Systematic Review and Meta-Analysis

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The renin–angiotensin system blockers and survival in digestive system malignancies

A systematic review and meta-analysis

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Abstract

Background: Accumulating pre-clinical and clinical studies suggested that the renin–angiotensin system blockers (RASBs) possess anti-carcinogenic properties, and their use is associated with favorable outcomes in many types of cancers.

Methods: A systematic literature search of relevant databases through January 2019 was conducted to identify studies assessing the RASBs on prognostic outcomes in digestive system malignancies patients on the basis of predetermined selection criteria for pooled hazard ratio (HR) with 95% confidence intervals (CIs). A total of 13 studies were included in the meta-analysis.

Results: The meta-analysis showed that the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) resulted in a significant improvement in overall survival (HR 0.79; 95%CI 0.70–0.89; $P < .000$), cancer-specific survival (HR 0.81; 95%CI 0.73–0.90; $P < .000$) and recurrence-free survival (HR 0.68; 95%CI 0.54–0.85; $P = .001$), but not progression-free survival (HR 0.88; 95%CI 0.73–1.07; $P = .183$) and disease-free survival (HR 0.50; 95%CI 0.11–2.39; $P = .103$). Subgroup analysis indicated that the use of RASBs has a significant improvement of overall survival (OS) in pancreatic cancer, liver cancer, and gastric cancer. Two studies evaluated the dose–response relationship between ACEIs/ARBs therapy and survival and showed higher doses and better survival [(1–364 defined daily doses: odds ratio (OR) 0.89, 95%CI 0.78–1.01, $P = .076$), (≥365 defined daily doses: OR 0.54, 95%CI: 0.24–1.24, $P = .148$].

Conclusions: Meta-analysis of studies supports a beneficial association between use of RASBs and survival of digestive system malignancies.

Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, CI = confidence interval, CSS = cancer-specific survival, CVD = cardiovascular disease, DDDs = defined daily doses, DFS = disease-free survival, HR = hazard ratio, OR = odds ratio, OS = overall survival, PFS = progression-free survival, RASBs = renin–angiotensin system blockers, RCT = randomised controlled trial, RFS = recurrence-free survival.

Keywords: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, digestive system malignancies, meta-analysis, survival

1. Introduction

Cancer is now becoming the leading cause of death in both developed and developing countries. Digestive system malignant tumors occupy most of the all-cancer incidence and mortality, with 3.4 million new diagnosed cases and 1.5 million deaths each year.[1] Recently, increasing attention has been put toward comorbid conditions and their associated medications as potential factors influencing digestive system malignancies progression, recurrence, and mortality.

The renin–angiotensin system (RAS) is involved with the regulation of arterial pressure. RAS inhibition represents a key target in the treatment of hypertension and heart failure.[2–4] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are some of the most widely used antihypertensive drugs. An estimated 200 million patients are treated with ARBs worldwide, representing 25% of all antihypertensive agents.[5] Previous studies showed that the angiotensin type 1 receptor is expressed in different malignancies, and has been reported to be significantly associated with tumor growth, metastasis, and angiogenesis.[6,7] Studies in vivo have indicated that inhibition of ACE activity could suppress tumor growth and angiogenesis.[8,9] Many meta-analysis also indicated that the long-

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term oral renin–angiotensin system blockers (RASBs) have a significant beneficial effect to cancer crowds.[10,11] Then there are not many studies about association between the survival of cancer patients and RASBs. Some meta-analysis just investigated association between all types of tumors and RASBs, and they did not have enough numbers' included studies. Some of them found no significant increase in survival,[12,13] which may be why different types of cancer have different physiological and pathological characteristics leading to different responses to RASBs. So, it is necessary to conduct system review about the long-term oral RASBs and digestive system malignancies.

2. Materials and methods

2.1. Information sources and search strategy

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library up to January 2019 without the language restriction. The search terms were as follows: "(cancer OR carcinoma OR adenoma OR tumor OR neoplasm OR malignance) AND (ACE inhibitor OR ACEI OR angiotensin-converting enzyme inhibitor OR angiotensin-converting enzyme inhibitor OR angiotensin receptor blocker OR angiotensin receptor antagonist OR angiotensin receptor blockade OR angiotensin-receptor blocker OR angiotensin-receptor antagonist OR ARB OR ARBs) AND (survival OR recurrence OR prognosis OR clinical outcome)" as well as their combinations. The references of retrieved articles were searched manually. When the same authors or laboratory reported the issue on the same group of people, only full-text articles of the most recent studies were included. One of the 13 studies was obtained by reading through related articles.[14]

2.2. Ethics statement

Given that the meta-analysis will not involve the collection of privacy information, ethical approval is not necessary for our research.

2.3. Study selection and eligibility criteria

After removal of duplicates, articles were screened by title and abstract for inclusion based on pre-specified eligibility criteria. Where it was not clear from the title or abstract if an article was relevant to the review, the full text was retrieved for further scrutiny. Articles were included if they met the following inclusion criteria:

(1) the study design was interventional (such as: a randomized controlled trial (RCT)) or observational (such as: a cohort or case–control study);
(2) the study assessed the association between the use of RASBs and survival or prognosis;
(3) the studies had to provide sufficient data for determining an estimate of log–hazard ratio (HR) and its 95% confidence interval (CI) for overall survival (OS) and/or cancer-specific survival (CSS) and/or progression-free survival (PFS) and/or recurrence-free survival (RFS) and/or disease-free survival (DFS).

2.4. Data extraction

Data were extracted by 2 authors working independently. Information on study design, location, year, study population, exposure ascertainment, classification of drug use (e.g., never, ever use and dose), outcome ascertainment, HR, odds ratio (OR) with 95%CI and confounders adjusted for was extracted from each of the included articles. Moreover, the outcomes were abstracted additionally according to dosage of ACEIs/ARBs to investigate the dose–response relationship.

2.5. Statistical analysis

Adjusted HRs were combined to estimate the overall effect if possible. If adjusted HRs were not directly available, survival curves could be used to extract HR.[15] One of 13 studies used OR as effect value to pool HR.[16] Two studies[16,17] calculated defined daily doses (DDDs) to investigate the dose–response relationship. A single DDD is the average maintenance dose per day of a drug used for its main indication in adults. One study[17] divided into 4 groups including: 1 to 182 DDDs, 183 to 364 DDDs, 365 to 729 DDDs, and ≥730 DDDs. We combined the first 2 groups and the last 2 as the other study[16] dividing 2 groups including: 1 to 364 DDDs and ≥365 DDs. The intention-to-treat meta-analysis was done in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, with Stata (version 12.0). Heterogeneity was assessed with the I^2 statistic. I^2 is the proportion of total variation observed with between the trials attributable to differences between trials rather than sampling error (chance); I^2 less than 25% was regarded as low and I^2 greater than 75% as high. We used the random model for HR and OR. Bias was estimated visually by funnel plots, and with the Begg's test and the weighted regression test of Egger.[18] A P value less than 0.05 was used to denote statistical significance.

3. Result

3.1. Studies identified

Figure 1 shows the stages of the systematic review process, which was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Of the 874 citations initially identified after duplicate citations were removed, full-text versions of 26 potentially relevant studies were retrieved for detailed evaluation. Finally, 13 relevant studies fulfilled the inclusion criteria for the meta-analysis.[16,17,19–29]

The characteristics of the studies included are summarized in Table 1.

3.2. Assessment of quality

The quality of the studies that were included in this systematic review was rated based on the standardized questionnaire in the Newcastle-Ottawa scale for cohort studies. Study quality was high with the exception of 3 studies which was found to be of moderate quality. All 3 of these studies[20,27,29] were limited by lack of adjustment for age or other key confounding variables such as diabetes, stage of cancer, and so on.

3.3. Study outcome

Pooling data from 13 studies showed that the use of ACEIs or ARBs resulted in a significant improvement in OS (HR 0.79; 95% CI 0.70–0.89; $P < .0001$), CSS (HR 0.81; 95%CI 0.73–0.90; $P < .0001$), and RFS (HR 0.68; 95%CI 0.54–0.85; $P = .001$)

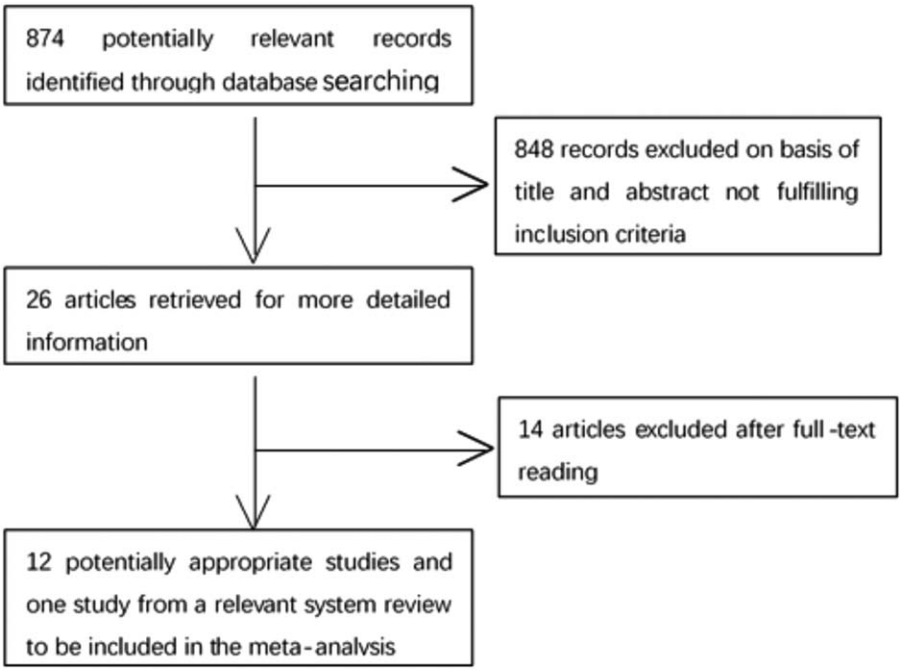

Figure 1. Flow diagram of the study selection.

apart from PFS (HR 0.88; 95%CI 0.73–1.07; $P=.183$) and DFS (HR 0.50; 95%CI 0.11–2.39; $P=.103$) (Fig. 2). The HR of OS was similar after removing the study[22] owning greater heterogeneity (HR 0.75; 95%CI 0.63–0.90; $P<.0001$). Because 10 studies for OS included 1 study using OR as effect value and 2 studies[20,26] in which HR was extracted from survival curves. Then, we recalculated the pooling HRs (HR 0.75; 95%CI 0.63–0.90; $P<.0001$) after removing those studies.

3.4. Subgroup analysis

In the subgroup analyses by drugs, the 7 studies[20,21,24–28] showed a significant protective effect when the analyses were restricted to studies that investigated the effect of ACEI or ARB (HR 0.78; 95%CI 0.64–0.94; $P=.009$). The 3 studies[16,19,22] showed a nonsignificant protective effect for analysis restricted to studies that investigated the effect of only ARB (HR 0.73; 95%CI 0.55–0.98; $P=.039$). There was a little improvement of beneficial effect compared to the use of only ACEI (HR 0.84; 95%CI 0.65–1.08; $P=.175$).[16,22] But the small numbers of subgroup analysis could lead to the doubt of truth of this conclusion (Table 2).

Analysis according to cancer type showed significant treatment effects in pancreatic cancer (HR 0.78; 95%CI 0.64–0.97; $P=.023$),[19,27,28] liver cancer (HR 0.52; 95%CI 0.31–0.87; $P=.012$),[22] gastric cancer (HR 0.55; 95%CI 0.31–0.97; $P=.039$),[25] oesophageal cancer (HR 0.57; 95%CI 0.35–0.93; $P=.026$),[20] and colorectal cancer (HR 0.90; 95%CI 0.82–0.98; $P=.021$) (Table 2).[16,21,24,26]

3.5. Dose–response relationship

Two studies[16,17] investigated the dose–response relationship between ACEIs/ARBs therapy and digestive system malignancies, the results of which are listed in Table 2. We calculated OR with 95%CI using the crude data from article because of the HR with 95%CI unavailable. The OR for 1 to 364 DDDs is 0.89 (95%CI: 0.78–1.01; $P=.076$) and for ≥365 DDDs is 0.54 (95%CI: 0.24–1.24; $P=.148$). There was not a very significant improvement for OS about 1 to 364 DDDs vs ≥365 DDDs (Table 2).

3.6. Sensitivity analysis

Due to the obvious heterogeneity for OS was found in our analysis. To assess whether any one study had a dominant effect in heterogeneity, the main summary estimate and I^2 (54.3%) was evaluated after removing each study (Fig. 3). There was no decrease in heterogeneity after removing the study one by one. In our analysis of OS, the HR and its 95% confidence intervals in some studies were extracted from Kaplan–Meier curve in 2 studies and was from OR and its 95% confidence intervals. So these extracted data was not accuracy. But then no evident heterogeneity changing was found. In subgroup analysis by cancer type, the heterogeneity of all cancer types subgroup has declined especially in colorectal cancer ($I^2=0.0\%$) and indicated that there was significant heterogeneity about different cancer site. In subgroup analysis by study-drugs, the heterogeneity has variation in ACEI/ARB ($I^2=44.2\%\%$), ACEI ($I^2=38.8\%$), and ARB ($I^2=80.1\%$). The heterogeneity for CSS ($I^2=0.0\%$), PFS ($I^2=7.9\%$), and RFS ($I^2=6.4\%$) is low.

3.7. Publication bias

There was no evidence of significant publication bias, both quantitatively (Egger's test, $P=.069$; Begg's test, $P=.011$) and on visual inspection of the funnel plot (Fig. 4).

4. Discussion

ACEI and ARB are a representative modality for RAS inhibition. ACEIs and ARBs are used as common antihypertensive agents

Table 1

Descriptive characteristics of studies included.

Reference	Location	Cancer type	Study-drugs	Age (exposure/control)	Male (exposure/control)	Study outcomes	Adjustments or match
Holmes et al (2013)[24]	Canada	Colorectal cancer	ACEI/ARB	65	NA	OS	Age, stage at diagnosis, gender, history of previous cancer, and urban/rural residence.
Cardwell et al (2014)[16]	England	Colorectal cancer	ACEI/ARB	NA	58%/58%	OS/CSS	Surgery, chemotherapy, radiotherapy, low dose aspirin, statins, comorbidities, and smoking.
Nakai et al (2014)[28]	Japan	Pancreatic cancer	ACEI/ARB	67	0.58	OS/PFS	Age, gender, PS, disease extension, tumor location, CA19-9, diabetes, smoking, and treatment protocol.
Busby et al (2018)[17]	England	Gastro-oesophageal cancer	ARB	NA	60%/68%	CSS	Age, deprivation, year of diagnosis, cancer site, cancer treatment within 6 mo, comorbidities, and other medication use.
Cerullo et al (2017)[17]	The United States	Pancreatic cancer	ARB	58/57	50.7%/48.9%	OS	Age, sex, region, charlson comorbidity, CVD, diabetes, hypertension, type of procedure, complications, nodal involvement, adjuvant chemotherapy, adjuvant radiation, neoadjuvant chemotherapy, neoadjuvant radiation
Engineer et al (2013)[21]	The United States	Colorectal cancer	ACEI/ARB	66/63	96.2%/97.1%	OS/PFS	Age, presence of diabetes, and hypertension, and stage
Facciorusso et al (2015)[22]	Italy	Liver cancer	ACEI/ARB	69/70	77.5%/79.7%	OS/RFS	Age, gender, blood hypertension, BMI, mellitus diabetes, etiology, Child–Pugh, portal hypertension, AFP, MELD, max diameter, BCLC, CLIP, number of nodules.
Kim et al (2012)[25]	South Korea	Gastric cancer	ACEI/ARB	67	66%/63%	OS/PFS	Age, gender, PS, disease status, grade.
Nakai et al (2010)[27]	Japan	Pancreatic cancer	ACEI/ARB	71/73	55%/44%	OS/PFS	NA
Chen et al (2015)[20]	Taiwan	Oesophageal cancer	ACEI/ARB	55	95%/97%	OS	NA
Morris et al (2016)[26]	Hawaii	Rectal cancer	ACEI/ARB	61.1/57.2	68%/54.4%	OS/RFS	Age, pretreatment hemoglobin, pretreatment CEA, sex, clinical stage, biopsy grade, radiation dose, concurrent chemotherapy, and pathological stage.
Yoshiji et al (2011)[29]	Japan	Liver cancer	ACEI	59.4/62.5	63%/61%	DFS	NA
Heinzerling et al (2007)[23]	The United States	Colorectal cancer	ACEI	NA	NA	DFS	Age, diabetes, stage of cancer, chemotherapy, radiation, and surgery

NA = not applicable; ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, CSS = cancer-specific survival, DFS = disease-free survival, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival.

and the reports of organ-protective effects of ACEIs, including inhibition of cardiac hypertrophy, diabetic nephropathy, and diabetic retinopathy, are increasing.[30] With respect to anticancer effects, large epidemiological studies suggest potential protective effects against cancer risk.[10,11,31,32] ACEI and ARB could act on tumor progression via different mechanisms, including: inhibition of cancer proliferation and inhibition of neovascularization and promoting of tumor cell apoptosis.[33] Some studies suggested that RASBs enhanced drug delivery about two-fold to three-fold.[34] Therefore, the anti-tumor effect of ACEIs and ARBs may be due to the accumulation and enhancement of anti-tumor drugs in tumor tissues, rather than the direct anti-tumor effect or the superposition of the 2 mechanisms.

Our meta-analysis was the first to analyze the relationship between RASBs and cancer recurrence, disease progression, and survival of patients with digestive system cancer. We included 13 studies, including 10 studies on the relationship with OS, 2 studies on the relationship with CSS[16,17], 4 studies on the relationship with PFS[21,25,27,28], 2 studies on the relationship with RFS,[22,26] and 2 studies on the relationship with DFS.[23,29] All of the results except for DFS (HR 0.50; 95%CI 0.11–2.39; $P = .02$) and PFS (HR 0.88; 95%CI 0.73–1.07; $P = .354$) groups showed significant improvements in survival in patients with digestive system malignancies. This may be due to the small number of literature included in the DFS and PFS groups. Thirteen studies included 12 cohort studies and a randomized controlled study with the research group of 19 persons and the control group of 26 persons, resulting in increased error in RCT. We analyzed the association of dose–response of RASBs. The ≥365 DDDs group (OR 0.54: 95%CI 0.24–1.24; $P < .001$) has a slight increase compared to the 1 to 364 DDDs group (OR 0.89; 95%CI 0.78–1.01; $P = .496$). This is more proof of our standpoint. People who take RASBs usually have high blood pressure and other heart problems, and are more likely to have diabetes, hyperlipidemia, obesity, and so on, which may increase non-cancer specific mortality and consequently made a negative impact to survival. Even though, survival improvement still appears in our analysis.

In the subgroup by cancer type, there are significant differences in OS. The exact relationship between survival and cancer type needs to be confirmed in future by carefully designed studies for few studies included in each subgroup. ACEI block both angiotensin II type-1 and type-2 receptors, whereas ARBs block only the type-1 receptor. The role of the angiotensin II type-2 receptor is less studied than that of the angiotensin II type-1

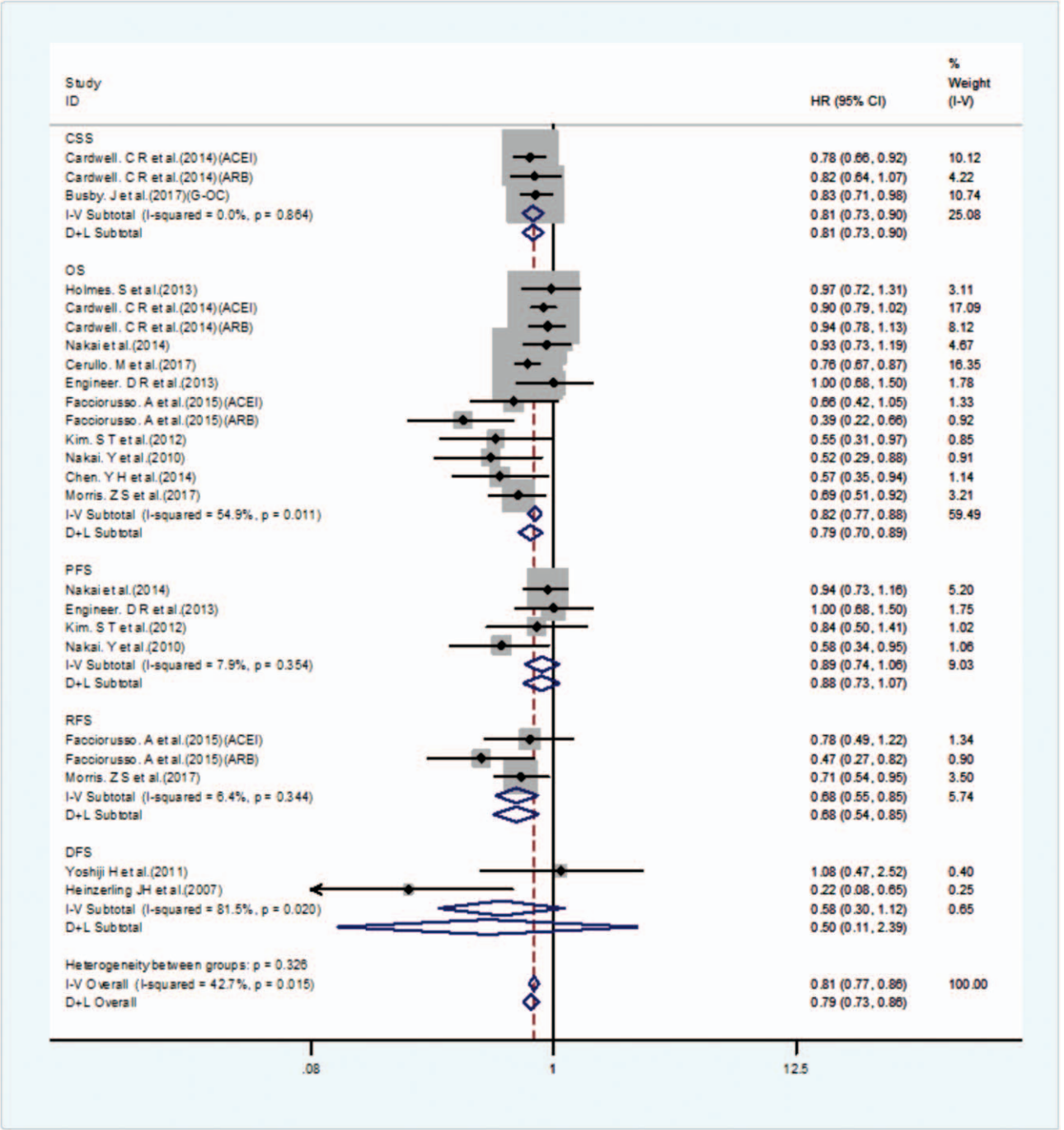

Figure 2. Digestive system malignancies and RASBs use, stratified by end points including: CSS, OS, RFS, PFS, and DFS. CSS = cancer-specific survival, DFS = disease-free survival, OS = overall survival, PFS = progression-free survival, RASBs = renin–angiotensin system blockers, RFS = recurrence-free survival.

receptor, which is known to induce angiogenesis, proliferation, and inflammation. This distinction between ACEI and ARB may have a different effect on cancer. So, we made a subgroup analysis by drug category and found that there were no significant differences possibly due to not enough sample size. Furthermore, more research is needed to prove our hypothesis.

The included studies were mainly retrospective cohort studies (12 cohort and 1 RCT). Retrospective cohort studies inevitably include confounding factors. Due to the inconsistency between the experimental group and the control group, there are various differences, which may affect the survival prognosis and tumor recurrence of patients. All retrospective cohort studies except 3 studies without data of adjustment and a RCT were adjusted for factors including age, gender, stage at diagnosis, therapy, diabetes, and so on, which to a great extent reduce confounding factors.

The present meta-analysis has the following limitations that must be taken into account. First, just a RCT owning 19 cases and 26 controls in all included studies incorporated into our study,

Table 2

Results of subgroup analysis of pooled hazard ratios of overall survival in patients of digestive system malignancies.

Stratifed analysis	No. of studies	Pooled HR (95%CI)	*P*-value	Heterogeneity	
				I^2 (%)	*P*-value
Cancer type	12	0.79 (0.70–0.89)	<.0001	0.543	.012
Colorectal cancer	5	0.90 (0.82–0.98)	.021	0	.428
Pancreatic cancer	3	0.78 (0.64–0.97)	.023	0.494	.139
Liver cancer	2	0.52 (0.31–0.87)	.012	0.519	.149
Gastric cancer	1	0.55 (0.31–0.97)	.039	NA	NA
Oesophageal cancer	1	0.57 (0.35–0.93)	.026	NA	NA
Study-drugs	12	0.79 (0.70–0.89)	<.0001	0.543	.012
ACEI/ARB	7	0.78 (0.64–0.94)	.009	0.442	.096
ACEI	2	0.84 (0.65–1.08)	.175	0.388	.201
ARB	3	0.73 (0.55–0.98)	.039	0.801	.007
Dose–response	2	0.69 (0.24–1.24)*	.049	0.936	<.0001
1–364 DDDs	2	0.89 (0.78–1.01)*	.076	0	.496
≥365 DDDs	2	0.54 (0.24–1.24)*	.148	0.973	<.0001

ACEIs = angiotensin-converting enzyme inhibitors, ARBs = angiotensin II receptor blockers, CI = confidence interval, CSS = cancer-specific survival, CVD = cardiovascular disease, DFS = disease-free survival, HR = hazard ratio, OR = odds ratio, OS = overall survival, PFS = progression-free survival, RASBs = renin–angiotensin system blockers, RCT = randomized controlled trial, RFS = recurrence-free survival.
* OR; DDDs = defined daily doses.

which may result in the low credibility of the results. Second, there are few studies in analysis of subgroup and dose–response association, which lead to an increase in the random errors of results. Third, some effect size of included studies were not from the calculation of raw data but from some other methods of estimation, which probably led to augment the error and heterogeneity in our meta-analysis.

Nevertheless, many of the included studies were based on a large prescription database. The people counting of them were very large to have smaller error. Many outcomes indicators incorporated OS, CSS, DFS, PFS, and RFS appeared in our analysis. We made a dose–response association to improve our conclusion. As far as known, this meta-analysis is firstly to investigate the association between RASBs and survival in patients of digestive system cancers.

The results of our meta-analysis suggested that the RASBs use had a significant beneficial effect in survival of digestive system cancers, which was proved by analysis dose–response association. The association between cancer patients' survival and the specific drugs type such as ACEI or ARB and specific cancer sites is still not very clear. Further investigations are required to confirm this relationship.

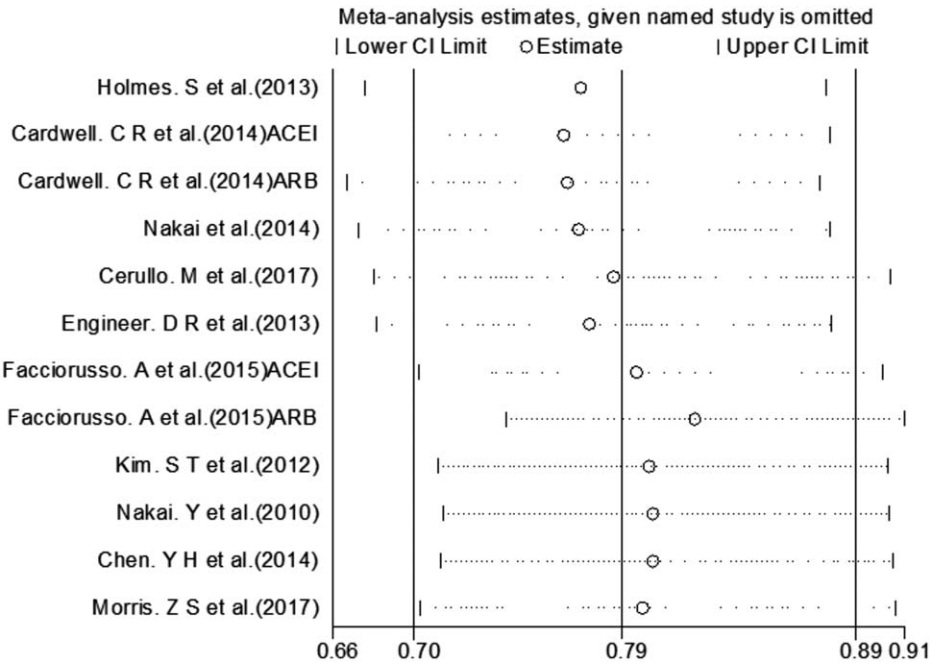

Figure 3. Sensitivity analysis in overall survival.

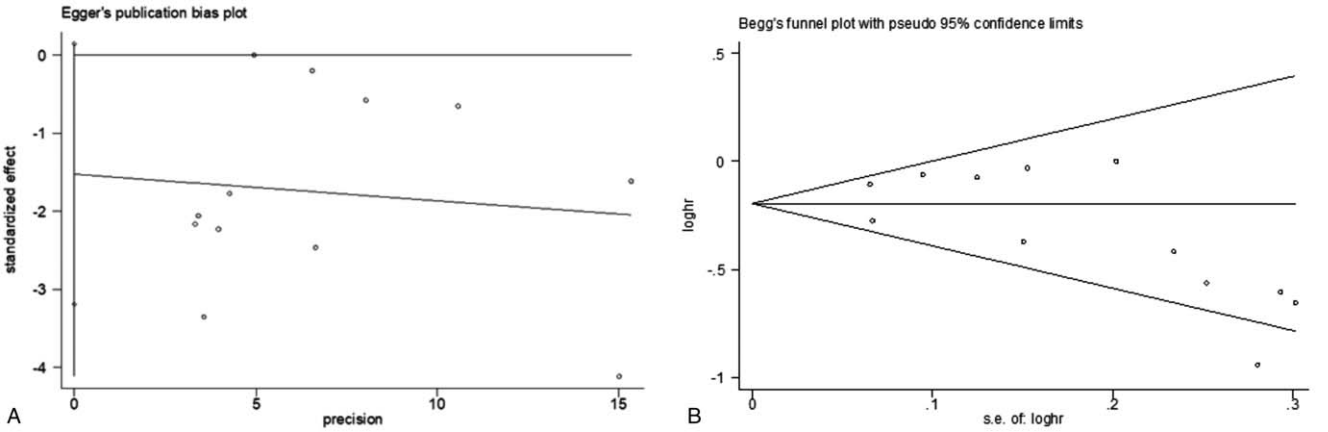

Figure 4. Meta-analysis of the pooled hazard ratios (HRs) of overall survival in patients of digestive system malignancies. (A) Begg's funnel plot. (B) Egger's publication bias plot.

Author contributions

Conceptualization: Lin Xin, Li-Qiang Zhou.
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Investigation: Li Liu, Shi-Hao Li.
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Validation: Yi-Wu Yuan.
Visualization: Di-Shi Chen.
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