Original Paper

Association Between Pretreatment Serum Apolipoprotein A1 and Prognosis of Solid Tumors in Chinese Population: A Systematic Review and Meta-Analysis

Jiayuan Wu^{a,b} Chuanmeng Zhang^c Gaohua Zhang^d Yufeng Wang^e
Zhanhui Zhang^e Wenmei Su^f Jun Lyu^a

^aClinical Research Center, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, ^bDepartment of Clinical Research, The Affiliated Hospital of Guangdong Medical University, Zhanjiang, ^cDepartment of Central Laboratory, People's Hospital of Taizhou, Taizhou, ^dHospital Office, People's Hospital of Gaozhou, Gaozhou, ^eSchool of Public Health, Guangdong Medical University, Zhanjiang, ^fDepartment of Oncology, The Affiliated Hospital of Guangdong Medical University, Zhanjiang, China

Key Words

Apolipoprotein A1 • Prognosis • Solid tumor • Chinese population • Meta-analysis

Abstract

Background/Aims: Serum apolipoprotein A1 (apoA1) has been reported to be abnormally expressed in several malignancies. However, the prognostic role of apoA1 in solid tumors is still controversial. We conducted this meta-analysis to obtain a more accurate evaluation of prognostic significance of apoA1 in Chinese patients with solid tumors. **Methods:** A comprehensive literature search of electronic databases was carried out up to August 2018. We included studies investigating the association between pretreatment serum apoA1 level and clinicopathological features, including survival outcomes, in solid tumors. Hazard ratios (HRs) and odds ratio (ORs) with 95% confidence intervals (CIs) were applied as effect size estimates. **Results:** A total of 13 studies and 8052 patients were included in our meta-analysis. Elevated level of pretreatment serum apoA1 was markedly associated with an improved OS (pooled HR = 0.608, 95% CI = 0.557 – 0.665, $P < 0.001$). The statistical significances were observed in all cancer types, including digestive system malignancies (pooled HR = 0.633; 95% CI = 0.550–0.727; $P < 0.001$), urinary system cancers (pooled HR = 0.471; 95% CI = 0.352–0.630; $P < 0.001$), nasopharyngeal cancer (pooled HR = 0.642; 95% CI = 0.538–0.766; $P < 0.001$) and non-small cell lung cancer (pooled HR = 0.526; 95% CI = 0.329–0.841; $P = 0.007$), but not in breast cancer (pooled HR = 0.573; 95% CI = 0.266–1.246; $P = 0.155$). Meanwhile, cancer patients with a low level of serum apoA1 suffered an unfavorable DFS (pooled HR = 0.714, 95% CI = 0.603 – 0.845, $P < 0.001$). Moreover, abnormal serum apoA1 was significantly correlated to tumor size (pooled OR = 0.640, 95% CI = 0.475 – 0.863, $P = 0.003$), tumor differentiation (pooled HR =

J. Wu, C. Zhang, and G. Zhang contributed equally to this work.

Jun Lyu
and Wenmei Su

Clinical Research Center, The First Affiliated Hospital of Xi'an Jiaotong University
Xi'an 710061, Shaanxi (China)
Tel. +86-029-85323614, E-Mail lujun2006@xjtu.edu.cn; suwenmei123@hotmail.com

0.724, 95% CI = 0.565 – 0.929, $P = 0.011$), and tumor stage (pooled HR = 0.493, 95% CI = 0.384 – 0.633, $P < 0.001$). **Conclusion:** Elevated level of pretreatment serum apoA1 was significantly associated with longer survival in patients with solid tumors. Pretreatment serum apoA1 could serve as a novel positive factor for malignant patient prognosis in Chinese population.

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Introduction

Metabolic reprogramming is one of the crucial hallmarks that distinguish cancer cells from normal cells and rewired to the demands of cell proliferation and survival [1]. This metabolic property of cancer cells not only meets the growth requirement of energy supplement but also supports the increased need of metabolic intermediates for the biosynthesis of cellular building blocks and signaling molecules [2]. A shift towards aerobic glycolysis with high glucose uptake even under sufficient oxygen is one of the most prominent characteristic of metabolic alterations in cancer. This phenomenon is called the “Warburg effect” [3]. Glucose was once considered as the major fuel, if not the only factor, that support tumor growth [4]. Malignant cells are now known to employ a wide variety of substrates to support their multiplication [5].

Lipids, also known as fats, are energy-rich molecules that serve as important energy sources for cellular metabolic processes when nutrients are limited. Lipids also function as structural components of all membranes and second messengers of cell signaling. Lipids in mammalian cells are mainly derived from *de novo* synthesis and food intake. Abnormality in lipid metabolism contributes to various metabolic diseases, such as cardiovascular diseases, obesity, hepatic steatosis, and diabetes [6-9]. Lipid metabolism is significantly enhanced during carcinogenesis, because most lipogenic enzymes are upregulated or activated in cancer cells [10]. Furthermore, lipids also promote cancer development, invasion, and metastasis, because highly proliferative malignant cells usually exhibit strong lipid avidity by increasing either the endogenous synthesis or the exogenous uptake of lipids [11]. Thus, targeting lipid metabolism reprogramming might be a promising strategy for anticancer therapy.

Extensive studies have shown that an abnormal level of lipid profile may influence carcinogenesis and is closely linked to tumor progression [12]. Cholesterol synthesis is raised in cancer cells compared with normal cells, as tumor cells require excess cholesterol and intermediates of the cholesterol biosynthesis pathway to sustain a high level of proliferation [13]. Cholesterol from non-hepatic peripheral tissues is transported through the hepatobiliary tract to the intestinal lumen. This process leads to fecal excretion, which is known as reverse cholesterol transport (RCT) mediated by high-density lipoprotein (HDL) at its initial step. As a major protein component of HDL, apolipoprotein A1 (apoA1) constitutes approximately 70% of the protein content of HDL particles, defining its size and shape, solubilizing its lipid component, and helping in RCT [14]. ApoA1 also functions as a cofactor of lecithin cholesterol acyltransferase (LACT) and participates in the formation of most plasma cholesteryl ester [15]. Accumulating evidence has revealed that serum apoA1 is inversely correlated with the risk of developing breast, colorectal, lung, and ovarian cancer [16-18]. Elevated apoA1 transgenic expression has shown a reduction of tumor burden and a survival benefit in mouse models of ovarian cancer and melanoma [19, 20]. The US Food and Drug Administration also approved the application of apoA1 along with transthyretin, transferrin, β 2-microglobulin, prealbumin, and CA125 for detecting early stage ovarian cancer, and these combined biomarkers test is known as OVA1® [21, 22]. Several publications have recently reported that low serum apoA1 level was associated with poor prognosis of solid tumors in Chinese population. However, several studies claimed that the connection was nonsignificant. Thus, the prognostic role of apoA1 in solid tumors has not yet been fully elucidated. Evidence from individual study is insufficient to conclude whether apoA1 can be

used as an effective predictive factor of prognosis. Hence, we conducted this meta-analysis to derive a more precise estimation of the role of apoA1 in the survival outcomes of patients with solid malignances.

Materials and Methods

Search strategy

This meta-analysis was strictly conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [23]. A comprehensive literature searching was performed in several computerized databases, such as PubMed, Embase, Web of Science, Science Citation Index, and Cochrane Library, as well as three Chinese databases, including China National Knowledge Internet (CNKI), Wanfang and Weipu databases. The key terms were used as follow: ("apolipoprotein A1" or "apoA1" or "apolipoprotein A-I" or "apo A-I") and ("cancer" or "tumor" or "carcinoma" or "neoplasm") and ("prognosis" or "survival" or "outcome"). The last search date was 1st Aug 2018. The references of the retrieved articles were also manually examined in order to discover additional relevant publications.

Study selection

Two researchers (WJY and ZCM) independently carried out the study selection, and all disagreements were resolved by discussion. Eligible studies for this meta-analysis had to meet the following criteria: 1) cohort studies investigated the association between pretreatment serum apoA1 levels and survival outcomes of solid tumors, such as overall survival (OS) and disease free survival (DFS); 2) studies originated from China and focused on Chinese population; 3) patients were divided into high apoA1 group and low (normal) apoA1 group, regardless of the cutoff value; 4) hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) could be extracted or estimated from the original data; and 5) publications were written in any language as full papers. Articles were excluded if they were: 1) case reports, reviews, conference abstracts, or nonoriginal articles; 2) articles of patients with hematological malignancies; 3) duplicate publications; and 4) basic research or animal experiments.

Data extraction and quality assessment

Two researchers (WYF and ZCM) independently extracted data from all enrolled studies, and any disagreement was resolved by a third person (WJY). The following data was collected: first authors, year of publication, study region, duration time, cancer type, follow-up period, primary treatment, sample size, cutoff value, analysis method, clinicopathological features, survival outcome, HR and the corresponding 95% CI, and quality score. In studies where the HR estimations were both provided in univariate and multivariate analyses, only the latter was applied to the data synthesis.

The quality of included studies was assessed by the Newcastle-Ottawa Scale (NOS) for cohort studies. The total score of NOS ranged from 0 to 9, and studies with at least seven scores were considered to be of high quality.

Statistical analysis

STATA 12.0 software (STATA Corp., College Station, TX) was adopted to perform the statistical analyses. Pooled HRs and their 95% CIs were applied to describe the association between apoA1 level and prognosis. HR values > 1 suggested an increased risk of poor survival, while HR values < 1 implied a survival benefit in patients with elevated serum apoA1 level. The result was considered statistically significant if the 95% CI did not overlap 1. Heterogeneity was qualitatively examined through the chi-squared *Q* test and quantitatively estimated using the *I*² metric (*I*² < 25%, no heterogeneity; *I*² = 25% – 50%, moderate heterogeneity; *I*² > 50%, extreme heterogeneity) [24]. When significant heterogeneity was observed (*P* < 0.05 or *I*² > 50%), a random-effects model was used to calculate the pooled HR estimation. Otherwise, a fixed-effects model was applied. Subgroup analyses and meta-regression analysis were performed to investigate the suspected factors for heterogeneity. Sensitivity analysis was conducted to evaluate the stability of the outcomes. Potential publication bias was quantitatively evaluated through Begg's and Egger's asymmetry tests [25], and was visually evaluated by funnel plots. If significant publication bias existed, trim and fill method was performed to validate the robustness of the meta-analysis results [26].

Results

Study characteristics

A total of 843 studies were identified from the initial electrical literature search, and then 732 papers were removed because of obvious irrelevance. After carefully screening the titles and abstracts, 78 papers were further excluded according to the inclusion and exclusion criteria. For the remaining potential candidate studies, 20 publications were removed after full text evaluation as follow: 11 articles that did not perform survival analysis; 5 papers that did not have sufficient data for HR calculation; 3 reports focused on other survival outcomes; and 1 study that originated from Caucasian population. Thus, 13 publications published from 2014 to 2018 were eligible for our meta-analysis [27-39]. The selection process is shown in Fig. 1.

The baseline characteristics of the included studies are summarized in Table 1. The included studies originated from Guangdong [27, 29-36, 39], Beijing [28], and Shanghai [37, 38]. A total of 8052 patients diagnosed with several kinds of cancers were including. These cancers included gastric cancer (GC) [27], bladder cancer [28], non small cell lung cancer (NSCLC) [29, 38], nasopharyngeal carcinoma (NPC) [30, 39], breast cancer [31, 32], colorectal cancer (CRC) [33], upper tract urothelial carcinoma (UTUC) [34], esophageal squamous cell cancer (ESCC) [35], renal cell carcinoma (RCC) [36], and hepatocellular carcinoma (HCC) [37]. Eleven studies were published in English [27-33, 35-37, 39], whereas the other two studies were in Chinese [34, 39]. One of these studies contained two cohorts [37]. Therefore, 14 cohorts were enrolled, and the sample sizes ranged from 99 to 1927. The outcomes of OS were reported in all 14 cohorts, and the end points of DFS were presented in 4 cohorts [30-32, 36]. Nine cohorts recruited patients with all disease stages (stage I – IV) [27, 29, 30, 32, 34-37], three cohorts included patients with advanced stage (including stage IV [33, 39], and stage IIB – IV [38]), one cohort contained patients with stage I – III [31], and the other one reported the data of patient with stage Tis – T1 [28]. The median follow-up time ranged from 20.3 months to 89 months, and even five studies did not report it. The primary treatments extremely varied among the 14 cohorts. These treatments included surgery [27, 28, 31, 32, 34-37], chemotherapy [33, 39], radiotherapy [30], and mixed treatment [29, 38]. The HRs and their 95% CIs in 11 cohorts were directly extracted from multivariate analyses, while those of the other cohorts were obtained from univariate analyses [27, 29, 31]. All cohort studies were of high quality and had seven scores or more in the quality criteria.

Fig. 1. Flow diagram of the study selection process. Abbreviation: HR, hazard ratio; OS, overall survival; DFS, disease free survival.

Table 1. Main characteristic of the eligible studies. ^a First of two cohorts in this study; ^b second of two cohorts in this study. Abbreviations: NR, none reported; GC, gastric cancer; NSCLC, non small cell lung cancer; NPC, nasopharyngeal carcinoma; CRC, colorectal cancer; UCUC, Upper tract urothelial carcinoma; ESCC, esophageal squamous cell cancer; RCC, renal cell cancer; HCC, hepatocellular carcinoma; OS, overall survival; DFS, disease free survival

Author (year)	Study region	Duration	Cancer type	Clinical stage	Primary treatment	Follow up (month)	Sample size	Cutoff, g/L (high/low)	Analysis method	Outcome	Language	Quality
Ma MZ (2018) [27]	Guangdong	2005–2010	GC	I ~IV	Surgery	Up to Mar 2017	1201	1.4 (246/955)	Univariate	OS	English	7
Shang ZH (2018) [28]	Beijing	2001–2011	Bladder cancer	Tis–T1	Surgery	Median 89 (10–154)	470	1.19 (114/326)	Multivariate	OS	English	9
Chen SL (2018) [29]	Guangdong	2008–2010	NSCLC	I ~IV	Mixed	Median 33	141	1.17 (85/56)	Univariate	OS	English	7
Chang H (2018) [30]	Guangdong	2010–2011	NPC	I ~IV	Radiotherapy	Median 66.2 (5.97–89.7)	1927	1.125 (1160/767)	Multivariate	OS, DFS	English	8
Li X (2017) [31]	Guangdong	2008–2011	Breast cancer	I ~III	Surgery	NR	1044	1.56 (197/847)	Univariate	OS, DFS	English	8
Lin XR (2017) [32]	Guangdong	2007–2011	Breast cancer	I ~IV	Surgery	Median 78	299	1.12 (244/55)	Multivariate	OS, DFS	English	7
Quan Q (2017) [33]	Guangdong	2005–2013	CRC	IV	Chemotherapy	Median 46 (1–131)	508	1.105 (254/254)	Multivariate	OS	English	8
Wen WJ (2016) [34]	Guangdong	2000–2012	UTUC	I ~IV	Surgery	Median 51.5 (11–159)	99	1.06 (61/38)	Multivariate	OS	Chinese	8
Wang XP (2016) [35]	Guangdong	2007–2009	ESCC	I ~IV	Surgery	Up to Oct 2015	210	1.21 (112/108)	Multivariate	OS	English	7
Guo SJ (2016) [36]	Guangdong	2000–2012	RCC	I ~IV	Surgery	Median 76.2 (50.0–107.5)	786	1.04 (579/207)	Multivariate	OS, DFS	English	7
Ma XL (2016) ^a [37]	Shanghai	2012	HCC	I ~IV	Surgery	Median 28.7 (0.6–37.0)	224	1.04 (82/142)	Multivariate	OS	English	7
Ma XL (2016) ^b [37]	Shanghai	2012–2013	HCC	I ~IV	Surgery	Median 20.3 (1.0–30.0)	219	1.04 (55/164)	Multivariate	OS	English	7
Shi H (2016) [38]	Shanghai	2009–2014	NSCLC	IIB–IV	Mixed	Up to Aug 2015	117	1.2 (67/50)	Multivariate	OS	Chinese	7
Jiang R (2014) [39]	Guangdong	2003–2009	NPC	IV	Chemotherapy	Up to Dec 2013	807	1.065 (549/258)	Multivariate	OS	English	7

Association between apoA1 and prognosis

The main results of this meta-analysis on the association between apoA1 and prognosis are listed in Table 2. We applied a fixed-effects model to pool the HRs because of the absence of significant heterogeneity ($I^2 = 19.3\%$, $P_h = 0.244$). The combined analysis of 14 cohorts in 13 studies showed that increased apoA1 level was significantly associated with improved OS (pooled HR = 0.608, 95% CI = 0.557–0.665, $P < 0.001$, Fig. 2). When subgroup analysis was conducted based on the cancer types, the overall results revealed that elevated serum apoA1 level significantly resulted in longer OS in patients with digestive system malignancies (i. e., GC, CRC, ESCC, and HCC; pooled HR = 0.633, 95% CI = 0.550–0.727, $P < 0.001$, fixed effects), urinary system cancers (i. e., bladder cancer, UTUC, and RCC; pooled HR = 0.471, 95% CI = 0.352–0.630, $P < 0.001$, fixed effects), NPC (pooled HR = 0.642, 95% CI = 0.538–0.766, $P < 0.001$, fixed effects), and NSCLC (pooled HR = 0.526, 95% CI = 0.329–0.841, $P = 0.007$, random effects), but this finding was not observed in patients with breast cancer (pooled HR = 0.573, 95% CI = 0.266–1.246, $P = 0.155$, random effects). In the subgroup analyses of clinical stage, higher apoA1 level was still obviously related to better OS for stage I – IV (pooled HR = 0.596, 95% CI = 0.521–0.680, $P < 0.001$, fixed effects), and advanced stage (i. e., stage IV and IIB – IV; pooled HR = 0.626, 95% CI = 0.536–0.731, $P < 0.001$, fixed effects), but not for early stage (i. e., stage I – III and Tis – T1, pooled HR = 0.539, 95% CI = 0.246–1.181, $P = 0.123$, random effects). Moreover, significant association between apoA1 level and OS was found in patients who underwent surgery (pooled HR = 0.596, 95% CI = 0.53–0.688, $P < 0.001$, fixed effects), chemotherapy (pooled HR = 0.626, 95% CI = 0.536–0.731, $P < 0.001$, fixed effects), radiotherapy (pooled HR = 0.646, 95% CI = 0.474–0.880, $P = 0.006$, random effects), or mixed treatment (pooled HR = 0.526, 95% CI = 0.329–0.841, $P = 0.007$, random effects). Furthermore, the results did not markedly change when the subgroup analyses were conducted based on the study region, cutoff value, sample size, and analysis method.

Four studies comprising 4045 patients reported the primary endpoint of DFS, and the overall outcome indicated that the upregulation of serum apoA1 was associated with an extended DFS (pooled HR = 0.714, 95% CI = 0.603–0.845, $P < 0.001$, fixed effects, Fig. 3), and significant heterogeneity did not exist ($I^2 = 32.0\%$, $P_h = 0.221$).

Table 2. Pooled and subgroup analysis of main results for the meta-analysis. Digestive system malignancies included gastric cancer, colorectal cancer, esophageal squamous cell cancer, and hepatocellular carcinoma. Urinary system cancers included bladder cancer, upper tract urothelial carcinoma, and renal cell cancer. Early stage included Stage I~III, and Stage Tis~T1. Advanced stage included Stage IV and Stage IIIB~IV.. Abbreviations: P_z denotes P value for statistical significance based on Z test; P_h denotes P value for heterogeneity based on Q test; P_m denotes P value for statistical outcome based on multivariate meta-regression analysis. HR, hazard ratio; CI, confidence interval; NPC, nasopharyngeal carcinoma; NSCLC non small cell lung cancer

Categories	Cohort (case)	Model	HR (95% CI)	Z	P_z	Heterogeneity I^2	P_h	P_m
Overall survival (OS)	14 (8052)	Fixed	0.608 (0.557~0.665)	10.97	< 0.001	19.3%	0.244	
Study region								0.782
Guangdong	10 (7022)	Fixed	0.626 (0.565~0.694)	8.94	< 0.001	5.9%	0.387	
Others	4 (1030)	Fixed	0.558 (0.468~0.666)	6.45	< 0.001	43.6%	0.150	
Cancer type								0.980
Digestive system	5 (2362)	Fixed	0.633 (0.550~0.727)	6.46	< 0.001	0.0%	0.435	
Urinary system	3 (1355)	Fixed	0.471 (0.352~0.630)	5.08	< 0.001	18.2%	0.294	
NPC	2 (2734)	Fixed	0.642 (0.538~0.766)	4.91	< 0.001	0.0%	0.961	
Breast cancer	2 (1343)	Random	0.573 (0.266~1.234)	1.42	0.155	63.8%	0.096	
NSCLC	2 (258)	Random	0.526 (0.329~0.841)	2.69	0.007	70.1%	0.068	
Clinical stage								0.743
Stage I ~IV	9 (5106)	Fixed	0.596 (0.521~0.680)	7.63	< 0.001	23.0%	0.239	
Early stage	2 (1514)	Random	0.539 (0.246~1.181)	1.54	0.123	78.2%	0.032	
Advanced stage	3 (1432)	Fixed	0.631 (0.556~0.716)	7.16	< 0.001	0.0%	0.946	
Primary treatment								0.955
Surgery	9 (4552)	Fixed	0.596 (0.517~0.688)	7.10	< 0.001	34.6%	0.141	
Chemotherapy	2 (1315)	Fixed	0.626 (0.536~0.731)	5.90	< 0.001	0.0%	0.771	
Radiotherapy	1 (1927)	Random	0.646 (0.474~0.880)	2.77	0.006	—	—	
Mixed	2 (258)	Random	0.526 (0.329~0.841)	2.69	0.007	70.1%	0.068	
Cut-off value								0.589
≥ 1.1 g/L	9 (5917)	Fixed	0.619 (0.558~0.688)	8.96	< 0.001	36.1%	0.130	
< 1.1 g/L	5 (2135)	Fixed	0.581 (0.492~0.687)	6.35	< 0.001	0.0%	0.526	
Analysis method								0.834
Univariate	3 (2386)	Random	0.621 (0.420~0.917)	2.39	0.017	64.4%	0.060	
Multivariate	11 (5666)	Fixed	0.595 (0.538~0.657)	10.16	< 0.001	0.0%	0.480	
Sample size								0.230
≥ 500	6 (6273)	Fixed	0.651 (0.583~0.727)	7.60	< 0.001	0.0%	0.829	
< 500	8 (1779)	Fixed	0.538 (0.464~0.624)	8.16	< 0.001	29.3%	0.194	
Disease free survival (DFS)	4 (4045)	Fixed	0.714 (0.603~0.845)	3.92	< 0.001	32.0%	0.221	

Association between apoA1 and clinicopathological parameters

The correlations of apoA1 with clinicopathological features of solid tumors are presented in Table 3. Four cohorts with 1011 patients reported the relationship between serum apoA1 and tumor size, and the pooled outcome showed that low apoA1 level was related to larger tumor size (pooled OR = 0.640, 95% CI: 0.475–0.863, $P = 0.003$, fixed effects). The correlation of serum apoA1 and tumor differentiation was reported in 5 studies with 1563 participants, and the conjoined result declared that decreased apoA1 level was positively correlated with poor histological grade (pooled OR = 0.724, 95% CI: 0.565–0.929, $P = 0.011$, fixed effects). Four studies enrolling 2425 cases exhibited the connection of apoA1 and tumor stage, and a significant association was found between low apoA1 level and advanced tumor stage (pooled OR = 0.493, 95% CI: 0.384–0.633, $P < 0.001$, fixed effects). However, serum apoA1 was not associated with age (pooled OR = 1.107, 95% CI: 0.951–1.289, $P = 0.191$, fixed effects), T stage (pooled OR = 0.746, 95% CI: 0.429–1.297, $P = 0.299$, random effects), lymph node metastasis (pooled OR = 0.785, 95% CI: 0.485–1.270, $P = 0.323$, random effects), and distant metastasis (pooled OR = 0.491, 95% CI: 0.179–1.346, $P = 0.167$, random effects).

Sensitivity analysis and meta-regression analysis

The overall HR estimates for OS (Fig. 4A) or DFS (Fig. 4B) did not significantly change after the sequential omission of each single cohort. This phenomenon indicated that no individual cohort influenced the pooled results.

Fig. 2. Forest plots of the association between serum apolipoprotein A1 and overall survival. Abbreviation: HR, hazard ratio; CI, confidence interval.

Fig. 3. Forest plots of the association between serum apolipoprotein A1 and disease free survival. Abbreviation: HR, hazard ratio; CI, confidence interval.

Table 3. Meta-analysis of apolipoprotein A1 levels and clinicopathological parameters in solid tumors. Notes: All pooled HRs were calculated from fixed-effect model except for cells marked with (random ^R). Abbreviations: P_h denotes P value for heterogeneity based on Q test; P denotes P value for statistical significance based on Z test

Categories	Studies (no. of patients)	OR (95% CI)	I ² (%)	P _h	Z	P
Age	7 (3541)	1.107 (0.951~1.289)	0.0%	0.587	1.31	0.191
Tumor size	5 (1128)	0.640 (0.475~0.863)	0.0%	0.588	2.93	0.003
Differentiation	5 (1563)	0.724 (0.565~0.929)	0.0%	0.413	2.54	0.011
T stage	4 (2888)	0.746 (0.429~1.297) ^R	85.3%	< 0.001	1.04	0.299
Tumor stage	4 (2425)	0.493 (0.384~0.633)	0.0%	0.587	5.56	< 0.001
Lymph node metastasis	4 (2198)	0.785 (0.485~1.270) ^R	57.1%	0.072	0.99	0.323
Distant metastasis	2 (1593)	0.491 (0.179~1.346) ^R	85.0%	0.010	1.38	0.167

Fig. 4. Sensitivity analysis of this meta-analysis. (A) Sensitivity analysis for overall survival. (B) Sensitivity analysis for disease free survival.

We performed meta-regression analysis to investigate the potential source of heterogeneity among studies for OS. The results listed in Table 2 demonstrated that the study region ($P = 0.782$), cancer type ($P = 0.980$), clinical stage ($P = 0.743$), primary treatment ($P = 0.955$), cutoff value ($P = 0.589$), analysis method ($P = 0.834$) and sample size ($P = 0.230$) did not contribute to the source of heterogeneity for OS. Moreover, we did not conduct meta-regression analysis concerning the outcome of DFS due to the insufficient number of literatures.

Publication bias

Both Begg's and Egger' tests suggested a potential publication bias with regard to the pooled outcome of OS (Begg's test, $P = 0.021$; Egger' test, $P = 0.005$), and the funnel plot also showed a certain degree of apparent asymmetry (Fig. 5A). However, the trim and fill analysis (no new studies added) showed no indication of publication bias. This phenomenon suggested that the results were robust and reliable. Moreover, Begg's test ($P = 0.308$), Egger' test ($P = 0.235$) and trim and fill method (no new studies added) showed no significant publication bias concerning the overall outcome of DFS (Fig. 5B).

Fig. 5. Funnel plots assessing the potential publication bias of the included studies. (A) Funnel plot of publication bias for overall survival. (B) Funnel plot of publication bias for disease free survival.

Discussion

ApoA1 is a vital mediator of plasma cholesterol transport and cellular cholesterol homeostasis. This molecule is primarily synthesized by the liver and intestine, and exists transiently in lipid-poor form. Serum apoA1 is generally included as part of the routine lipid test panel at admission and before treatment in Chinese hospitals. Thus, this biomarker is a convenient and reproducible laboratory parameter. In addition to simply serving as a shuttle of cholesterol cargo during RCT, an expanded range of physiological functions of apoA1 have been described, including anti-inflammatory, anti-apoptotic, anti-parasitic, anti-bacterial, anti-viral, and anti-oxidant activities [40]. Chronic inflammation, infection, oxidative stress, and lipids have been related to tumorigenesis [41-43]. Given the beneficial role of apoA1 against atherogenic process and cardiovascular disease, apoA1 may also be protective against cancer. Numerous studies have associated the serum levels of apoA1 with the risk of developing a broad spectrum of cancers [44]. However, the prognostic value of serum apoA1 in solid tumors remained ambiguous. Thus, we performed this first meta-analysis to investigate the prognostic significance of serum apoA1 based on a data synthesis of 13 studies involving 8052 Chinese patients with various cancers. High serum apoA1 level predicted an improved OS and DFS in solid tumors, which suggested that apoA1 might serve as a positive prognostic biomarker for solid tumors. Although publication bias and sensitivity analysis have confirmed the robustness and reliability of the meta-analysis outcomes, different baseline characteristics of individual studies might lead to inter-study heterogeneity. We performed meta-regression analysis using the factors of study region, cancer type, clinical stage, primary treatment, cut-off value, analysis method, and sample size. However, none of these factors could complain the heterogeneity of OS.

Despite the robustness of the pooled results, the findings of this research should be interpreted with caution. When subgroup analysis of OS was conducted based on the cancer type, no statistical significance was found in the pooled results from patients with breast cancer, which indicated that the function of apoA1 might be tissue specific. One of the two studies that reported the association between serum apoA1 and OS in breast cancer collected 299 patients with stage I – IV and exhibited an obvious correlation [32]. The other study employed 1044 cases with stage I – III and obtained a nonsignificant relationship [31]. Thus, the inconsistencies between these studies were possibly due to the bias of sample selection and sample size. Moreover, numerous reports have focused on the role of apoA1 in breast cancer, but extremely diverse conclusions were drawn. A prospective study based on 7557 subjects [45] declared that the serum level of apoA1 was inversely associated with breast cancer risk, contrary to a recent publication by Martin [46]. Furthermore, a study has indicated that breast cancer cells with elevated apoA1 level were more sensitive

to chemotherapy than cells with lower apoA1 level [47]. By contrast, Hodgkinson [48] demonstrated that high apoA1 level contributed to chemotherapy resistance in breast cancer tissue with positive estrogen receptor (ER) expression. These conflicting results might be attribute to the difference in study populations and suggested that the impact of apoA1 on breast cancer might be related to ER expression. Therefore, the role of apoA1 in breast cancer remains controversial. Similarly, when the tumor stage was classified, no statistical significance was found in cancer patients with early stage (stage I – III and stage Tis – T1). Given that only two studies with 1514 cases were enrolled based on this subgroup, more well-designed studies are warranted to explore the real effect.

To verify the prognostic role of apoA1 on malignant tumors, we further analyzed the correlation between apoA1 level and clinicopathological features that may affect survival outcomes. The synthesized data suggested that decreased level of serum apoA1 was significantly correlated with some phenotypes of tumor progression, such as larger tumor size, poor histological grade, and advanced clinical stage. All these aggressive tumor behaviors have been documented to be independent factors related to tumor progression and compromise survival outcome [49, 50]. Herein, apoA1 played an important role in the inhibition of tumor progression through different pathways. Thus, this molecule contributes to better survival in malignant patients. Therefore, cancer patients with large tumor size, poor histological grade, or advanced clinical stage may primarily benefit from serum apoA1 evaluation to make clinical decisions.

The exact mechanisms of apoA1 anti-tumor activity remain unclear, but are undoubtedly multifactorial. First, apoA1 has been proved to negatively alter tumor-permissive features of tumor microenvironment through multiple pathways. These pathways include but are not limited to the following: suppressing the increase in myeloid-derived suppressor cells to decrease tumor volume [51]; reducing the matrix metalloproteinase-9 protein level and activity to inhibit tumor metastasis [52]; increasing the recruitments of tumor cell killing macrophages and CD8 T cells [53]; reducing the level of surviving, a anti-apoptotic protein, responsible for tumor regression [54]. Second, apoA1 and apoA1 mimetic peptides can bind pro-inflammatory or pro-angiogenic phospholipids, such as lysophosphatidic acid. Moreover, these peptides can subsequently clear the phospholipids from the blood, thereby controlling cell proliferation in tumor growth [55]. Third, apoA1 affects the innate and adaptive arms of the immune system to suppress tumor-related angiogenesis, and inversely influences the migration of tumor cells. ApoA1 induces the conversion of tumor-associated macrophages from a pro-tumor M2 phenotype to an anti-tumor M1 phenotype. This process aids in cancer rejection [56]. Moreover, apoA1 also inhibits inflammation which has been inferred to participate in tumor metastasis [57].

Some potential limitations should be clarified in this meta-analysis. First, several individual HRs were obtained from univariate analysis, which have not adjusted the confounding factors and might overestimate the effect size [58]. Second, due to no acknowledged threshold, the cut-off values for defining “high” level of apoA1 were extremely different among the included studies, which might affect the availability of serum apoA1 as a prognostic biomarker in malignances. Third, the fact that studies with positive results tended to be published than works with null or negative outcomes, might lead to reporting bias and potentially exaggerate the overall outcomes. Fourth, the present meta-analysis concentrated on the Chinese population, and the results may not be able to apply to other populations. Fifth, our meta-analysis focused on pretreatment level of serum apoA1, and the clinical significance of posttreatment level, which reflects the dynamic variance of apoA1 level during tumor progression, is still unclear. Finally, the present meta-analysis only provided evidence for correlation study, which could not be simply interpreted as causal relationship.

Conclusion

In conclusion, this meta-analysis of currently available evidences supports the notion that elevated level of pretreatment serum apoA1 is significantly associated with improved prognosis in Chinese patients with solid tumors. Serum apoA1 could serve as a reliable, convenient, and low-cost biomarker for predicting the prognosis and tumor progression of solid tumors in Chinese population because of its availability as a blood routine test in daily clinical practice. In future, more experiments and clinical trials with well designs and large samples are required to verify and strengthen the prognostic significance of apoA1 in malignancies.

Acknowledgements

This study was supported by National Natural Science Foundation of China (No. 81702270), and Guangdong Province Science and Technology Development of Special Funding Support (No. 2016A020215151).

Disclosure Statement

The authors declare no conflicts of interest.

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