The impact of Renin-angiotensin system blockers on lung cancers prognosis: A prisma-compliant systematic review and meta-analysis.

Ning Wang, Jia Liu, Wenting Wang, Jinguang Qin, Dianjie Lin*

The Olympic Mid Road, Lixia District Jinan Shandong, China

Abstract

Background and objective: The impact of antihypertensive medications angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on the clinical outcomes of lung cancer patients remains controversial. This meta-analysis was conducted to investigate the association between ACEIs/ARBs usage and survival of lung cancer patients.

Methods: Eligible studies were identified by searching Pubmed, Embase and Cochrane library up to February, 2017. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for the effect of ACEIs/ARBs on survival of lung cancer. Heterogeneity and sensitivity were also analyzed.

Results: We finally included 9 eligible studies (8 articles) with the total number of 29,156 patients in this meta-analysis. Our results showed that ACEIs/ARBs usage was associated with favorable overall survival (OS) (HR, 0.86; 95% CI, 0.76–0.98) in lung cancer patients. Moreover, the significant association was found in subgroup of advanced clinical stage (IIIb to IV) (HR, 0.77; 95% CI, 0.64-0.92) and non-small cell lung carcinoma (NSCLC) (HR, 0.78; 95% CI, 0.65–0.93). However, no significant association was revealed between ACEIs/ARBs usage and progression-free survival (PFS) (HR, 0.84; 95% CI, 0.70–1.02).

Conclusions: ACEIs/ARBs statistically significantly prolong OS of lung cancer patients, especially in advanced clinical stage or patients with NSCLC. However, it has no demonstrable impact on PFS.

Keywords: Renin-angiotensin system blockers, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, Lung cancer, Survival, Meta-analysis.

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Introduction

Lung cancer is the leading cause of cancer death among men and the second leading cause of cancer death (after breast cancer) among women worldwide, responsible for an estimated 1.6 million deaths a year [1]. Despite of the advances in diagnosis and treatment in recent years, the prognosis of lung cancer patients is still unsatisfactory [2]. In order to further palliate symptoms and prolong survival time, significant efforts have been taken to seek potentially effective agents. Recently, increasing attention has been paid to renin-angiotensin system blockers (RASBs) as potential factors influencing lung cancer progression and mortality [3,4].

The renin-angiotensin system (RAS) has been found associated with tumor growth and its key signaling molecule is angiotensin II (Ang II). The tumor-promoting effect of Ang II seems to be mediated by a G-protein coupled receptor known as angiotensin type 1 receptor (AT1R), the expression of which has been reported to be increased in cancer tissues [5,6]. Indeed, a positive correlation has been found between the expression level of AT1R in tumor tissues and the clinical stage of the cancer. Namely, higher level has been detected in advanced stage [7]. Although the concrete mechanism behind the tumor-promoting process of Ang II remains unclear, several relevant aspects have been discussed: (1) Ang II binds with AT1R and then the G-protein pathway is activated, followed by enhanced expression of cell growth-related factors, such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF1) and basic fibroblast growth factor (bFGF) [8-10]. These factors can promote tumor proliferation and angiogenesis [11]. (2) The interaction of Ang II and AT1R leads to some receptors transactivation, such as epidermal growth factor receptor (EGFR) [12]. The increased expression and activity of these receptors has already been demonstrated to be associated with angiogenesis and metastasis of tumor cells [13-15]. (3) The inflammation and oxidative stress are also regulated by Ang II binding with AT1R, releasing a series of pro-inflammatory mediators like TNF-α, ROS and various prostaglandins. Furthermore, the inflammatory cytokines are connected to cancer cachexia [16]. Collectively, as showed in Figure 1, Ang II and AT1R play crucial roles in tumor initiation and development by stimulating proliferation, angiogenesis and inflammation. The effects of Ang II can be inhibited by renin-angiotensin system blockers (RASBs), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). ACEIs prevent the generation of angiotensin II by inhibiting angiotensin-converting enzymes (ACEs) while ARBs selectively block angiotensin II binding to the AT1R. In addition, as a kind of metalloproteinase inhibitors, ACEIs might prevent the progression of cancer directly since metalloproteinase is related to tumor metastasis [17]. Therefore, ACEIs/ARBs hold great promise for antitumor activity.

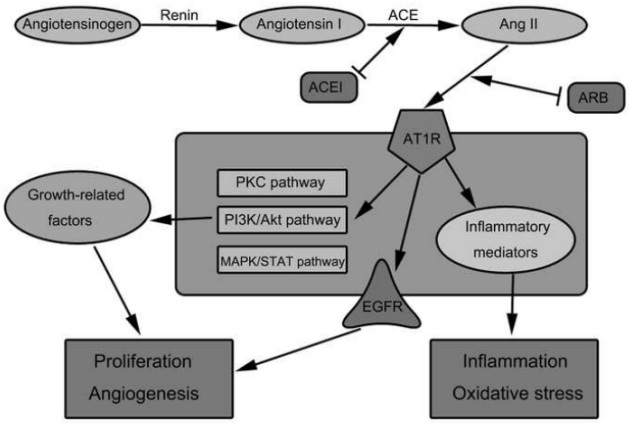

Figure 1. Tumor-promoting effect of AngII binding with AT1R. Ang II angiotensin II, AT1R angiotensin type 1 receptor, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, PKC protein kinase C, PI3K/Akt phosphatidylinositol-3-kinase, MAPK/STAT mitogen-activated protein kinase/signal transducer and activator of transcription, EGFR epidermal growth factor receptor

Preclinical studies have suggested that RASBs might decrease tumor growth, inhibit tumor-associated angiogenesis and improve cancer survival [18-21], but clinical data have been mixed [4,22-24]. Results from observational studies in lung cancer patients are controversial and the potentiality of ACEIs/ARBs in cancer treatment is still not fully understood. In order to shed light on possible roles of ACEIs/ARBs in antitumor treatment, we conducted the meta-analysis to determine the impact of ACEIs/ARBs on progression-free survival (PFS) and overall survival (OS) in lung cancer patients.

Material and Methods

Systematic literature search and quantitative analysis were conducted and reported according to a predefined protocol following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines [25].

Literature search

A systematic literature search for eligible studies was conducted in Pubmed, Embase, and Cochrane library from inception to February, 2017. The following keywords and medical subject headings (MeSH) terms were used: anti-hypertensive, renin-angiotensin system blockers, RASBs, angiotensin-converting enzyme inhibitors, ACEIs, angiotensin receptor blockers, ARBs, angiotensin II type 1 receptor blockers, angiotensin receptor antagonists AND pulmonary neoplasm, lung neoplasm, lung cancer, pulmonary cancer, cancer of the lung, AND observational study, cohort study, case-control study, clinical trial. Reviews, case reports and editorials were considered unqualified. We also searched the reference lists of all relevant articles to identify any further potentially eligible articles.

Eligibility criteria

Two reviewers independently screened the articles by title and abstract based on pre-specified eligibility criteria. Studies were included if they met the following inclusion criteria: (1) the study design was cohort study or case-control study or randomized controlled trial; (2) the study assessed the usage of ACEIS/ARBs in the study population; (3) the study used clinically relevant outcomes such as PFS, OS, tumor recurrence or metastasis. Discrepancies between the two reviewers' lists of articles for inclusion were resolved with discussion. When two or more studies had overlapping study samples, only the most recent or the most complete study was involved in the analysis.

Data extraction

Two authors conducted the data extraction independently with disagreements resolved by consensus or an experienced third author. Data extracted included the name of the first author, publication year, country, age, histology type, cancer stage, population according to the ACEIs and ARBs type, follow-up period, outcomes, hazard ratios (HRs) with corresponding 95% confidential intervals (95% CIs) and covariates adjusted. If multiple HRs were reported, we chose the one with the most comprehensive adjustment for our meta-analysis. If only Kaplan-Meier curves were available, data were calculated from survival curves and estimation of the HR was then performed by the method reported by Tierney et al. [26].

Quality assessment

Quality assessment for studies included in this meta-analysis was evaluated by using the Newcastle Ottawa Scale (NOS) criteria [27]. The higher score out of a total of nine points indicated the higher quality, and the studies that met 5 or more of the NOS criteria were considered of adequate quality for the meta-analysis.

Statistical analysis

In this meta-analysis, we calculated pooled HRs with their corresponding 95% CIs to assess the prognostic significance of ACEIs/ARBs use in lung cancer patients, and the HR greater than 1 implied an inferior prognosis for patients with ACEIs/ARBs use. We used a random effects model approach for our meta-analyses to account for both within and between study heterogeneity. Statistical heterogeneity of effect estimates was carried out using Cochran's Q test and Higgins I-squared statistic, and the I2 values $\geq$ 50% indicated significant heterogeneity. For additional analyses, subgroup meta-analysis was performed according to the histology (NSCLC or pan-lung cancer), medication type (ACEIs or ARBs) and the tumor stage (I-IIIa or IIIb-IV) respectively. Sensitivity analysis was performed by sequential omission of individual studies to examine the stability of the outcomes in this meta-analysis. Publication bias was evaluated by Egger's test and Begg's funnel plot. We performed all analyses using STATA software (version 12.0, Stata Corp, College Station, Texas, USA). A

two-tailed P value less than 0.05 was considered significant in statistical tests.

Results

Study selection and characteristics

The results of the search strategy for studies were showed in Figure 2 Nine hundred and forty-seven potentially relevant abstracts were found out. One additional article by Linhai et al. was identified from our peers' study, which was not published but accepted for publication. Most of the exclusive abstracts were researches without correlation between ACEIS/ARBs and lung cancers. One hundred and sixty articles were related to cell lines or animals. Twelve were excluded due to insufficient survival data for calculating HRs. Finally, Linhai et al. and the other 7 articles were eligible for this meta-analysis [4,19,23,24,28-30], of which one article had two available statistical data [28]. It examined whether concomitant ACEIs/ARBs usage during basic chemotherapy of carboplatin and paclitaxel (CP) or carboplatin and paclitaxel with bevacizumab (CPB) is associated with improved overall survival in patients with NSCLC.

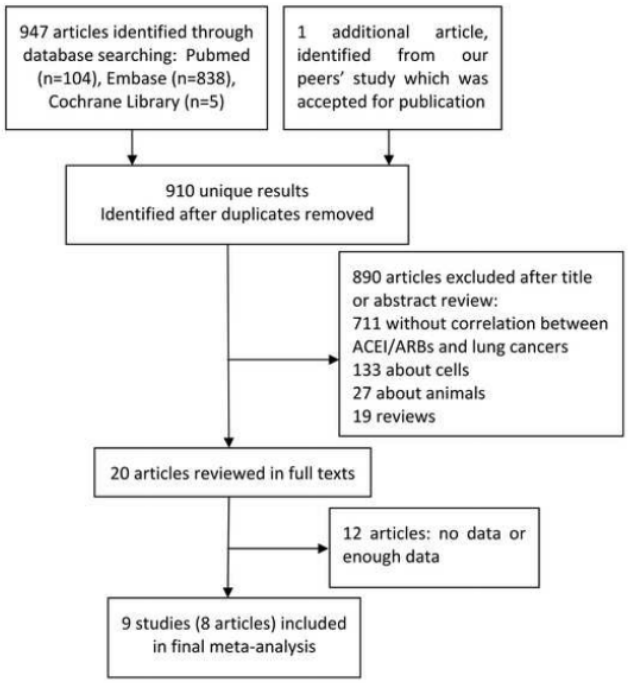

Figure 2. Flow chart of searching the relevant studies used in this meta-analysis.

The general characteristics of the studies, as well as the results of quality assessment were summarized in Table 1. A total number of 29,156 patients were recruited in the meta-analysis, with study sizes ranging from 117 to 19,592. All the studies were retrospective cohort studies. Three of the studies were based in China; two were based in America and the rest in Germany, Canada and Turkey. Five studies pathologically confirmed NSCLC while the other three had no specific histology. Three studies provided information and discussed the different effect between ACEIs and ARBs. As for the tumor stage, one study was about stage I to IIIa, four studies were of stages IIIB to IV, and two studies were of all stages. Of the nine studies, five directly reported HRs on OS, while the other four studies provided it by survival curves or from the authors by letters. Four studies showed that ACEIs/ARBs had a favorable prognosis while one study showed a poor prognosis, and the rest four studies showed no significant impact of ACEIs/ARBs usage on survival. The qualities of all nine studies were considered high enough for the meta-analysis.

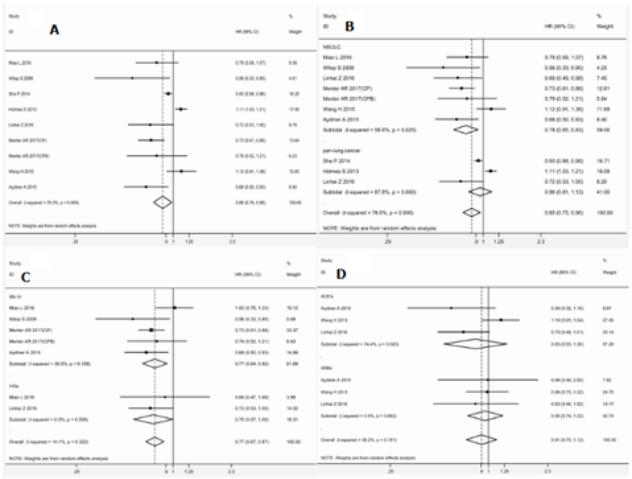

Figure 3. Forest plot with random-effects model for the association between ACEIs/ARBs and OS of lung cancer: (A) Forest plot for the association in all 9 eligible studies. (B, C, D) Forest plot for the association in subgroups by tumor histology, stage and medication type. CI: Confidence Interval; HR: Hazard Ratio.

Meta-analysis of ACEIs/ARBs and patients' survival

To explore the prognostic effect of ACEIs/ARB drugs on lung cancers, a meta-analysis was performed on HRs of OS and PFS/DFS. The pooled HR and corresponding 95% CI of OS in all 9 studies were 0.86 (95% CI: 0.76-0.98) (Figure 3A). A random effects model was used due to the significant heterogeneity (I2=79.3%, P<0.001). Figure 3 shows the results of main subgroup meta-analyses. When grouped by tumor histology, ACEIs/ARBs users showed favorable OS in NSCLC group (HR, 0.78; 95% CI, 0.65-0.93; p=0.005) and not significantly in pan-lung cancer group (HR, 0.96; 95% CI, 0.81-1.13) (Figure 3B). These results indicated that there might be a significant positive prognostic effect on OS in lung cancer patients, especially in NSCLC patients. Meantime, five studies were included in subgroup of stage IIIb to IV and two studies in stage I to IIIa, with combined HRs were 0.77 (95% CI, 0.64-0.92) and 0.751 (95% CI, 0.565-0.998) respectively (Figure 3c). However, as for medication type, the pooled HR of OS in ACEIs usage group and ARBs usage group are 0.83 (95% CI, 0.53-1.30) and 0.95 (95% CI, 0.74-1.22), indicating no significant association was found when we grouped by medication type (Figure 3d).

Table 1. Characteristics of the included studies.

Author Year	Country	Years of diagnosis	No. of patients	Age (years)	Follow-up (month)	Histology	Stage	ACEI/ARBs type	Outcomes	HR estimation	NOS score
Miao [4]	China	2000-2014	52/249	69(35-89)	NA	NSCLC	I-IV	ACEi 25, ARB 27	OS, PFS	survival curve	7
Wilop [19]	Germany	1996-2007	52/235	62(31-83)	NA	NSCLC	IIIb-IV	ACEi 43, ARB 9	OS	survival curve	7
Sha [23]	Taiwan	2003-2010	11207/8353	NA	NA	pan-lung cancer	I-IV	NA	OS, PFS	given by author	6
Holmes [24]	Canada	2004-2008	1256/2985	71	84	pan-lung cancer	I-IV	NA	OS	given by author	7
Linhai	China	2006-2012	143/1320	58.72	120	pan-lung cancer	I-IIIa	ACEi and ARB 5, ACEi 108, ARB 30	OS, PFS	given by author	7
Menter [28] (CP)	America	2005-2011	255/255	67	96	NSCLC	IIIb-IV	ACEi 199, ARB 56	OS	given by author	8
Menter [28] (CPB)	America	2005-2011	61/61	62	96	NSCLC	IIIb-IV	ACEi 45, ARB 16	OS	given by author	8
Wang [29]	America	1998-2010	138/1204	65(34-95)	50(1-155)	NSCLC	III	ACEi 76, ARB 66	OS, PFS	given by author	8
Aydiner [30]	Turkey	2003-2011	37/80	61.8/60.4	18.9(1-102)	NSCLC	IV	ACEi 16, ARB 21	OS	survival curve	8

OS: Overall Survival; PFS: Progression-free Survival; NA: Not Available; NSCLC: Non-small Cell Lung Cancer, ACEI: Angiotensin-converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; HR: Hazard Ratio: NOS: Newcastle-Ottawa Scale; CP: Carboplatin and Paclitaxel; CPB: Carboplatin and Paclitaxel with Bevacizumab

Four studies with PFS were also pooled into the meta-analysis. The combined HRs of the PFS was 0.84 (95% CI: 0.70-1.02, P=0.076) with heterogeneity (I2=66.3%, p=0.031), suggesting that ACEIs/ARBs usage is not significantly associated with favorable PFS.

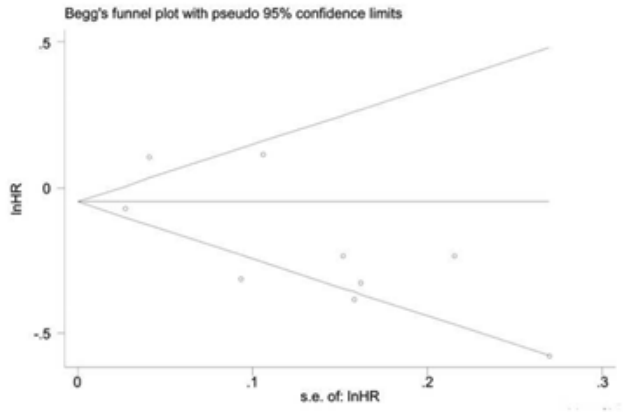

Figure 4. Begg's funnel plot of the 9 evaluable studies assessing ACEIs/ARBs in lung cancer for overall survival. HR: Hazard Ratio; SE: Standard Error.

Sensitivity analysis

In order to gauge results stability, a sensitivity analysis was performed by sequential omission of individual studies. The pooled HR for OS and PFS were not significantly changed when we omitted any single study, suggesting that the results of the meta-analysis for OS and PFS were stable.

Publication Bias

The Egger's test and Begg's funnel plot were applied for detecting publication bias in the meta-analysis. The shapes of the Begg's funnel plot (Figure 4) indicated the absence of publication bias. In other words, there was no evidence of publication bias as suggested by Egger's and Begg's tests for OS (Egger's test, p=0.151; Begg's test, p=0.602) and PFS (Egger's test, p=0.368; Begg's test, p=0.308).

Discussion

The factors that influence the prognosis of lung cancer patients haven't been completely understood so far. Preclinical findings have reported that RASBs such as ACEIs or ARBs can suppress tumor cell growth and cancer metastasis in some cancers, including lung cancer [21,31-34]. However, the correlation between ACEIs/ARBs and prognosis in lung cancer patients remained inconsistent and controversial in some survival studies. Therefore, we performed this clinical meta-analysis trying to determine the value of ACEIs/ARBs on the prognosis in lung cancer patients.

The results of this systematic review and meta-analysis demonstrate the therapeutic significance of ACEIs/ARBs in lung cancer patients. In the overall pooled analysis of the association between ACEIs/ARBs use and survival of lung cancer patients, the pooled HR and 95% CI of OS were 0.86 (95% CI: 0.76-0.98, p=0.022), supporting the hypothesis that the use of ACEIs/ARBs may prolong patients' survival with lung cancer. Additionally, a considerable degree of heterogeneity (I2=79.3%) was noticed after the HR were pooled in OS of all nine studies, and so subgroup analyses were essential.

In the subgroup of tumor histology, the result suggested a favorable prognosis in patients with NSCLC, while no statistical association was found in the pan-lung cancer group. For advanced-stage NSCLC, radical surgery cannot be carried out and platinum-based doublet chemotherapy now is considered to be the standard treatment [35,36]. However, this standard treatment approach can prolong survival by no more than several weeks to several months [37,38]. But the good news is, our research suggests ACEIs/ARBs may have synergistic anti-tumor effect in chemotherapy. Our meta-analysis indicates ACEIs/ARBs prolong survival of NSCLC patients and this result is consistent with previous studies, e.g., in Menter et al. [28] analysis, for CP (carboplatin and paclitaxel) patients with concomitant ACEIs/ARBs receipt, the HRs (HR 0.73, 95% CI, 0.61-0.88) demonstrated statistically significant OS benefit, relative to patients with no ACEIs/ARBs receipt. The Wilop et al. [19] also showed that addition of ACEIs/ARBs to platinum based first-line chemotherapy may contribute to prolonged survival in patients with advanced lung cancer (HR 0.56, P=0.03). These results support preclinical evidence that inhibition of Ang II or the Ang II receptor resulted in decompressing blood vessels and improving chemotherapy delivery [39,40]. Overall, these findings suggest ACEIs/ARBs as an effective adjuvant therapy to basic chemotherapy, which needs to be confirmed by further studies before clinical application. Meantime, we noticed that monoclonal antibody against VEGF were usually added to the basic chemotherapy for advanced-stage NSCLC, such as bevacizumab. And a randomized phase III study demonstrated a 2-month improvement in median OS [41]. However, Menter et al. [28] suggested that no synergistic benefit was found between ACEIs/ARBs and bevacizumab in lung cancer patients. A prospective study with a larger population needs to be performed for confirming this hypothesis. As for the pan-lung cancer subgroup, the result suggests no statistical association between ACEIs/ARBs use and survival of patients. The pan-lung cancer group contained both NSCLC and SCLC and we detected that the heterogeneity was increased in this group. As the characteristic and reaction to medication are not significantly consistent between NSCLC and SCLC, no wonder there were some differences among individuals in pan-lung cancer group. Considering the significant heterogeneity and small sample (only three studies were included in this subgroup), the result of pan-lung cancer may be suspectable.

Subgroup analyses also showed that there was no statistical significance between ACEIs usage group and ARBs usage group. However, similar to the pan-lung cancer group, the both subgroups had few studies included. We must be cautious when interpret the results because of the small number of studies contained. In terms of anti-tumor mechanism, ACEIs seem to be more effective in the treatment of cancer. That is, as mentioned above, both ACEIs and ARBs can block the effects of RAS to exert anti-tumor activity, while ACEIs also have a direct impact on tumor cells. Prontera et al. found, in mice bearing Lewis-lung-carcinoma cells, captopril (a kind of ACEIs) decreased the synthesis of gelatinase-A, which plays a role in tumor metastasis [17]. Besides, sulfhydryl-containing ACEIs have antioxidant properties, beneficial to tumor inhibition. Nevertheless, the underlying anti-tumor mechanism of RASBs remains unclear and the difference in anti-tumor effect between ACEIs and ARBs is still unknown.

Five studies were included in subgroup of stage IIIb to IV with combined HRs were 0.77 (95% CI, 0.64-0.92; I2=39.5%), ignoring the HRs of stage I to IIIa due to a small number of studies included. Since the expression level of AT1R, as we have mentioned in the introduction, is much higher in advanced cancer, it is reasonable to presume that the impact of ACEIs/ARBs is more significant on patients in advanced stage. Our study data were too deficient to evaluate this kind of relationships, remaining an undefined issue for further research.

The combined HR of the PFS provided in 4 articles was 0.84 (95% CI: 0.70-1.02, P=0.076), which meant that no statistical significant association between ACEIs/ARBs usage and favorable PFS was found in our study. It is unclear if this insignificance is the result of a true underlying effect or a bias due to small sample, heterogeneity and inaccurate data extracted from original literature. Because the deficient number of studies impacted the credibility of the result in PFS analysis and OS is the most widely-used endpoints in oncology trails, we did not conduct a further analysis of PFS with existing studies.

Despite we made efforts to conduct a comprehensive analysis, some inevitable limitations of this meta-analysis need to be acknowledged. First, the number of eligible studies searched is low. We had tried to collect as many researches related to our topic, imperfectly, only 9 studies (8 articles) were eligible for our meta-analysis, consequently the outcomes should be interpreted with caution. Second, the outcomes were limited by a presence of heterogeneity among the studies. We noticed the heterogeneity reduced in the subgroup analyses of tumor stage, NSCLC and medication type, which may partly indicate the source of heterogeneity. However, heterogeneity can also derive from many other aspects, such as the influence of previous treatment, years of publication, length of recruitment period, inclusion criteria, endpoint definition, follow-up period and so on. Moreover, despite being undertaken by two reviewers, the inaccuracy was inevitable for HRs extracted from the survival curves, which can also generated heterogeneity. Third, not all articles included the multivariate survival analysis, and if these data were not available, data calculated from survival curves by univariate analysis were included. Insufficient retrievable HR data adjusted might not convincingly guarantee the independent prognostic significance of ACEIs/ARBs in lung cancer. Furthermore, this study was based on the findings of observational studies, which are less persuasive than randomized controlled trials. Finally, publication bias may occur because positive results tend to be accepted by journals, although no publication bias was indicated from both funnel plot and Egger's test.

Conclusion

In conclusion, despite the limitations, our meta-analysis has identified that ACEIs/ARBs are significantly associated with favorable outcomes for lung cancer patients. The outcome is

much better in NSCLC and advanced lung cancer patients. To strengthen our findings, more prospective multi-center and well-matched cohort researches should be performed to clarify the prognostic effect of ACEIs/ARBs in lung cancer patients.

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***Correspondence to**

Dianjie Lin,

The Olympic Mid Road,

Lixia District Jinan Shandong,

China,

Tel: +86-0531-68773269

E-mail: lindianjiesd@163.com