

# The renin-angiotensin system blockers as adjunctive therapy for cancer: a meta-analysis of survival outcome

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**Abstract.** – **OBJECTIVE:** The renin-angiotensin system blockers (RASBs), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are widely used to reduce cardiovascular disease (CVD) events. Accumulating pre-clinical and clinical studies suggested that RASBs possess anti-carcinogenic properties, and their use is associated with favorable outcomes in several type cancers. To conduct a meta-analysis to evaluate the effect of adjunctive therapy of renin-angiotensin system blockers combined with chemotherapeutic agents in cancer patients.

**MATERIALS AND METHODS:** Data from a total of 2436 patients from 7 retrospective studies investigating chemotherapeutic agents in combination with RASBs agents versus chemotherapeutic agents were included in this meta-analysis. Publication bias was assessed by the Begg's Test, Egger's test and funnel plot. Subgroup analysis was conducted when the chemotherapeutic agents were the same.

**RESULTS:** A significant reduction in overall mortality in favor of chemotherapeutic agents in combination with RASBs agents was observed, hazard ratio (HR) 0.80 (95% CI: 0.69-0.92); there was a significant decrease in the risk of disease progression in favor of chemotherapeutic agents in combination with RASBs regimens, HR 0.79 (95% CI: 0.66-0.94), compared with those who only used chemotherapeutic agents. Subgroup analysis indicated that platinum-based agents plus ACEI/ARB could increase significantly the survival outcome (HR = 0.56; 95% CI: 0.38-0.82).

**CONCLUSIONS:** Our results suggest that RASBs combined with chemotherapeutic agents may improve outcomes in multiple types' cancer patients. More research and well-designed, rigorous, large clinical trials are required to address these issues.

## Key Words

Angiotensin converting enzyme inhibitors, Angiotensin II receptor blockers, Cancer, Combination therapy, Meta-analysis.

## Introduction

The renin-angiotensin system (RAS) is known for controlling the homeostasis of the organism and extensively studied in the physiological regulation of systemic arterial pressure. One major RAS regulatory component is biologically active peptide angiotensin II (AngII), which via activation of angiotensin II type 1 receptor, regulates cell proliferation<sup>1</sup> and migration<sup>2</sup> and induces angiogenesis by up-regulating the vascular endothelial growth factor receptor<sup>3,4</sup>. Thus, the potential role of the local RAS in carcinogenesis has attracted substantial attention. Accumulating pre-clinical and clinical studies suggested that blockade of the renin-angiotensin pathway with their inhibitors may inhibit tumor growth in several type cancers. Large epidemiological researches revealed that RASBs have the potential protective effects against cancer risk<sup>5,6</sup>. ACEI/ARB showed antiproliferative effects in breast cancer cells<sup>7,8</sup>; reduce the incidence of advanced adenomatous colon polyps<sup>9</sup>; trigger apoptotic cell death in human pancreatic cancer cells<sup>10</sup>; restrain tumor growth and decreasing the extent of colorectal cancer liver metastases<sup>11</sup> and delay progression of pancreatic intraepithelial neoplasia and cancer formation<sup>12</sup>; even though the results remain controversial.

Cancer is a major health problem. Despite recent improvements in surveillance protocols and diagnostic tools, cancer represents the leading mortality in entire world. A growing body of evidence suggests that ACEI/ARB in combination with gemcitabine might improve clinical outcomes in patients with advanced pancreatic cancer<sup>13</sup>. Platinum-based chemotherapy in combination with ACEI/ARB can improve the survival in patients with advanced non-small-cell lung cancer<sup>14</sup>. Combined gemcitabine and ARB showed

synergistic inhibition of tumor growth in murine pancreatic cancer<sup>15</sup>; ACEI with or without cisplatin was also reported to inhibit tumor growth in a human gastric xenograft<sup>16</sup>. Thus, ACEI/ARB in combination with chemotherapeutic agents may improve survival outcomes in cancer patients. For this reason, we performed a comprehensive meta-analysis of currently available relevant studies to quantify the effect of RASBs plus chemotherapeutic agents on the survival outcomes of multiple cancer patients.

The present meta-analysis aims to quantify the treatment effect of chemotherapeutic agents plus ACEI/ARB in the treatment of multiple types' cancer using retrospective studies. The main outcome of interest was overall survival (OS) and progression-free survival (PFS).

## Materials and Methods

### Information Sources and Search Strategy

We searched PubMed, ScienceDirect and web of science from 1991 to 2015 with the language restriction in English. The search terms were related to Angiotensin II receptor blocker (Angiotensin II receptor blocker, angiotensin II type-1 receptor blocker, ARB); angiotensin converting enzyme inhibitor (angiotensin converting enzyme inhibitor, ACEI, ACE-I); and cancer (oncology; cancer; carcinogenesis; tumor; carcinoma; tumor; neoplasm; neoplasia; tumour; malignancy). A manual review of references from primary and review articles was performed to identify any other relevant studies that were not captured through the initial database searches.

### Study Selection and Eligibility Criteria

We selected clinical studies which include a treatment arm of ACEI/ARB plus chemotherapeutic agents, and at least one treatment arm of chemotherapeutic agents. We primarily excluded reviews, case reports, pre-clinical studies, editorials, letters without sufficient data, and non-peer reviewed sources (e.g., author replies, conference and abstracts). When multiple reports based on the same study were published, only the most recent or complete report would be used. Abstracts were reviewed for relevance. All studies had to provide sufficient data for determining an estimate of Log-Hazard ratio (HR) and its 95% CI for overall survival (OS) and/or progression-free survival (PFS).

### Data Extraction

All potentially relevant articles were independently evaluated by two independent investigators; disagreements were resolved by consensus or consultation with a third author. HR and its 95% CI was either directly collected from original article or calculated by the Kaplan-Meier survival curves of survival outcomes<sup>7,18</sup>. We recorded the following information from eligible studies: first author, publication year, cancer type, patients' age, length of follow-up, number of patients in each group, and treatment.

### Statistical Analysis

We calculated a pooled HR with 95% CI from those reported in individual studies. But these statistical data was not given explicitly in the Aydinler et al study<sup>19</sup>. We calculated the necessary statistics on the basis of available numerical data with methods developed by Parmar et al<sup>17</sup>, Williamson et al<sup>20</sup>, and Tierney et al<sup>18</sup>. The calculation was accomplished by the software designed by Jayne Tierney et al<sup>18</sup>. We performed a meta-analysis of OS and/or PFS; the subgroup research was given when the study number  $\geq 2$ .

The statistical heterogeneity between studies was evaluated by Chi-squared Q-test and expressed by  $I^2$  index. Heterogeneity was defined as  $I^2 > 50\%$ <sup>21</sup>. When homogeneity was fine ( $I^2 \leq 50\%$ ), a fixed effect model was used. If not, a random effect model was used. We considered a favor survival outcome when observed HR  $< 1$  for the chemotherapeutic agents plus ACEI/ARB group compared to the alone chemotherapeutic agents group, and would be considered statistically significant if the 95% CI did not overlap 1.

The potential publication bias was assessed using the Begg's test, Egger's test, and funnel plot also was used when the study number  $\geq 5$ .  $p > 0.05$  was considered that there was no potential publication bias. All statistical analyses were performed with Stata version 12.1.

### Eligible Studies

After screening the titles and abstract of the potentially relevant studies, eleven studies met our eligible criteria. After reviewing the full text of the remaining articles, three studies had insufficient reported data, and the data could not be retrieved from the investigators<sup>22-24</sup>; we excluded these three studies from the meta-analysis. Another one study<sup>25</sup> was excluded because ACEI/ARB in combination with  $\beta$ -adrenoceptor blockers. The remaining seven studies<sup>13,14,19,26-29</sup> were

included in the final analysis. Characteristics of the included studies were summarized in Table I. These studies were published between the year of 2009 and 2015. The total number of included patients was 2436, ranging from 28 to 1449 patients per study (median, 348). Six studies had reported the HR with 95% confidence intervals for overall and/or progression-free survival; only one study<sup>19</sup>

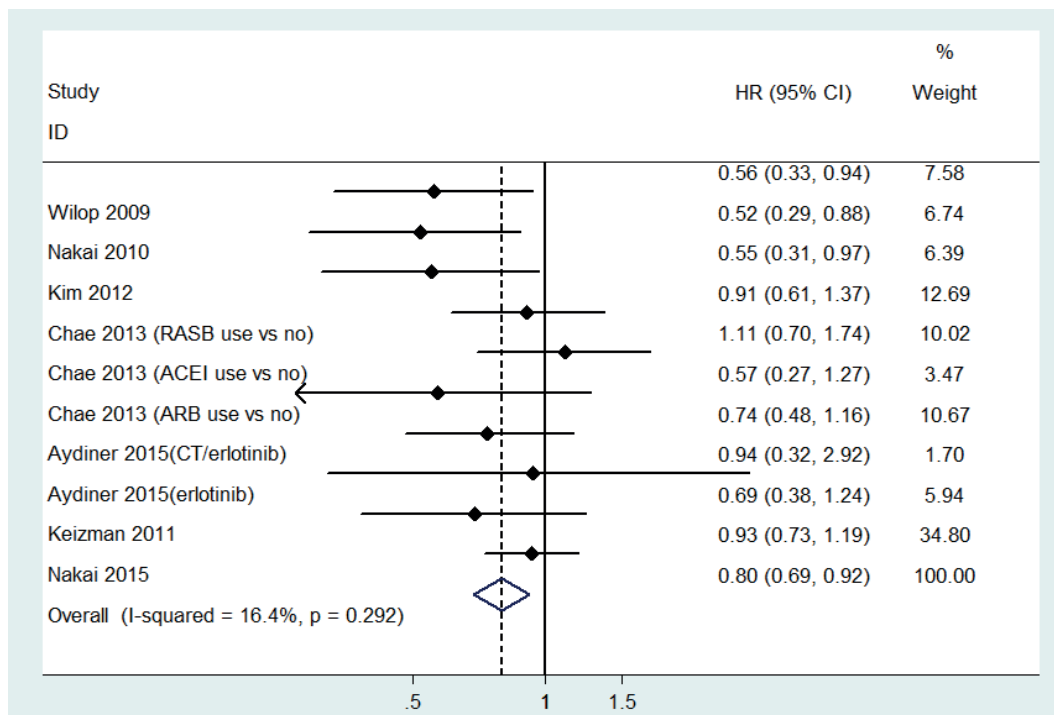
report the survival data, Kaplan-Meier curve of overall survival, did not reported HR with 95% confidence intervals.

### Overall Survival

Data on 10 comparisons were available from 7 eligible studies, including 2436 patients, 378 in the chemotherapeutic agents plus ACEI/ARB

**Table I.** Characteristics of the included studies.

Author	Year	Case	Control size	Median age	Cancer type	Treatment	Follow-up	Period
Stefan	2009	52	253	ACEI/ARB group: 69.5; non-ACEI/ARB group: 65.5	Non-small-cell lung cancer	First-line platinum-based chemotherapy; and the ACEI or ARB was administered from the start of the first cycle until the end of the last cycle simultaneously to first-line chemotherapy	9.4 months	1996-2007
Nakai	2010	27	128	ACEI/ARB group: 71; non-ACEI/ARB with HT group: 73; non-HT group: 63	Advanced pancreatic cancer	The patients received gemcitabine monotherapy, which was administered at a dose of 1000mg m-2 in a 30min intravenous infusion on day 1, 8, and 15 in 4-week cycles. The ACEI or ARB was administered during their chemotherapy.	9.5 months	2001-2009
Kim	2012	30	33	67	Advanced gastric cancer	Patients received platinum-based combination chemotherapy. Chemotherapy was repeated every 2–4 weeks according to the regimen. The ACEI or ARB was administered during their chemotherapy.	12.6 months	2002-2010
Chae	2013	160	1289	non-ACEI/ARB group: 48; ACEI/ARB group: 58	Invasive primary breast cancer	Patients were treated with anthracycline and taxane-based neoadjuvant systemic therapy (NST). The ACEI or ARB was administered during their chemotherapy.	55 months	1995-2007
Aydiner	2015	37	80	61	Metastatic non-small cell lung cancer	The patients in RASB group received an RASB agent during chemotherapeutics or erlotinib treatment at any time after the diagnosis of the malignancy.	18.9 months	2003-2011
Keizman	2011	44	83	60.7	Metastatic renal cell carcinoma	Patients received ACEI/ARB, before or within one month of sunitinib treatment.	81 months	2002-2010
Nakai	2015	28	210	67	Advanced pancreatic cancer	Patients received gemcitabine-based chemotherapy, and the patients in ARB group were on clinical trials of gemcitabine and candesartan combination therapy.	9.6 months	2001-2013



**Figure 1.** Forest plots for pooled hazard ratio (HR) and the corresponding 95% CI of overall survival with chemotherapeutic agents plus ACEI/ARB versus chemotherapeutic agents.

arms and 2058 in the comparator treatment arms. The estimated pooled HR for overall survival of all studies was 0.80 (95% CI: 0.69-0.92;  $I^2 = 16.4%$ ,  $p = 0.29$ ), indicating the favor for the treatment of chemotherapeutic agents plus ACEI/ARB (Figure 1).

**Subgroup analysis:** when there was more than one study focusing on the same chemotherapeutic agents, we conducted a subgroup analysis. As two articles<sup>26,14</sup> investigated the clinical effect of platinum-based agents plus ACEI/ARB; and another two studies<sup>3,29</sup> reported the gemcitabine in combination with ACEI/ARB. We separately summarized them in the subgroup analysis. The subgroup of platinum-based agents included 193 patients, 57 in the ACEI/ARB plus platinum-based agents' arms and 136 in the comparator treatment arms. The HR for platinum subgroup was 0.56 (95% CI: 0.38-0.82;  $I^2 = 0.0%$ ,  $p = 0.96$ ), indicating a significant benefit for the survival outcome of platinum-based agents plus ACEI/ARB (Figure 2A). The subgroup of gemcitabine-based agents included 393 patients, 55 in the ACEI/ARB plus gemcitabine-based agents' arms and 338 in the comparator treatment arms. The pooled HR for gemcitabine subgroup was 0.85 (95% CI: 0.68-

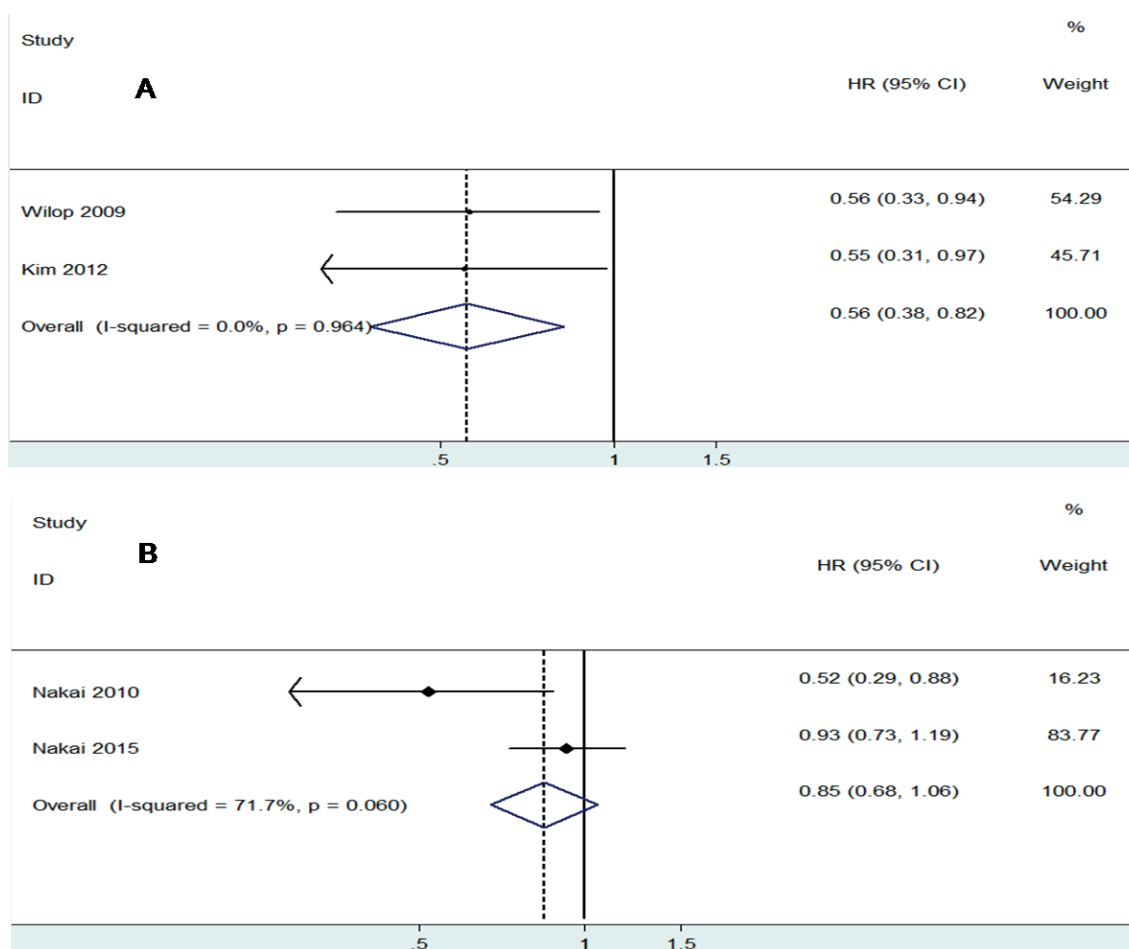
1.06), its 95% CI overlap 1, indicating the result was not statistically significant; and its  $I^2$  was 71.7%, also indicating their heterogeneity was significant (Figure 2B).

### Progression-free Survival

Data on four comparisons were available from the eligible studies, including 558 patients, 129 in the chemotherapeutic agents plus ACEI/ARB arms and 429 in the comparator treatment arms. A summary of individual studies and pooled results from the primary analysis of progression-free survival were presented in Figure 3. The pooled HR for progression-free survival was 0.79 (95% CI: 0.66-0.94;  $I^2 = 50.7%$ ,  $p = 0.11$ ), indicating a significant benefit for the treatment of chemotherapeutic agents plus ACEI/ARB.

### Sensitivity Analysis

In the analysis of overall survival, the HR and its 95% confidence intervals for OS were extracted from Kaplan-Meier curve in one study<sup>19</sup>; these extracted data was not accuracy, and may affect the meta-analysis. We rejected this study and estimated pooled HR for overall survival of the remaining studies; and its HR was 0.80 (95% CI:



**Figure 2.** Forest plots for subgroup analysis. Pooled hazard ratio (HR) and the corresponding 95% CI for the platinum subgroup (A) and gemcitabine subgroup (B) with chemotherapeutic agents plus ACEI/ARB versus chemotherapeutic agents.

0.69-0.93;  $I^2 = 33.8\%$ ,  $p = 0.16$ ; Figure 4A). This indicated that the error which comes from HR being extracted from K-M curve had a non-significant impact on the outcome of meta-analysis.

In the meta-analysis of progression-free survival, its  $I^2 > 50\%$ , indicated there was significant heterogeneity. We rejected the Nakai's (2015) study<sup>29</sup> because its weight was maximum, and estimated the pooled HR for progression-free survival in the remaining studies; and the HR was 0.63 (95% CI: 0.47-0.83;  $I^2 = 0.0\%$ ,  $p = 0.41$ ; Figure 4B); indicating this work was the source of heterogeneity.

**Assessment of Publication Bias**

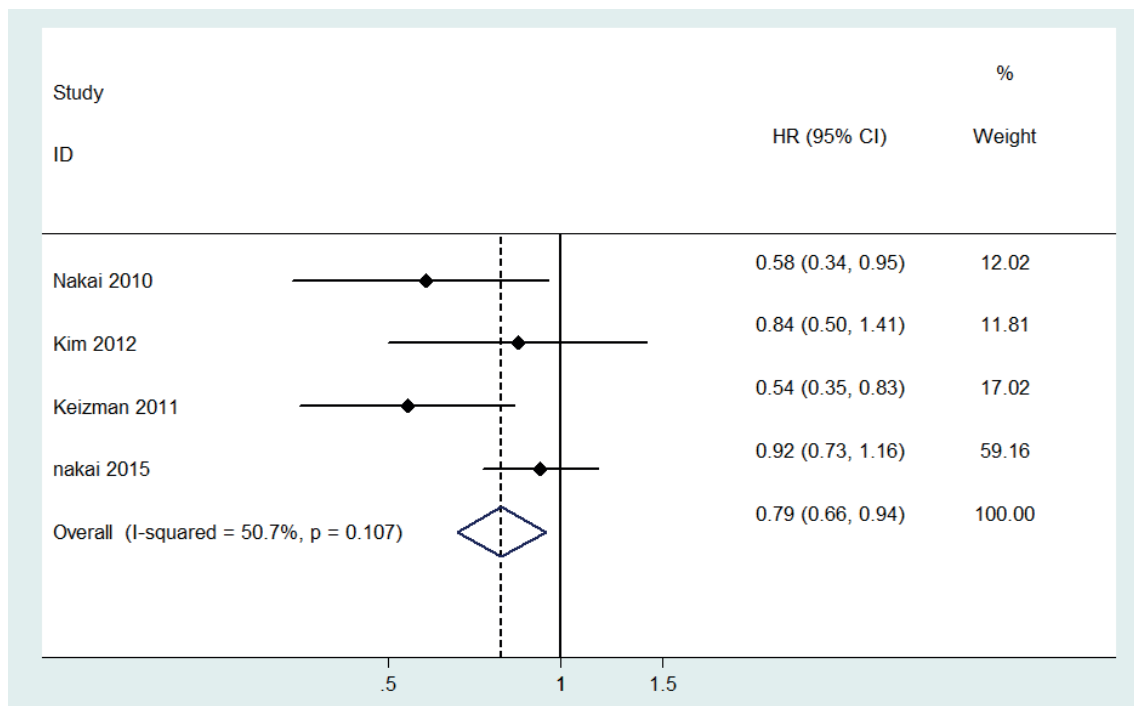
Begg's and Egger's test were used to examine publication bias. No significant publication biases were found in results of HR for OS ( $p = 0.283$  and  $0.097$ ); as for PFS, we obtained similar results ( $p$

$= 1.0$  and  $0.257$ ). Furthermore, a funnel plot was undertaken which also indicates the absence of publication bias (Figure 5).

**Discussion**

This meta-analysis of 7 retrospective studies, investigated the efficacy of RASBs agents when co-administered with conventional therapy in cancer patients. To our knowledge, it was the first time that a detailed meta-analysis revealed that the combination of chemotherapeutic agents and ACEI/ARB can improve the survival outcome and progression-free survival of diverse types cancer patients.

Treatment of cancer has been a major challenge for oncologists due to its sustaining proliferative signaling, evading growth suppressors,



**Figure 3.** Forest plots for pooled hazard ratio (HR) and the corresponding 95% CI for progression-free survival with chemotherapeutic agents plus ACEI/ARB versus chemotherapeutic agents.

resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion and metastasis<sup>30</sup>. ACEIs/ARBs are the most active drugs approved for treatment of hypertension, heart failure, and diabetic nephropathy. ACEIs and ARBs were combined into one group because of the similar mechanism of action, and there were no differences in relevant outcomes between the two groups. Some epidemiological researches demonstrated that the expression of the renin-angiotensin system is associated with an increased cancer risk and preclinical data also support the concept that ACEI/ARB exerts anti-carcinogenic effect<sup>31,13</sup>. The main mechanism underlying this effect as follow: RAS signaling increases tumor cell proliferation and modulating the growth of vascular cells during angiogenesis<sup>32</sup>; and the local RAS is related to fibrosis<sup>33</sup>. Therefore, the use of ACEI/ARB theoretically increases the efficacy of chemotherapy by enhancing delivery of chemotherapeutics.

Our data support the hypothesis that chemotherapeutic agents plus ACEI/ARB can improve the survival outcome of diverse types' cancer patients, and suggests that well-designed prospec-

tive studies are warranted to confirm these findings. Our study also had some limitations, such as all the included studies were retrospective; we found no evidence of publication bias in this meta-analysis, inherent bias may exist because small studies with null results are unlikely to be published.

## Conclusions

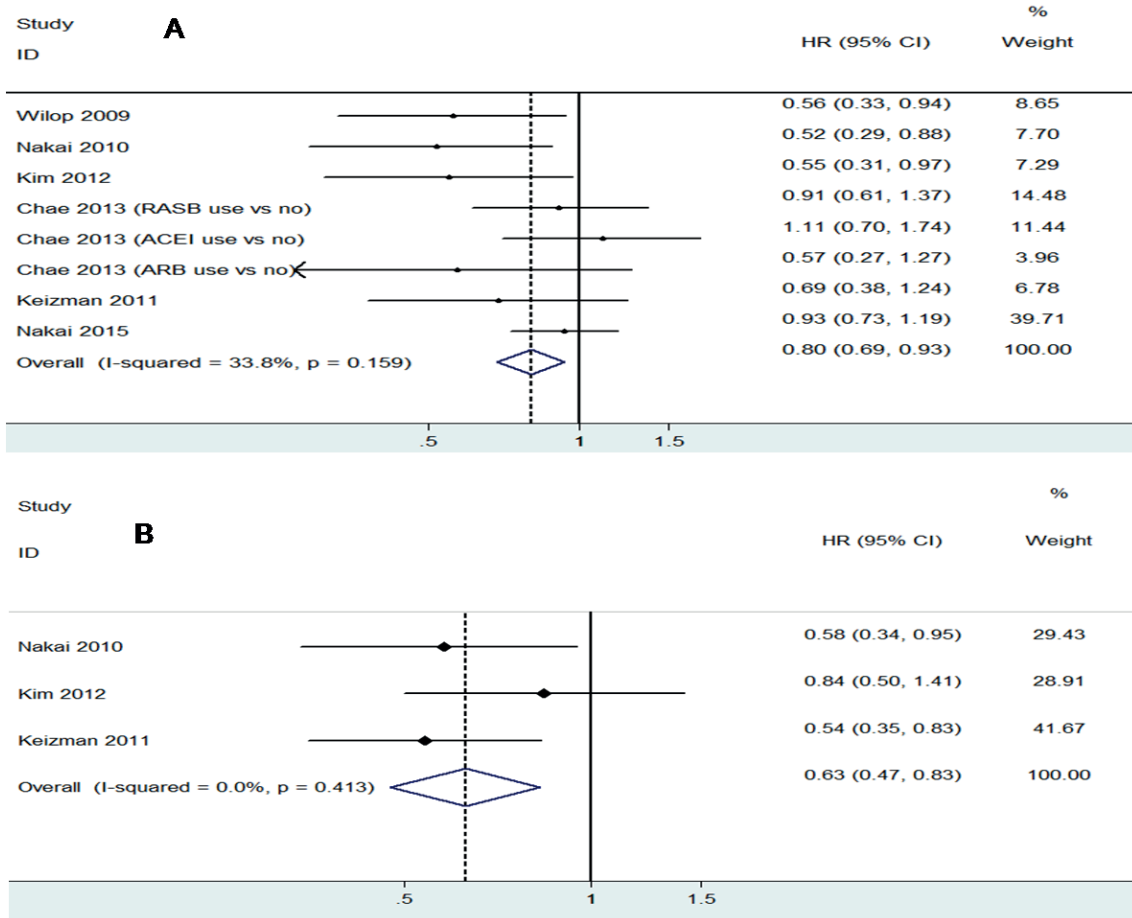
Our findings suggest a potential efficacy of the combination of RASBs and chemotherapeutic agents for multiple types' cancer therapy. More research and well-designed, rigorous, large clinical trials are required to address these issues.

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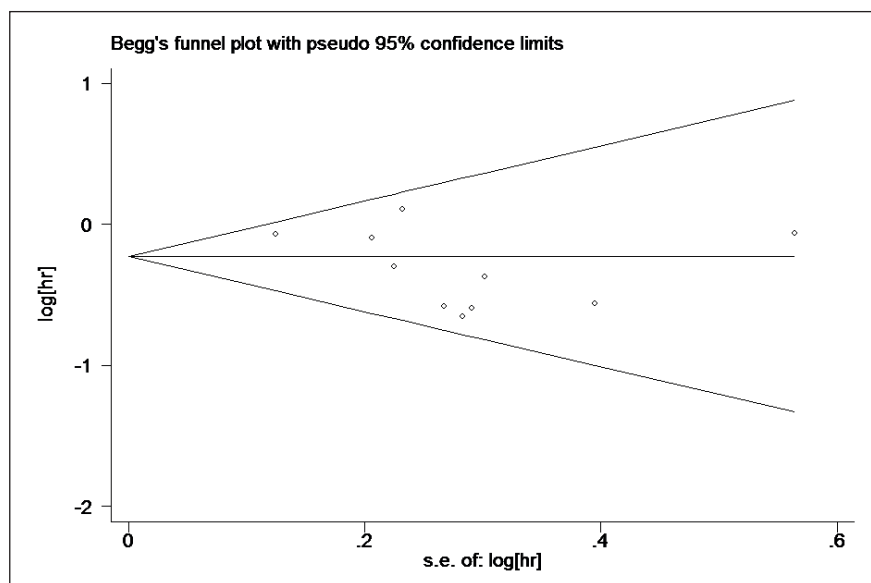
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## Conflict of interest

The authors declare that no conflicts of interest exist.



**Figure 4.** Sensitivity analysis. Pooled hazard ratio (HR) and the corresponding 95% CI for the overall survival (A) and progression-free survival (B) with chemotherapeutic agents plus ACEI/ARB versus chemotherapeutic agents.



**Figure 5.** Begg's funnel plot with 95% confidence limits for overall survival among the included studies.

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