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Angiotensin receptor blockers use and lung cancer risk in Chinese patients with chronic obstructive pulmonary disease: a population-based cohort study

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is one of the most prevalent specific chronic respiratory diseases. It could worsen the development of cardiovascular diseases (CVD) and lung cancer. We aimed to elucidate the relationship between the use of angiotensin receptor blockers (ARBs) and the incidence of lung cancer among the COPD population in China.

Methods This retrospective cohort included COPD patients identified by the international classification of diseases 10th edition (ICD-10) codes in the Yinzhou Regional Health Care Database. The use of ARBs was defined according to the use and cumulative use. The lung cancer was defined by ICD-10 code (up to 2023). Time-varying Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the use of ARBs on the risk of lung cancer.

Results This population-based COPD cohort comprised 25,436 patients with an average age of 68.2 years (standard deviation [SD]: 12.59 years), of which 60.6% were male. A total of 8,611 patients received at least one prescription for ARBs. After adjusting for multiple covariates, the results showed that cumulative annual exposure to ARBs was associated with a reduced risk of lung cancer (HR: 0.93, 95% CI: 0.90–0.97). The results of sensitivity analyses and negative control exposure analyses indicated that the associations were largely consistent and less likely to be influenced by unobserved confounding.

Conclusions The use of ARBs may reduce the risk of lung cancer among patients with COPD.

Keywords Angiotensin receptor blockers, Lung cancer, Chronic obstructive pulmonary disease, Cohort study

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous airway disease characterized by persistent respiratory symptoms, airflow limitation, and local and systemic inflammation [1]. It is the most prevalent specific chronic respiratory disease both globally and in China, and it is also the chronic respiratory disease with the highest mortality rate [2–4].

Cardiovascular disease (CVD) is a comorbidity in patients with COPD [5, 6], and the pulmonary and systemic inflammation caused by COPD is one of the risk factors for CVD [6].

Hypertension is considered one of the most common comorbidities among cancer patients, with a prevalence of up to 37% [7]. Studies have suggested a potential association between hypertension and cancer incidence [8].

COPD is also a comorbidity of lung cancer, both sharing common etiological factors such as smoking. ARBs are not only effective in treating CVD but also improve the prognosis of COPD patients [9], potentially influencing the incidence of lung cancer. ARBs exert their primary anti-inflammatory and antifibrotic effects by inhibiting the renin-angiotensin system [9]. These effects may help regulate airway inflammation and the pro-tumor inflammatory microenvironment in COPD patients [10]. However, previous studies primarily focused on the relationship between ARBs and the risk of lung cancer [11]. Few studies have addressed this issue in the Chinese population [12], and none have specifically examined this association among COPD cohort [13].

Considering the insufficient evidence in previous research, the objective of this cohort study was to assess the association between ARBs use and lung cancer risk based on a cohort of COPD patients in China.

Methods

Data source and participants

We conducted a retrospective new-user cohort study using the Yinzhou Regional Health Care Database (YRHCD). The YRHCD covered data from health information systems in public hospital, community health center, health surveillance system, and death registry, and integrated longitudinal information of population census, electronic medical records, disease surveillance and management, health check, death registry, and other healthcare services in the Yinzhou District, Ningbo City, Zhejiang Province, China [14, 15]. Since 2009, the YRHCD has covered nearly all health-related activities of all residents in this region, from birth to death [14]. In 2008, disease registry and management systems were established for COPD patients, diabetes mellitus, cancer, CVD, and hypertension [15]. The Yinzhou database was standardized to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) version 5, which is maintained by the Observational Health Data Sciences and Informatics (OHDSI) Network [16, 17].

The study population consisted of real-world COPD patients captured in the YRHCD. Patients were screened between January 1, 2010, and June 1, 2022 (the screening period). Patients meeting the following criteria were considered eligible: (1) At least one primary diagnosis codes for COPD (the international classification of diseases 10th edition (ICD-10) code: J44)in the outpatient setting, or at least one primary or secondary diagnosis item/code for COPD in the inpatient setting during the screening period; (2) Age ≥ 40 years at the time of the first identified COPD diagnosis code; (3) Baseline data continuously available for at least 12 months prior to the first identified COPD diagnosis code. The date of the first identified COPD diagnosis (occurring within the screening period) was defined as the index date. Baseline data were derived from the 12-month baseline period prior to the index date (including the index date).

Exposure

The use of ARBs was defined based on outpatient and inpatient prescriptions, as well as medication information from the disease registry and management system. Patients who were diagnosed with COPD and had been prescribed ARBs prior to the diagnosis of lung cancer or the end of follow-up date were classified as the ARBs treatment group; otherwise, they were designated as the control group. Patients who had used ARBs during the baseline (washout period) were excluded (Supplementary Figure S1).

We employed two distinct analytical approaches to define medication exposure:

1. Binary ARBs exposure: Patients who had filled a prescription for ARBs medications at any given time during the follow-up period.
2. Cumulative years of use: The total years supplied for each ARBs prescription were aggregated for each patient during the follow-up period.

The ARBs exposures were treated as time-dependent variables to enhance statistical power for detecting moderate effects and minimize the risk of biases, such as immortal time bias [18].

Outcome

The study results focused on newly diagnosed lung cancer cases identified through outpatient or inpatient records, primarily using ICD-10 codes (**C34**). The date of first diagnosis was defined as the outcome date. Given the prolonged preclinical phase of lung cancer, our primary analysis assumed a one-year latency period prior to the

onset of the disease; thus, all lung cancer cases diagnosed within one year following the index date were excluded from the analysis.

Covariates

Covariates included demographic covariates comprised age, gender, and educational attainment. Additionally, factors such as smoking status, alcohol consumption, COPD-related medications, other antihypertensive drugs, cardiac drugs, COPD exacerbation status, comorbidities, and the number of hospital admissions were incorporated. Detailed definitions of these covariates can be found in Supplementary Table S1.

COPD exacerbation status was categorized into moderate and severe exacerbations. A moderate exacerbation was defined as an outpatient visit (by a general practitioner, pulmonologist, or internist) for COPD exacerbation during which a new prescription for systemic corticosteroids (administered intravenously or orally) and/or antibiotics for respiratory infections was issued. A severe exacerbation was defined as a record of hospitalization for COPD exacerbation, with specific codes listed in Supplementary Table S1.

Statistical analyses

The distribution of covariates between the exposed group and the control group was examined. Continuous variables were compared using t-tests, while categorical variables were analyzed using chi-square tests.

Immortal time bias is a common form of time-related bias in cohort studies, primarily arising when the start of exposure is not aligned with the beginning of the cohort follow-up period [19, 20]. To address this issue, time-varying Cox regression models was employed to estimate the risk of ARBs on lung cancer. Follow-up time was selected as the timescale which started from index date and ended at the time of lung cancer, loss to follow-up (the date of the last recorded clinical event in the database), death (death data traceable up to June 30, 2023), or data deadline (June 30, 2023), which occurred first (Fig. 1). Four models with different combinations of covariates were conducted to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between ARBs use and the risk of lung cancer. The four models were as follows: model 1 estimated crude HR; model 2 was adjusted for age and gender; model 3 was further adjusted for incorporates comorbidities; model 4 was further adjusted for education levels, smoking status, drinking status, COPD exacerbation status, the number of hospital admissions, and comedications.

Based on this fully adjusted model, subgroup analysis was performed by age (< 65 and ≥ 65) [21]and hospitalizations (CVD and COPD).

Sensitivity analyses

To assess the robustness of the primary analysis results, we conducted a series of sensitivity analyses. First, in the primary analysis, the latency period for lung cancer was defined as one year following the index date. To test the robustness of this period, sensitivity analyses were conducted by resetting the latency period to: (1) zero month, (2) six months, and (3) two years. Second, we replaced the non-ARBs control group with Angiotensin-converting enzyme inhibitor (ACEI) users. Third, to address time-dependent confounding, we employed inverse probability of treatment weighting (IPTW) within the G-method framework for validation of time-varying Cox regression models [22]. Fourth, to explore the impact of a longer duration of ARBs use on the incidence of lung cancer, we compared baseline ARBs users and non-users under the main analysis model.

Negative control

As one of the effective approaches for addressing unmeasured confounding or other biases, negative controls are increasingly applied in epidemiological studies. Negative controls are classified into negative control exposures (NCEs) and negative control outcomes (NCOs). A NCE variable is not causally associated with the outcome [23]; in the context of this study, a drug unrelated to lung cancer can be selected as the NCE., A NCO is defined as an outcome variable that was not causal affected by the exposure of interest [24], and for this study, a disease unrelated to ARBs use may serve as the NCO.

If an association is found between the NCE and lung cancer, or between the NCO and ARBs use, this would suggest that the observed association in the primary analysis may be due to confounding or other biases. Based on findings from prior studies, calcium channel blockers (CCBs) were chosen as the NCE, given the evidence indicating no association with lung cancer risk [25–27]. Similarly, glaucoma and fractures were selected as NCOs, as research has shown no relationship between these conditions and ARBs use [28, 29].

Results

ARBs use and baseline characteristics

A total of 25,436 COPD patients meeting the inclusion criteria were identified for this study. The mean age of patients at the index date was 68.28 (standard deviation [SD]: 12.59) years, with 60.6% of the cohort being male. The mean follow-up period for COPD patients was 4.59 (SD: 3.44) years. The average actual duration of ARBs use during the follow-up period was 2.70 (SD: 2.96) years. Among these patients, 470 (1.85%) new cases of lung cancer were identified. Kaplan-Meier curves of ARBs and no ARBs groups were shown in Supplementary Figure S2.

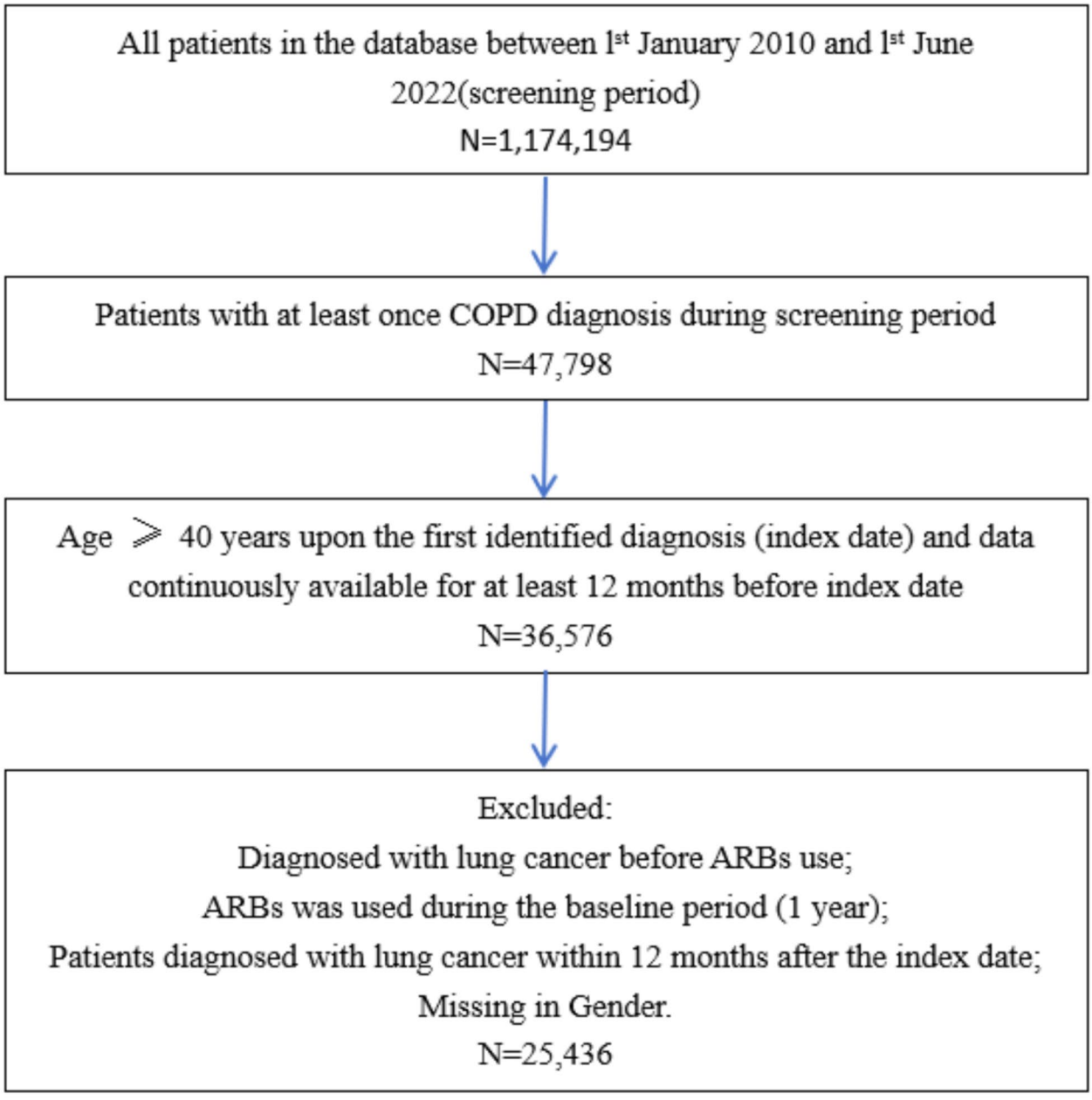

Fig. 1 Flowchart of participants in the study cohorts

8,611 COPD patients received at least one prescription for ARBs, with a total of 143,063 ARBs prescriptions issued, averaging approximately 17 prescriptions per patient. The most commonly prescribed angiotensin receptor blockers were telmisartan, irbesartan, losartan, and valsartan, accounting for 28%, 25%, 24%, and 21% of prescriptions (Supplementary Table S2).

At baseline, compared with non-ARBs users, the ARBs user group was notably older, had lower educational attainment, and experienced higher hospitalization rates. Differences were also observed between groups in terms of diabetes, hyperlipidemia, hypertension, ischemia, arrhythmia, CVD, COPD, and long-acting medication use (Table 1). Baseline characteristics stratified by quantiles of cumulative years of ARBs use were shown in Supplementary Table S5.

Effect of ARBs on lung cancer

For binary ARBs exposure, no significant associations were observed between ARBs use and lung cancer risk across models. For exposure defined by cumulative years of ARBs use, a significant and protective association with

Table 1 Baseline characteristics of the study cohort

Characteristics	Total	ARBs use		*P* value
		Yes	No	
Participants	25,436	8611	16,825	
Age (mean (SD)), year	68.28(12.59)	69.85(11.35)	67.48(13.11)	< 0.001
Male (%)	15,422(60.6)	5140(59.7)	10,282(61.1)	0.029
Education Level (%)				< 0.001
Illiteracy	3399(13.4)	1337(15.5)	2062(12.3)	
Elementary school	8600(33.8)	3337(38.8)	5263(31.3)	
Secondary school and above	9237(36.3)	3238(37.6)	5999(35.7)	
Unknown	4200(16.5)	699(8.1)	3501(20.8)	
Smoking (%)	4455(17.5)	1489(17.2)	2966(17.6)	0.539
Drinking (%)				< 0.001
Drinker	6182(24.3)	2156(25.0)	4026(23.9)	
Non-drinkers	13,318(52.4)	4874(56.6)	8444(50.2)	
Unknown	5936(23.3)	1581(18.4)	4355(25.9)	
Hospitalization (%)				< 0.001
Any Reason	13,826(54.4)	5864(68.1)	7962(47.3)	
CVD_related	3290(12.9)	1933(22.4)	1357(8.1)	
COPD_related	4532(17.8)	1946(22.6)	2586(15.4)	
Comorbidities (%)				
Diabetes	1244(4.9)	484(5.6)	760(4.5)	< 0.001
Hyperlipidemia	3495(13.7)	1419 (16.5)	2076(12.3)	< 0.001
Mental	2165(8.5)	739(8.6)	1426(8.5)	0.791
Hypertensive	8377(32.9)	4186(48.6)	4191(24.9)	< 0.001
CKD	349(1.4)	112(1.3)	237(1.4)	0.520
Ischaemic heart diseases	3875(15.2)	1511(17.5)	2364(14.1)	< 0.001
Venous thromboembolism	148(0.6)	48(0.6)	100(0.6)	0.780
Arrythmia	2334(9.2)	886(10.3)	1448(8.6)	< 0.001
Heart failure	2167(8.5)	750(8.7)	1417(8.4)	0.451
Cerebrovascular disease	3160(12.4)	1173(13.6)	1987(11.8)	< 0.001
Asthma	4562(17.9)	1514(17.6)	3048(18.1)	0.302
Comedications				
COPD drug - Long-acting treatments	5194(20.4)	1401(16.3)	3793(22.5)	< 0.001
COPD drug - Short-acting treatments	3448(13.6)	1213(14.1)	2235(13.3)	0.080
Cardiac drugs	11,765(46.3)	4305(50.0)	7460(44.3)	< 0.001
Other Antihypertensive drugs	8965(35.2)	3922(45.5)	5043(30.0)	< 0.001
AECOPD				
Moderate Exacerbation	0.37(0.51)	0.42(0.51)	0.35(0.50)	< 0.001
Severe Exacerbation	0.07(0.27)	0.08(0.28)	0.07(0.27)	0.121

ARBs angiotensin receptor blockers, SD standard deviation, CVD cardiovascular diseases, CKD chronic kidney disease

Table 2 Association between ARBs use and risk of lung cancer

Models	Binary ARBs exposure		Cumulative Years of Use	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model1	1.06(0.87,1.29)	0.5713	0.95(0.92,0.98)	0.0046
Model2	1.03(0.84,1.25)	0.7742	0.95(0.92,0.98)	0.0039
Model3	1.00(0.82,1.23)	0.9777	0.94(0.91,0.98)	0.0012
Model4	0.95(0.77,1.16)	0.5907	0.93(0.90,0.97)	0.0002

Model 1 estimated crude HR; model 2 was adjusted for age and gender; model 3 was further adjusted for incorporates comorbidities; model 4 was further adjusted for education levels, smoking status, drinking status, COPD exacerbation status, the number of hospital admissions, and comedications

lung cancer risk was found, suggesting that prolonged ARBs use is associated with a lower incidence of lung cancer (HR 0.93, 95% CI 0.90–0.97) (Table 2). Results of the time-dependent Cox model for cumulative years of use were shown in Supplementary Table S4.

In a further analysis, the COPD cohort was restricted to patients aged 65 and older, reflecting the typical age of lung cancer onset. The estimated HR for cumulative ARBs use (HR: 0.91, 95% CI: 0.87–0.95) suggested a protective effect against lung cancer in this age group. Among patients hospitalized for CVD and COPD, the CVD subgroup showed results in line with the main analysis, while the COPD subgroup showed no significant

Table 3 Results of sensitivity analyses

	Multivariable Regression	
	HR (95% CI)	***P* value**
Different latency Periods		
None		
Binary ARBs exposure	0.95(0.78,1.15)	0.6081
Cumulative Years of Use	0.89(0.84,0.94)	0.0001
6 months		
Binary ARBs exposure	0.93(0.76,1.13)	0.4524
Cumulative Years of Use	0.93(0.90,0.96)	0.0001
1 year		
Binary ARBs exposure	0.95(0.77,1.16)	0.5907
Cumulative Years of Use	0.93(0.90,0.97)	0.0002
2 years		
Binary ARBs exposure	0.90(0.72,1.13)	0.3744
Cumulative Years of Use	0.94(0.91,0.98)	0.0018
ARBs vs. ACEI		
Binary ARBs exposure	1.33(0.85,2.08)	0.2155
Cumulative Years of Use	0.91(0.86,0.96)	0.0009
Inverse-Probability-of-Treatment Weighting[1]		
Binary ARBs exposure	0.53(0.43,0.64)	< 0.0001
Cumulative Years of Use	0.89(0.85,0.93)	< 0.0001
Baseline ARBs vs. non-ARBs[1]		
Binary ARBs exposure	0.74(0.57,0.95)	0.0204
Cumulative Years of Use	0.89(0.86,0.92)	< 0.0001

[1] The Cox proportional hazards model

association for either exposure measure (Supplementary Table S3).

The dose-response relationship between ARBs and lung cancer is illustrated in Supplementary Figure S3, indicating that short-term use may have no significant effect or exhibit unstable effects. As the duration of use increases, the hazard ratio shows a declining trend, suggesting that long-term use may be associated with a lower risk.

Sensitivity analysis

The sensitivity analysis, modifying the latency period, yielded results consistent with the primary analysis (Table 3). Whether the latency was reduced to zero or six months or extended to two years, the findings remained comparable to the main analysis.

To minimize potential differences between patients receiving ARBs treatment and those not receiving ARBs treatment, a sensitivity analysis was conducted using patients treated with ACEI as the control group. These patients also had hypertension and were presumed to have similar baseline characteristics to those receiving ARBs treatment. The analysis revealed that, compared to the ACEI group, the ARBs group exhibited a protective effect against lung cancer incidence (HR 0.91, 95% CI 0.86–0.96).

To address time-dependent confounding, the relationship between ARBs exposure and lung cancer risk was further examined using G-methods, specifically IPTW combined with a marginal structural Cox model. The results consistently demonstrated a protective effect of ARBs exposure on lung cancer incidence across both exposure definitions (HR 0.89, 95% CI 0.85–0.93).

To account for the potential limitation of insufficient cumulative ARBs exposure duration, an additional analysis directly compared lung cancer risk between ARBs users and non-users at baseline. The results further confirmed the protective association between ARBs exposure and lung cancer incidence (HR 0.89, 95% CI 0.86–0.92) (Table 3).

Table 4 Results of negative control analyses

	Multivariable Regression	
	HR (95% CI)	***P* value**
Negative Control Exposure		
CCB		
Binary CCB exposure	1.16(0.95,1.42)	0.1440
Cumulative Years of Use	0.98(0.95,1.02)	0.2697
Negative Control Outcome		
Glaucoma		
Binary ARBs exposure	1.44(1.08,1.92)	0.0140
Cumulative Years of Use	0.96(0.91,1.01)	0.1025
Fracture		
Binary ARBs exposure	1.23(1.14,1.33)	< 0.001
Cumulative Years of Use	0.99(0.98,1.00)	0.0696

Negative control

To assess whether unmeasured confounding and biases could affect the primary analysis results, negative control analyses were also performed. The NCE primarily explored the association between time-dependent calcium channel blockers exposure and lung cancer risk in a multivariable model. No association was found between binary CCBs exposure and lung cancer (HR: 1.16, 95% CI: 0.95–1.42), and the relationship between cumulative CCBs use and lung cancer was also not significant (HR:0.98, 95% CI:0.95–1.02). The negative control outcomes selected were glaucoma and fractures. No significant relationship was found between cumulative ARBs use and either glaucoma (HR:0.96, 95% CI:0.91–1.01) or fractures (HR:0.99, 95% CI: 0.98-1.00). However the associations between binary ARBs and negative control outcomes were observed (Table 4).

Discussion

This study assessed the relationship between ARBs exposure and the risk of lung cancer among patients with COPD in China. A significant protective association was observed between cumulative ARBs and the risk of lung cancer. The results of sensitivity analyses and the negative control analyses showed that the findings were consistent

with the main findings and less influenced by unmeasured confounding.

Research on the relationship between hypertension and cancer risk is most commonly focused on renal cancer. A review indicated that hypertension increases the risk of renal cancer in both men and women [8]. Additionally, a study demonstrated an association between hypertension and an increased risk of breast cancer, particularly in postmenopausal women [30]. Furthermore, a meta-analysis suggested that hypertension may be linked to an elevated risk of prostate cancer [31]. These findings highlight the potential for hypertension control through antihypertensive medications to also reduce the risk of cancer development.

Existing studies have examined the relationship between ARBs use and cancer risk [32], including studies specifically addressing ARBs and lung cancer risk. Pasternak et al. (2011) conducted a retrospective cohort study using Danish registry data with 42,585 participants, finding no significant association between ARBs and cancer risk overall (relative risk [RR]: 0.99, 95% CI: 0.95–1.03) or lung cancer risk (RR: 0.92, 95% CI: 0.82–1.02) [33]. A meta-analysis based on RCTs in 2019 similarly reported no association between ARBs and lung cancer risk (odds ratio [OR]: 1.02, 95% CI: 0.87–1.19; $P = 0.803$) [34]. Using the UK General Practitioner database, Lau et al. conducted a nested case-control study within a hypertension cohort from 1995 to 2008. They selected patients diagnosed with lung, colorectal, breast, and prostate cancer as cases to examine the association between ARBs use and the risk of these cancers, with findings showing no significant associations for any cancer type [35]. In contrast, Bhaskaran et al. (2012), utilizing the same database, analyzed a retrospective cohort of 377,649 patients with a median follow-up of 4.6 years, observing no overall significant effect of ARBs on cancer risk after covariate adjustment (HR: 1.03, 95% CI: 0.99–1.06, $P = 0.10$), though protective effects were observed in cancer subgroups (HR: 0.84, 95% CI: 0.75–0.94). Their study also showed a significant cumulative duration effect of ARBs on lung cancer ($P < 0.001$) [36]. More recently, Wang et al. (2023) published a meta-analysis specifically analyzing ARBs and lung cancer risk, concluding that ARBs use was associated with a reduced risk of lung cancer (RR: 0.85, 95% CI: 0.76–0.95). Among ARBs, valsartan had the most substantial effect in lowering lung cancer risk (RR: 0.78, 95% CI: 0.62–0.98, $P = 0.139$) [13].

Although existing evidence is not entirely consistent, studies have shown mixed results on the association between ARBs and cancer risk, with findings indicating increased risk, reduced risk, and no significant effect [13, 37, 38]. However, recent studies predominantly suggest a risk reduction, particularly among Asian populations, where protective associations are more frequently observed [39, 40]. Studies have shown that the G allele variant of rs4975616 is negatively associated with lung cancer, with a stronger negative correlation observed in Caucasians compared to Asians. Therefore, Caucasians may have a higher likelihood of lung cancer and LUAD risk due to rs4975616 variation [41].This study contributes important insights into the relationship between ARBs use and lung cancer risk.

Previous research has indicated that ARBs use among COPD patients may slow lung function decline [42] and reduce respiratory morbidity and all-cause mortality risks [43]. These findings suggest a potential pleiotropic effect of ARBs in COPD patients.

In addition to statistical significance, the minimal clinically important difference (MCID) using Cohen's d was used to better reflect clinical relevance [44]. For a d value of 0.2 (small MCID), the corresponding HR is 0.83. However, the HR of cumulative ARBs use in our study was 0.93, which means that our findings were statistically significant but not clinically significant.

The findings are supported by previously reported biological mechanisms suggesting that, beyond cardiovascular benefits, ARBs may improve COPD outcomes, potentially affecting lung cancer risk. Pulmonary and systemic inflammation associated with COPD is a known CVD risk factor and might also contribute to COPD itself. Studies indicate that COPD remains an independent risk factor for lung cancer, even after adjusting for age, gender, and smoking status [45, 46]. Chronic inflammation in COPD patients' airways, particularly the small airways, involves cellular recruitment and activation, creating a pro-tumor inflammatory microenvironment linking COPD to lung cancer. Inflammatory mediators play a central role in both COPD and lung cancer development [10]. Activation of neurohumoral pathways, particularly the renin-angiotensin system (RAS), triggers local and systemic inflammation, resulting in parenchymal changes across organs.

ARBs influence the RAS by blocking the AT1 receptor, thereby mitigating the effects of angiotensin II (Ang II), which is known to promote inflammation, fibrosis, and oxidative stress. By inhibiting the Ang II/AT1 receptor axis, ARBs help restore the balance in favor of the protective ACE-2/Ang-(1–7)/Mas receptor pathway, which exerts anti-inflammatory and antifibrotic effects [9]. This modulation of the RAS system reduces the recruitment and activation of immune cells—such as macrophages, T cells, and dendritic cells—that contribute to the formation of a chronic inflammatory microenvironment in the lungs. In this microenvironment, the enhanced activity of nuclear factor κB (NF-κB) and the predominance of M2-polarized tumor-associated macrophages facilitate cell proliferation, inhibit apoptosis, and promote tumor development. Therefore, by attenuating the RAS-driven

inflammatory cascade, ARBs may decrease chronic inflammation and its associated pro-tumorigenic effects, ultimately reducing the risk of lung cancer, particularly in patients with COPD who are already predisposed to an elevated inflammatory state [10]. This action not only benefits cardiovascular health but may also impact lung cancer risk in COPD patients.

To address time-dependent confounding, we applied a time-dependent Cox proportional hazards model and conducted sensitivity analysis validation using IPTW within the G-method framework. The results were consistent with those of the primary analysis. To assess unmeasured confounding, we employed negative control outcomes and negative control exposures for detection, and the findings remained consistent with the primary analysis. To mitigate potential reverse causation between exposure and outcome, we excluded patients who developed lung cancer within the first year of cohort entry and tested different latency periods in the sensitivity analysis. The results were consistent with those of the primary analysis.

In the negative control analyses, the effect of the binary exposure is associated with an increased risk of negative control outcomes. This maybe because that binary exposure was only collected at a fixed time point, which failed to incorporate cumulative medication information. Additionally, it may be associated with the inconsistency in the starting time of the exposure group compared to the control group after addressing time-dependent treatment.

Considering COPD and CVD were with higher levels of inflammation, and also important confounders among associations between ARBs and lung cancer, in the subgroup analysis, we stratified patients into two subgroups based on hospitalization due to COPD or CVD to explore whether the impact of ARBs on cancer incidence would be more pronounced under higher levels of inflammation [47, 48]. The results showed a significant association in the CVD subgroup but not in the COPD subgroup, which does not provide direct evidence to support this hypothesis.

Our study has several strengths. First, we utilized a time-dependent Cox proportional hazards model, effectively avoiding immortal time bias and minimizing confounding by adjusting for various potential confounders [49]. Second, we explored the association between ARBs use and lung cancer risk in COPD patients through two exposure definitions. Subgroup and sensitivity analyses on cumulative exposure duration consistently showed protective effects, reinforcing the reliability of our findings. Third, incorporating NCE (CCBs exposure) and NCOs (glaucoma and fractures) to assess unmeasured confounding and other biases was a crucial advantage, enhancing the robustness of the association between ARBs exposure and lung cancer risk.

This study has some limitations. First, the study population was limited to a single metropolitan area in China, warranting caution when generalizing our findings to other populations. Further studies are needed with more representative populations. Additionally, this study is a retrospective observational study primarily aimed at elucidating the association between ARBs exposure and the risk of lung cancer development, and thus cannot establish a causal relationship. Caution is also warranted when extrapolating the findings. Second, covariates, such as family history of cancer, Forced Expiratory Volume in 1 second (FEV1), exercise, dietary factors, alcohol consumption and smoking dose, were not adjusted due to lack of data, which may have influenced the positive findings. Third, drug dosage information was insufficiently documented, preventing calculation of standardized time-specific doses for each drug, which led us to use cumulative exposure years as a measurement. Additionally, information about ARBs discontinuation and switching, which may have influenced the final results. Fourth, although the diagnosis of lung cancer and COPD was based on the ICD codes in the hospital medical record system, the possibility of misdiagnosis could not be entirely ruled out. Fifth, the average follow-up time of 4.59 years and ARBs usage duration of 2.7 years in our study were relatively short, which to some extent may impede a more comprehensive assessment of the relationship between ARBs and lung cancer.

Conclusions

This study suggests that the use of ARBs in COPD patients may reduce the risk of lung cancer. In subgroup analyses, ARBs exposure was significantly associated with a reduced risk of lung cancer in patients aged 65 years and older. This conclusion was further strengthened by analyses using negative control exposures and negative control outcomes to detect residual confounding or bias.

These findings support the hypothesis that among COPD patients, there may be a subset with higher levels of inflammation who could significantly benefit from ARBs treatment. Hence, this subgroup could be considered in the clinical management of hypertension in COPD patients. Future studies on this topic should collect more abundant and accurate data about ARBs and cancer outcomes. And future studies could expand the population scope and conduct more powerful designs and analyses to explore their associations and clarify the causality of observed associations. In addition, basic scientific studies are required to investigate the specific mechanisms for the observed associations.

Supplementary Information

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Supplementary Material 1

Author contributions

Wenhao Li was responsible for the overall research design, implementation, and manuscript preparation; Qingqing Yang, Yahong Chen, Feng Sun, and Jinzhu Jia provided guidance on research design and analysis. Yexiang Sun and Peng Shen contributed to the preliminary data preparation.

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Data availability

Data used in this study are available to the scientific community and the requests should be sent to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. The study was approved by the ethical review board of Peking University Health Science Center (approval number: IRB00001052-23112). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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