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Research Article

The Preventive and Prognostic Value of ACEIs/ARBs in Hepatocellular Carcinoma Patients

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Abstract

Background and Aim: Hepatocellular carcinoma (HCC) represents most of the primary liver tumors and the process of neo angiogenesis is thought to be a significant malignant characteristic of HCC. Due to their anti-angiogenic and anti-fibrinogenic properties, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II blockers (ARBs) may play a substantial role as adjuvant therapy in prevention of HCC. The purpose of this systematic review is to better understand the therapeutic role of ACEIs and ARBs in HCC.

Methods: We conducted literature search using the most widely used internet databases (Medline, EMBASE, and Cochrane) to retrieve all the articles evaluating the use of ACEI/ARBs in the prevention or treatment of hepatocellular carcinoma, using the following keywords: "angiotensin-converting enzyme inhibitors", "ACE inhibitors", "ACE-I", "angiotensin II type 1 receptor blockers", "ARBs", "hepatocarcinoma", and "hepatocellular carcinoma". The following criteria were used to determine eligibility: (1) prospective or retrospective observational studies; and (2) clinical trials. We restricted our search to English-language papers and omitted animal studies, conference abstracts, review articles, case reports, case series, editorial letters, and irrelevant studies.

Results: The results of the two RCTs conducted by Yoshiji., *et al.* demonstrated a significant difference ($p < 0.01$) in recurrence rates between the control group and the group of patients who used ACEI and vitamin K2 combination therapy followed by the curative therapy, as well as a significant decline in recurrence rates i.e. $p < 0.01$ was observed among patients who underwent treatment with ACEIs in conjunction with branched chain amino acids (BCAA) when compared to the control group. ACEIs/ARBs treatment demonstrated a significant overall survival i.e. OS = 11.9 months vs. 6.8 months ($p = 0.014$) in patients diagnosed with HCC with a Child-Pugh class A in a cohort study conducted by Printer., *et al*. Another study conducted by Facciorusso., *et al*. reported a significantly improved response to Sartan therapy in terms of increased duration of recurrence ($p = 0.001$) and overall survival ($p = 0.15$). Kaibori., *et al.* analyzed certain metabolic factors as risk factors for the poor prognosis in patients with HCC and found that hypertension was associated with worse overall and disease-free survivals and demonstrated a significant increase in the overall and disease-free survivals in patients with HCC treated with angiotensin II blockade. However, three studies by Ho., *et al,* Walker., *et al.* and Hagberg., *et al*. found no protective effect of ACEIs/ARBs among patients diagnosed with HCC.

Conclusion: ACEIs/ARBs have a prognostic role in HCC, increasing survival and reduced recurrence rates and lengthening the time to recurrence; nevertheless, angiotensin II blockade for primary prevention against the development of hepatocellular carcinoma is not of considerable benefit.

Keywords: *Hepatocellular Carcinoma (HCC); Non-Alcoholic Fatty Liver Disease (NAFLD); Angiotensin-Converting Enzyme (ACE); Renin-Angiotensin System (RAS)*

Introduction

Hepatocellular carcinoma (HCC), which accounts for the vast majority of primary liver tumors, is reported to be the second leading cause of cancer-related deaths world-wide, as well as the leading cause of mortality among patients with advanced liver disease caused by chronic viral hepatitis, alcoholic liver disease, or non-alcoholic fatty liver disease (NAFLD) [1,2]. Patients with HCC have a high mortality rate since they are typically asymptomatic and are identified at an advanced tumor stage [2].

HCC is a hypervascular tumor, and studies have revealed that angiogenesis plays a key role in a variety of pathological processes, including liver fibrogenesis and tumor progression [3]. The angiotensin-converting enzyme (ACE) is a key component of the renin-angiotensin system (RAS) that plays a crucial role in the regulation of circulatory homeostasis and angiogenesis. Antiangiogenic drugs were proposed to limit tumor development and progression owing to the association between vasculogenesis and high tumor grade/poor prognosis [4,5]. Therapies aimed at destroying tumor vasculature can result in rapid regression of experimental tumors, where anti-angiogenic drugs have been demonstrated to greatly accelerate tumor cell death [6-8].

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are usually used as antihypertensive drugs and may also have beneficial effects in cancer patients. ACEIs/ARBs were associated with longer overall survival (OS) in patients with pancreatic, lung, and brain cancer, reduced risk of breast cancer relapse and increased tumor response in rectal cancer [9-11]. However, not all studies have reached the same conclusion. For example, a 2016 study by Sorich., *et al*. discovered that the use of renin-angiotensin system inhibitors (RASi) was not a significant predictor of mortality in patients with metastatic renal cancer [12].

HCC treatment is becoming increasingly expensive as new anti-angiogenic drugs become available, rendering it unaffordable for many patients. Because of their anti-angiogenic and anti-fibrogenic effects, ACEIs and ARBs appear to be suitable adjuvant therapy for HCC. As a result, the goal of this systematic review is to comprehensively analyze the data on the prognostic benefit (if any) of using ACEIs/ARBs in patients with HCC, as well as any preventative potential they may have.

Materials and Methods

We conducted an electronic literature search using the most widely used internet databases (Medline, PMC, and Scopus) to retrieve all the articles evaluating the use of ACEIs or ARBs in the prevention or treatment of hepatocellular carcinoma using the following keywords: “angiotensin-converting enzyme inhibitors”, “ACE inhibitors”, “ACE-I”, “angiotensin II type 1 receptor blockers”, “ARBs”, “hepatocarcinoma”, and “hepatocellular carcinoma”.

The following criteria were used to determine eligibility: (1) prospective or retrospective observational studies; and (2) clinical trials. We restricted our search to English-language papers and omitted animal studies, conference abstracts, review articles, case reports, case series, editorial letters, and irrelevant studies.

Study variables such as sample size and follow-up durations, baseline factors such as age, gender, comorbidities, and outcome characteristics such as incidence of HCC (or association, depending on study design), survival, and recurrence were all compiled into a standardized excel sheet.

We avoided a quantitative synthesis of the data because pooling the research data was not ideal due to the variety of research design and the unpredictability of reported results. As a result, we present a qualitative evaluation of the included research findings, merits, and limitations.

Results

Our literature search retrieved 198 articles. Following duplicates removal (n = 60) and the exclusion of irrelevant records through screening (n = 108), we reviewed the remaining 30 articles. Eight articles qualified for the final analysis, which included four retrospective cohort studies, two case-control studies, and two randomized controlled trials (RCTs). Figure 1 shows the detailed PRISMA flow diagram.

There was a total of 22,096 patients in the eight studies. Table 1 presents the baseline demographics and comorbidities, and results of the individual studies. The mean age of the population was 70 years. Most patients were treated with ACEIs (n = 10973, 49.6%), and ARBs (n = 10694, 48.4%). The remaining received sorafenib (n = 151, 0.7%), vitamin K (n = 87, 0.4%), branched chain amino acid (BCAA) (n = 61, 0.3%) or no treatment (n = 130, 0.6%). The population primarily consisted of patients with advanced cirrhosis (Stages B and C).

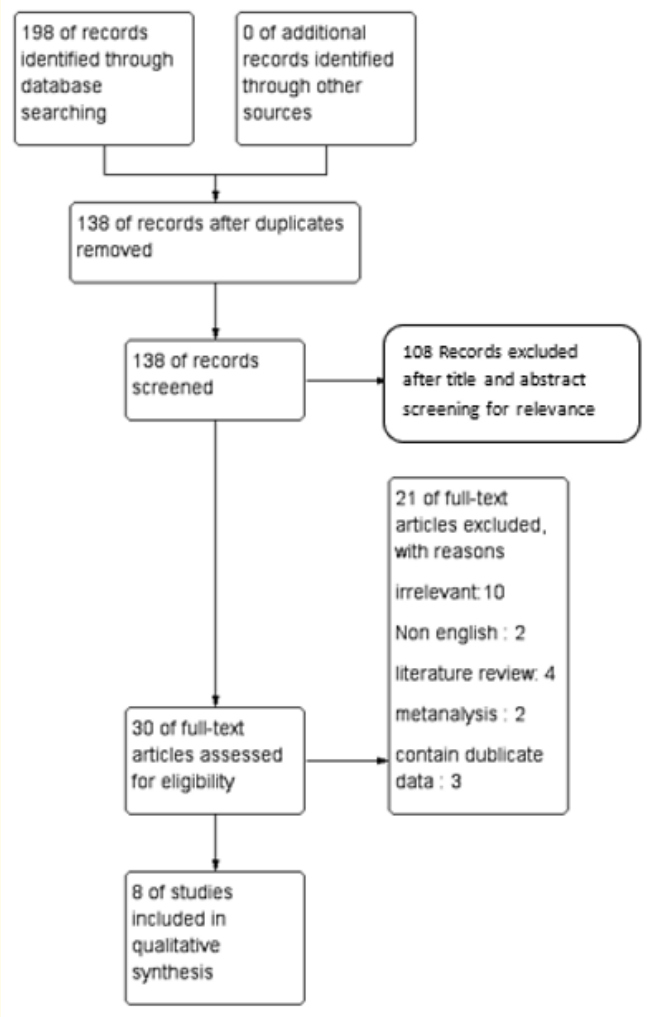

Figure 1: *PRISMA flow diagram.*

	Demographics				Comorbidities (%)						Results				
Study	**Age in years, Mean (SD)**	**Gender (Male, %)**	**Number of patients**	**Adjuvant HCC* Therapy**	**Hepatitis B**	**Hepatitis C**	**Cirrhosis**	**Hypertension**	**Diabetes**	**Agents used**	**Association, OR (95% CI)**	**Incidence, HR (95% CI)**	**Survival HR (95% CI)***	**Recurrence HR (95% CI)***	**Follow-up (Months)**
Primary Prevention Ho 2018															
HBV** + ACEI/ARB***	57.5 (11.2)	68.8	3575				77.8		43.8	ACEI/ARB					
HBV Control	57.3 (11.5)	63.9	4149				79.8		30.4	ACEI/ARB		0.97 (0.81 to 1.16)			48
HCV† + ACEI/ARB	59.7 (9.3)	51.8	3349				87.0		45.7	ACEI/ARB					
HCV Control	59.3 (9.0)	47.4	4524				88.8		28.6	ACEI/ARB		0.97 (0.80 to 1.16)			55.2
Hagberg 2016															
Cases	70.9 (9)	72.2	490		3.9			100	43.5	ACEI					
Controls	70.9 (8.)	72.4	1909		0			100	19.5	ACEI					
Walker 2011															
Cases		61.8	224												
Control		61.6	2313												
Secondary Prevention Pinter 2017 (Vienna)				Sorafenib											96.6
ACEI/ARB	69 (8.9)	74	43		35$ 42$			100		ACEI/ARB			0.6 (0.4 to 0.9)		
Control	64 (10.6)	83	113				----								
Pinter 2017 (Mainz)				Sorafenib											48.9
ACEI/ARB	69.4 (7.4)	89	38		50$			100		ACEI/ARB			0.6 (0.3 to 1.0)		
Control	67 (10.1)	11	38		34$			----							

Facciorusso 2015														88
ACEI	69 (11.8)[$$]	77.5	49	Radioablation		18.3	51	32.6	40.8	ACEI			0.66 (0.42 to 1.05)	0.78 (0.49 to 1.22)	
ARB	72 (8.5)[$$]	83.9	31			19.3	48.3	54.8	43.2	ARB			0.39 (0.22 to 0.66)	0.47 (0.27 to 0.82)	
Control	70 (6.3)[$$]	79.5	73			24.6	42.4	40	34.2						
Yoshiji 2011														
Controls	62.5 (11.5)	61.5	26		23.1	69.2							NS	30	48
ACEI	59.4 (12.3)	63.2	19		36.8	63.2				Perindopril, 4mg/day				56.5**	
ACEI + BCAA[††]	64.8 (10.6)	64.3	28		28.6	67.9				Perindopril, 4mg/day & BCAA granules 12g/day				63**	
Kaibori 2010															
ACEI/ARB	66.5 (7.6)	86.5	37			100		100	38	ACEI/ARB			60.1 & 59.7***		7
Control	67.1 (6.9)	92.9	42			100		100	14	ACEI/ARB			52.8 & 31.1***		
Yoshiji 2009															
Controls	60.5 (8.5)	68	25		12	4								72	
ACEI	59.4 (8.3)	52.6	19		5.9	88.2				Perindopril, 4mg/day			NS	52**	48
ACEI + Vitamin K	63.4 (7.6)	68.2	25		9.1	86.4				Perindopril, 4mg/day & Vitamin K 45mg/day				36**	

Table 1: *A description of the baseline characteristics of the included studies as well as the main findings.*

**HCC = Hepatocellular Carcinoma; ** HBV = Hepatitis B Virus; ***ACEI/ARB = ACE Inhibitor or Angiotensin Receptor Blocker; † HCV = Hepatitis C Virus; †† BCAA = Branched Chain Amino Acid.*

Quality of included studies

Two authors (A.S. and A.K.) independently assessed the quality of included studies. Based on the Newcastle Ottawa Scale (NOS) (22) and the Cochrane Risk-of-bias (ROB) II tool respectively (23), we deemed the methods of the observational studies to be high (score of 7-8), and risk of bias of the two RCTs to be low. Although the retrospective nature of the cohort studies can lead to selection bias, some studies matched the baseline characteristics of their cohorts alleviating this risk to some extent. Selection bias may have affected the two randomized control trials (RCTs), but they were sound in other domains, and therefore judged to be at an overall low risk of bias. Table 2 details the NOS assessment of observational studies and figure 2 summarizes the ROB assessment of the RCTs.

Study	Selection				Comparability	Exposure			Total
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts	Total number of stars
Pinter., *et a*l. 2017	*	*	*	*	*	*	*	*	8
Ho., *et al*. 2018	*	*	*	*	*	*	*	*	8
Facciorusso., *et al*. 2015	*	*	-	*	**	*	*	*	8
Kaibori., *et al*. 2010	*	*	*	*	*	*	*	*	8
Walker., *et a*l. 2011	*	*	-	*	*	*	*	*	7
Hagberg., *et al*. 2016	-	*	*	*	*	*	*	*	7

Table 2: *Newcastle-Ottawa Scale (NOS) for assessing the quality of observational studies.*

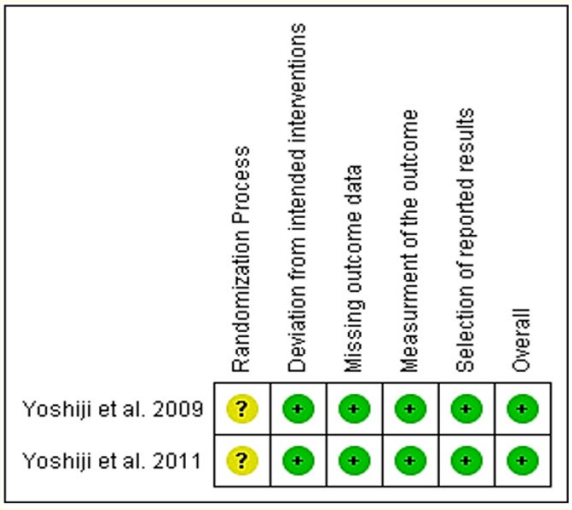

Figure 2: *Summary of risk of bias assessment of the randomized control trials.*

Design and setting

Yoshiji., *et al*. conducted the two RCTs at Nara Medical University, Japan to study ACEIs, vitamin K or BCAA. Pinter., *et al*, Facciorusso., *et al.* and Kaibori., *et al*. performed three cohort studies at the Medical University of Vienna, Austria, University of Foggia, Italy, and Hirakata Hospital, Kansai Medical University, Hirakata, Osaka, Japan, respectively. Ho., *et al*. performed the fourth cohort study using three Taiwanese databases (National Health Insurance Research Database (NHIRD), the Registry for Catastrophic Illness Patient Database (RCIPD), and Taiwan's Cause of Death Database). Data collection was over 21 years for Pinter., *et al*. 6 years for Facciorusso, 15 years for Kaibori., *et al*. and 9 years for Ho., *et al*. All four cohort studies were performed retrospectively. Walker., *et al.* used the General Practice Research Database, while Hagberg., *et al*. used the United Kingdom's Clinical Practice Research Datalink database respectively to conduct their case-control studies.

Primary prevention

Walker., *et al*. 2011

A case control study conducted by Walker., *et al*. revealed that prior use of ACEIs was associated with HCC however the association was minimal and non-significant (OR = 1.16, CI = 0.67-2.00). However, no protective effect of ACEIs use in HCC patients was found either. In conclusion, there was no clear preventive benefit of using ACE inhibitors for short or long periods of time against the development of HCC.

Hagberg., *et al*. 2016

A case-control study conducted by Hagberg., *et al*. found no association between the use of ACEIs and/or beta-blockers (β-blockers) with lowering the risk of developing liver cancer. Cases included patients with documented hypertension (HTN) and HCC and were compared to controls from the study population with documented HTN without HCC. Study results revealed an OR of 1.14 (95% CI 0.85 - 1.55) among ACEIs or β-blockers users compared to the non-users. Further analysis revealed that in comparison to non-users, the OR for the use of ACEIs and β-blockers in combination was 1.27 (95% CI 0.88 - 1.82) vs. 1.13 (95% CI 0.79 - 1.60) for ACEIs alone and 1.08 (95% CI 0.75 - 1.55) for β-blockers alone.

Ho., *et al*. 2018

The authors studied two cohorts with Hepatitis B virus (HBV) and Hepatitis C Virus (HCV) respectively, matched for baseline characteristics including pre-study exposure to ACEIs or ARBs (46.3% vs 42.5%) and the median duration (36.4 months vs 38.9 months) of initial exposure. Initial and non-exposure subgroups had a median exposure of 41.8 and 18.3 months in the HBV cohort and 46.4 and 22.7 months in the HCV cohort. The HCC hazard ratios (HRs) in the treatment group were 0.97 (95% confidence interval [CI]: 0.81 - 1.16) and 0.96 (0.80 - 1.16) in the HBV and HCV cohorts, respectively. In HCV patients without cirrhosis, diabetes mellitus and hyperlipidemia, the use of ACEIs and ARBs increased the risk of HCC (HR: 4.53, 95% CI: 1.46 - 14.1).

Secondary prevention

Yoshiji., *et al*. 2009

The authors tested the combined and individual inhibitory effects of ACEIs and vitamin K2 against HCC recurrence in two separate sub-studies. These medications have anti-angiogenic effects that could inhibit tumor growth. The study recruited a total of 87 patients with HCC admitted to the hospital for curative radiofrequency ablation (RFA) therapy. The first study compared the combined effects of ACEIs and Vitamin K2 for 48 months while the second study compared the effects of ACEIs and Vitamin K2 monotherapies for 36 months. Although the authors assigned the patients randomly to treatment and control groups, they did not use placebo for the control group. They found a significant difference ($p < 0.01$) in the recurrence rates between the two groups in the first study.

	Cumulative recurrence rates in percentage	
Time of follow-up (in months)	**Treatment group (ACEIs + Vitamin K2)**	**Control group**
12	12	24
24	28	48
36	32	68
48	36	72

Table 3

The combination of ACEIs and vitamin K2 suppressed alpha-fetoprotein-L3 (AFP-L3) and vascular endothelial growth factor (VEGF) levels, which corresponded to a decrease in HCC recurrence rates. In the two studies, the authors found no significant difference in mortality between treatment and control groups. They believe that future studies should follow a larger number of patients for longer periods of time to determine whether the combination treatment with ACEIs and Vitamin K2 results in improved survival rates.

Yoshiji., *et al*. 2011

The authors randomized 89 patients with HCC that received curative radiofrequency ablation (RFA) therapy into a control group and three treatment groups receiving ACEIs monotherapy, branched chain amino acids (BCAA) monotherapy and combined ACEIs and BCAA monotherapy and followed them up for 48 months. These drugs act against angiogenesis which contributes to HCC tumor growth. Furthermore, high levels of BCAA persistently activates mTOR complex 1 which results in insulin resistance, resulting in progression of HCC tumor growth. Unlike monotherapy with either drug, the combination treatment significantly reduced the cumulative recurrence of HCC compared to the control group ($p < 0.01$). VEGF, a central angiogenic factor, and one of its soluble receptors, sVEGFR2 decreased significantly ($p < 0.01$) six and three months after the combined treatment, indicating their potential use as biomarkers. Insulin resistance, as measured by a homeostasis model, was also significantly improved by this regimen, implying that the improved insulin resistance and anti-angiogenic properties contribute to the tumor suppressive effects to some extent.

	Cumulative recurrence rates in percentage	
Time of follow-up (in months)	**Treatment group (ACEIs + BCAA)**	**Control group**
12	14.3	15.4
24	21.4	30.8
36	25	46.2
48	32.14	61.5

Table 4

The decreased recurrence rates of HCC in the combined treatment group, as in the previous study, did not translate into improved survival rates; the authors recommended a longer study on a larger scale to detect any such improvement.

Pinter., *et al*. 2017

To determine the effect of RAS inhibitors on survival in patients with HCC, authors observed two cohorts with HCC and Child-Pugh class A liver disease, one treated with sorafenib, experimental therapy or supportive care (Vienna) and the other with sorafenib (Mainz). The authors performed multivariate analyses within each cohort on variables that had log rank p values < 0.1 on univariate analysis, including RAS inhibitor use.

In the Vienna cohort, the patients who received RAS inhibitors had an overall survival of 11.9 months compared with 6.8 months (p = 0.014) and a lower hazard ratio in multivariate analysis (HR = 0.6; 95% CI 0.4-0.9; p = 0.011). Subgroup analysis (Kaplan-Meyer survival curves) performed in this cohort showed that the median overall survival was the highest in those treated with sorafenib and RAS inhibitors (19.5 months), followed by sorafenib (10.9 months) and RAS inhibitor (9.7 months) monotherapy (p = 0.043).

The authors verified the effect of RAS inhibitor on overall survival in the second cohort, which received sorafenib treatment (HR = 0.5; 95% CI = 0.3-1.0, p = 0.038).

The main limitations of the study were the small number of subjects and unknown confounders associated with the retrospective nature. However, the results are supported by their alignment with results of phase 3 SHARP trial and the multivariate analysis of the second cohort in this study.

Facciorusso., *et al*. 2015

Facciorusso., *et al*. reviewed data on 215 patients to evaluate the role of sartans in delaying the recurrence and increasing overall survival in patients with HCC following radiofrequency ablation. Patients were divided into three groups based on their treatment, with Group A receiving neither ARBs or ACEIs, group B receiving ACEIs, and group C receiving sartans only. Facciorusso., *et al*. reported a significantly improved response to sartan therapy in terms of increased recurrence duration and overall survival, with the median time to recurrence in Group C being 51months, compared to 33 and 41 months in group A and B (p = 0.001), respectively. Furthermore, patients treated with sartan had significantly better overall survival than the other two groups with 63 months in Group C compared to 48 and 51 months in group A and B (p = 0.15), respectively.

Kaibori., *et al.* investigated metabolic factors such as hypertension, obesity and diabetes and found that hypertension was a risk factor for poor prognosis following surgical treatment in patients diagnosed with HCV related HCC, with the 5-year disease free and overall survival in patients with hypertension was 13.4% and 50.0% compared to those without hypertension, i.e. 18.4% and 62.4% (p = 0.028 and p = 0.039), respectively. Furthermore, patients with HCV HCC were divided into three groups, group I included patients without hypertension, group II with documented hypertension receiving angiotensin II blockers (ACEIs or ARBs) and patients who received anti-hypertensive agents other than angiotensin II-block agents (ABA) were included into group III. Group III had considerably lower disease-free survival rates compared to group I and group II, with rates of 14.7% compared to 49.3%, and 31.9% at 3 years and 9.2% compared to 25.8%, and 8.9% at 5 years (P = 0.0001 and P = 0.0033), respectively. Similarly, the overall survival rates at 3, 5 and 7 years of group III compared to group I and II were 58.3%, 79.6%, and 96.6%, as well as 27.2%, 71.3%, and 80.5%, and 17.0%, 60.1%, and 52.8% (P < 0.0001 and P = 0.0002), respectively.

Discussion

The renin-angiotensin system (RAS) is frequently activated in patients with chronic liver diseases. Thus emerged the controversial role of RAS inhibitors for both inhibiting angiogenesis by reducing vascular endothelial growth factor (VEGF) production [13] and improvement of the overall prognostic outcome in these patients. Promising preliminary data have been recently published on the use of angiotensin-converting enzyme inhibitors (ACEIs) in the setting of adjuvant therapies for HCC, because of their well-known antiangiogenic and antifibrogenic activity [14,15]. The oral multikinase inhibitor sorafenib, a pan-vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (TKI), remains an efficacious treatment as first line and provides a modest prolongation of median overall survival (OS) (2.8 months) against progression of HCC [16]. A closely related TKI drug, regorafenib, recently showed increased OS in second line [17]. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely prescribed antihypertensive drugs and may also have beneficial effects in cancer patients. ACEIs/ARBs use was associated with reduced risk of breast

cancer recurrence, increased tumor response in rectal cancer, and longer OS in patients with pancreatic, renal cell (RCC), lung, and brain cancer [9-11,18-21].

Three studies assessed the association between ACEIs/ARBs and the risk of primary occurrence of hepatocellular carcinoma. The largest study we included, Ho., *et al.* [24], a cohort study, followed up 16,000 patients for up to 5 years retrospectively. About 80% of subjects with hepatitis B had cirrhosis compared to 90% of subjects with hepatitis C. The study found that the use of ACEIs and ARBs did not significantly affect the incidence of HCC in these patients.

Interestingly, in the subgroup of patients without cirrhosis, diabetes, or hyperlipidemia, the use of ACEIs/ARBs was associated with a statistically significant increase in the risk of developing HCC in the HCV cohort (HR: 4.53; 95% CI: 1.46 to 14.1) and a non-statistically significant risk increase in the HBV cohort (HR: 1.65; 95% CI: 0.60 to 4.55). Given the non-randomized nature of this study, we must be cautious to interpret these results as associations rather than causal effects.

On a smaller scale, two case-control studies conducted by Hagberg., *et al.* [25] and Walker., *et al.* [26], assessed the associated between the use of ACEIs and ARBs and HCC, however found no significant evidence linking the two together. Walker., *et al*. found a positive association between short-term (< 6 months) use of ACEIs and the development of HCC, though the study's observational nature makes drawing causal conclusions difficult.

Taking the evidence available, there does not appear to be any strong evidence that ACEIs/ARBs provide a primary protective benefit in patients at risk of developing HCC. The two students by Ho., *et al*. and Walker., *et al*. on the other hand, found positive associations between ACEIs/ARBs use and HCC in certain subgroups, however again the observational designs do not allow us to draw causal link.

The remaining five studies examined the relationship between ACEIs/ARBs and clinical outcomes in patients with pre-existing HCC. Some studies looked at ACEIs/ARBs as monotherapy, while others looked at them in combination with other treatments. Pinter., *et al.* [27] carried out the largest of these studies, where they discovered a significant improvement in overall survival in patients receiving ACEIs/ARBs and sorafenib in comparison to either drug alone. In the second cohort, the effect of RAS inhibitor therapy on overall survival was also confirmed. Furthermore, study conducted by Facciorusso., *et al.* [28] also found that RAS inhibition was beneficial in HCC. Although the point of estimates for both ACEIs and ARBs suggested a protective association, the confidence intervals of only the latter reached statistical significance. ARBs exhibited lower point estimates than ACEIs, implying that the differences in the effects of the two medication classes may be a key component in determining the overall efficacy of RAS inhibitors in HCC. Facciorusso., *et al*. not only studied survival but also recurrence and found a similar pattern, ARBs had lower point estimates and achieved statistical significance but ACEIs did not.

Kaibori., *et al.* [29] in a small observational study published in 2011, examined the effects of ACEIs/ARBs therapy on HCC in HBV and HCV patients with and without comorbidities. The hypertensive patients had poor prognosis that reached statistical significance only in the HCV cohort. The investigators also found that in the hypertensive HCV cohort, the use of ACEIs/ARBs, improved the prognosis to some extent compared to the other antihypertensive medications. A major limitation of the study was that the blood pressure was not adjusted for, where the improved survival seen in patients who received ACEIs/ARBs may simply reflect better blood pressure control in that cohort.

Two smaller scale RCTs, conducted by Yoshiji., *et al.* in 2009 and 2011 [14,30], where the first study compared the efficacy of a perindopril monotherapy and perindopril plus vitamin K combination therapy to a placebo-free control group. The combination of perindopril (ACEIs) and vitamin K was associated with a significant reduction in recurrence, with the recurrence rate being half that of the control group. They discovered no statistically significant differences in survival among the three. Whether this is due to a smaller

statistical power due to the smaller sample size and shorter follow-up, or a true reflection of the treatment's inefficacy could be answered by appropriately planned future studies.

Yoshiji., *et al*. used a similar design in the second study, but instead of vitamin K, they used branched chain amino acids (BCAA) as adjunctive treatments. Only the group receiving the combination of ACEIs and BCAA showed statistically significant decreases in the recurrence rate, as in the previous study. Similarly to the previous study, no differences in survival were observed between the three groups.

Overall, the majority of the evidence supporting the use of ACEI/ARBs in patients with HCC is derived from observational data that is susceptible to confounder influence, and the two RCTs that showed evidence of benefit were relatively small single-center trials that only showed benefit when ACEIs/ARBs were combined with adjuncts (Vitamin K and BCAA respectively).

All in all, our meta-analysis included 22096 patients and eight clinical studies, including two RCTs that helped overcome heterogeneity. Unlike Baron's metanalysis in 2019, which included numerous experimental and epidemiological studies as well as animals in addition to humans, all of these studies increased heterogenicity, resulting in unreliable results and conclusions. Furthermore, Asgharzadeh's metanalysis in 2020 included a small number of studies, resulting in inconclusive results, as well as more variables, resulting in more heterogeneous populations and, as a result, heterogeneous results.

This meta-analysis assessed the risk of bias and attempted to overcome heterogeneity by examining a larger number of clinical studies, including two RCTs and excluding animals. Given these constraints, and despite our previous trials to reduce heterogeneity, the potential benefit of ACEIs/ARBs (in combination with other therapies) requires confirmation in larger multi-center randomized trials. If beneficial, the relative affordability and accessibility of these drugs could improve the lives of millions of liver cancer patients around the world, particularly in areas where access to more expensive therapeutics is limited.

Conclusion

ACEIs/ARBs have a prognostic value for hepatocellular carcinoma in terms of improved survival and time to recurrence. Furthermore, hypertension was discovered to be a poor prognostic predictor of HCC. Thus, in people with HCC and hypertension, blocking angiotensin II has a dual benefit. It has a survival rule in addition to its antihypertensive properties. The preventive and prophylactic effects of ACEIs/ARBs were not found to be significant, but the lack of studies addressing this role raises the possibility that this role is still uncertain, and more research is needed to confirm its value in prevention.

Ethics Approval and Consent to Participate

N/A.

Consent for Publication

N/A.

Availability of Data and Material

All materials and data are available.

Competing Interests

Authors declare no conflict or competing interests.

Funding Support

N/A.

Authors' Contributions

Daad Hassan SharafEldin, MD. for her contribution in reviewing the manuscript and appraisal.

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