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Research Paper

# Angiotensin-converting Enzyme Inhibitors Decrease the Incidence of Radiation-induced Pneumonitis Among Lung Cancer Patients: A Systematic Review and Meta-analysis

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## Abstract

**Background:** Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been demonstrated to mitigate radiation-induced lung damage in animal models and preclinical studies. Our study aims to evaluate whether ACEIs or ARBs reduce the incidence of radiation-induced pneumonitis (RP) in lung cancer patients.

**Methods:** Publications were searched from EMBASE, PubMed and Web of Science databases. Seven studies published from April 2000 to August 2016 met inclusion criteria and included 1412 patients in total. Only patients with grade 2 and above pneumonitis within 12 months after radiotherapy were analyzed.

**Results:** Patients taking ACEIs had a lower risk of developing radiation pneumonitis compared with non-users (OR = 0.46, 95%CI = 0.31-0.67, $p < 0.0001$). While the use of ARBs couldn't reduce the incidence of RP (OR = 1.42, 95%CI = 0.94-2.14, $p = 0.10$). Elderly patients (age ≥ 70) benefited more from ACEIs (OR = 0.12, 95%CI = 0.02-0.67, $p = 0.02$). In addition, smokers were found to have a lower risk of developing RP than non-smokers (OR = 0.49, 95%CI = 0.30-0.81, $p = 0.005$), but sex and the use of statin or NSAID had no influence on the appearance of RP ($p = 0.59$, $p = 0.70$, $p = 0.40$, respectively).

**Conclusions:** ACE inhibitors could decrease the incidence of symptomatic RP among lung cancer patients. However, the use of ARBs has a slight trend to develop RP but not above statistical significance. Elderly patients (age ≥ 70) benefited the most from ACEIs.

Key words: angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; lung cancer; radiotherapy; radiation pneumonitis.

## Introduction

Lung cancer accounts for the leading cause of death from cancer around the world.[1] The morbidity of lung cancer remains high and most patients require radiotherapy. Thus, radiation-induced injury especially radiation pneumonitis (RP) is becoming a common problem, despite progress achieved in radiation planning and technique. Pneumonitis is the main dose-limiting toxicity encountered after radiotherapy.[2] Symptomatic RP significantly reduces patients' quality of life and limits the therapeutic

effect of radiation treatment. In recent years, scientists have gained new insights into the pathogenesis of RP.

Transforming growth factor β (TGF-β), Tumor necrosis factor alpha (TNF-α), IL-6, IL-8 and other cytokines play a vital role in the development of RP.[3-6] TGF-β is upregulated early and persistently in lung tissue damaged by radiation.[7] The elevation of TGF-β is highly associated with the risk of radiation pneumonitis.[8] Regulating the levels of TGF-β and other cytokines could provide effective prevention and treatment for RP. ACE inhibitors and ARBs are commonly used to treat hypertension and several cardiac diseases. ACE inhibitors and ARBs have been found to regulate TGF-β, VEGF and other cytokines which could decrease tissue damage and radiation necrosis, inhibit angiogenesis, attenuate tumor growth, and even improve survival of cancer patients.[9-14] Similar protective effects have been demonstrated in animal models and preclinical trials.[15-18] One clinical study reported either pre-RT or during-RT, ACE levels were significant lower in an RP group compared with a non-RP group,[19] which means that lower plasma ACE is likely a risk factor for RP. In another study, Wang *et al*.[20] concluded that neither ACEIs or ARBs could reduce the incidence or delay the appearance of symptomatic RP among lung cancer patients. In addition, randomized control trial NRG Oncology Radiation Therapy Oncology Group 0123 was aimed to test the ability of captopril to affect the incidence of pulmonary damage after radiotherapy, but this study closed early due to the low accrual.[21]

In recent years, articles regarding the role of ACEIs and ARBs in mitigating lung toxicity after radiation therapy have reached differing conclusions, so that the role of these two drugs in preventing RP remains unclear. Hence our study was designed to determine whether ACEIs or ARBs decrease the incidence of radiation induced pneumonitis among lung cancer patients.

## Material and Methods

### Literature search

We conducted our meta-analysis using PRISMA statement guidelines. [22] Publications were searched from PubMed, EMBASE and Web of Science databases. Seven articles published from April 2000 to August 2016 met inclusion criteria and all were human trials. All patients from included studies have had lung computed tomography (CT) scan or 4-dimensional free-breathing CT scan or positron emission tomography (PET). RP was scored by the Common Terminology Criteria for Adverse Events v4.0 and was divided into 5 grades.[23] For the requirements of our analysis, symptomatic RP was defined as grade 2 and above.

### Study selection and quality assessment

In the experimental group, patients took either ACEIs or ARBs, while patients in the control group did not. Inclusion criteria were as follows: (1) Studies concerned lung cancer patients. (2) ACE inhibitors and/or ARBs were used. (3) Patients had received radiation therapy. (4) Only grade 2 or higher pneumonitis were included.

Exclusion criteria were as follows: (1) Studies did not involve lung cancer patients. (2) Patients did not take ACEIs or ARBs. (3) No active follow up (less than 12 months). (4) Systematic review with data absent.

Methodological quality of the included studies was evaluated by the Newcastle–Ottawa Scale (NOS) of nonrandomized studies. The NOS consisted of 3 parameters: selection, comparability and outcome with a maximum score of 9. We defined studies with a score of 6 and above as high quality studies.

### Data extraction

Two reviewers independently searched the potential relevant articles by scanning titles and eligible abstracts. Any disagreements were resolved by discussion with a third reviewer. Data extracted from all involved studies were summarized as follows: first author's last name, year of publication, age, number of patients, radiotherapy dose, follow up, incidence and number of RP in the experimental group and the control group.

### Statistical analysis

We used Review Manager 5.3 software for statistical analysis and forest plots to show the results. ACEIs and ARBs were compared with each control group to estimate the odds ratios and 95% confidence intervals. A statistically significant difference was shown by $p < 0.05$. For heterogeneity, an $I^2$ test was used to measure the variation among studies. The $I^2$ ranged from 0 to 100% according to the Cochrane Handbook for Systematic Review of Intervention Version 5.1.0 (0 to 40%: the heterogeneity might be unimportant; 30 to 60%: might represent moderate heterogeneity; 50 to 90%: substantial heterogeneity exists; and 75 to 100%, considerable heterogeneity). [24] A fixed-effect model was used when $I^2$ was below 40%, otherwise, a random effect model was used. We did sensitivity analysis to test the stability and reliability of the results. Publication bias was presented by Funnel plots and assessed by Egger's test. For Egger's test, $p > 0.10$ was considered to mean no obvious publication bias.

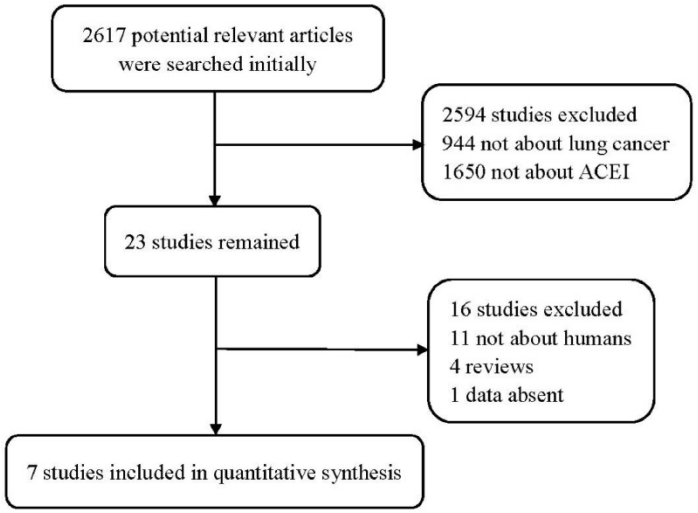


**Figure 1. Flow diagram of the study selection process.**

**Table 1.** Main characteristics of the included studies.

| study | Median age | Median follow up (month) | Median dose or range(Gy) | patients | | total | NOS score |
|---|---|---|---|---|---|---|---|
| | | | | ACEI use | nonusers | | |
| Bracci 2016 | 72 | 13.8 | 30 | 33 | 125 | 158 | 8 |
| Wang 2013 | 66 | 18 | ≥60 | 65 | 348 | 413 | 8 |
| Alite 2016 | 71 | 24.8 | 48-60 | 49 | 140 | 189 | 7 |
| Kharofa 2012 | 65 | Not given | Not given | 62 | 100 | 162 | 7 |
| Harder 2015 | 75 | ≥12 | 54 | 70 | 187 | 257 | 8 |
| Wang 2000 | 66 | 24 | 50-80 | 26 | 187 | 213 | 8 |
| Small 2016 | 65 | >16 | ≥45 | 7 | 13 | 20 | - |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; NOS, the Newcastle–Ottawa Scale of cohort studies.

# Results

## Search results

Total of 2617 publications were searched initially. After irrelevant and duplicate papers were excluded, 23 studies remained. Then, 16 articles were abandoned for further reasons: 11 studies were animal studies rather than human; 4 were review articles; and data from 1 study was absent. After applying the inclusion and exclusion criteria, 7 studies including 1412 patients were included for analysis (Figure 1). Their main characteristics are summarized in Table 1.

## Quality assessment

The results of quality assessment were evaluated by the NOS of cohort studies and presented in Supplementary Table S1. All included studies with a NOS score greater than 6 were determined as high quality studies. Most studies had a good representativeness except Kharofa *et al.*[25] which included men only. There were no statements about adequacy of follow up in all included studies. All other factors met our requirements.

## Efficacy assessment

In the ACEIs group, 39 of 312 patients developed RP compared with 285 of 1100 patients in the non-ACEIs group (12.5% vs. 25.9%). The use of ACE inhibitors showed a significant effect to reduce the risk of radiation-induced pneumonitis compared with the non-ACEIs group (OR = 0.46, 95%CI = 0.31-0.67, $p < 0.0001$) and low heterogeneity was identified ($I^2 = 26\%$). However, 44 of 144 ARBs users developed RP compared with 250 of 1021 nonusers (30.6% vs. 24.5%). ARBs not only failed to decrease the incidence of RP, but also showed a slight trend to promote the appearance of RP, although the difference was not statistically significant (OR = 1.42, 95%CI = 0.94-2.14, $p = 0.10$). Considering ACEIs and ARBs as a whole, this difference remained below statistical significance. (OR = 0.54, 95%CI = 0.12-2.44, $p = 0.43$). (Figure 2). The results of freedom from symptomatic radiation pneumonitis (FFSRP) at 6 month and 12 month follow-ups are shown in Figure 3. At 6 months, the use of ACE inhibitors freed 141 of 144 (97.9%) ACEI users of RP compared with 302 of 333 (90.7%) nonusers ($p = 0.01$). At 12 months, 163 of 178 (91.6%) ACEI users compared with 502 of 607 (82.7%) nonusers were freed from RP ($p < 0.0001$). Both initially and long term, ACE inhibitors proved effective at decreasing the incidence of RP.

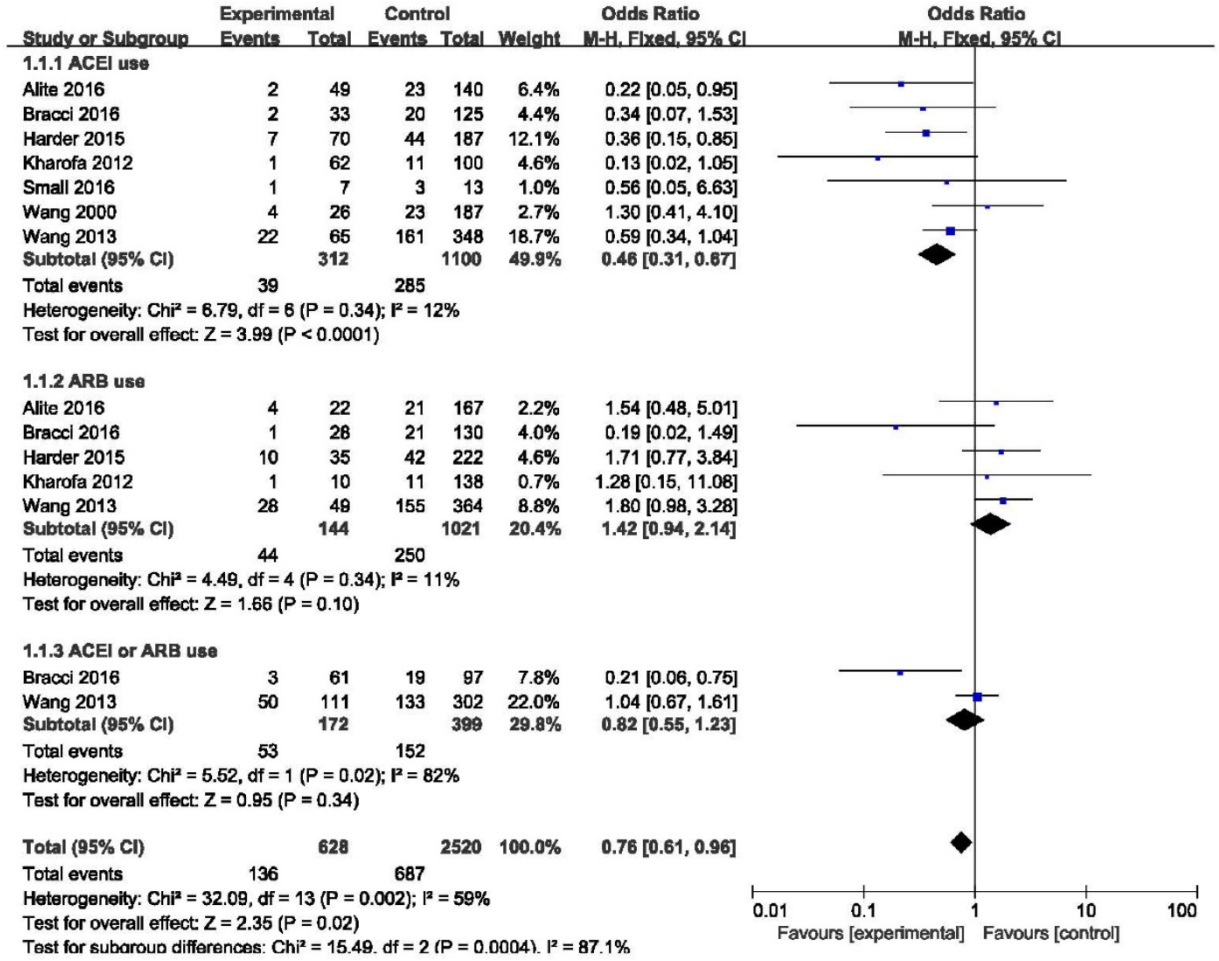


**Figure 2. Forest plot of the use of ACEI, ARB, ACEI or ARB.** Abbreviations: CI, confidence interval; OR, odds ratio; Event, radiation pneumonitis; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ACEI or ARB, consider the use of ACEI and ARB as a whole.

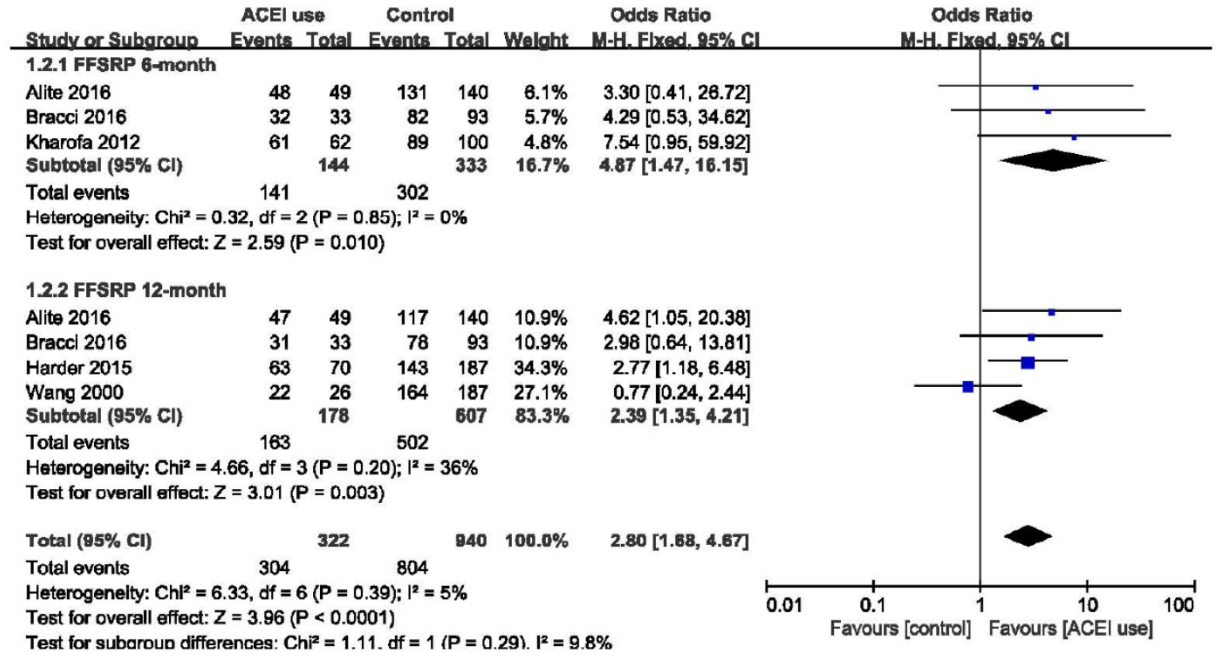


**Figure 3. Forest plot of the odds ratio (OR) of FFSRP at 6 months and 12 months.** Abbreviations: CI, confidence interval; OR, odds ratio; Event, radiation pneumonitis; ACEI, angiotensin-converting enzyme inhibitor; FFSRP, freedom from symptomatic radiation pneumonitis.

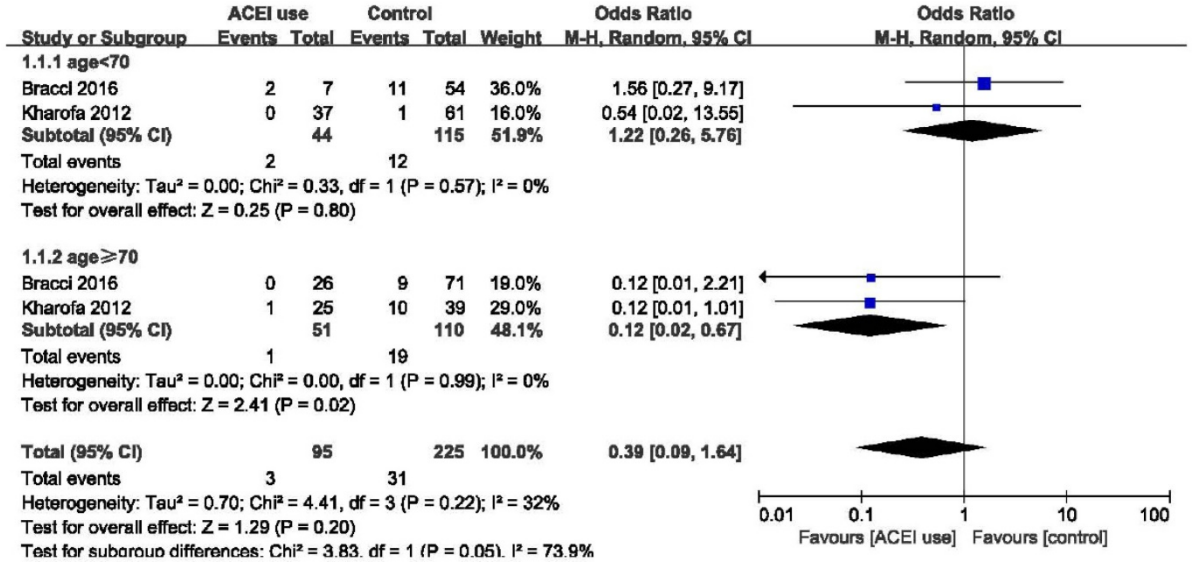


**Figure 4. Forest plot of the comparison of age < 70 and age ≥ 70.** Abbreviations: CI, confidence interval; OR, odds ratio; Event: radiation pneumonitis.

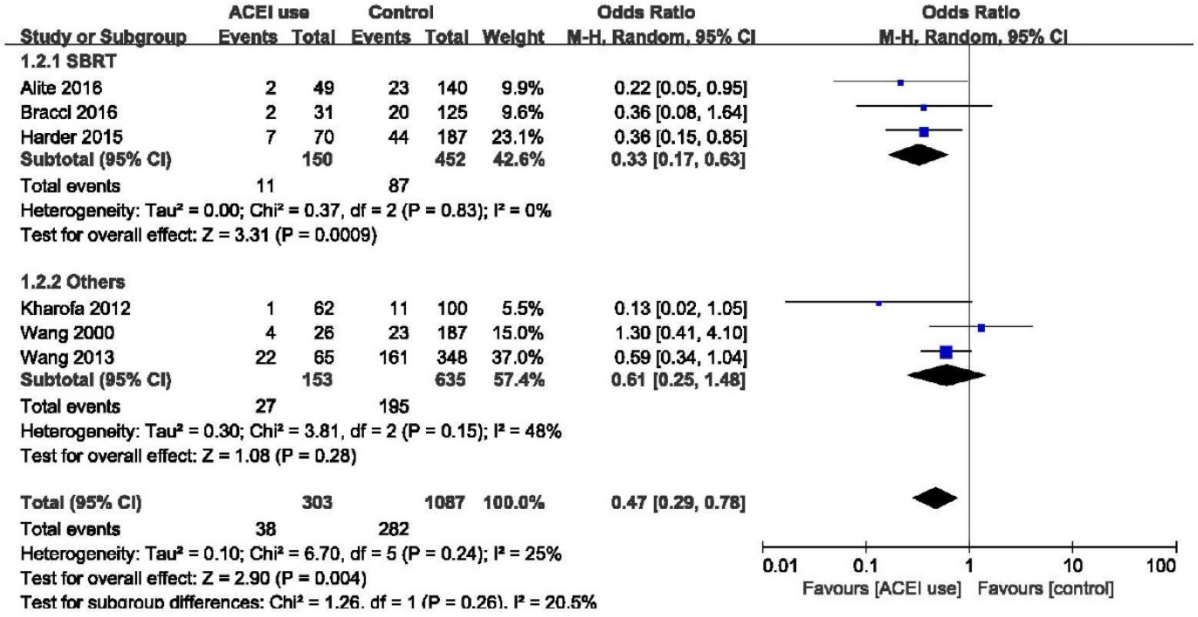


**Figure 5. Forest plot of the comparison of SBRT and other radiation techniques.** Abbreviations: CI, confidence interval; OR, odds ratio; Event, radiation pneumonitis; SBRT: Stereotactic body radiotherapy.

## Subgroup analysis

Elderly patients are those most at risk of developing pneumonitis after radiation therapy.[26] However, we found that elderly patients (age ≥ 70) may benefit more from the use of ACE inhibitors (OR = 0.12, 95%CI = 0.02-0.67, $p$ = 0.02) than patients age < 70 years (OR = 1.22, 95%CI = 0.26-5.76, $p$ = 0.80), although the difference between these two group was only slightly statistically significant ($p$ = 0.05) (Figure 4). Stereotactic body radiotherapy (SBRT) was reported to be more beneficial than 3D-CRT or IMRT in treating early stage non-small cell lung cancer (NSCLC). In patients treated with SBRT, ACEIs were clearly effective as we demonstrated (OR = 0.33, 95%CI = 0.17-0.63, $p$ = 0.0009). High heterogeneity existed in the group treated with other radiation techniques ($I^2$ = 48%), and there was no obvious statistical significance in this group (OR = 0.61, 95%CI = 0.25-1.48, $p$ = 0.28). And no statistical significance was found between these two groups ($p$ = 0.26). In overall effect, ACEIs were effective for all patients regardless of the radiation technique they accepted (OR = 0.47, 95%CI = 0.29-0.78, $p$ = 0.004). (Figure 5). Sex, smoking status, and the use of statin and nonsteroidal anti-inflammatory drugs (NSAID) were abstracted from included studies to evaluate the relationship between radiation pneumonitis and these factors. We found that patients who smoked previously or currently had a lower risk of RP than

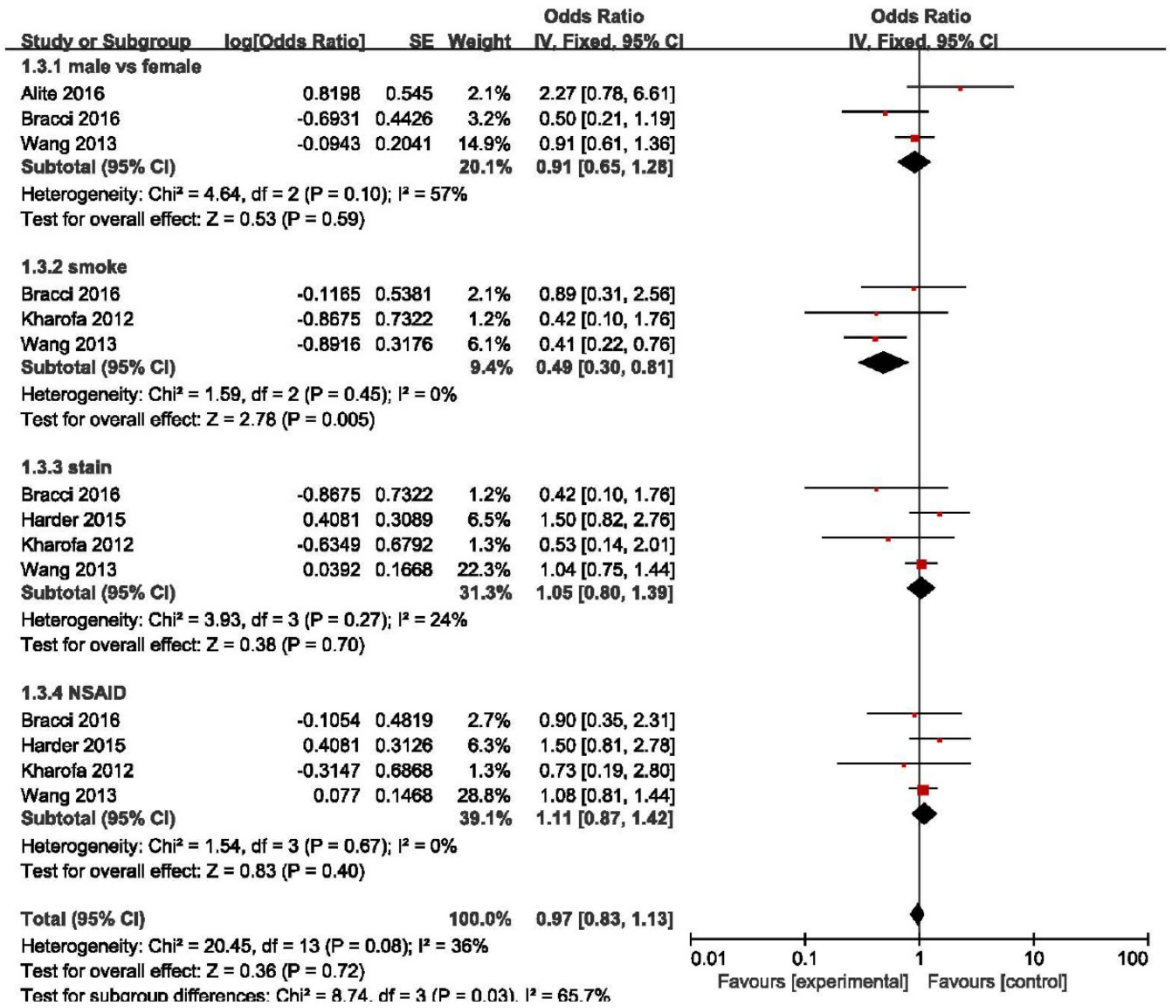


**Figure 6. Forest plot of the log(OR) of sex, smoking status, use of statins and NSAIDs.** Abbreviations: CI, confidence interval; NSAID, nonsteroidal Anti-inflammatory Drugs.

non-smokers (OR = 0.49, 95%CI = 0.30-0.81, $p$ = 0.005), but sex and the use of statin or NSAID had no influence on the appearance of RP ($p$ = 0.59, $p$ = 0.70, $p$ = 0.40, respectively). (Figure 6).

### Publication bias and sensitivity analysis

Figure 7 shows the results of publication bias, which were evaluated by funnel plots and Egger's test. No obvious publication bias was identified (Egger's test: $p$ = 0.225 for analysis of ACEIs use). We observed that the overall results were still stable and reliable when each study was excluded or included, so that the sensitivity of our results was low.

## Discussion

To our knowledge, this is the first meta-analysis to analyze the effect of ACEIs and ARBs in preventing radiation pneumonitis among lung cancer patients. Pertinent findings were summarized as follows. In our analysis, we found that the use of ACE inhibitors was associated with a significant reduction in the risk of radiation-induced pneumonitis among lung cancer patients ($p$ < 0.0001), especially elderly patients. On the contrary, ARBs not only failed to reduce the incidence of RP, but have a slight trend to promote RP, though the difference was not statistically significant. In addition, patients who have a smoking history or smoke currently have a lower risk than non-smokers for developing RP.

In the past few decades, radiation techniques have developed rapidly, including 3D-CRT, IMRT, IGRT, SBRT, proton and particle beam therapy[27]. But radiation- induced pneumonitis still cannot be completely prevented, which restricts the therapeutic dose and effectiveness of treatment. ACE inhibitors and ARBs have been demonstrated to help reduce the risk of RP among some animal models and preclinical trials.[15, 28] ACEIs but not ARBs also proved useful for preventing pneumonia (but not radiation induced pneumonitis) in one analysis with a large number of patients.[29] Whether ACEIs or ARBs could play a protective role in radiation-induced pneumonitis has remained controversial.

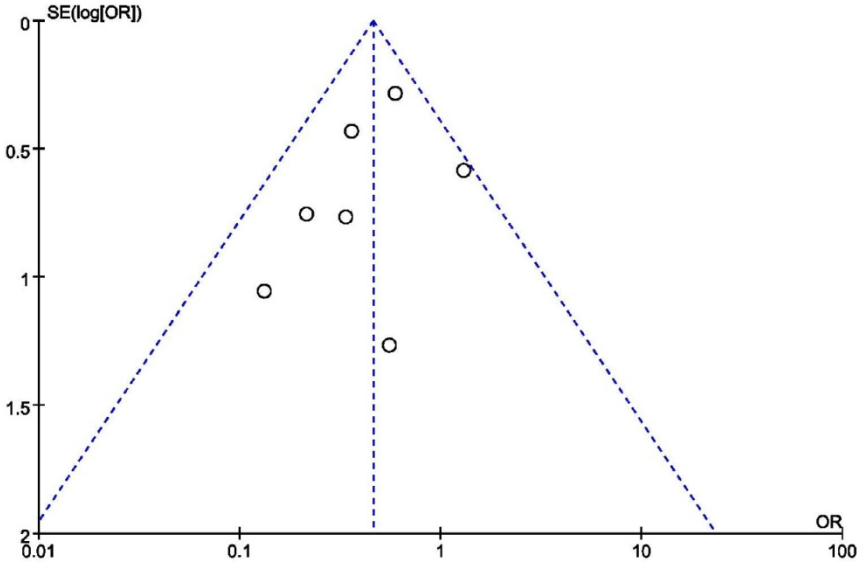


**Figure 7. Funnel plot based on odds ratio.**

Wang *et al.*[20] reported a cohort study including 213 patients, but most patients were accepted with 2D non-conformal RT between 1994 and 1997, and no difference was found between the ACEIs group and non-users group (15% vs. 12%, $p$ = 0.75). In our opinion, the low efficacy of ACEIs in this study may be associated with the imperfection of 2D-CRT and the high radiotherapy dose. Afterwards, Kharofa *et al.*[25] reported a study with 162 patients who were treated with radiation from 2004 to 2009. The incidence of Grade ≥ 2 pneumonitis was lower in ACEI users compared with non-users (2% vs. 11%, $p$ = 0.03), ARBs did not have this effect. Wang *et al.*[30] retrospectively analyzed 413 patients of NSCLC treated with at least 60 Gy and found that the rate of grade ≥ 2 RP was lower in ACEI users than non-users (34% vs. 46%), although the apparent difference was not statistically significant ($p$ = 0.06). After evaluating 189 patients with a median follow-up of 24.8 months, Alite *et al.*[31] found a significant association between ACEI use and decreased risk of clinical pneumonitis. In another study, a total of 257 patients were included, and this study concluded that use of ACE inhibitors during SBRT was associated with significantly greater freedom from grade ≥2 RP on univariate (vs nonusers, 89.8% vs. 76.3% at 12 months, $p$ = 0.029) and multivariate analysis (hazard ratio 0.373, 95%CI = 0.156-0.891, $p$ = 0.026).[32] Consistent with Harder[32], Bracci *et al.*[33] demonstrated that ACE inhibitors were associated with a decreased incidence of RP after SBRT. However, they expressed different opinions in the effectiveness of ARBs for preventing RP. Bracci *et al.* combined ACEIs with ARBs groups into one group and concluded that RAS inhibitors were associated with a reduction of incidence for patients undergoing SBRT. There may be some biases because of the combination of ACEIs and ARBs. One clinical RCT of NRG Oncology Radiation Therapy Oncology Group 0123 was aimed to test the ability of the angiotensin-converting enzyme inhibitor captopril to alter radiation-induced pulmonary damage for lung cancer patients, but due to low accrual and a large number loss of patients, this study closed early.[34] Only 20 patients were analyzed in this study, so that it is failed to evaluate patients' quality of life who have taken ACEIs and the long-term effects of captopril. The length and frequency of the medication may need to be improved, but this study did show the safety of the use of ACEIs among lung cancer patients who received radiotherapy. The results of our study suggested that ACEIs were useful for preventing RP, but ARBs were not. Whether in the short term or long term, ACE inhibitors had a significantly protective effect.

SBRT delivers a high radiation dose to the tumor so that a high local control rate is achieved.[35, 36] SBRT is the best choice for inoperable early stage NSCLC currently and may be preferable to surgery.[37, 38] In subgroup analysis, we did not find a statistical difference between SBRT and other radiation techniques using ACE inhibitors. High heterogeneity was identified in the other radiation techniques group. When the data of patients treated with SBRT were analyzed specifically, ACEIs was shown to be effective rather than ARBs, and the difference was slightly above statistical significance. However, since the radiation therapy dose, range of $V_{20}$, and technique was highly variable among these studies, the strength of this subgroup analysis was a little weakened and should be evaluated by be verified by further studies.

As well as its overall effect, the morbidity of RP was significantly reduced in elder patients who took ACEIs compared with non-users. Older age was considered as a risk factor of pulmonary toxicity for patients treated with thoracic radiation.[39, 40] And elderly patients were observed to have an increased risk of symptomatic pneumonitis after radiotherapy.[26] Notably, we found that elderly patients could benefit more from ACE inhibitors than younger patients. This does not mean that younger patients do not benefit from ACE inhibitors; after all, the overall effect suggests a protective effect of ACEIs to prevent RP for the majority of patients.

Interestingly, we found that patients who have a smoking history or smoke currently have a lower risk than non-smokers for developing RP. Consistent with our result, Palma *et al.*[41] reported that smokers have a protective effect on radiation pneumonitis (OR =0.39, 95%CI = 0.19-0.80, $p$ = 0.01). The protection mechanism of smoking in preventing RP remains unclear, but further studies may help to determine this. Bjermer *et al.* [42] found that smokers displayed a weaker inflammatory reaction than non-smokers, possibly due to lower levels of lymphocytes and mast cells. Furthermore, radiation would undoubtedly injure the normal structure of DNA, and the repair state would affect the injury of tissues. The polymorphisms of DNA repair genes may play a different role based on smoking status. XRCC1 and ERCC2 are two DNA repair genes, and polymorphisms of these two genes are considered as a risk in non-smokers but have a protective effect in smokers. [43]This may be due to the fact that polymorphisms of these repair genes were overwhelmed in heavy smokers.[44]

Several limitations exist in our study. First, there were only one clinical randomized controlled trial and most included studies were cohort studies, it limited the result to evaluate the effect of ACEIs or ARBs for mitigating the toxicity or reducing the incidence of radiation-induced pneumonitis. Second, the data we analyzed were extracted from published articles rather than original records. Due to some data being absent and the different range of $V_{20}$ and MLD in their papers, such as overall survival and the known factors of RP, chemotherapy and $V_{20}$, cannot be analyzed. Furthermore, as only 7 studies met our inclusion criteria, safety and efficacy should be verified by further studies. In the future, we will continue to explore these questions.

Our meta-analysis demonstrated that the use of ACEIs but not ARBs effectively reduced the incidence of radiation pneumonitis for most lung cancer patients. That has important clinical implications. Lung cancer patients accepting thoracic radiation could take an appropriate dose of ACEIs to prevent RP during or after the period of radiotherapy, which would greatly improve quality of life and therapeutic effect. By contrast, the more expensive ARBs are ineffective for preventing RP. Whether ARBs could promote the appearance of RP should be tested cautiously. For elderly lung cancer patients, ACEIs may help them to avoid radiation pneumonitis after radiotherapy, but we cannot neglect the specific conditions and potential adverse effects of ACEIs. We hope our results help pave the way for using ACE inhibitors to decrease the incidence of RP in future clinical trials and will inspire further research into preventing radiation induced inflammation in other organs.

## Supplementary Material

Supplementary table.
http://www.jcancer.org/v09p2123s1.pdf

## Acknowledgements

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## Competing Interests

The authors have declared that no competing interest exists.

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