, DSS = disease-specific survival, OS = overall survival, RFS = recurrence-free survival.

with 9 different cancer types in this meta-analysis. The pooled results showed that ATAD2 over-expression was significantly associated with shorter OS, RFS, DFS, and DSS. There was no significant heterogeneity in the pooled secondary outcomes, but it was observed in OS. Subgroup analyses were implemented to search the possible causes about heterogeneity. The subgroup analysis by the region indicated that the heterogeneity of non-Asian group significantly declined compared with Asian countries. Heterogeneity of the both subgroups including estrogen-dependent and gastrointestinal tumors was lower than that of hepatocellular carcinoma, and the heterogeneity of subgroup with few samples also decreased. The phenomenon suggested that heterogeneity of studies was likely to be caused by the differences of Region, tumor type, or sample size. Fortunately, most of survival data were directly extracted from multivariate analysis in the included studies, which greatly ensured the reliability of the results. The number of studies is so limited in the subgroup analysis that more available studies are needed to support the conclusion. However, we conducted the sensitivity analysis for the primary and secondary outcomes, which indicated that both results were not affected after removing any study. In addition, 2 vital causes cannot be ignored. On one hand, the cut-off values and scoring method used to define ATAD2 expression have no uniform standard, on the other hand, the testing environment of each study is quite different.

ATAD2 gene is located at chromosome 8q24 and encodes for a predicted protein of 1390 amino acids, of which molecular mass is 158.5 kDa. For many different types of tumors, the 8q24 is considered the most frequently amplified region.[23] The retinoblastoma protein pathway plays an important role in the control of cells proliferation. Therefore, deregulation of the retinoblastoma protein pathway or specific amplification of the ATAD2 locus may cause the high levels of ATAD2 in many human tumors. E2F target genes (such as MYC, cyclin E1, and EZH2) are a class of oncogenes, which usually amplify and over-express in human tumors. ATAD2 combines the E2F and MYC pathways, and involves in the development of aggressive tumor through enhancing the MYC-dependent transcription.[8,24] ATAD2 gene expression at protein level is likely to be enhanced by the AR and E2F1, indicating that ATAD2 is a direct target of AR and E2F1.[2,8] AR binding sequence and E2F DNA binding sites are respectively located at the distal enhancer of ATAD2 regulatory region and ATAD2 promoter sequence. So both AR and E2F1 may regulate human ATAD2 gene expression via binding with corresponding binding site.[8,25] ATAD2 over-expression is correlated with aggressive and proliferative tumor cells and appears to act as a driver of proliferation. It was reported that ATAD2 mainly expresses in G1/S phase of the cell cycle in tumor cells and is likely to be involved in DNA repair.[26,27] Furthermore, ATAD2 is upregulated in the S phase

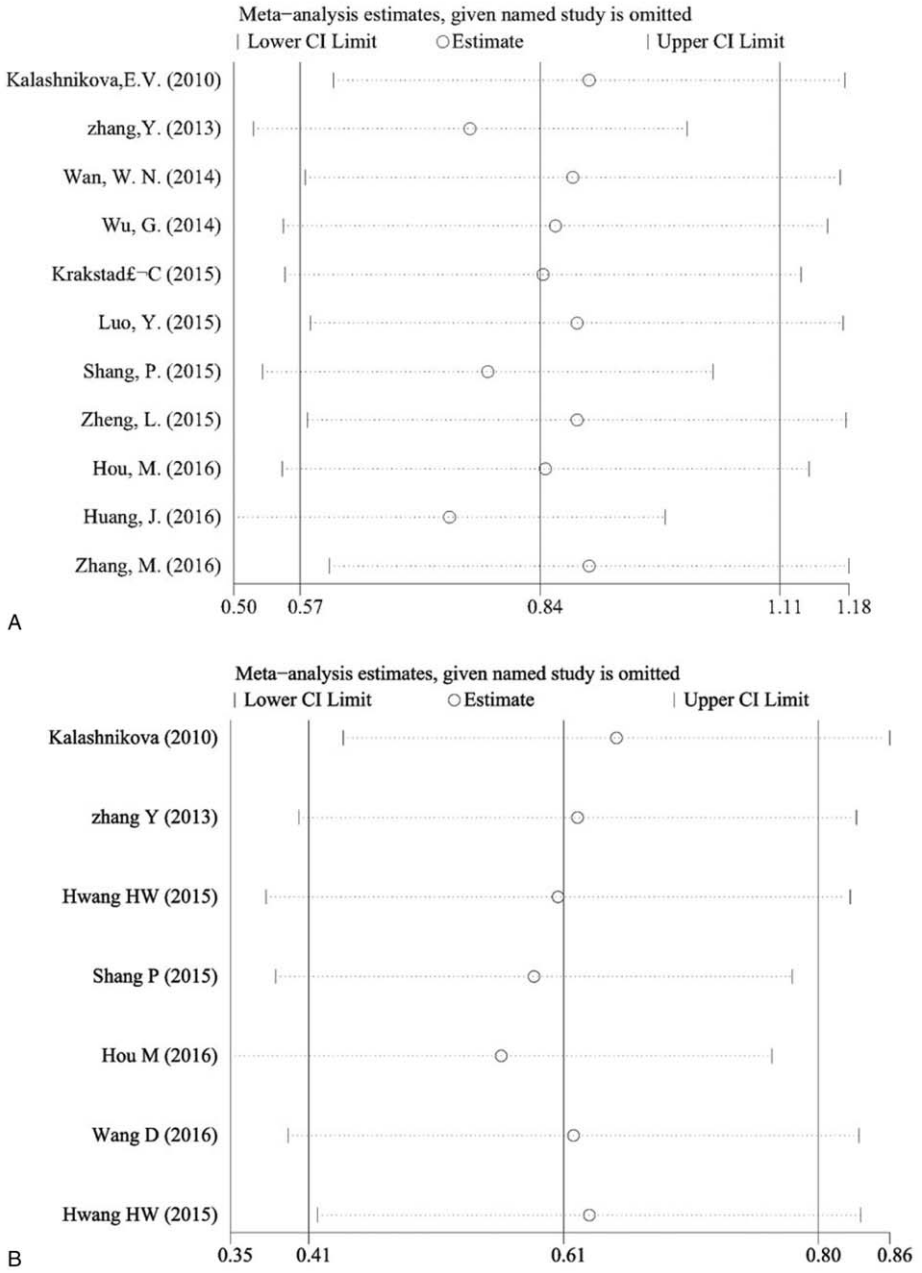

Figure 5. Sensitivity analysis of the meta-analysis. Included studies in OS (A). Included studies in RFS, DFS, and DSS (B). DFS = disease-free survival, DSS = disease-specific survival, OS = overall survival, RFS = recurrence-free survival.

and functions as a coactivator for E2F transcription factors to promote the transitions of G1 to S phase. High ATAD2 expression, together with some S-phase expressed multifunctional chromatin remodeling proteins, forms functional loops to drive tumor cells proliferation.[27] ATAD2 acts on upstream and basic cellular processes, and controls chromatin dynamics and genome transcriptional activities to enhance oncogenesis in a variety of cell types.[28]

As mentioned previously, although ATAD2 is induced by estrogen and acts as a coregulator for ER and AR, high expression is not limited to hormone-dependent tumors.[9–21] In 2007, investigators evaluated the prognostic value of 8 identified drug-regulated candidate genes on osteosarcoma therapy outcome, and the results showed that the event-free survival was significantly decreased in the patients with ATAD2 over-expression (6.3-fold), which demonstrated that ATAD2 gene was a valuable marker for the prediction of osteosarcoma therapy outcome.[29] Two years later, ATAD2 was reported that the expression levels were correlated with clinical outcomes of breast cancer patients.[8] Thereby, ATAD2 possibly participates in the progress of human tumors. After that ATAD2 over-expression was reported by other studies in different cancer types. In this study, multivariate analysis of Hwang et al[20] showed that ATAD2 over-expression was correlated with poor RFS, but was correlated with favorable DSS in hepatocellular carcinoma patients. However, Wang et al[21] showed significantly poor

DSS in squamous cell lung carcinoma patients, which suggested ATAD2 expression in different cancer types may cause different clinical outcomes. In addition, several aspects, including the assay conditions, the cut-off values, and scoring method used to define ATAD2 expression, are possible limiting factors and cannot be neglected. Other included studies showed obvious correlation between high ATAD2 expression and primary and secondary outcomes. Wan et al and Zheng et al[10,13] reported that knockdown of ATAD2 in tumor cell lines was found to reduce cells proliferation, invasion, and migration, which is consistent with a recent related study in colorectal cancer.[30]

According to our pooled results, the ATAD2 over-expression was significantly correlated with poor OS, RFS, DFS, and DSS, which suggested that both primary and secondary outcomes were indicative measurements for the prognostic significance of ATAD2 over-expression in human cancers, and no significant heterogeneity was observed in the analysis for RFS, DFS, and DSS. Based on the results of subgroup analyses for OS, the correlation between high ATAD2 expression and poor prognostic was consistent in Asian and non-Asian regions. The capacity that over-expression/knockdown of ATAD2 regulates the proliferation and migration to affect clinical outcomes establishes a therapeutic target for human cancers. Luo et al[14] showed that suppression of ATAD2 expression with siRNA could significantly inhibit growth in colorectal cancer cells. Lu et al[31] showed that suppression of ATAD2 expression in hepatocellular carcinoma cell lines decreased cells viability, migration, and invasion by using RNA interference. All of these views are in agreement with the literature published by Hong et al and Koo et al.[30,32] Furthermore, the bromodomain, a functional domain of ATAD2 gene, may be a potential epigenetic therapeutic target which is inhibited by small-molecule inhibitors. In the last few years, researchers attempt to develop bromodomain inhibitors about ATAD2 and have achieved preliminary effective results.[33–35] However, the development of effective therapeutic strategies against human cancers with high ATAD2 expression currently remains a challenging task. Therefore, this study is likely to provide effective evidence for the clinical treatments of progressive cancers.

This meta-analysis has several limitations. First, except English papers, the articles in other languages were not included. Second, the number of studies included for the pooled analysis was limited. Third, there was significant heterogeneity among the included studies, although subgroup analyses explain the reasons of heterogeneity, the difference including the cut-off values and scoring method used to define ATAD2 expression and the testing environment of each study, cannot be excluded. Finally, Begg funnel plot and Egger test have shown that there was publication bias among the studies for OS.

5. Conclusion

In a conclusion, this study showed a strong association between increased ATAD2 expression and clinical outcomes among human cancers. It is clear that ATAD2 is a novel prognosis biomarker for the patients of different cancer types, although prognostic feature among cancer types may be different. As mentioned above, more adequate clinical trials are demanded to support the prognosis value of ATAD2 over-expression, especially in a single cancer type. We first evaluate the relationship between increased ATAD2 expression and prognosis significance to establish its prognostic biomarker value for clinical treatment and look forward to improving the prognosis of cancer patients.

Author contributions

Conceptualization: Hua-Jing Han, Qi-Zhi Diao.
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Project administration: Hua-Jing Han, Qian-Yi Huang.
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Supervision: Hua-Jing Han.
Validation: Hua-Jing Han.
Visualization: Hua-Jing Han.
Writing – original draft: Hua-Jing Han.
Writing – review & editing: Hua-Jing Han.

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