



## The Association between oral antihypertensive drug use and lung cancer risk in adults: a systematic review

Shadman Newaz <sup>1\*</sup>, Ali Ahmed Shaju <sup>2</sup>, Moontasir Ahmed <sup>1</sup>, Ayesha Noor <sup>3</sup>, Sarwar Jahan Ratul <sup>1</sup>, Marjia Islam Tisha <sup>1</sup>, Samin Sadaf <sup>2</sup>, Bohnishikha Saha <sup>1</sup>

<sup>1</sup> Tangail Medical College, Tangail, Bangladesh

<sup>2</sup> Dinajpur Medical College, Dinajpur, Bangladesh

<sup>3</sup> Department of Pharmacy, Jahangirnagar University, Dhaka, Bangladesh

### Abstract

**Introduction:** Hypertension is a widespread cardiovascular condition often managed with antihypertensive medications, including ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and others. Emerging evidence suggests these medications may influence cancer risk, particularly in lung cancer, a leading cause of cancer-related mortality worldwide. This systematic review aims to evaluate the relationship between antihypertensive drugs and lung cancer risk, focusing on both protective and risk-increasing effects of these drugs.

**Materials and methods:** A comprehensive search was conducted across multiple databases for studies published between January 2015 and February 2025. Eligible studies included cohort studies, case-control studies, clinical trials, and observational studies. The review followed PRISMA guidelines for transparency and comprehensive reporting.

**Results:** A total of 14 studies—including cohort and case-control designs—met the inclusion criteria. The findings suggest that ACEIs were associated with an increased risk of lung cancer, especially with prolonged use, while ARBs seem to offer protective effects, particularly in certain populations such as heavy drinkers and males. CCBs, when used in combination with other antihypertensive drugs, may increase cancer risk, while  $\alpha$ -blockers combined with aspirin show promise in reducing cancer risk, particularly in older adults. Doxazosin and felodipine have potential in reducing cancer aggression and improving outcomes through modulation of tumor microenvironments and immune responses.

**Conclusion:** The relationship between antihypertensive medications and lung cancer risk is complex, with ACEIs potentially increasing the risk and ARBs offering protective effects. Future research should focus on larger prospective studies, exploring molecular mechanisms and developing personalized treatment strategies to minimize cancer risk in hypertensive patients. Regular screenings and careful management of drug interactions are essential for improving clinical outcomes.

**Keywords:** Antihypertensive drugs, ACE inhibitors, ARBs, Lung cancer, Calcium channel blockers, Cancer risk, Systematic review

Corresponding Author: Shadman Newaz

✉ Email: [shadmannewaz11@gmail.com](mailto:shadmannewaz11@gmail.com)

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## Introduction

Hypertension, a prevalent cardiovascular condition affecting millions globally, is characterized by persistently elevated blood pressure levels (1–4). The management of hypertension often involves the use of antihypertensive medications, which encompass a variety of drug classes, including diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (5–8). While the primary aim of these medications is to reduce cardiovascular morbidity and mortality, emerging evidence suggests that they may also have implications beyond blood pressure control, particularly in the context of cancer (5, 9–13).

Lung cancer, one of the leading causes of cancer-related mortality worldwide, presents a significant public health challenge (14–19). The complex interplay between hypertension, antihypertensive therapy, and cancer outcomes has garnered increasing attention in recent years (20,21). Emerging evidence suggests that antihypertensive medications may influence cancer incidence, progression, and survival—particularly in lung cancer due to its high prevalence and morbidity (22–24). Some studies report protective effects of certain antihypertensives, possibly through modulation of the renin-angiotensin system, anti-inflammatory actions, or alterations in the tumor microenvironment. Others, however, associate specific agents with increased lung cancer risk or poorer clinical outcomes (25, 26).

Given the conflicting evidence and the clinical significance of understanding the implications of antihypertensive therapy in lung cancer patients, a systematic review is warranted. This review aims to synthesize the current literature on the relationship between antihypertensive medications and lung cancer, evaluating both the potential benefits and risks associated with their use. By providing a comprehensive overview of existing studies, this review seeks to inform clinical practice and guide future research directions in this critical area of oncology and cardiovascular health.

## Methods

## Study Design and Protocol Registration

This systematic review was conducted following a predefined protocol that was registered on the Open Science Framework. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and comprehensive reporting throughout the review process.

## Inclusion and Exclusion Criteria

The review included studies published between January 2015 and February 2025 that investigated the relationship between antihypertensive medications and lung cancer outcomes. Eligible studies were of various designs, including clinical trials, cohort studies, case-control studies, and observational studies. Only studies published in English were considered. Studies were included if they focused on patients diagnosed with hypertension and explored the use of antihypertensive medications in relation to lung cancer outcomes. Exclusion criteria included non-English studies, those lacking sufficient data for extraction, study protocols, and studies addressing other cancer types without specific reference to lung cancer and hypertension or antihypertensive use. Studies published prior to 2015 were excluded to ensure the inclusion of more recent and methodologically rigorous research, reflecting advances in diagnostic techniques, drug classification, and cancer surveillance practices that have emerged over the past decade.

## Search Strategy

A comprehensive and refined search was conducted across four major electronic databases: PubMed, ScienceDirect, Cochrane Central Register of Controlled Trials (CENTRAL), and Mendeley. The search strategy involved a combination of Medical Subject Headings (MeSH) and free-text terms to capture studies related to antihypertensive medications and lung cancer outcomes. The primary concepts of the search were antihypertensive medications, lung cancer, and hypertension. Specific search terms included:

- Antihypertensive classes: "angiotensin-converting enzyme inhibitors" OR "ACE inhibitors" OR "angiotensin II receptor

blockers" OR "ARBs" OR "beta-blockers" OR "calcium channel blockers" OR "diuretics" OR "renin-angiotensin system" OR "antihypertensive agents."

- Lung cancer terms: "lung cancer" OR "lung carcinoma" OR "pulmonary carcinoma" OR "non-small cell lung cancer" OR "small cell lung cancer" OR "lung neoplasms."
- Lung cancer subtypes: "adenocarcinoma" OR "squamous cell carcinoma" OR "small cell lung cancer" OR "non-small cell lung cancer."

Additionally, keywords such as "lung cancer incidence," "lung cancer progression," "lung cancer recurrence," "lung cancer mortality," and "lung cancer survival" were combined with terms related to antihypertensives. To capture a broader range of relevant studies, terms were also expanded to include related side effects, mechanisms, and risk assessments, such as:

- "hypertension treatment" OR "cardiovascular drugs" AND "lung cancer risk."
- "antihypertensive side effects" AND "lung cancer survival."
- "risk of lung cancer" AND "antihypertensive drugs."

A second search iteration targeted grey literature sources by searching databases like Web of Science, Scopus, and Google Scholar. Reference lists of key studies and reviews were also screened to ensure no relevant studies were overlooked. The search covered studies published from January 2015 to February 2025, and the database searches were initially performed on January 26, 2025, with an update conducted on February 26, 2025.

### Screening and Data Extraction

The screening process was managed using Rayyan software, which allowed for the removal of duplicates and facilitated the title and abstract screening. Two independent reviewers (MA and SR) conducted the initial screening, with disagreements resolved by a

third reviewer (MT). Full-text reviews were conducted for studies that met the inclusion criteria.

Data extraction was performed using a predesigned Excel spreadsheet that captured key details, including study design, patient population, type of antihypertensive medications used, lung cancer outcomes, and major findings. Data extraction was carried out by SN, with 50% of the data verified independently by AS and SS to ensure accuracy.

### Quality Appraisal

Although the primary aim of this systematic review was to summarize and map the existing evidence rather than to critically appraise study quality, a descriptive evaluation of study limitations and potential biases was performed for each study. Formal quality appraisal tools, such as the Newcastle-Ottawa Scale (for cohort and case-control studies), were applied where appropriate, but no studies were excluded based on quality criteria.

### Data Synthesis

Due to the heterogeneity in study designs and outcomes, a narrative synthesis was conducted. A meta-analysis (quantitative pooling of data) was not performed due to variations in study methods, populations, and outcome measures across the included studies. Heterogeneity was assessed qualitatively by comparing study designs, patient characteristics, interventions, and outcome definitions across studies.

For the purpose of this review, "lung cancer outcomes" encompassed a range of endpoints, including cancer incidence, disease progression, treatment response, survival rates (overall and disease-specific), and mortality.

The results were synthesized to provide a broad overview of the available evidence on the relationship between antihypertensive medications and lung cancer outcomes.

### Assessment of Bias

Bias assessment was carried out using established tools and guidelines to ensure a rigorous evaluation process.

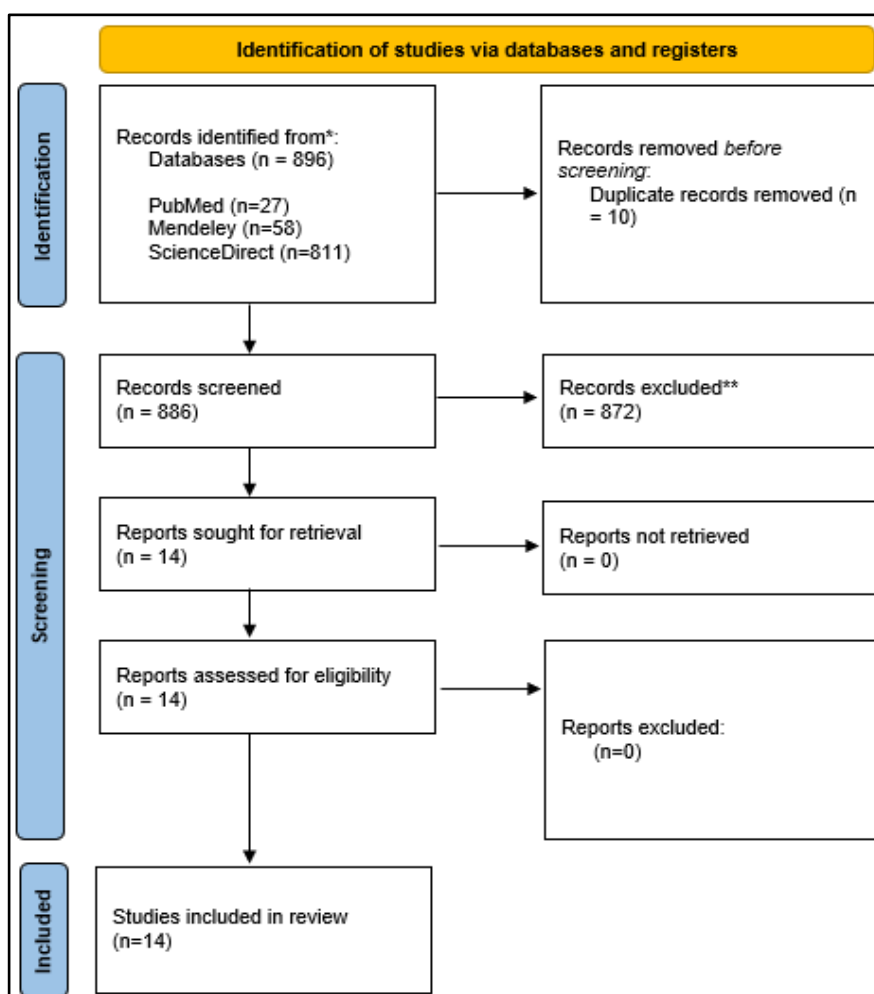
The ROBINS-I tool was employed to assess the quality and risk of bias in the included studies. This evaluation considered various factors, such as selection bias, performance bias, detection bias, and reporting bias. Multiple researchers independently reviewed each study to maintain consistency and objectivity in the assessment.

Although no studies were excluded based on bias ratings, findings from studies assessed as having a high risk of bias were interpreted with caution during synthesis. Where applicable, subgrouping and narrative comparisons were used to explore differences in outcomes based on risk of bias. No formal sensitivity analysis was performed; however, the level of bias was qualitatively considered when drawing final conclusions about the strength and reliability of the evidence.

This methodological approach aimed to provide a comprehensive understanding of potential biases influencing study outcomes and to enhance the reliability of the systematic review's findings.

## Results

The review process details are depicted in the PRISMA flowchart (Figure 1). A total of 896 records were identified through database searches, including Science Direct (n=811), PubMed (n=27), and Mendeley (n=58). After removing 10 duplicate records, 886 records remained for title and abstract screening. Following this initial screening, 872 records were excluded based on irrelevance to the study objectives. Subsequently, 14 full-text articles were assessed for eligibility. Ultimately, all 14 studies were included in the systematic review for further in-depth analysis of the core relationship between antidiabetic drugs and the risk of developing liver cancer.



**Figure 1.** Prisma flow diagram illustrating the study selection process.

Below table (Table 1) summarizes the geographical distributions of the included studies.

**Table 1.** Country distribution of included studies.

| Country        | Count |
|----------------|-------|
| Korea          | 2     |
| Hong Kong      | 2     |
| East Asia      | 1     |
| Shanghai       | 1     |
| United Kingdom | 1     |
| Unidentified   | 7     |

Seven studies lack country identification, while five studies are from Korea, Hong Kong, East Asia, Shanghai, and the United Kingdom. The lack of geographical information in these seven studies limits the ability to generalize the findings across different populations and healthcare systems. Further details on the study locations would improve the applicability of the results. The studies included in this review employed a variety of designs (Table 2), with the majority being cohort studies. Additionally, there were case-control studies, a Mendelian randomization study, a case report, a pre-clinical model, and an in-vitro model. This diverse range of study designs provides valuable insights, though the observational nature of many studies may introduce potential biases.

Among the included studies, one case report, one pre-clinical model, and one in vitro study were identified alongside larger epidemiological studies. These studies were synthesized separately from cohort and case-control studies to preserve interpretive clarity and account for methodological heterogeneity. While they did not contribute directly to population-level outcome trends, they provided valuable mechanistic insights into potential biological pathways through which antihypertensive medications may influence lung cancer development or progression. Their findings

were used to support or contextualize associations observed in clinical studies but were interpreted cautiously due to inherent limitations in generalizability.

**Table 2.** Methodological Designs of Included Studies.

| Study design                  | Count |
|-------------------------------|-------|
| Cohort                        | 9     |
| Case-control                  | 2     |
| Mendelian randomization study | 1     |
| Systematic review             | 1     |
| Case report                   | 1     |
| Pre-clinical Model            | 1     |
| In-vitro Model                | 1     |

**Key Characteristics of the Included Studies**

The table (Table 3) below summarizes the key characteristics of the studies included in this review, including country, study design, total participants, age, gender, and limitations. This provides an overview of the diversity in study contexts and methodologies. While most included studies reported comprehensive data such as country of origin and participant demographics, a few lacked such details. These studies were retained to ensure inclusivity of all relevant evidence on the relationship between antihypertensive medications and lung cancer outcomes. Despite the missing contextual information, these studies provided valuable outcome data and mechanistic insights that contributed meaningfully to the overall synthesis. Their inclusion was justified by their relevance to the review question and methodological adequacy in other areas, as assessed through the bias appraisal process. To minimize potential impact, findings from these studies were interpreted with appropriate caution in the narrative synthesis.

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

| References | Country   | Design                        | Total Participants                              | Age       | Gender | Limitations                                                                                                              |
|------------|-----------|-------------------------------|-------------------------------------------------|-----------|--------|--------------------------------------------------------------------------------------------------------------------------|
| (27)       | East Asia | Cohort                        | 228                                             | N/A       | Both   | Non-randomized, retrospective design with small sample size, potential biases, and lack of molecular exploration.        |
| (28)       | N/A       | In-vitro                      | N/A                                             | N/A       | N/A    | In vitro model limits accuracy, no in vivo confirmation, lacks consideration of drug interactions or adverse effects.    |
| (29)       | N/A       | Pre-clinical model            | N/A                                             | N/A       | N/A    | Small sample size, reliance on preclinical models, and insufficient mechanistic evidence.                                |
| (30)       | Korea     | Cohort                        | 0.3 million                                     | ≥40 years | Both   | Residual confounding, retrospective design, and limited generalizability due to a specific population.                   |
| (31)       | N/A       | Mendelian randomization study | N/A                                             | N/A       | N/A    | Long-term genetic impact focus, limited generalizability, and lack of RCTs weakening causal conclusions.                 |
| (32)       | N/A       | Case-control                  | 178                                             | ≥18       | Both   | Small sample size, retrospective design, and unaddressed comorbidities/genetic factors.                                  |
| (33)       | Hong Kong | Cohort                        | 6,592 anti-hypertensive users, 84,116 non-users | N/A       | Both   | Lack of smoking status consideration, unmeasured confounders, and potential inapplicability to the Hong Kong population. |
| (34)       | Shanghai  | Cohort                        | 4,970 cancer cases                              | N/A       | Both   | Missing dosage information, pharmacological classes, and limited applicability outside Shanghai.                         |
| (35)       | Worldwide | Systemic review               | N/A                                             | N/A       | N/A    | Potential biases (selection, recall), and inconsistent prior research affecting causality and generalizability.          |
| (36)       | Hong Kong | Cohort                        | 6,592 and 84,116 lung cancer cases              | N/A       | N/A    | Lack of causality data and missing data on rare tumors and medication details.                                           |

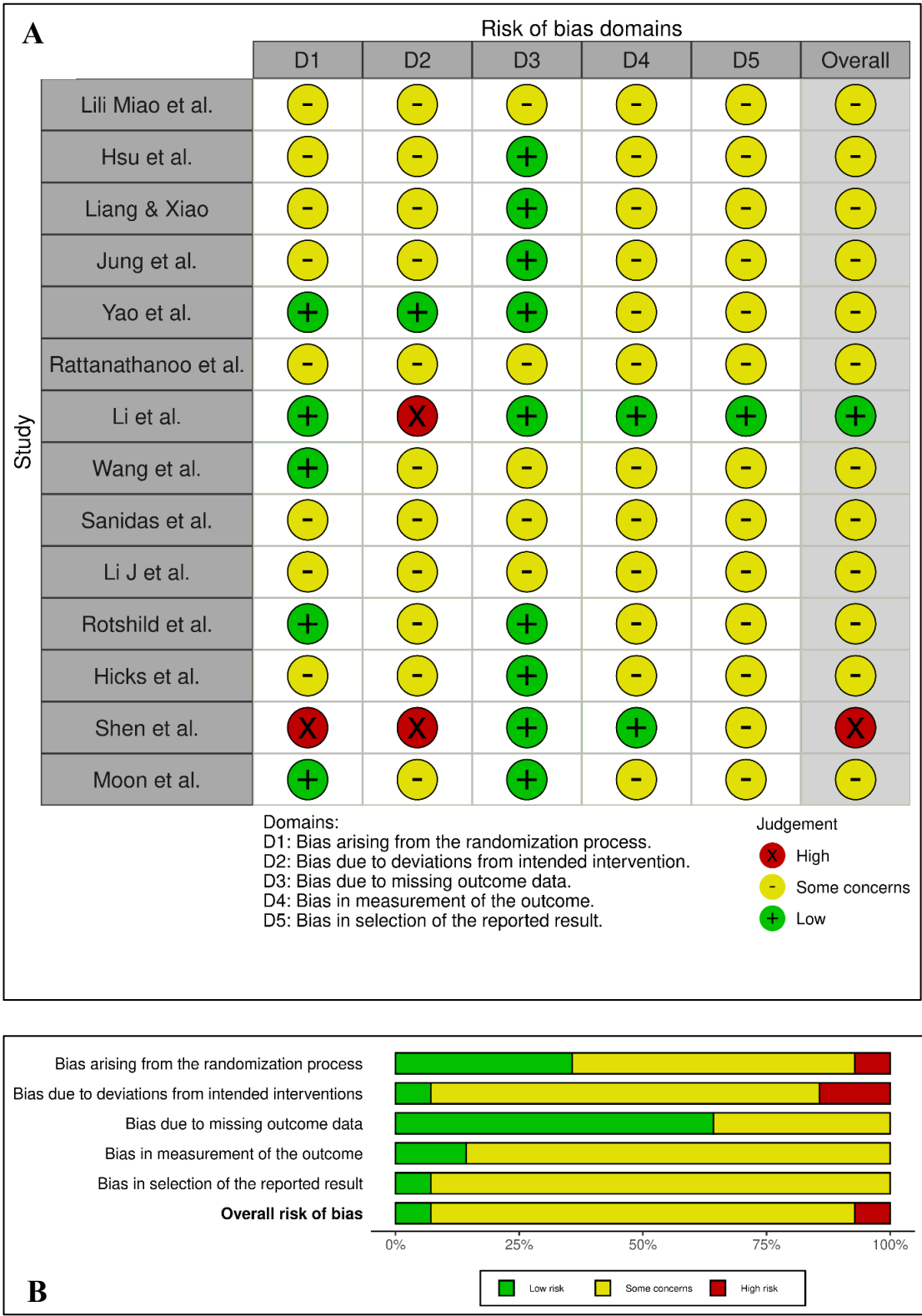
|      |                |              |                         |     |        |                                                                                           |
|------|----------------|--------------|-------------------------|-----|--------|-------------------------------------------------------------------------------------------|
| (37) | N/A            | Case-control | 4,174 lung cancer cases | N/A | N/A    | N/A                                                                                       |
| (38) | United Kingdom | Cohort       | 992,061                 | N/A | N/A    | Missing smoking data, unmeasured confounders, and potential misclassification of results. |
| (39) | N/A            | Case report  | 1                       | N/A | Female | Unaccounted genetic/environmental factors and no long-term data on cancer outcomes.       |
| (40) | South Korea    | Cohort       | 60,469 subjects         | N/A | Both   | Observational design with potential misclassification and missing subtype-specific data.  |

**Risk of Bias Assessment**

The risk of bias across the included non-randomized studies was evaluated using the ROBINS-I tool. Overall, most studies demonstrated concerns regarding bias risk in multiple domains. The most frequent issues were related to the selection of participants, deviations from intended interventions, and reporting of outcomes, where many studies lacked sufficient information or exhibited methodological concerns. A few studies were judged to have a high risk of bias, mainly due to confounding and missing outcome data. Only a limited number of studies were rated as low risk across all domains. The domain-wise distribution of the risk of bias is visually summarized in the figures (Figure 2 A and B) below. Figure 2 presents a comprehensive summary of the risk of bias assessment across included studies. Figure 2 A provides a visual overview of the risk of bias for each individual study,

categorized into five domains. Each domain is evaluated using a traffic light color-coding system—green (+) for low risk, yellow (–) for some concerns, and red (×) for high risk. Most studies exhibit “some concerns” across multiple domains, with a smaller number rated as “low risk” throughout. High risk assessments are predominantly observed in D2, indicating deviations from intended interventions.

Figure 2B illustrates the distribution of risk of bias judgments across all studies by domain, represented as a bar chart. The highest proportion of “some concerns” is seen consistently across most domains. Domains D1 and D2 show the greatest frequency of “high risk” assessments, while domain D3 (missing outcome data) has the fewest concerns, with a relatively higher proportion rated as “low risk.” Overall, only a limited number of studies are free from bias across all domains.



**Figure 2.** Summary and domain-level distribution of risk of bias in included non-randomized studies (27–40).

Legend (Applicable to Both Figures): Green (+): Low risk of bias. Yellow (-): Some concerns regarding bias. Red (x): High risk of bias. D1: Bias arising from the randomization process. D2: Bias due to deviations from intended interventions. D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result. Overall: Combined assessment of all domains for each study.

**Main Findings of the Studies based on Antihypertensive Drugs Classification**

Key findings of the included studies are given below (Table 4) according to the different classes of anti-diabetic drugs.

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

| Drug Class                      | Specific Findings                                                                                                                               | References |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| ACE Inhibitors (ACEIs)          | ACEIs linked to increased lung cancer risk, especially with prolonged use. Risk observed in non-smokers and higher after five years.            | (31,38)    |
| ARBs                            | ARBs reduced lung cancer risk compared to ACEIs, particularly in men and heavy drinkers, with stronger effects after prolonged use.             | (30,40)    |
| Calcium Channel Blockers (CCBs) | CCBs associated with a slightly higher risk of lung cancer, especially thyroid and lung cancers, when multiple antihypertensive drugs are used. | (33,34,37) |
| $\alpha$ -blockers              | $\alpha$ -blockers, especially when combined with aspirin, reduced lung cancer risk, with the greatest benefit seen in older adults.            | (33,36)    |
| Doxazosin                       | Doxazosin reduced cancer cell aggression and metastasis in NSCLC models, showing promise as a therapeutic option.                               | (28)       |
| Felodipine                      | Felodipine slowed tumor growth and improved outcomes when combined with immune therapies, possibly by influencing NFAT1.                        | (29)       |

**Summary of Findings:**

- **ACEIs** are associated with an increased risk of lung cancer, particularly with prolonged use (31,38).

- **ARBs** offer a protective effect, reducing lung cancer risk compared to ACEIs, particularly in certain populations (30,40).
- **CCBs** may increase cancer risk, especially with multi-drug antihypertensive combinations (33,34,37).
- **$\alpha$ -blockers** and **aspirin** combination enhance cancer prevention, especially in older adults (33,36).
- **Doxazosin** and **Felodipine** have promising potential in reducing cancer cell aggression and improving outcomes (28,29).

Table below (Table 5) includes influencing factors for lung cancer due to hypertension management. The influencing factors identified in the studies include the impact of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on survival outcomes in NSCLC patients (27), and the role of vasculogenic mimicry (VM) pathways in NSCLC, influenced by molecules like VEGF-A and VE-cadherin (28). Additionally, the effectiveness of felodipine in lung squamous cell carcinoma (LUSC) is associated with immune modulation and tumor resistance (29). Prolonged ARB use has been shown to reduce the risk of lung, hepatic, and gastric cancers, especially in males and heavy drinkers (30), while genetic variants and ACEI-induced cough may increase lung cancer risk in Europeans (31). Factors such as dyslipidemia and family history of lung cancer are significant for cancer risk in hypertensive patients, while calcium channel blockers (CCBs) do not show an association (32). Long-term use of antihypertensives like ACEIs, ARBs, and  $\alpha$ -blockers has been linked to reduced lung cancer risk (33), although the use of multiple antihypertensive drugs increases cancer risk (34). The study suggests various mechanisms by which different antihypertensive drugs may influence cancer risk (35), with ACEI use over five years increasing lung cancer risk (38). Drug-drug interactions and genetic factors can impact treatment outcomes in cancer patients (39), while lifestyle factors such as smoking, alcohol, and comorbidities influence the effectiveness of antihypertensive treatments (40).

**Table 5.** Influencing factors for lung cancer due to hypertension management according to the included studies.

| References | Influencing factor                                                                                                                                                                                                                                                       |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (27)       | Use of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in NSCLC patients to evaluate their effect on survival outcomes.                                                                                                                                  |
| (28)       | Vasculogenic mimicry (VM) in NSCLC is influenced by VEGF-A, VE-cadherin, EphA2/AKT/mTOR/MMP pathway, and epithelial-mesenchymal transition (EMT) markers (vimentin, fibronectin). Doxazosin inhibits VM by targeting these pathways.                                     |
| (29)       | Felodipine's effectiveness in lung squamous cell carcinoma (LUSC) is impacted by NFAT1 expression, immune system modulation, tumor resistance to immune checkpoint blockers (ICBs), and its role in treating both hypertension and cancer.                               |
| (30)       | Prolonged ARB use significantly lowers the risk of lung, hepatic, and gastric cancers, especially in males and heavy drinkers, by inhibiting AT1 receptors while preserving AT2 receptor benefits. Effects vary by cancer type and demographics.                         |
| (31)       | Genetic variants (e.g., rs118121655, rs360206) and ACEI-induced cough increase lung cancer risk, particularly in Europeans with small-cell lung cancer (SCLC) and adenocarcinoma. Bradykinin and protachykinin-1 accumulation may contribute to this risk.               |
| (32)       | Dyslipidemia and family history of lung cancer significantly elevate cancer risk in hypertensive patients, while calcium channel blockers (CCBs) show no association. Smoking and comorbidities were not linked to lung cancer.                                          |
| (33)       | Long-term use of ACEIs, ARBs, and $\alpha$ -blockers reduces lung cancer risk, with greater benefits observed in older adults (above 65) and males. Aspirin combined with $\alpha$ -blockers further lowers risk, but smoking status was not considered in the analysis. |
| (34)       | Increased cancer risk is linked to the use of multiple antihypertensive drug classes, with hazard ratios of 1.22 for two-drug combinations and 1.22 for three or more classes.                                                                                           |
| (35)       | Cancer risk is associated with ACEIs, ARBs, CCBs, beta-blockers (BBs), and diuretics. Research also examines rare side effects and potential links between antihypertensive drugs and malignancy.                                                                        |
| (36)       | Cancer risk varies based on drug mechanisms (RAS inhibitors may protect, while CCBs and thiazides might increase risk), treatment duration, dosage, and patient-specific factors such as comorbidities, lifestyle, and genetics.                                         |
| (37)       | Prolonged ACEI use (over five years) is associated with an increased lung cancer risk, peaking at 10 years. The accumulation of bradykinin and substance P in the lungs may contribute to tumor growth. Risk persists in non-smokers and is higher than with ARBs.       |
| (38)       | Drug-drug interactions (CYP3A4-mediated competition between gefitinib, nifedipine, and simvastatin), genetic factors (wild-type CYP3A4, weak CYP2D6 metabolism), and patient non-compliance impact drug toxicity and treatment outcomes.                                 |
| (39)       | ARB use lowers lung cancer risk more than CCBs, particularly in women, never-smokers, non-drinkers, and those without COPD. Lifestyle factors (smoking, alcohol) and comorbidities (diabetes, dyslipidemia) influence treatment effects.                                 |

## Discussion

The relationship between antihypertensive medications and cancer risk has been explored across various studies with mixed results (41–43). Some evidence suggests that angiotensin-converting enzyme inhibitors (ACEIs) may be associated with an increased risk of lung cancer, particularly after prolonged use beyond five years (31,38), although confidence intervals vary and causality remains uncertain. Conversely, angiotensin receptor blockers (ARBs) appear to offer a protective effect against lung cancer, especially in subpopulations such as men and heavy drinkers, with hazard ratios ranging from 0.7 to 0.85 in these groups (30,40). Calcium channel blockers (CCBs) have been linked to an increased risk of certain cancers, notably lung and thyroid cancers, primarily when used in combination with other antihypertensive agents (33,34,37). This association appears to be dose- and duration-dependent, with studies reporting stronger correlations in patients receiving higher cumulative doses or treatment extending beyond three years (adjusted hazard ratios ranging from 1.15 to 1.35; 95% CI: 1.05–1.50). However, these findings are limited by inconsistent control for important confounders such as smoking status, which may influence cancer risk independently. Moreover, data on specific CCB subtypes remain sparse, limiting precise conclusions about individual drug effects. A notable finding is the potential protective role of  $\alpha$ -blockers combined with aspirin, particularly in older adults, with relative risk reductions reported around 15–20% (33,36). Mechanistic studies support this, with doxazosin demonstrated to inhibit vasculogenic mimicry (VM) in non-small cell lung cancer (NSCLC) cells, suggesting a possible therapeutic benefit (28). Similarly, felodipine has shown promise in preclinical models by slowing tumor growth and enhancing outcomes when combined with immune therapies, although clinical evidence remains limited (29). While these findings offer important insights, they must be interpreted cautiously due to limitations including small sample sizes, predominantly retrospective study designs, and insufficient adjustment for key confounders such as smoking status, environmental exposures, and lifestyle factors. Given the observational nature of the data, any potential therapeutic implications—such as the use of

specific antihypertensives for cancer risk modification—remain speculative and require validation through well-designed prospective trials.

## Recommendations of the Studies

Recommendations from the included studies with their key insights are given in the table below (Table 6). The recommendations across the studies emphasize the need for more extensive research and careful patient management. Larger prospective trials should be conducted to confirm findings, reduce bias, and explore the biological mechanisms behind observed effects (27–29,34). Monitoring genetic factors (31) and considering patient-specific factors such as lifestyle (32,33,40) can help personalize treatment strategies, particularly when using ACEIs and ARBs. Additionally, the combination of antihypertensives and aspirin (33) or other newer drugs like sacubitril/valsartan (36,38) should be explored for their potential in cancer prevention. Regular screenings for high-risk patients and careful management of drug interactions (39) are critical for improving outcomes.

## Clinical Implications of the Study

This study highlights the importance of considering the long-term effects of antihypertensive drugs on cancer risk, particularly in lung cancer. ACE inhibitors (ACEIs) may increase the risk, while angiotensin receptor blockers (ARBs) show protective effects. The findings suggest that clinicians should evaluate the type of antihypertensive prescribed based on patient demographics, comorbidities, and potential cancer risks. Additionally, drugs like doxazosin and felodipine, which show promise in reducing cancer aggression and improving immune responses, may offer new therapeutic options.

## Limitations of the Study

The study's limitations include reliance on observational designs, small sample sizes in some studies, lack of long-term follow-up data, and potential biases such as confounding factors (e.g., smoking, alcohol use, genetic variations). Additionally, the studies did not fully address the molecular mechanisms of antihypertensives' effects on cancer development.

The generalizability of findings is also limited due to specific population settings and regional differences.

**Table 6.** Key recommendations of selected studies.

| References | Recommendations                                                                                                                                                                       | Key Insights                                                                                                                                        |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| (27)       | Conduct larger, prospective randomized trials to validate findings and reduce bias. Explore biological mechanisms and ensure diverse patient populations to improve generalizability. | Larger trials and exploration of biological mechanisms are necessary to confirm the results and improve clinical applicability.                     |
| (28)       | Conduct further preclinical and clinical trials to confirm doxazosin's anti-vasculogenic mimicry effects and its potential as an add-on therapy for NSCLC.                            | Doxazosin should be investigated further, particularly for its potential in combination therapies targeting cancer metastasis.                      |
| (29)       | Repurpose felodipine for cancer therapy and assess its combination with immune checkpoint blockers (ICBs). Explore NFAT1 as a target for treatment.                                   | Felodipine shows promise for enhancing immune responses in cancer therapy, and its use in combination therapies warrants further investigation.     |
| (30)       | Consider ARBs as a safer option for long-term use to reduce cancer risks in hypertensive patients, particularly in men and heavy drinkers.                                            | ARBs offer protective effects against certain cancers, especially in specific demographic groups like men and those who consume alcohol.            |
| (31)       | Monitor genetic variants (e.g., rs360206) in ACEI users and consider ARBs for those who experience ACEI-induced cough.                                                                | Genetic monitoring could help reduce lung cancer risk in patients taking ACEIs, while ARBs should be considered as an alternative.                  |
| (32)       | Continue using CCBs for hypertension management, as they do not increase lung cancer risk. Focus on managing dyslipidemia and family history of lung cancer.                          | Managing other risk factors like dyslipidemia and family history is critical, as CCBs do not contribute to increased lung cancer risk.              |
| (33)       | Explore the combination of antihypertensives (ACEIs, ARBs, $\alpha$ -blockers) with aspirin for lung cancer prevention, especially in older adults and males.                         | The combination of antihypertensives with aspirin could be beneficial for lung cancer prevention, particularly in older adults and males.           |
| (34)       | Conduct randomized controlled trials to confirm causality and explore the impact of different drug combinations on cancer risk.                                                       | More large-scale RCTs are needed to clarify the link between antihypertensives and cancer risk, with a focus on drug combinations.                  |
| (35)       | Monitor long-term use of certain antihypertensive drugs like CCBs and thiazides, and perform regular cancer screenings for high-risk patients.                                        | Regular monitoring and cancer screening are essential for hypertensive patients, particularly those on certain antihypertensive medications.        |
| (36)       | Replicate findings on ACEI-related lung cancer risks in other settings and monitor long-term use. Explore newer drugs like sacubitril/valsartan.                                      | Long-term monitoring of ACEI users is crucial, with a focus on alternative treatments like ARBs and newer medications such as sacubitril/valsartan. |

|      |                                                                                                                                   |                                                                                                                                                                            |
|------|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (37) | Investigate the risk increase of lung cancer with prolonged CCB use, and consider patient-specific factors in treatment.          | Prolonged use of CCBs may increase lung cancer risk, making individualized treatment decisions essential.                                                                  |
| (38) | Consider alternative treatments to ACEIs, particularly for patients with long-term use, and explore newer antihypertensive drugs. | Prolonged use of ACEIs was associated with increased lung cancer risk; ARBs and newer drugs like sacubitril/valsartan could offer safer alternatives.                      |
| (39) | Avoid CYP3A4-mediated drug interactions in cancer patients and foster multidisciplinary collaboration for managing drug toxicity. | Drug-drug interactions should be avoided by choosing alternative medications like valsartan and rosuvastatin, and collaboration between healthcare providers is essential. |
| (40) | Consider ARBs for hypertensive patients at high risk of lung cancer, particularly non-smokers, women, and non-drinkers.           | ARBs are recommended for hypertensive patients at higher risk for lung cancer, especially those with specific lifestyle factors.                                           |

Conclusion

This study provides valuable insights into the potential relationship between antihypertensive medications and cancer risk. While ACEIs were associated with increase cancer risk, particularly lung cancer, ARBs seem to have protective effects. The use of calcium channel blockers (CCBs) may increase the risk of certain cancers, especially when multiple antihypertensive medications are combined. Future research should focus on conducting larger prospective studies, exploring molecular mechanisms, and developing personalized treatment strategies to minimize cancer risk in hypertensive patients.

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, lung cancer outcomes, and major findings. Additionally, SN oversaw the entire review process and coordinated the writing of the manuscript. AS independently verified 50% of the extracted data to ensure accuracy and consistency. MA 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. MA contributed to refining the search strategy, participated in the full-text review process, and assisted in synthesizing the extracted data. MA also built the tables and diagrams for the manuscript and helped review the methodology section. AN independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. AN also conducted the full-text review for studies meeting the inclusion criteria and wrote the discussion section. SR independently verified 50% of the extracted data alongside MA to enhance data accuracy. SR also contributed to refining the study methodology and participated in manuscript revisions. MT wrote the introduction section and assisted in optimizing the search strategy. MT also played a role in screening full-text articles and contributed to drafting and reviewing the discussion section. SS independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. SS also wrote the conclusion section and participated in discussions regarding study inclusion and exclusion criteria. BS contributed to writing the discussion section and provided critical revisions to improve clarity and coherence. BS also participated in reviewing the final

manuscript to ensure consistency and accuracy. NT played a role in the quality assessment of included studies and assisted in synthesizing the extracted data. NT 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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