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Antihypertensive medications and hepatocellular carcinoma risk: a systematic review

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Abstract

Introduction: Emerging evidence suggests that antihypertensive medications may influence the risk, progression, and survival outcomes of hepatocellular carcinoma (HCC). However, findings across studies remain inconsistent. This systematic review aims to evaluate and synthesize current data on the associations between different classes of antihypertensive drugs and liver cancer outcomes.

Materials and methods: A systematic review was conducted, incorporating randomized controlled trials, cohort studies, retrospective analyses, and in vitro studies that investigated the relationship between antihypertensive medications and HCC. Extracted data included study design, population characteristics, drug categories, primary outcomes, and study limitations.

Results: Nine studies met the inclusion criteria, encompassing diverse study designs and patient populations. Renin-angiotensin system (RAS) inhibitors—including ACE inhibitors and angiotensin receptor blockers (ARBs)—were most consistently associated with reduced HCC incidence and improved survival. Thiazide diuretics demonstrated potential protective effects in genetic studies, though results were mixed in larger population-based analyses. Beta-blockers yielded inconclusive evidence: while some studies linked them to increased HCC risk, others found neutral or beneficial effects, particularly for non-selective Beta-blockers in patients with established HCC. Additionally, one preclinical study highlighted possible anti-cancer activity of agents like chlorpromazine and prazosin.

Conclusion: RAS inhibitors show the strongest and most consistent evidence for a protective effect against HCC development and progression among antihypertensive drug classes. Certain non-selective Beta-blockers may also offer survival benefits in specific patient populations. However, conflicting findings and methodological limitations across studies underscore the need for high-quality prospective research to confirm these associations and inform clinical practice

Keywords: Hepatocellular carcinoma, Antihypertensive drug, ACE inhibitors, ARBs, Beta-blockers, Diuretics, Liver cancer

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Introduction

Hypertension is a widespread global health concern and a primary contributor to cardiovascular disease (1–4). Globally, approximately 1.28 billion adults aged 30 to 79 are affected by hypertension (5), which is recognized as the leading risk factor for mortality worldwide (5,6). In parallel, liver cancer continues to pose a major global health challenge. As of 2024, it ranks as the sixth most common cancer and the fourth leading cause of cancer-related deaths, accounting for nearly 800,000 fatalities each year. Hepatocellular carcinoma (HCC) constitutes about 90% of all primary liver cancers (7,8).

Most individuals diagnosed with stage 1 hypertension or higher are treated with antihypertensive medications (9–11). Common first-line agents include Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin II Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), and thiazide diuretics. Other medications such as Beta-blockers, loop diuretics, vasodilators, and α-blockers are typically used as second-line treatments in particular clinical contexts (12,13). Research exploring the relationship between antihypertensive therapies and cancer risk has produced inconsistent findings. These variations may be influenced by geographic location, preexisting conditions, concurrent comorbidities, and unknown underlying mechanisms.

Specifically, the connection between antihypertensive drug use and liver cancer has not been extensively studied, and current data do not establish a definitive causal link (14–16). Nevertheless, the relationship is believed to be multifactorial and remains under investigation. Some studies suggest that certain antihypertensive drug classes may influence tumor development (17–20). The Renin-Angiotensin-Aldosterone System (RAAS), for instance, has been implicated in cancer biology beyond its role in blood pressure regulation. It is hypothesized that modulation of Angiotensin II activity by drugs like ACEIs and ARBs could affect angiogenesis (21–24) and thereby influence liver tumorigenesis.

ACEIs and ARBs have been associated with reduced cancer incidence and improved survival in several observational studies (25–27). Moreover, Beta-blockers, thiazide diuretics, and some CCBs have demonstrated anti-angiogenic properties, which could influence tumor growth (27,28). Conversely, other research—such as one case-control study—reported a slight increase in colorectal cancer risk with ACEI and ARB use, raising concerns about potential implications for liver metastasis (29).

Given the conflicting data and the absence of definitive conclusions, a significant research gap persists regarding the role of blood pressure medications in HCC development (25,27,28,30). The potential interactions between antihypertensive agents and liver cancer remain underexplored (31,32). This review seeks to evaluate both the direct and indirect roles of these medications in HCC, examine the conflicting effects of ACEIs and ARBs and their clinical implications, address gaps in current knowledge, and highlight new directions for future research aimed at clarifying these associations.

Materials and methods

Study Design and Protocol Registration

This systematic review was guided by a pre-established protocol registered on the Open Science Framework. The review process adhered strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparent and rigorous reporting.

Eligibility Criteria

Studies published between 1st January 2015 and 28th February 2025 were eligible for inclusion if they explored the association between antihypertensive medications and liver cancer-related outcomes. Included study designs comprised randomized controlled trials, cohort and case-control studies, and observational research. Only articles published in English were considered. To be included, studies had to focus on individuals with hypertension and assess the effects of antihypertensive drugs on liver cancer risk, progression, or mortality. Studies were excluded if they were non-English, lacked extractable data, were protocols only, or discussed other cancer types without

clear relevance to liver cancer in hypertensive patients. Research published before 2015 was also excluded.

Search Strategy

An extensive literature search was conducted using four prominent electronic databases: PubMed, ScienceDirect, the Cochrane Central Register of Controlled Trials (CENTRAL), and Mendeley. The search employed a mix of Medical Subject Headings (MeSH) and keyword-based queries focused on antihypertensive drugs, liver cancer, and hypertension. Key search terms included:

- For drug types: "ACE inhibitors" OR "angiotensin-converting enzyme inhibitors" OR "ARBs" OR "angiotensin II receptor blockers" OR "beta-blockers" OR "calcium channel blockers" OR "diuretics" OR "renin-angiotensin system" OR "antihypertensive agents"
- For cancer: "liver cancer" OR "hepatocellular carcinoma" OR "liver carcinoma" OR "hepatic neoplasms"
- Subtypes: "hepatocellular carcinoma" OR "cholangiocarcinoma" OR "liver metastasis"

The search was broadened using additional terms such as:

- "liver cancer incidence," "progression," "recurrence," "mortality," and "survival"
- Combined queries like "hypertension treatment" OR "cardiovascular drugs" AND "liver cancer risk," and "antihypertensive side effects" AND "liver cancer survival"

Reference lists from key studies and relevant reviews were manually screened to capture any overlooked studies. The initial database search was conducted on January 26, 2025, and updated on February 26, 2025.

Screening and Data Extraction

The screening process was conducted using Rayyan software to facilitate duplicate removal and streamline the title/abstract screening phase. Two independent reviewers (JT and FT) conducted the initial screening, and any disagreements were resolved through consultation with a third reviewer (SS). Full-text articles of potentially eligible studies were retrieved and reviewed for final inclusion.

Data extraction was carried out using a structured Excel template, which collected information on study design, sample population, drug class, liver cancer outcomes, and key findings. Extraction was primarily handled by SN, with independent verification of 50% of the data entries by FZ and PD for quality assurance.

Quality Assessment

Although the review primarily aimed to summarize the breadth of available evidence rather than perform a critical quality assessment, potential limitations and sources of bias in each study were noted descriptively. Where applicable, formal tools such as the Newcastle-Ottawa Scale were used to appraise the quality of cohort and case-control studies. No studies were excluded based on quality scores alone.

Data Synthesis

Due to substantial heterogeneity in the included studies—across study design, sample demographics, drug classification, outcome measurement, and follow-up duration—a meta-analytic approach was not feasible. While formal statistical heterogeneity (e.g., I^2) could not be calculated, qualitative indicators of variability such as differing comparator groups, inconsistent effect directionality, and variation in drug dosage/timing were noted across studies. As a result, findings were synthesized narratively to provide a comprehensive overview of the relationships between different classes of antihypertensive medications and liver cancer outcomes. This approach allowed for thematic comparison across diverse methodologies and helped contextualize apparent contradictions in the literature.

Bias Assessment

To evaluate potential biases in the included studies, recognized assessment frameworks were used. The Cochrane Risk of Bias tool was applied to analyze aspects such as selection, performance, detection, and

reporting bias. Each study underwent independent review by multiple researchers to enhance objectivity and consistency. This process aimed to thoroughly explore and report the possible biases affecting study outcomes and to support the credibility of the review's conclusions.

Results

The selection process for this systematic review, as outlined in the PRISMA flow diagram (Figure 1), aimed to determine the potential effects of antihypertensive drugs on liver cancer outcomes. A total of 1,376 records were retrieved from three databases: PubMed (10), ScienceDirect (1,000), and Mendeley (366). After removing 66 duplicates, 1,310 records were screened by title and abstract. Following this, 1,299 records were excluded due to irrelevance or not meeting the inclusion criteria. 11 full-text articles were reviewed, with 2 subsequently excluded for being unrelated, leaving 9 studies that met the eligibility criteria and were included in the final review. This systematic selection approach promotes transparency and methodological rigor (Figure 1).

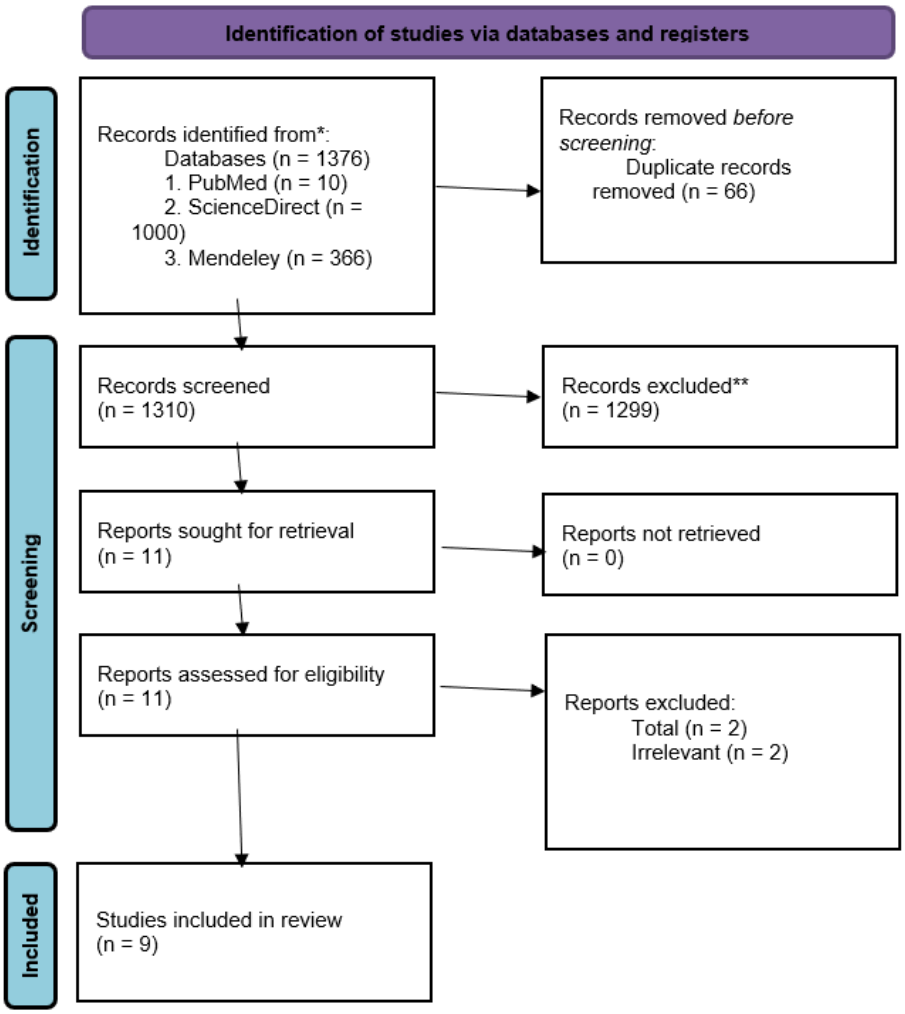

Figure 1. Prisma flow diagram illustrating the study selection process. The flow diagram outlines the systematic selection of studies included in this review. A total of 1,376 records were identified through database searches (PubMed: 10, ScienceDirect: 1,000, Mendeley: 366). After removing 66 duplicates, 1,310 records were screened by title and abstract. Of these, 1,299 were excluded for not meeting the inclusion criteria. Eleven full-text articles were assessed for eligibility, and two were excluded for being unrelated to liver cancer outcomes. Ultimately, nine studies were included in the qualitative synthesis. This structured screening process ensured methodological transparency and adherence to PRISMA guidelines.

The geographical distribution of the included studies (Table 1) indicates a predominance of research conducted in high-income countries. The United States accounted for the highest number of studies (n = 2). Additionally, one study each originated from the United Kingdom, South Korea, Spain, Sweden, and Germany. One study was broadly categorized under the region of Europe and East Asia.

Table 1. Country distribution of included studies.

Country Name	Total Count
United States	2
Europe & East Asia	1
United Kingdom	1
South Korea	1
Spain	1
Sweden	1
Germany	1

The summary presented in (Table 2) outlines the distribution of different study designs included in the dataset. Randomized controlled trials (RCTs) are the most frequently reported, accounting for three out of nine studies. Retrospective cohort studies appear twice, while each of the following designs is represented once: standard cohort study, longitudinal cohort study with repeated measures, in-vitro experimental study, and regression analysis. This reflects a diverse mix of research methodologies, with a slight predominance of experimental approaches, particularly RCTs, which are widely regarded as the benchmark for evaluating clinical interventions.

Table 2. Methodological designs of included studies.

Study Design	Total count
Randomized controlled trial	3
Retrospective cohort study	2
Cohort study	1
Regression analysis	1
In-vitro experimental study	1
Longitudinal cohort study (repeated measures)	1

Key Characteristics of Included Studies

This table (Table 3) presents the basic features of each study, providing context for evaluating the study populations, methodologies, and limitations. These elements help interpret the results and assess the risk of bias.

Table 3. Key characteristics of studies included in the systematic review.

References	Country	Design	Total Participants	Age	Gender	Limitations
(27)	Europe and East Asia	Randomized control trial	N/A	N/A	Both male and female	MR assumptions, lack of clinical data, limited generalizability
(33)	United Kingdom	Longitudinal cohort study	2399	>35	Both male and female	Observational design, adherence uncertainty, residual confounding
(34)	U.S.	Randomized controlled trial	2733	60 ± 9.9	Both male and female	Selection bias, loss to follow-up, confounding
(35)	South Korea	Randomized control trial	32,692	50–60 (avg 58)	Comparison	Retrospective data, adherence bias, ethnic limitations
(36)	Spain	Retrospective cohort study	153	39–86	Majority Child-Pugh	Lack of RCTs, pharmacological

						interactions, genetic variability
(37)	Not Applicable	Retrospective cohort study	Not applicable	Not applicable	Comparison	Not specified
(38)	United States	In vitro experimental study	Not applicable	Not applicable	Not applicable	In vitro only, no apoptosis mechanism confirmed
(39)	Sweden	Cohort study	2104	30–94	Not applicable	Observational design, adherence uncertainty, confounding
(40)	Germany	Regression analysis	349,210	Not applicable	Comparison	Lifestyle data missing, short follow-up, selection bias

Figure 2 displays the risk of bias assessment for the nine studies included in this review, evaluated across six methodological domains: participant selection, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Several studies demonstrated a high risk of bias in multiple domains, particularly in areas such as selective reporting and participant selection. Some studies showed predominantly unclear risks, often due to insufficient reporting of study methods. A few studies exhibited low risk across most domains, particularly in measurement and blinding. Overall, the figure highlights substantial variation in study quality, emphasizing the need for cautious interpretation of findings due to methodological inconsistencies.

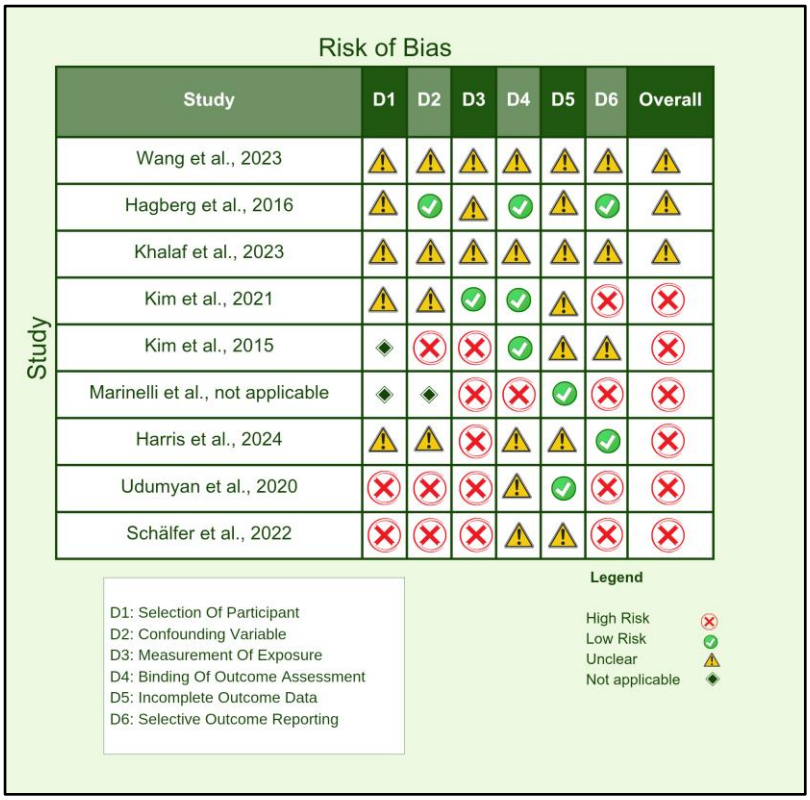

Figure 2. Risk of bias assessment among studies. This figure summarizes the domain-specific risk of bias for each included study using six criteria: D1—Selection of Participants, D2—Confounding Variables, D3—Measurement of Exposure, D4—Blinding of Outcome Assessment, D5—Incomplete Outcome Data, and D6—Selective Outcome Reporting. Risk levels are indicated by symbols: red (✕) for high risk, green (✓) for low risk, yellow (▲) for unclear risk, and gray diamonds (◆) for not applicable. Overall risk reflects the cumulative assessment across all domains.

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Main Findings of the Studies on the Basis of Antihypertensive Drugs Classification

This table (Table 4) categorizes the main findings according to antihypertensive drug classes with serial numbers referencing specific studies.

Table 4. Main findings of the studies based on antihypertensive drugs classification.

Drug Class	Findings	References
Thiazide Diuretics	Associated with decreased HCC risk in both Europeans and East Asians.	(27)
Beta-Blockers (BBs)	Increased HCC risk in Europeans; No association in UK study; Reduced liver cancer mortality in Sweden (non-selective BBs better).	(27,33,39)
ACE Inhibitors (ACEIs)	No significant association with HCC risk.	(33,40)
Angiotensin II Receptor Blockers (ARBs)	Reduced recurrence and improved outcomes in HCC patients following radiofrequency ablation (RFA) (study 5); Increased prostate cancer risk (study 9).	(36,40)
Renin-Angiotensin System (RAS) Inhibitors	Reduced HCC risk with long-term use in patients with hypertension and liver disease.	(35)
Diuretics (General)	Associated with increased liver and hematopoietic cancer risks; decreased prostate and skin cancer risk.	(40)
Calcium Channel Blockers (CCBs)	No significant cancer association.	(40)
Others (Prazosin, Chlorpromazine)	Reduced viability in HCC cell lines; potential cytotoxic effect in vitro.	(38)
Non-Classified (e.g., Sorafenib)	Adverse hepatic effects not linked to treatment duration or response.	(37)

Summary of Findings (Table 4)

- Thiazide diuretics demonstrated a potential protective effect against hepatocellular carcinoma (HCC) in both European and East Asian populations (27).
- Beta-blockers demonstrated inconsistent associations with hepatocellular carcinoma (HCC) outcomes across studies. One study reported an increased risk of HCC among European users (27), while another conducted in the UK found no significant protective effect (33). In contrast, a Swedish study observed reduced liver cancer mortality, particularly with the use of non-selective beta-blockers (39). These conflicting results may be due to differences in beta-blocker type (selective vs. non-selective), patient populations, study design, or unmeasured confounding factors.
- ACE inhibitors and calcium channel blockers (CCBs) were not significantly associated with liver cancer outcomes in the reviewed studies (33,40).
- Angiotensin receptor blockers (ARBs) provided supportive benefits when used alongside radiofrequency ablation in HCC management (36,40); however, one extensive cohort study noted an increased risk of prostate cancer linked to ARB use (40).
- Renin-angiotensin system (RAS) inhibitors, as a broader class, were associated with a decreased risk of HCC with prolonged use in a South Korean cohort (35).
- Diuretics, when not categorized into specific subtypes, were linked with an elevated risk of liver cancer in a large German regression analysis (40), suggesting outcomes may depend heavily on drug subclass and patient context.
- Prazosin and chlorpromazine, evaluated in vitro, exhibited promising anti-tumor activity, implying potential for drug repurposing, though clinical evidence is still lacking (38).

- Sorafenib was associated with hepatic side effects regardless of treatment duration or response, warranting caution when used in patients with liver impairment (37).

Influencing Factors in the Relationship Between Antihypertensive Drugs and Hepatocellular Carcinoma (HCC)

Table below (Table 5) includes influencing factors for liver cancer due to hypertension management.

Table 5. Influencing factors in the relationship between antihypertensive drugs and hepatocellular carcinoma (HCC).

References	Influencing Factors
(27)	Genetic variants, pleiotropy, ethnic differences, hypertension and liver health, drug metabolism.
(33)	Hypertension, diabetes, liver disease, alcohol use, obesity, smoking, viral hepatitis, medication adherence, and exposure definition.
(34)	Age, gender, cause of cirrhosis, liver function, comorbidities, surveillance, and medical management.
(35)	Underlying hypertension and liver disease, medication adherence, comorbidities (diabetes, obesity), demographics, smoking, alcohol consumption.
(36)	Tumor characteristics, liver cirrhosis and fibrosis, comorbidities (renal and cardiovascular health), and pharmacokinetics of ARBs.
(37)	Pre-existing arterial hypertension (AH).
(38)	Oxidative stress, IC_{50} concentrations of tested drugs (chlorpromazine and prazosin).
(39)	Type of Beta-blocker used, liver condition, cancer stage.
(40)	Drug type, comorbidities, large sample size, unaccounted lifestyle factors, combination therapies.

Potential Effect Modifiers

The studies reviewed highlighted several categories of factors that may modify the relationship between antihypertensive medications and hepatocellular carcinoma (HCC) outcomes:

- Metabolic and Genetic Factors: Genetic variability and metabolic differences—including liver-specific drug metabolism—were noted as possible reasons for differential drug responses across populations.

- Comorbid Conditions: Common coexisting diseases such as hypertension, diabetes, chronic liver disease, obesity, and cardiovascular disorders were frequently identified as confounders.

- Behavioral and Lifestyle Factors: Alcohol use, smoking, and dietary patterns were recognized as important but inconsistently measured modifiers of HCC risk.

- Treatment-Related Factors: Characteristics such as pharmacokinetics, medication adherence, and the specific class of antihypertensive drug (e.g., ACE inhibitors, ARBs, β-blockers, diuretics) were central to observed variations in outcomes.

- Tumor-Specific Variables: Clinical features of the tumor—such as size, stage, and vascular invasion—were shown to influence the impact of antihypertensives when used as adjuncts in HCC therapy.

- Study and Population Heterogeneity: Variability in data collection methods, patient demographics, and study design also contributed to bias and limited comparability across studies.

Discussion

The relationship between antihypertensive medications and liver cancer remains controversial. While most studies report no significant association, some have identified links involving common antihypertensives such as ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and diuretics. Among these, ARBs have shown a potential protective effect against liver cancer. This is hypothesized to result from inhibition of the renin-angiotensin system, particularly the angiotensin II type 1 receptor (AT1R), allowing unopposed stimulation of AT2R, which may exert anti-proliferative and anti-angiogenic effects (27,41,42).

Experimental models, such as the rat liver perfusion model, suggest that hyperosmolarity-induced upregulation of the miR-15/107 family and miR-141-3p may influence liver cell apoptosis and proliferation (40).

Diuretics have also been associated with increased liver cancer risk in some studies, with Cox regression analyses indicating a positive correlation (40).

Additionally, in patients with pre-existing liver conditions like hepatic steatosis, antihypertensives—particularly CCBs, ARBs, and ACEis—have been linked to disease progression and elevated liver cancer risk (43).

This systematic review highlights the nuanced and multifactorial nature of the association between antihypertensive drugs and HCC. Certain medications, such as thiazide diuretics, were found to reduce HCC risk in both European and East Asian populations (27). Similarly, renin-angiotensin system inhibitors—including ACE inhibitors and ARBs—were linked to improved progression-free survival and lower HCC incidence in South Korean cohorts (35,36). Evidence from Sweden further suggested that non-selective Beta-blockers may lower liver cancer mortality (39).

Conversely, some findings raised caution. A German regression analysis indicated a positive relationship between diuretics and liver cancer risk (40), which contradicts results from a Mendelian randomization study (27). Similarly, Beta-blockers were associated with increased HCC risk in Europeans (27), while other studies either found no association (33) or reported a protective effect (39). These inconsistencies may stem from differences in drug subtypes, patient characteristics, and methodological design. Importantly, the observational design of most included studies (33,36,37,39) limits causal inference and leaves room for residual confounding.

Some studies also examined the repurposing of non-conventional agents. For instance, in vitro analyses of chlorpromazine and prazosin revealed cytotoxic effects against liver cancer cells (38), though clinical application remains premature. Additionally, the adjunctive use of ARBs with radiofrequency ablation was associated with better outcomes in HCC patients (36), suggesting a potential role in combined treatment strategies.

In summary, while specific antihypertensive drugs—especially RAS inhibitors and diuretics—may impact HCC risk or progression, findings are heterogeneous across drug types and populations. These discrepancies likely reflect variations in underlying liver conditions, genetic backgrounds, drug mechanisms, and study quality (27,33,35,36,39,40). Carefully designed longitudinal studies are needed to clarify causality and identify which patient populations may benefit—or be harmed—by specific antihypertensive therapies in the context of liver cancer.

Recommendations of the Studies

To guide future research and clinical decision-making, Table 6 summarizes the key recommendations and insights from each included study, highlighting suggested directions for improving antihypertensive use in the context of hepatocellular carcinoma (HCC) prevention and management.

The reviewed evidence collectively underscores the importance of cautious interpretation regarding the association between antihypertensive medications and hepatocellular carcinoma (HCC) risk. Several studies (27,35,36,38–40) suggest that specific drug classes—including thiazide diuretics, Beta-blockers, ARBs, and renin-angiotensin system (RAS) inhibitors—may influence HCC risk, either positively or negatively.

These preliminary associations highlight the need for further exploration through rigorously designed prospective studies and randomized controlled trials. Concurrently, multiple authors (33,34,40) advocate against modifying existing clinical guidelines based solely on these early findings. Instead, they emphasize maintaining standard cancer prevention approaches while expanding future research to incorporate broader risk factors such as genetic predispositions, lifestyle behaviors, and socioeconomic determinants. Methodological refinements—including the use of standardized data collection protocols, inclusion of diverse patient populations, and multi-national study designs—are vital for improving the reliability and generalizability of future evidence (34).

Table 6. Key recommendations of selected studies.

References	Recommendations	Key Insights
(27)	Thiazide diuretics may reduce HCC risk; Beta-blockers may increase it. Consider individual risk factors and personalize treatment. Further studies are needed.	Potential drug-specific impact on HCC risk; need for personalized treatment and further research.
(33)	No protective effect of ACE inhibitors or Beta-blockers against liver cancer. Continue using them for cardiovascular indications, not cancer prevention. Emphasize established preventive strategies.	Antihypertensives not indicated for cancer prevention; focus on established prevention (e.g., alcohol reduction, hepatitis management).
(34)	Recommendations for future research: improve cohort diversity, ensure follow-up, analyze broader risk factors, and conduct international, standardized studies.	Methodological improvements to enhance validity and generalizability of findings.
(35)	Need for prospective studies on renin-angiotensin system inhibitors for liver protection. Encourage tailored approaches in high-risk patients.	Possible protective role of RAS inhibitors; importance of personalized medicine and longitudinal studies.
(36)	ARBs may be beneficial in HCC patients undergoing RFA. Recommend further RCTs to confirm efficacy and safety.	Potential adjunct role for ARBs in HCC treatment; requires validation through RCTs.
(38)	Further studies on chlorpromazine and prazosin for HCC treatment, including mechanism exploration. Repurposing may expedite therapeutic development.	Drug repurposing opportunity; need for mechanistic and clinical studies.
(39)	Recommend further clinical trials on Beta-blockers' survival benefits and their mechanisms in HCC. Investigate long-term use.	Investigate Beta-blockers' therapeutic potential and long-term outcomes.
(40)	Recommend future studies on long-term cancer risks of antihypertensives, especially diuretics and ARBs. Consider lifestyle and genetics. Don’t change clinical guidelines yet.	Cautious interpretation of current findings; need for comprehensive risk assessment and further validation.

Clinical Implications of the Study

This review underscores the importance of considering both drug class and patient-specific factors when

evaluating the potential oncologic effects of antihypertensive medications. Among these, agents targeting the renin-angiotensin system (RAS) may play a particularly favorable role, especially in individuals with preexisting liver conditions. Non-selective β-blockers also showed promise in reducing liver cancer mortality in patients already diagnosed with HCC. By contrast, diuretics demonstrated inconsistent effects, with some evidence suggesting benefit while other studies reported increased cancer risk—emphasizing the need for individualized therapeutic decisions based on clinical context. Overall, these findings suggest the potential to expand the therapeutic scope of certain antihypertensive drugs, though careful patient selection and further validation are essential before clinical application.

Limitations

This review incorporates studies with considerable methodological and clinical heterogeneity. Included studies range from randomized controlled trials to observational cohort analyses and in vitro experimental research. A notable limitation is the frequent reliance on prescription databases rather than direct confirmation of medication adherence, which may lead to misclassification of exposure. Additionally, several studies lacked detailed clinical or lifestyle data, increasing the risk of residual confounding.

Confounding by indication—where the underlying reason for prescribing an antihypertensive (e.g., cardiovascular disease or cirrhosis) may itself influence liver cancer risk—was a common challenge in observational studies and often not adequately controlled for. Selection bias was also a concern, particularly in studies using region-specific or institution-based cohorts (e.g., UK-only populations or U.S. veterans), which may not reflect broader patient demographics. Furthermore, immortal time bias—where patients must survive a certain period to receive treatment and thus appear to have better outcomes—may have affected studies lacking clearly defined exposure windows and time-to-treatment analyses.

Other issues included small sample sizes in certain studies, variations in follow-up duration, differences in liver disease staging, and inconsistent classification of antihypertensive drug categories. These limitations complicate direct comparisons across studies and emphasize the need for cautious interpretation. Future research should aim to address these biases through more rigorous study designs, ideally using prospective, longitudinal data with standardized outcome definitions.

Conclusion

This systematic review highlights the complex and nuanced associations between antihypertensive drug use and hepatocellular carcinoma. Certain classes—most notably RAS inhibitors and non-selective β-blockers—emerge as promising candidates for further exploration in cancer prevention or adjunctive therapy, though definitive conclusions remain premature. Mixed results for other drug types, such as diuretics and selective β-blockers, reflect underlying heterogeneity across study populations, designs, and outcome measures. The evidence, though promising in parts, is tempered by significant methodological limitations that prevent definitive conclusions. Nevertheless, these findings offer a foundation for future research and suggest a potential role for repurposing certain antihypertensive agents in liver cancer prevention and treatment. To move the field forward, high-quality, long-term clinical trials that incorporate diverse populations and standardized methodologies are essential. These efforts will help determine whether specific antihypertensive therapies can be safely and effectively integrated into personalized strategies for patients at risk for or living with HCC.

Author contribution

SN developed the methodology and wrote the methodology section. **SN** also conducted data extraction using a predesigned Excel spreadsheet, capturing key study details, including study design, patient population, type of antihypertensive medications used, liver cancer outcomes, and major findings. Additionally, **SN** oversaw the entire review process and coordinated the writing of the manuscript. **FZ** independently verified 50% of the extracted data to ensure accuracy and consistency. **FZ** also wrote the results section, contributed to the final review of the

manuscript, played a role in developing the study design, and assisted in refining the methodology section. **AN** contributed to refining the search strategy, participated in the full-text review process, and assisted in synthesizing the extracted data. **AN** also built the tables and diagrams for the manuscript and helped review the methodology section. **PD** independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. **PD** also conducted the full-text review for studies meeting the inclusion criteria and wrote the discussion section. **FT** independently verified 50% of the extracted data alongside **MA** to enhance data accuracy. **FT** also contributed to refining the study methodology and participated in manuscript revisions. **MR** wrote the introduction section and assisted in optimizing the search strategy. **MR** also played a role in screening full-text articles and contributed to drafting and reviewing the discussion section. **ML** independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. **ML** also wrote the conclusion section and participated in discussions regarding study inclusion and exclusion criteria. **JT** contributed to writing the discussion section and provided critical revisions to improve clarity and coherence. **JT** also participated in reviewing the final manuscript to ensure consistency and accuracy. **SS** played a role in the quality assessment of the included studies and assisted in synthesizing the extracted data. **SS** also contributed to reviewing the discussion and conclusion sections to ensure alignment with the study objectives. All authors contributed to the conception and design of the study, provided input on data interpretation, and participated in manuscript revisions. All authors approved the final version before submission.

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Conflicts of interest

There are no conflicts of interest.

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