Impact of ACEI/ARB use on the survival of hypertensive patients with cancer: A meta-analysis

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Received April 7, 2024; Accepted July 1, 2024

DOI: 10.3892/ol.2024.14667

Abstract. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly used antihypertensive drugs. However, the impact that the use of ACEI and ARB drugs will have on the survival of patients with hypertension and cancer is still unclear. Therefore, the present study aimed to investigate the effects of ACEI and ARB use on the survival of patients with cancer. The Embase, PubMed and Web of Science databases were used to systematically analyze the survival of hypertensive patients with cancer treated with ACEIs or ARBs. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to evaluate the association between ACEI and ARB use and patient survival. The relationship between the survival of patients with certain types of cancer and ACEI and ARB use was evaluated using the calculated HRs. Patients with ovarian, pancreatic, prostate, hepatocellular, lung, esophageal, gastric, colon, nasopharyngeal, head and neck tumors, gallbladder and rectal cancers that used ACEI and ARB analogs had significantly increased survival times, except for patients with breast cancer (HR, 1.04; 95% CI, 0.90-1.19; P<0.01) and uroepithelial carcinoma (HR, 1.15; 95% CI, 0.69-1.94; P<0.01), who had significantly decreased survival times, when compared with patients who did not use these drugs. Analysis of the relationship between the use of ACEIs or ARBs alone or in combination on the overall survival of hypertensive patients with cancer demonstrated that the use of ACEIs alone (HR, 1.00; 95% CI, 0.93-1.08; P<0.01) did not have a significant effect on the survival of these patients. By contrast, the survival time was increased in hypertensive patients with cancer who used either ARBs alone (HR, 0.89; 95% CI, 0.84-0.94; P<0.01) or a combination of ACEIs and ARBs (HR, 0.84; 95% CI, 0.78-0.91; P<0.01). The present meta-analysis demonstrated the potential effects of ACEI and ARB use on the overall survival of patients with cancer. Therefore, investigation of the underlying mechanisms of action of ACEIs and ARBs, as well as the identification of specific groups of patients who may benefit from these interventions, could potentially lead to novel therapeutic options and improve the prognosis of patients with cancer in the future.

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Key words: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, hypertension, tumor, cancer

Introduction

Hypertension is a common risk factor for cardiovascular diseases (1). A previous multi-center prospective cohort study that included 17,712 patients from the US population with prostate cancer, respiratory cancer, breast cancer, digestive system cancers, gynecological cancers, urinary system cancers, and head and neck cancers reported that 37% of the patients with cancer were diagnosed with hypertension and needed to take both anti-cancer drugs and antihypertensive drugs (2). Previous studies have shown that the use of antihypertensive drugs during cancer treatment is correlated to a certain extent with prognosis and may affect the occurrence and development of tumors (3,4). The renin-angiotensin-aldosterone system (RAAS) serves a critical role in the maintenance of cardiovascular homeostasis and the RAAS of local tissues may also be involved in the development of tumors (5). Lung, thyroid, breast, stomach and colorectal cancer have been reported to express components of the RAAS, renin and angiotensin (Ang) II receptors (6,7). According to the classical viewpoint, angiotensin II (Ang II) is the main element of the RAAS generated by angiotensin-converting enzyme (ACE), and its various effects, mainly mediated by the angiotensin type 1 (AT1) receptor, include vasoconstriction, detrimental remodeling, and oxidative stress in various tissues (8). It has been reported that Ang II can also serve as a growth factor, promoting tumor cell proliferation through paracrine signal transduction, and can facilitate angiogenesis by stimulating VEGF expression through activation of the angiotensin I receptor (AT1) (9).

Angiotensin-converting enzyme inhibitors (ACEIs) and AT1 receptor antagonists (ARBs), which inhibit the generation of angiotensin II, are classical inhibitors of the RAAS (10). Previous experimental and clinical investigations have reported the potential impact of these medications on tumor development and progression. For example, in a mouse model of colon cancer with liver metastases, the co-administration of ACEI, captopril, and the angiotensin receptor blocker (ARB) irbesartan, reduced the size of metastatic foci (11). However, in clinical studies, results regarding the relationship between the use of ACEIs and cancer prognosis in randomized trials and observational studies are contradictory. In a 2003 clinical trial the impact of ARB (candesartan) on the morbidity and mortality of patients with heart failure reported that the cancer incidence increased in patients using candesartan compared with those treated with placebo (12). By contrast, a retrospective study of 287 patients conducted in 2009 reported that the addition of an ACEI or an ARB to platinum-based chemotherapy could extend the survival of patients with advanced lung cancer (13). This indicates that the application of RAAS inhibitors, such as ACEI/ARB drugs, may have certain effects on the survival and prognosis of tumor patients.

Therefore, the present meta-analysis analyzed cohort and case-control studies that investigated the relationship of the use of ACEIs and ARBs, and the prognosis of patients with cancer and aimed to evaluate whether the use of ACEIs and ARBs alone or in combination can influence the overall survival (OS) of patients with cancer.

Materials and methods

Protocol registration and guidance. The study protocol was registered in the PROSPERO database (registration no. CRD42023487852; https://www.crd.york.ac.uk/prospero). The present study was performed in accordance with the Cochrane handbook (14) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (15).

Literature retrieval. Literature published in English was retrieved from the Embase (https://www.embase.com), PubMed (https://pubmed.ncbi.nlm.nih.gov) and Web of Science databases (https://access.clarivate.com) and studies that examined the association between the use of ACEIs and ARBs and the OS of patients with cancer were selected. The retrieval period was from the establishment of the aforementioned databases to July 10 2023. Databases with the following search algorithm: ('ACE inhibitor' or 'angiotensin converting enzyme inhibiting agent' or 'angiotensin converting enzyme inhibitor' or 'angiotensin converting enzyme inhibitors' or 'angiotensin I converting enzyme inhibitor' or 'angiotensin-converting enzyme inhibitors' or 'converting enzyme inhibitor' or 'angiotensin II type 1 receptor blockers' or 'angiotensin-converting enzyme inhibitors' or 'captopril' or 'cilazapril' or 'enalapril' or 'fosinopril' or 'imidapril' or 'lisinopril' or 'moexipril' or 'perindopril' or 'perindopril' or 'quinapril' or 'ramipril' or 'trandolapril' or 'eprosartan' or 'irbesartan' or 'irbesartan' or 'Olmesartan' or 'telmisartan' or 'valsartan' or 'candesartan' or 'ARB' or 'angiotensin receptor antagonists') and ('cancer' or 'cancers' or 'malignant neoplasia' or 'malignant neoplastic disease' or 'malignant tumor' or 'malignant tumour' or 'neoplasia' or 'malignan' or 'neoplasmic malignancy' or 'neoplastic malignancy' or 'oncologic malignancy' or 'oncological malignancy' or 'tumor' or 'malignant' or 'tumoral malignancy' or 'tumorous malignancy' or 'tumour' or 'malignant' or 'malignant neoplasm').

A comprehensive literature search of published studies was performed in January 2016 based on PubMed, Web of Science, and the Chinese National Knowledge Infrastructure (CNKI) databases with the following search algorithm: ('hypertension' or 'blood pressure' or 'systolic pressure' or 'diastolic pressure') and ('prostate cancer' or 'prostate neoplasm') and ('cohort' or 'case control' or 'case-control'). In addition, the lists of references from retrieved articles and reviews were also checked to identify any additional eligible studies. No limitations on language or publication date were applied. This systematic review and meta-analysis was designed, performed, and reported based on the standards of quality for reporting meta-analyses.

Inclusion and exclusion criteria. The present meta-analysis included studies in which: i) Participants were diagnosed with tumors by pathological examination; ii) the relationship between ACEI and ARB use and the OS of patients with cancer with hazard ratios (HR) and 95% CIs were reported, or studies in which the HRs and CIs could be calculated from the data provided in the studies; and iii) cohort and case-control studies.

The following studies were excluded: i) Reviews, conference minutes, case reports and systematic reviews; ii) The use of non-standard scoring criteria for outcome indicators; iii) studies in which the participants had distant metastasis or other malignant tumors at the time of diagnosis; and iv) studies for which the full text could not be accessed.

Literature screening and data extraction. The literature was independently screened by two investigators, who extracted the data and cross-checked the results. In cases of disagreement, a third party was consulted to arbitrate discrepancies and, when possible, the authors of the included studies were contacted to supplement missing information. Literature was screened through the removal of duplicate studies, reading of the titles and abstracts to exclude publications irrelevant to the research topic and evaluation of the full text to determine whether each study should be included. The extracted data included: Author(s), tumor type, country, year, sex, sample size, follow-up duration, types of drugs used, study type, HRs and 95% CIs. The quality of the screened literature was assessed using the Newcastle-Ottawa scale (NOS) (16) with a total score of 9 points, which included assessments on the selection of study groups (4 points), comparability between groups (2 points) and outcome measures (3 points). Studies with a score of ≥6 points were considered to be of high quality.

Data analysis. The STATA software (version 16.0; StataCorp LP) was used to perform the meta-analysis. The HR and 95% CI of each outcome measure were weighted and combined by calculating the log HR and SElog HR, which used the general inverse variance method to construct a forest plot. The heterogeneity of the studies were assessed quantitatively based on I^2 values. Due to the potential heterogeneity in the intervention

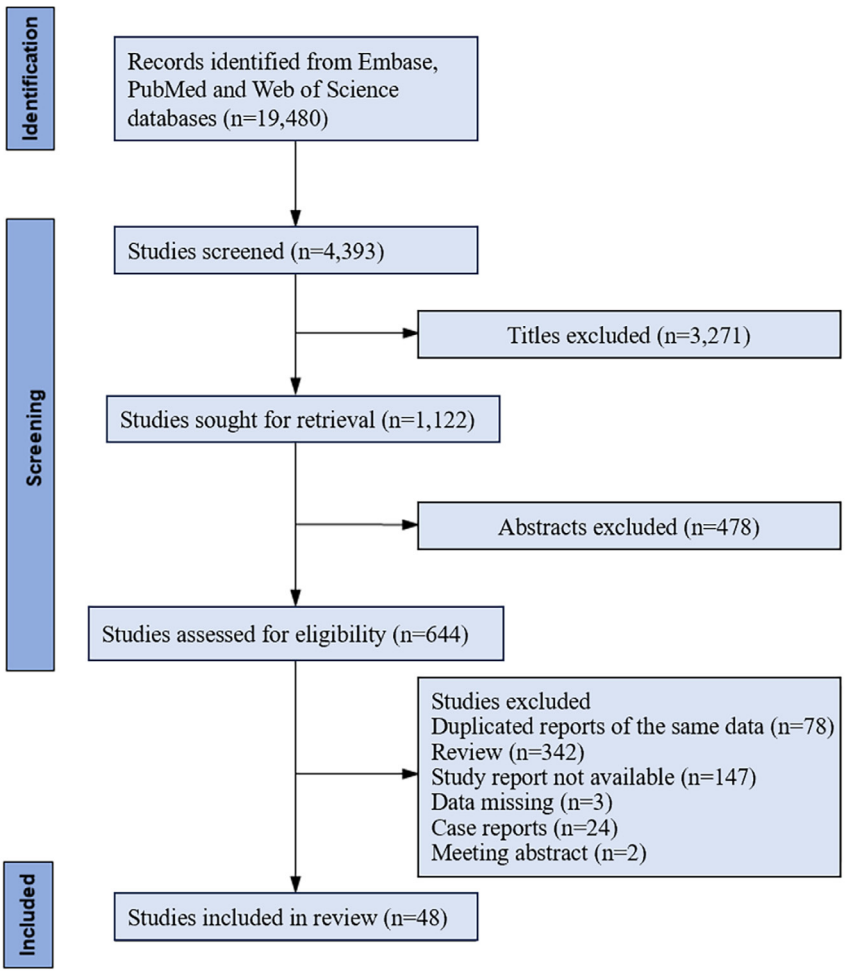


Figure 1. Flowchart of the literature screening process.

effects across different populations and geographic locations, a random effects model was used and subgroup analyses was performed. Egger's funnel plots and linear regression tests were used to assess publication bias. The robustness and reliability of the obtained results were tested through sensitivity analysis. All statistical tests performed were two-sided and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Literature retrieval. A total of 19,480 articles were obtained during the initial retrieval (Fig. 1). Following the initial screening process, 4,393 articles were identified for the present meta-analysis. Subsequently, 644 articles were selected after reading the titles and abstracts. After reading the full texts, 48 articles that met the inclusion and exclusion criteria were included in the present meta-analysis.

Characteristics of the included studies. The present meta-analysis included a total of 48 studies, which involved 923,134 participants (13,17-63). All included studies reported the HRs and 95% CIs which were calculated using the Cox regression model. The included studies were published between 2011 and 2023. Among these, 12 studies were conducted in the United States, 7 in Japan, 7 in Finland, 6 in China, 2 in England, 2 in Canada, 2 in the Czech Republic, 3 in Italy and 1 each in Denmark, Germany, South Korea, North Korea, Norway, Oman and Poland (Table I). Furthermore, there were 34 cohort studies and 14 case-control studies among the included studies. Of the total included studies, 7 reported the use of ACEIs alone, 8 on the use of ARBs alone and 33 on the combined use of ACEIs and ARBs. Based on the NOS, all included studies scored ≥6 points, which indicated the included studies were of high quality.

Impact of ACEI and ARB use on the OS of patients with cancer. The use of ACEIs or ARBs alone and in combination on the OS of patients with cancer over the past decade was analyzed in the 48 included studies (Fig. 2). Meta-analysis indicated that patients who used ACEIs or ARBs, either alone or in combination, had a significantly increased OS compared with that of patients with cancer who did not use ACEI or ARB drugs (HR, 0.91; 95% CI; 0.87-0.95; $P<0.01$).

Impact of ACEI and ARB use on the OS of patients in specific types of cancer. A subgroup analysis was performed on the data from the included studies according to the site of tumor (Fig. 3). Among patients with ovarian (HR, 0.85; 95% CI, 0.74-0.971; $P<0.01$), pancreatic (HR, 0.86; 95% CI, 0.73-1.01;

Table I. Characteristics of the studies included in the present meta-analysis.

First author, year	Type of cancer	Patient sex	Median age, years ± SD (range)	Country of residence	Study population, n	Diagnosis period	Follow-up period	Treatment	Study design	Newcastle-Ottawa quality score	(Refs.)
Anderson *et al*, 2021	Lung	Mix	60.2±15.1	United States	187,060	1996-2018	7.1 years	ACEI/ARB	Cohort	≥6	(17)
Aydiner *et al*, 2015	Non-small cell lung	Mix	61±1 (42-75)	Japan	117	2003-2011	18.9 months	ACEI/ARB	Case-control	≥6	(18)
Balkrishnan *et al*, 2021	Colorectal	Mix	(³65)	United States	13,982	2007-2012	6.0 years	ACEI/ARB	Cohort	≥6	(19)
Botteri *et al*, 2013	Breast	Female	62 (48-80)	Italy	800	1997-2008	72 months	ARB	Case-control	≥6	(20)
Busby *et al*, 2017	Gastro-esophageal	Mix	-	England	5,124	1998-2012	1.4 years	ARB	Cohort	≥6	(21)
Cardwell *et al*, 2014	Multi-cancer	Mix	-	England	51,507	1998-2006	6.0 years	ACEI/ARB	Cohort	≥6	(22)
Chae *et al*, 2013	Breast	Female	58	United States	1,449	1995-2007	55 months	ACEI	Case-control	≥6	(23)
Cho *et al*, 2020	Ovarian	Female	-	Korea	878	2001-2014	120 months	ARB	Cohort	≥6	(24)
Cui *et al*, 2019	Multi-cancer	Mix	(40-74)	China	2,891	1996-2006	3.4 years	ACEI/ARB	Cohort	≥6	(25)
Engineer *et al*, 2013	Colorectal	Mix	66.48 (³18)	United States	262	2000-2009	4,364 days	ACEI/ARB	Cohort	≥6	(26)
Eskelinen *et al*, 2022	Renal	Mix	-	Finland	13,873	1995-2012	6.2 years	ACEI/ARB	Cohort	≥6	(27)
Fiala *et al*, 2019	Colorectal	Mix	62.3 (28.0-86.1)	Czech Republic	514	2005-2019	22.3 months	ACEI	Cohort	≥6	(28)
Fiala *et al*, 2021	Renal cell carcinoma	Mix	37.5-83.1	Czech Republic	343	2007-2020	96 months	ACEI/ARB	Cohort	≥6	(29)
Fryzek *et al*, 2005	Renal cell carcinoma	Mix	62 (30-85)	Denmark	113,298	1989-2002	10.0 years	ACEI/ARB	Cohort	≥6	(30)
Ganz *et al*, 2011	Breast	Female	-	United States	1779	1997-2000	8.2 years	ACEI	Cohort	≥6	(31)
Harding *et al*, 2019	Ovarian	Female	(³66)	United States	2,195	2007-2012	12 months	ACEI	Cohort	≥6	(32)
Holmes *et al*, 2013	Multi-cancer	Mix	(³65)	Canada	15,582	2004-2008	6.0 years	ACEI/ARB	Cohort	≥6	(33)
Huang *et al*, 2021	Ovarian	Female	-	United States	743	1994-2017	1.0 years	ACEI	Cohort	≥6	(34)
Keith *et al*, 2022	Pancreatic	Mix	74.4 (66.3-81.5)	Italy	8,158	2003-2011	6.2 months	ACEI/ARB	Cohort	≥6	(35)
Keizman *et al*, 2011	Renal cell carcinoma	Mix	66 (47-79)	United States	127	2004-2010	60 months	ARB	Case-control	≥6	(36)
Kim *et al*, 2012	Gastric	Mix	67 (37-85)	South Korea	63	2002-2010	60 months	ACEI/ARB	Case-control	≥6	(37)
Iede *et al*, 2022	Pancreatic	Mix	73 (42-80)	Japan	56	2015-2020	50 months	ACEI/ARB	Case-control	≥6	(38)
Li *et al*, 2022	Gastro-esophageal	Mix	(³50)	China	4,577	2008-2016	10.0 years	ACEI/ARB	Cohort	≥6	(39)
Lin *et al*, 2021	Nasopharyngeal carcinoma	Mix	-	China	927	2008-2017	5.0 years	ARB	Cohort	≥6	(40)
Lorona *et al*, 2021	Breast	Female	(20-69)	United States	4,557	2004-2015	5.0 years	ACEI	Cohort	≥6	(41)
Mafiana *et al*, 2019	Colorectal	Mix	-	Oman	301	2006-2014	8.0 years	ACEI/ARB	Case-control	≥6	(42)
Ho *et al*, 2018	Hepatocellular carcinoma	Mix	-	China	15,597	2005-2014	9.0 years	ACEI/ARB	Cohort	≥6	(43)
Morris *et al*, 2016	Rectal	Mix	-	United States	216	1999-2012	4.1 years	ACEI/ARB	Case-control	≥6	(44)
Nakai *et al*, 2010	Pancreatic	Mix	71 (53-87)	Japan	155	2001-2009	9.5 months	ACEI/ARB	Case-control	≥6	(45)
Nakai *et al*, 2015	Pancreatic	Mix	67 (39-89)	Japan	349	2001-2014	9.6 months	ACEI/ARB	Cohort	≥6	(46)

Table I. Continued.

First author, year	Type of cancer	Patient sex	Median age, years ± SD (range)	Country of residence	Study population, n	Diagnosis period	Follow-up period	Treatment	Study design	Newcastle-Ottawa quality score	(Refs.)
Nayan *et al*, 2018	Kidney	Mix	(≥65)	Canada	9,124	1997-2013	16.0 years	ACEI/ARB	Cohort	≥6	(47)
Osumi *et al*, 2015	Colorectal	Mix	61.5 (38-75)	Japan	181	2007-2010	70 months	ARB	Case-control	≥6	(48)
Ozawa *et al*, 2019	Colorectal	Mix	-	Japan	461	2009-2014	57 months	ACEI/ARB	Case-control	≥6	(49)
Santala *et al*, 2019	Urothelial	Mix	75 (44-96)	Finland	14,065	1995-2012	4.1 years	ACEI/ARB	Cohort	≥6	(50)
Santala *et al*, 2020	Breast	Female	67 (27-102)	Finland	73,170	1995-2013	20.0 years	ACEI/ARB	Cohort	≥6	(51)
Santala *et al*, 2019	Prostate	Male	63 (40-93)	Finland	14,422	1995-2013	9.9 years	ACEI/ARB	Cohort	≥6	(52)
Siltari *et al*, 2020	Prostate	Male	68 (64-72)	Finland	8,253	1996-2016	7.6 years	ACEI/ARB	Cohort	≥6	(53)
Santala *et al*, 2021	Ovarian	Female	70 (18-101)	Finland	12,122	1995-2013	19.0 years	ACEI/ARB	Cohort	≥6	(54)
Siltari *et al*, 2018	Prostate	Male	59 (55-63)	Finland	78,615	1996-2015	20.0 years	ACEI/ARB	Cohort	≥6	(55)
Støer *et al*, 2021	Pancreatic adenocarcinoma	Mix	67 (60-74)	Norway	2,614	2007-2015	7.0 years	ARB	Cohort	≥6	(56)
Stokes *et al*, 2021	Head and neck	Mix	(^{3}66)	United States	5,000	2008-2015	24 months	ACEI/ARB	Cohort	≥6	(57)
Tamburrino *et al*, 2021	Pancreatic adenocarcinoma	Mix	-	Italy	430	2015-2019	3.0 years	ACEI/ARB	Cohort	≥6	(13)
Wilk *et al*, 2021	Prostate	Male	69 (43-88)	Poland	93	2014-2018	9.8 months	ACEI/ARB	Case-control	≥6	(58)
Wilop *et al*, 2009	Non-small cell lung	Mix	62 (31-83)	Germany	287	1996-2007	8.1 months	ACEI/ARB	Cohort	≥6	(59)
Wu *et al*, 2021	Oral squamous cell carcinoma	Mix	58 (51.7-66)	China	714	2007-2018	11.0 years	ARB	Case-control	≥6	(60)
Yoshida *et al*, 2017	Bladder	Mix	70 (39-91)	Japan	269	1995-2014	44.5 months	ACEI/ARB	Case-control	≥6	(61)
Zhang *et al*, 2022	Colorectal	Mix	-	United States	2,343	1976-2014	28.0 years	ACEI	Cohort	≥6	(62)
Yang *et al*, 2022	Multi-cancer	Mix	-	China	253,491	2002-2019	6.5 years	ACEI/ARB	Cohort	≥6	(63)

ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; -, age group not indicated.

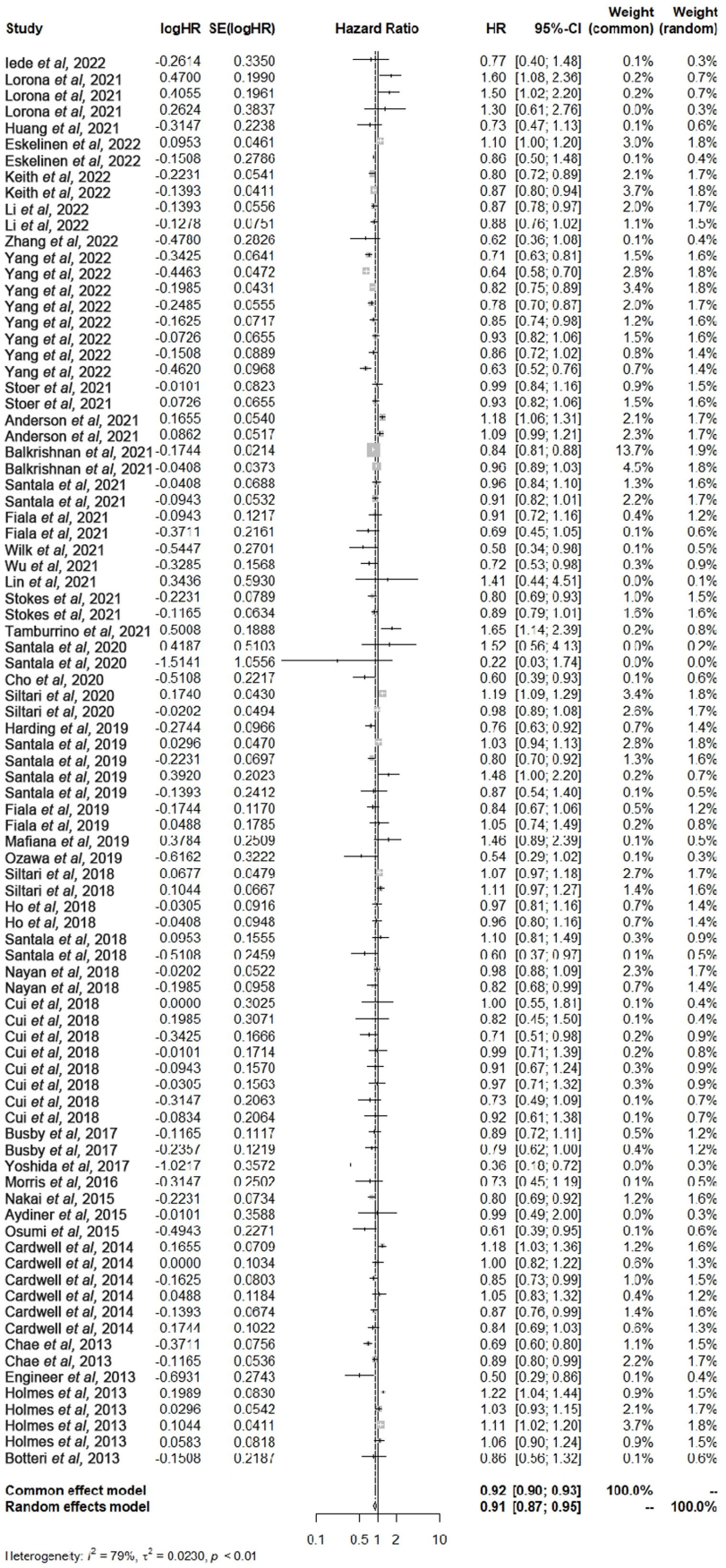
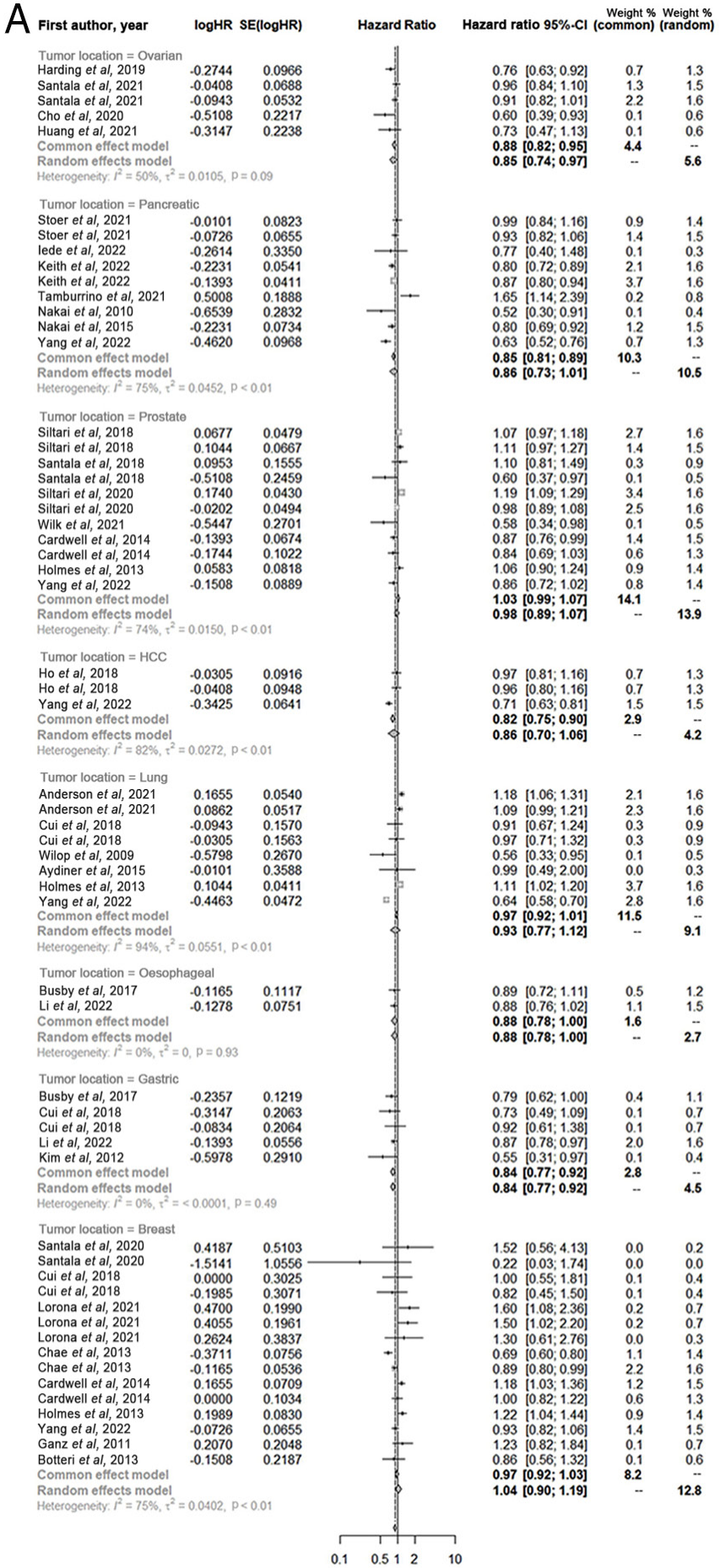


Figure 2. Forest plot of the impact of the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on the overall survival of tumor patients over the past decade. Within this graphical representation, each block corresponds to an individual study, with the size of the block reflecting its relative weight in the analysis. The horizontal line through each block represents the 95% CI for the observed effect. At the bottom of the plot, the diamond represents the pooled effect calculated across all included studies, with the width of the diamond indicating the 95% CI. HR, hazard ratio; CI, confidence interval; SE, standard error.



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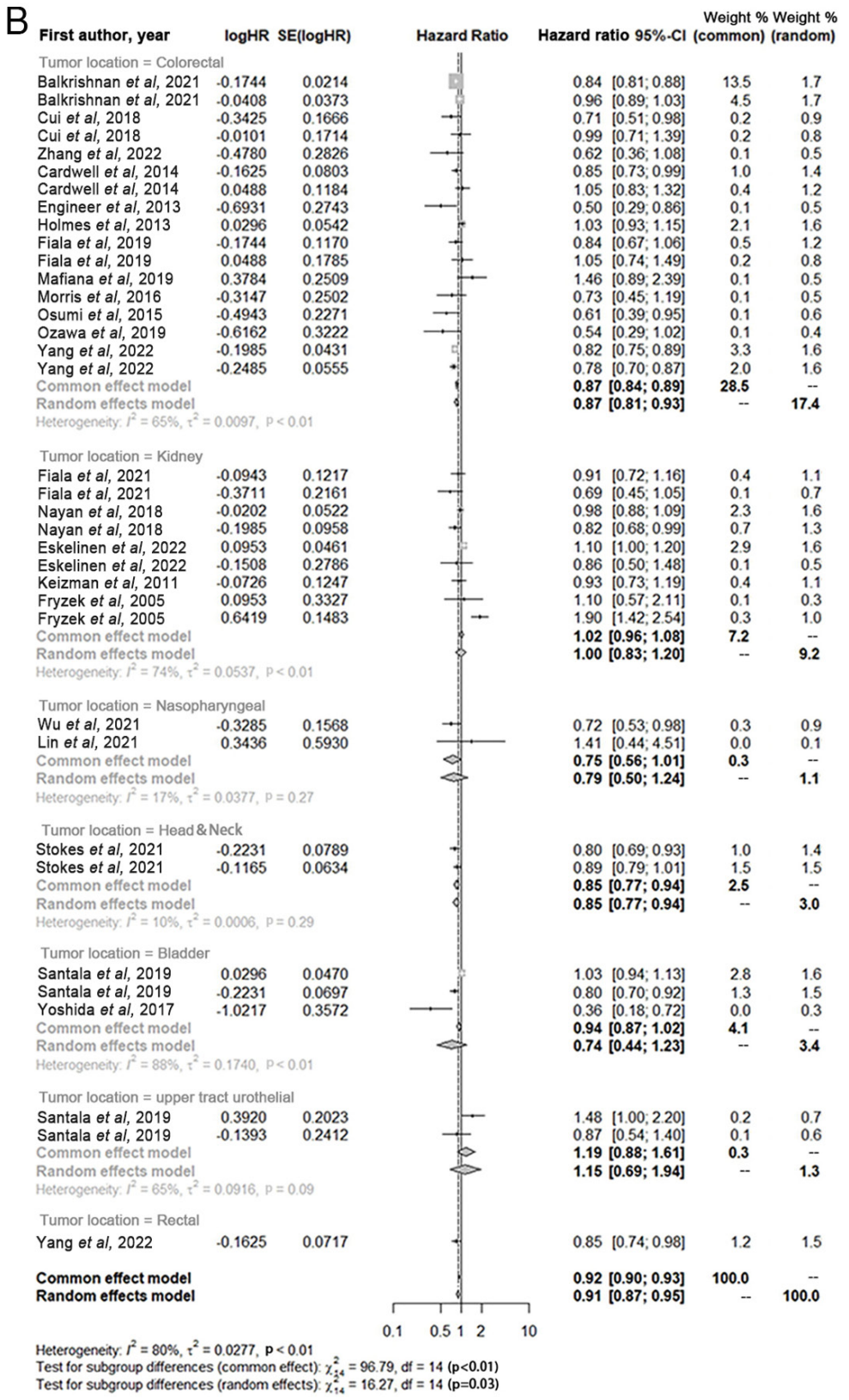

Figure 3. Forest plot of the impact of the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on the overall survival of patients with different tumors. (A) Outlines the impact of the use of ACEI/ARB drugs on the overall survival of patients with ovarian, pancreatic, prostate, HCC, lung, oesophageal, gastric and breast cancers. (B) Outlines the impact of the use of ACEI/ARB drugs on the overall survival of patients with colorectal cancer, kidney cancer, nasopharyngeal, head□neck, bladder, upper tract urothelial and rectal cancers. Within this graphical representation, each block corresponds to an individual study, with the size of the block reflecting its relative weight in the analysis. The horizontal line through each block represents the 95% CI for the observed effect. At the bottom of the plot, the diamond represents the pooled effect calculated across all included studies, with the width of the diamond indicating the 95% CI. HR, hazard ratio; CI, confidence interval; SE, standard error.

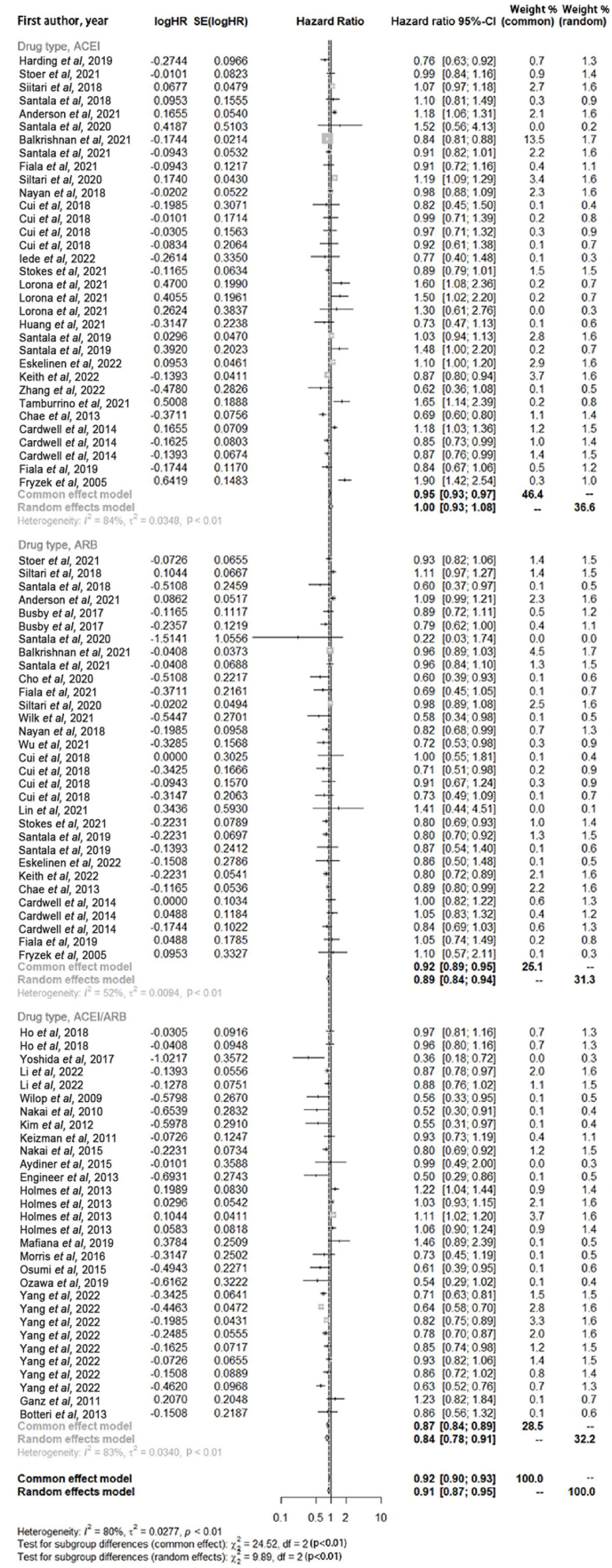

Figure 4. Forest plot of the impact of the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers alone or in combination on the overall survival of patients with tumors. Within this graphical representation, each block corresponds to an individual study, with the size of the block reflecting its relative weight in the analysis. The horizontal line through each block represents the 95% CI for the observed effect. At the bottom of the plot, the diamond represents the pooled effect calculated across all included studies, with the width of the diamond indicating the 95% CI. HR, hazard ratio; CI, confidence interval; SE, standard error.

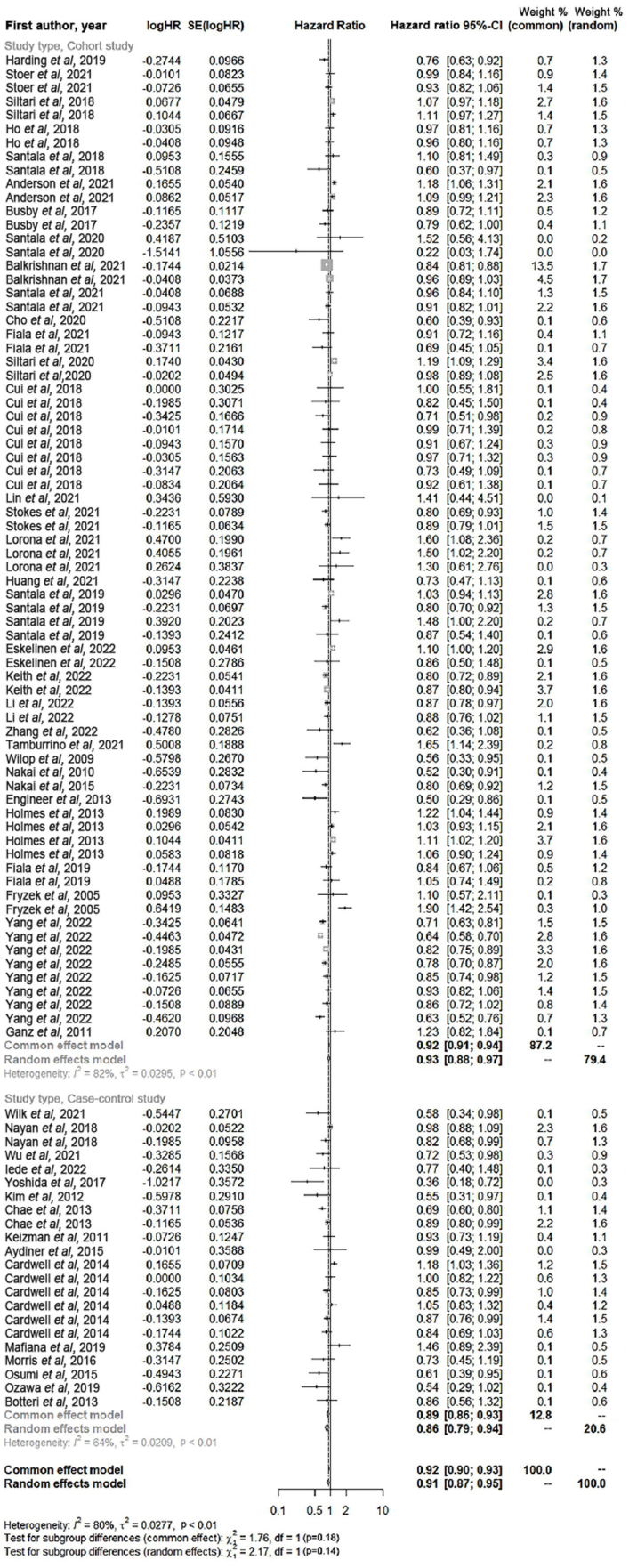

Figure 5. Forest plot of the impact of the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on the overall survival of patients according to data from different study types. Within this graphical representation, each block corresponds to an individual study, with the size of the block reflecting its relative weight in the analysis. The horizontal line through each block represents the 95% CI for the observed effect. At the bottom of the plot, the diamond represents the pooled effect calculated across all included studies, with the width of the diamond indicating the 95% CI. HR, hazard ratio; CI, confidence interval; SE, standard error.

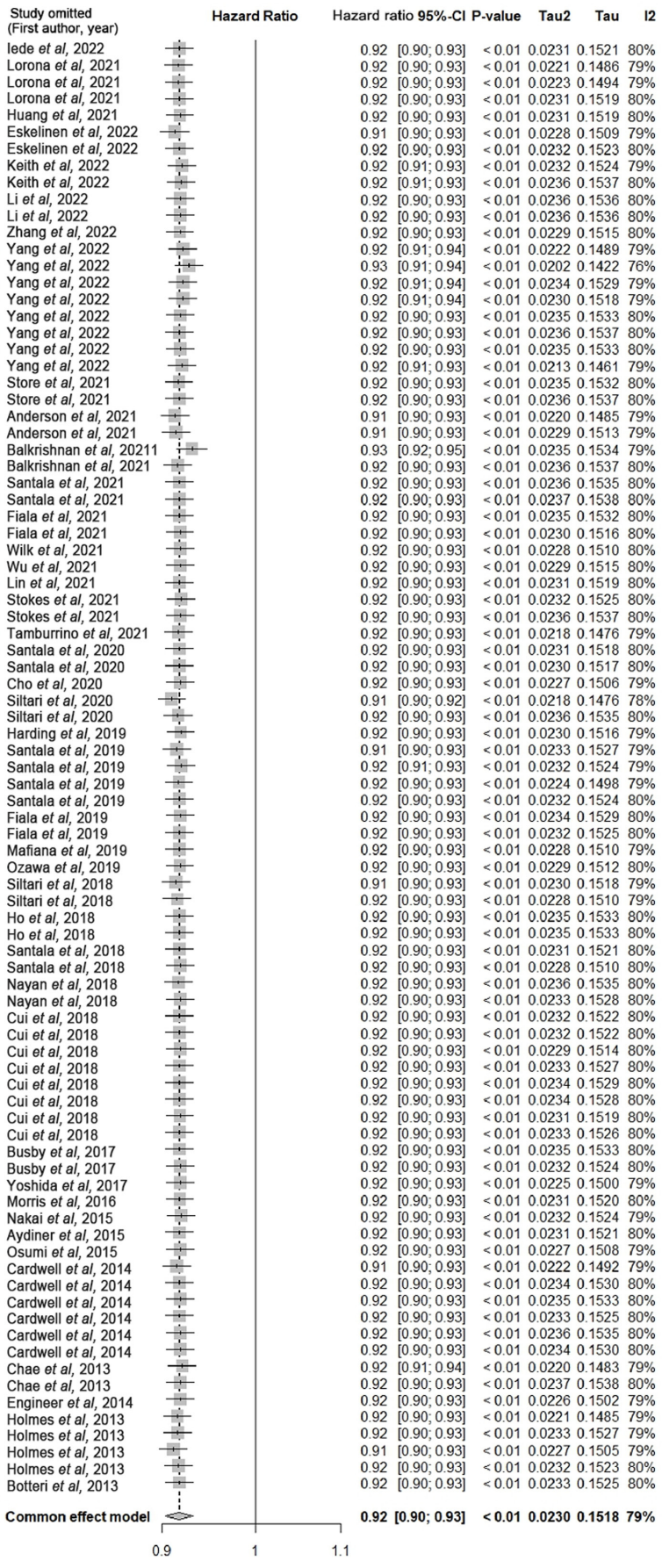

Figure 6. Hazard ratio for the primary outcome in prespecified Subgroups. Within this graphical representation, each block corresponds to an individual study, with the size of the block reflecting its relative weight in the analysis. The horizontal line through each block represents the 95% CI for the observed effect. At the bottom of the plot, the diamond represents the pooled effect calculated across all included studies, with the width of the diamond indicating the 95% CI. HR, hazard ratio; CI, confidence interval; SE, standard error.

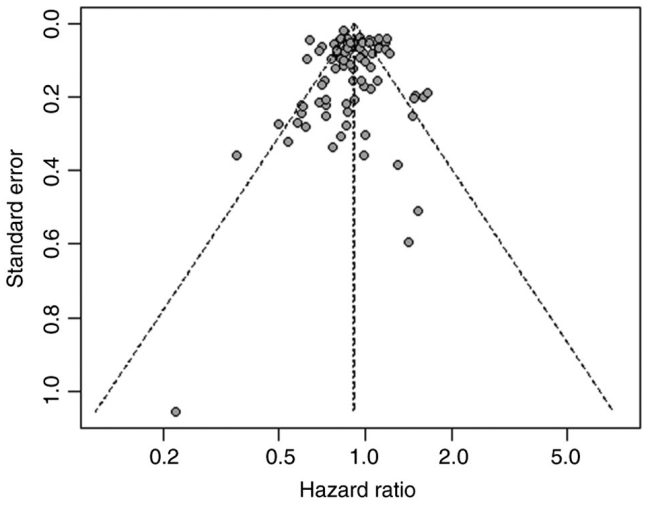

Figure 7. Funnel plot for publication bias. Circles, an individual study; diagonal lines, pseudo 95% CI; middle vertical line, pooling hazard ratio.

P<0.01), prostate (HR, 0.98; 95% CI, 0.89-1.07; P<0.01), hepatocellular carcinoma (HR, 0.86; 95% CI, 0.70-1.06; P<0.01), lung (HR, 0.93; 95% CI, 0.77-1.12; P<0.01), esophageal (HR, 0.88; 95% CI, 0.78-1.00; P<0.01), gastric (HR, 0.84; 95% CI, 0.77-0.92; P<0.01), colonic (HR, 0.87; 95% CI, 0.81-0.93; P<0.01), nasopharyngeal (HR, 0.79, 95% CI, 0.50-1.24; P<0.01), head and neck (HR, 0.85; 95% CI, 0.77-0.94; P<0.01), gallbladder (HR, 0.74; 95% CI, 0.44-1.23; P<0.01) and rectal (HR, 0.91; 95% CI, 0.87-0.95; P<0.01) cancers, patients who used ACEIs or ARBs, either alone or in combination, had a significantly increased OS compared with that of patients who did not use the aforementioned drugs. By contrast, the use of ACEIs or ARBs, either alone or in combination, did not show no significant benefit in the OS of patients with renal cancer (HR, 1.00; 95% CI, 0.83-1.20; P<0.01) and significantly decreased the OS of patients with breast cancer (HR, 1.04; 95%CI, 0.90-1.19; P<0.01).

Impact of ACEI and ARB use alone or in combination on the OS of patients with cancer. Subgroup analysis was performed on the included studies according to the use of the drugs, either alone or in combination (Fig. 4). The use of ACEI drugs alone did not lead to an significant extension of the overall survival period of cancer patients (HR, 1.00; 95% CI, 0.93-1.08; P<0.01), while the use of ARB drugs alone (HR, 0.89; 95% CI, 0.84-0.94; P<0.01) or the combined application of ACEI/ARB drugs (HR, 0.84; 95% CI, 0.78-0.91; P<0.01) significantly improved the survival period of tumor patients compared with patients with hypertension and cancer who did not use ARB drugs or who were not taking ACEI/ARB drugs.

Impact of ACEI and ARB use on the OS of patients with cancer according to study type. Subgroup analysis was performed on the included studies according to study type (Fig. 5). Among the 34 cohort studies, the use of ACEIs or ARBs, alone or in combination, significantly increased the OS of patients with cancer (HR, 0.92; 95% CI, 0.88-0.97; P<0.01) compared with those who were not treated. The use of ACEIs or ARBs, alone or in combination, significantly increased the OS of patients with cancer among the 14 case-control studies (HR, 0.86; 95% CI, 0.79-0.94; P<0.01).

Sensitivity and publication bias analyses. Sensitivity analysis was performed through the individual elimination of each included study from the merged studies (Fig. 6). The results of this analysis indicated no significant change in the combined effect size.

Egger's regression test was used to conduct a publication bias analysis of the 48 articles that explored the correlation between neutrophil-lymphocyte ratio and the OS and no significant publication bias was demonstrated (Fig. 7; P=0.321).

Discussion

Hypertension is a common and frequently occurring disease (64), and in clinical practice, the prognosis of a number of patients with cancer with concurrent hypertension is subject to potential effects of the antihypertensive drugs, such as ACEIs and ARBs (65). However, the impact of ACEIs and ARBs on prognosis is currently unclear. The present meta-analysis included 48 studies, which involved the data of 923,134 patients and demonstrated that patients who used ACEIs and ARBs had a significantly increased OS compared with patients with cancer who did not use these drugs. The increase in OS was significant in patients with ovarian, pancreatic, prostate, hepatocellular, lung, esophageal, gastric, colon, nasopharyngeal, head and neck, gallbladder and rectal cancers. However, the OS of patients with breast tumors and urothelial carcinoma, was significantly decreased with the use of ACEIs and ARBs compared with the OS of patients who did not use them. No significant differences in overall survival were observed among patients with renal tumors, regardless of whether they were treated with ACEI or ARB drugs. In terms of the specific drugs used and the method of administration, the use of ACEIs alone did not significantly change the OS of patients with cancer; however, the use of ARBs alone and the combined use of ACEIs and ARBs significantly increased the OS of patients.

The effects of antihypertensive drugs on the development and progression of tumors is a topic of notable importance. Previous studies have shown that Ang II and AT1 are upregulated in a number of types of cancer tissues and that RAAS disorders are closely associated with hypertension (66). Therefore, the present study aimed to investigate whether the administration of RAAS-inhibiting antihypertensive drugs in hypertensive patients with cancer affects their prognosis. In comparison with a number of previous studies on the effect of RAAS inhibitors on the prognosis of patients with cancer (21,32), the present study incorporated data from a large number of types of cancer, which included ovarian, pancreatic, prostate, hepatocellular carcinoma, lung, esophageal gastric, colon, nasopharyngeal, head and neck, gallbladder cancer, rectal, renal, urothelial carcinoma and breast cancers. The impact of ACEI and ARB use on the OS of hypertensive patients with various types of cancer was systematically analyzed. The present study evaluated the survival rate following the diagnosis of cancer, collecting information on the use of medication in patients with cancer, which may provide a better reflection of the impact of hypertension treatment drugs

on cancer risk and prognosis. In 2019, Cui *et al* (25) utilized a time-dependent Cox regression model to examine the association between common antihypertensive drugs and the OS in breast, colorectal, lung and gastric cancers, and used data from 2 large prospective cohort studies in Shanghai, China. By contrast, the present study included sample information on patients with different types of cancer from the United States, Japan, Finland, China, England, Canada, the Czech Republic, Italy, Denmark, Germany, South Korea, North Korea, Norway, Oman and Poland. This approach was used to minimize the analytical errors that could result from different races of the patients included in the studies. In contrast to the study conducted by Mc Menamin *et al* (67), which assessed the impact of RAAS inhibitors on overall survival in patients with pancreatic cancer, lung cancer, renal cell carcinoma, breast cancer, colorectal cancer, prostate cancer, and multiple myeloma by assessing 10 relevant studies, the present study included 48 relevant studies and used a larger sample to conduct a more comprehensive analysis of overall survival in patients with pancreatic cancer, lung cancer, renal cell carcinoma, breast cancer, colorectal cancer, prostate cancer, and multiple myeloma who had used ACEI/ARB drugs, making the results more generalizable. In contrast to a number of studies on that evaluated the impact of antihypertensive drugs on the prognosis of cancer patients (68,69), in terms of drug type, the present study investigated RAAS inhibitors, which have a well-established mechanism of action in tumor tissues. However, ACEIs and ARBs, which both act as inhibitors in the various steps of the RAAS cascade reaction, may not have the same effect on tumors. By analyzing the impact of using ACEI/ARB drugs alone or in combination on the overall survival of cancer patients, it was found that inhibiting different steps of the RAAS cascade may have different effects on the overall survival of cancer patients of different types, these results may help to guide future research.

The RAAS is an endocrine pathway that participates in the regulation of cardiovascular and neuroendocrine functions and is closely associated with the pathogenesis of hypertension (70). In the RAAS, the angiotensin-converting enzyme (ACE) is a key enzyme that primarily converts Ang I into Ang II. Ang II binds to the AT1 and AT2 receptors, playing a role in various physiological pathways, including vasoconstriction, aldosterone and vasopressin release, sodium and water retention, and sympathetic activation (71,72). Previous studies have reported that some tumor cells express renin and Ang II receptors, and the activation or deactivation of these receptors plays distinct physiological roles in the development of cancer through various signaling pathways (73). The activation of AT1 receptor and PRR receptor signaling leads to the activation of MAPK, PI3K/AKT/MTOR, NF-κB and JAK/STAT signaling pathways, as well as an increase in VEGF, TGFβ1, EGFR, and fibronectin, ultimately leading to cell proliferation, angiogenesis, fibrosis, tumor invasion and metastasis (74). These pathways are inhibited by the AT2 receptor and angiotensin-(1-7)-mediated Mas signaling. Therefore, the AT1 receptor is considered to serve a role in the promotion of tumorigenesis (7,66). By contrast, the AT2 receptor has a direct antiproliferative effect (75,76) and Ang (1-7) directly inhibits angiogenesis and cell proliferation (77). ACEIs inhibit ACE, which thereby prevents the conversion of Ang I into Ang II and indirectly inhibits the binding of Ang II to AT1 and AT2. By contrast, ARBs directly block the binding of Ang II to AT1. Both ACEIs and ARBs may exert their effects by directly or indirectly inhibiting the signaling pathways of AT1 and AT2 receptors, which leads to the inhibition of tumor cell growth and formation of peripheral vessels (78).

A previous analysis of various types of cancer demonstrated that patients with breast cancer had a decreased survival period after the use of ACEIs or ARBs (32). However, a cohort analysis including 1,435 cases of breast cancer, 1,511 cases of colorectal cancer and 1,184 cases of prostate cancer demonstrated that in all patients, the use of ACEIs or ARBs did not increase the cancer-specific risk of death; therefore, ACEIs and ARBs drugs were considered to be safe for patients diagnosed with breast, colorectal and prostate cancer (21). A previous meta-analysis suggested that ARBs have antiproliferative effects on breast cancer (79). There are a number of molecular types of breast cancer, and the specific type is determined from the expression levels of indicators such as estrogen and progesterone receptors, HER2 and Ki-67 through IHC; the clinical features, degree of malignancy, treatment and prognosis vary among the different molecular types of breast cancer (80). It could be suggested that the differential results reported on the prognosis and OS of hypertensive patients with breast cancer after treatment with ACEI and ARB analogs may be because endocrine therapy is preferred in patients with high levels of estrogen and progesterone receptors in the molecular typing of breast cancer (81). In the present study, analysis of ACEIs and ARBs use, alone or in combination, on the OS of patients with cancer, ACEIs alone had no significant effect on the survival of these patients, whereas the use of ARBs or ACEI and ARB in combination increased patient survival. The mechanism of action of ACEIs against hypertension is to inhibit the ACE and bradykinin-degrading enzymes, reduce the conversion of Ang I to Ang II, and through vasodilatory effects, slow down the degradation of bradykinin through and promote the release of prostaglandins, which together leads to vasodilatation and blood pressure reduction (82). However, it has been reported that kinins are not only involved in blood pressure regulation, but also serve a role in the regulation of physiological functions of the cardiovascular system, kidneys and nervous system. Kinins are closely related to the occurrence of diseases such as heart disease, kidney disease, inflammatory reactions and cancer (83). Previous studies reported that bradykinin mediates the migration and invasion of various human cancer cells (84,85). Hsin-Shan Yu *et al* found that bradykinin induced VEGF expression and promoted angiogenesis in human prostate cancer through activation of the B2 receptor and the Akt, mTOR, and NF-k AP-1 signaling pathways. Bradykinin promotes gastric cancer cell proliferation, migration, invasion and tumor growth through the ERK signaling pathway (86). The mechanism of action of ARBs against hypertension, by contrast, is to selectively block the binding of Ang II to AT1, which leads to a dose-dependent reduction in peripheral vascular resistance and a decrease in blood pressure (87). This could potentially be due to the previous studies on breast or gynecological cancers on the impact of hormones and hormone therapies where the status of estrogen receptors were unclear, which may have impacted the subsequent analysis. Analysis of the impact of the use

of ACEIs and ARBs alone or in combination on the OS of patients with cancer in the present study demonstrated that the use of ACEIs alone did not significantly affect the OS of these patients. ACEIs block Ang II production by suppressing ACE and indirectly inhibiting Ang II binding to AT1 and AT2 (88). ARBs selectively block the binding of Ang II to AT1, the AT1 receptor is upregulated in cancer tissues and promotes cell proliferation and angiogenesis (89). Previous studies have reported that AT1 receptor antagonists can significantly slow the progression of tumors, and in the maintenance of blood pressure, water and electrolyte homeostasis, AT1 and AT2 receptors antagonize each other to maintain a regulatory balance (89). The present analysis demonstrated no significant impact of the use of ACEIs alone on the OS of patients with cancer, whereas the use of ARBs alone significantly the OS of these patients. Therefore, determining the specific roles of AT1 and AT2 receptors in tumors could potentially increase the understanding of the increased OS of patients with cancer who used ARBs alone or in combination with an ARB or ACEI. Hence, conducting further investigation into the involvement of the RAAS in local tumors by selectively inhibiting AT1 and AT2 receptors in hypertensive cancer patients through experimental studies may yield deeper insights into this mechanism.

The impact of antihypertensive drugs on the prognosis of cancer patients may be influenced by multiple factors, with a key constraint being heterogeneity, as well as factors such as race, lifestyle, geographical environment, underlying diseases, comorbidities, health status and therapeutic methods. Simultaneously, specific types of bias should be considered, for example, in a previous study where hypertension history was collected through self-report, there may be a few cases of recall bias among patients; the data collected in this way will be partially biased (90). Additionally, the potential effects of changes in the therapeutic regimen for hypertension on the analysis results should be considered. For example, in a previous study, a number of patients started using thiazide diuretics or calcium channel blockers due to poor blood pressure control or the subsequent development of other diseases (91). However, the effect of other antihypertensive drugs on the previous stages of cancer is currently unclear. Furthermore, the present study demonstrated that the inclusion and exclusion criteria for single tumor studies varied among populations. A study by Wilk *et al* (58) with stringent exclusion criteria included 93 patients with metastatic castration-resistant prostate cancer who had received docetaxel and androgen deprivation therapy and had developed metastases, all of whom had a clear pathological diagnosis and radiological evidence of metastasis, and had received docetaxel prior to the start of ABI to evaluate the impact of prior chronic diseases and concomitant medications on the abiraterone acetate treatment process in this patient cohort. It was reported that the use of ACEI/ARB drugs may prolong the survival of these patients; however, the aforementioned study requires further support through prospective studies. Another previous study investigated the relationship between antihypertensive drugs and prostate cancer prognosis through a survey of 8,253 patients with prostate cancer and reported that the use of RAS inhibitors, ACEIs and AT receptor blockers were associated with improved survival rates in patients with prostate cancer (52). Although the aforementioned study had a large sample size, the inclusion and exclusion criteria were not set for the study population's age, disease stage or treatment received. Therefore, the aforementioned study may only represent the overall prognosis trend of patients with prostate cancer who use antihypertensive drugs to a certain extent and cannot accurately reflect the impact of antihypertensive drugs use on the prognosis of certain specific groups of prostate cancer patients (52). The present meta-analysis is a preliminary study of the prognostic impact of ACEIs and ARBs in hypertensive patients with cancer; therefore, the inclusion and exclusion criteria were set broadly. With an increase in the number of randomized controlled trials and clinical studies on the use of ACEIs and ARBs in hypertensive patients with different types of cancers, meta-analyses for a single type of tumors could be performed with more stringent exclusion criteria to obtain accurate study conclusions in the future. For instance, to further investigate the impact of ACEI/ARB drugs on the overall survival of a specific subtype of breast cancer patients with comorbid hypertension undergoing endocrine therapy, establishing inclusion criteria for individuals diagnosed with this subtype of breast cancer and receiving endocrine therapy. Subsequently, it would be possible to prospectively assess the prognosis of this cohort to yield more valuable research findings.

ACEIs and ARBs may increase the survival of hypertensive patients with cancers and the specific mechanism underlying this effect may be associated with the promotion of cell proliferation and angiogenesis by AT1 (73). In the future, further clinical and biological research could potentially improve the understanding of the mechanisms underlying the anticancer effects of ACEIs and ARBs, demonstrate the potential of ACEIs and ARBs in adjunctive cancer therapy, identify the patient populations that benefit the most from these treatments and provide novel treatment options to improve the prognosis of hypertensive patients with cancer.

Acknowledgments

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YX was responsible for the study methodology, software use, data curation, manuscript writing, review and editing. YX and XC contributed to study conceptualization. XC contributed to formal analysis of the data. WL participated in data investigation. WL and XC curated the data. YX, XC and WL performed data validation. WZ and XL contributed significantly to the conceptualization and design of the study, and supervised the research activities, and validated the integrity of all primary data. WZ and XL confirm the authenticity of all the raw

data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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