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Original Article

The impact of hypertension and renin-angiotensin system blockers on outcomes of lung cancer patients: a population-based retrospective cohort study

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Abstract: Previous studies suggest that renin-angiotensin system blockers (RASBs) have anti-proliferative effects in several types of cancer. The aim of this study was to evaluate the impact of RASBs on outcomes of lung cancer. A total of 1463 patients with histologically confirmed lung cancer were retrospectively analyzed. We compared the clinical characteristics and survival among "non-hypertension", "hypertension without RASBs" and "hypertension with RASBs" groups. For lung cancer patients, hypertension had no significant impact on overall survival (OS) and progression-free survival (PFS) of lung cancer, while RASBs use was associated with smaller tumor size, reduced lymph node metastasis, decreased stage and improved survival in lung cancer. In the subgroup analysis based on histological type, RASBs seemed to have positive impacts on NSCLC rather than SCLC. In the NSCLC group, it was angiotensin-converting enzyme inhibitors (ACEIs) rather than angiotensin receptors-1 blockers (ARBs) playing a protective role in the survival of NSCLC patients. The use of ACEIs may significantly improve the survival of NSCLC patients through suppressing tumor growth, reducing lymph node metastasis and decreasing tumor stage. The impact of RASBs on lung cancer should be investigated in more comprehensive studies with larger population.

Keywords: Lung cancer, hypertension, RASBs, survival

Introduction

Lung cancer is the common cause of cancer-related deaths in the world [1]. At present, surgical resection is the most effective treatment modality for the early stage lung cancer patients. However, most postoperative patients are still suffering from poor prognosis due to metastasis. Lung cancer mainly shows a preference for the lymph node, liver, contralateral lung, brain, and bone marrow [2]. Inhibition of metastasis of lung cancer is regarded as one of the important therapeutic strategies.

Hypertension is the most common comorbid disease in cancer survivors and appears to affect survival of certain cancers [3, 4]. It is reported that hypertension leads to excessive mortality from stroke and heart disease [4], but whether hypertension increases the risk of death through promoting the recurrence and metastasis of lung cancer is unknown.

The renin-angiotensin system (RAS) that includes angiotensin (AT), angiotensin-converting enzyme (ACE), angiotensin receptors 1 and 2 (AT1R and AT2R) is mainly associated with the regulation of arterial pressure [5]. RAS components are expressed in a number of cancer types, such as carcinomas of the lung, pancreas, and ovary, but their roles are not fully understood [6-8]. It is reported that RAS could promote tumor proliferation and angiogenesis by inducing epidermal growth factor receptor (EGFR) expression and vascular endothelial growth factor (VEGF) generation [9, 10]. Furthermore, the activated AT1R can trans-activate EGFR signaling, which stimulates pro-oncogenic pathways [11]. Emerging data suggests that tumorous local RAS produces AT2, which induces tumor proliferation and angiogenesis [12].

The renin-angiotensin system blockers (RASBs) include ACE inhibitors (ACEIs) and AT1R block-

ers (ARBs). ACEIs inhibit the RAS by reducing the production of AT2, while ARBs selectively block the activation of AT1R. RASBs have been commonly prescribed drugs which have anti-hypertensive and end-organ protective properties [13, 14]. Preclinical studies have suggested that RASBs might decrease tumor-associated angiogenesis and inhibit metastasis [15, 16]. Recent epidemiological studies also have reported that RASBs could reduce metastasis and improve survival in colon cancer, pancreatic cancer and breast cancer [17-19]. In light of the available data, hypertension and RASBs use might affect the outcomes of lung cancer, but the data was limited. Therefore, we conducted the retrospective study to identify the impact of hypertension and RASBs use on the outcomes of lung cancer.

Patients and methods

Ethic permission

Informed consent for the use of medical records of lung cancer patients was obtained at the time of surgery. This retrospective study was approved by the ethics committee of Shandong Provincial Hospital affiliated to Shandong University.

Study populations and clinical data

Between January 2006 and July 2012, 1534 lung cancer patients undergoing complete resection were consecutively selected from the Shandong Provincial Hospital. Of the selected patients, 71 patients were excluded for the following reasons: prior diagnosis of other cancer (n=44); positive margin (n=24); incomplete clinical data (n=3). The hospital's electronic database contains all individual results of any laboratory test during in- or outpatient care administered by our institution, detailed data on drugs, doses and timing of any chemotherapy applied and hospital discharge reports. Follow-up data was obtained by telephone contact with the patients or their families. Patients were generally followed every 3 months for the first 2 years after surgery, and annually thereafter according to schedule.

Demographic and clinical information of patients was collected from the medical records. The histological type and TNM stage were assigned according to the classification criteria for lung tumors of the World Health Organization and International Association for the Study of Lung Cancer (WHO/IASLC). The definition of hypertension was determined by elevated blood pressure (≥130/85 mmHg) or a history of anti-hypertension medication. For the analysis, the variables were divided into categories: gender (male or female), age (≤60 or >60), smoking history (never or ever), histological type (non-small cell lung cancer, NSCLC or small cell lung cancer, SCLC), tumor size (≤3 cm or >3 cm), lymph node metastasis (absent or present), pathological grade (well, moderately, poorly or unknown), pathological stage (I, II, or IIIa), hypertension status (absent or present) and RASBs use (absent or present). Patients were assigned to three groups: "patients without a history of hypertension"; "patients with hypertension and any anti-hypertension medication except RASBs"; and "patients with hypertension and RASBs use".

In the subgroup analysis, we subdivided the lung cancer patients into 2 groups by histological type: NSCLC and SCLC groups. For each subdivided group, the effects of hypertension and RASBs use on outcomes of patients were evaluated. We also conducted subgroup analyses according to the RASBs type (AECIs or ARBs) in NSCLC group.

The study endpoints were overall survival (OS) and progression-free survival (PFS). OS was calculated from surgery to the date of death from all causes or the date of the last follow-up. PFS was defined as the period from surgery till progression or death or the date of the last follow-up.

Statistical analysis

Associations of hypertension with or without RASBs use with the clinical characteristics were evaluated using Chi-square test and/or analysis of variance (ANOVA) test. The OS and PFS curves were constructed using the Kaplan-Meier methods and log-rank test was applied for pairwise comparison of survival. Cox proportional hazards models were used to assess the effects of clinicopathological factors on survival. All analyses were performed using SPSS software (version 19.0, SPSS Inc., Chicago, IL, USA). A two-tailed *P* value less than .05 was considered significant in statistical tests.

Table 1. Association of hypertension and RASBs use with the clinicopathologic characteristics of 1463 patients with lung cancer treated with surgery

Characteristic	Total, n=1463	Non-Hypertension, n=1077	Hypertension, non-RASBs, n=243	Hypertension, RASBs, n=143	*P*-value
Gender, n (%)					
Male	1027 (70.2)	762 (70.8)	171 (70.4)	94 (65.7)	0.467
Female	436 (29.8)	315 (29.2)	72 (29.6)	49 (34.3)	
Age, years					
Mean (SD)	58.72 (9.86)	57.44 (9.98)	65.73 (8.44)	61.52 (8.84)	<0.001
≤60	795 (54.3)	644 (59.8)	91 (37.4)	60 (42.0)	<0.001
>60	668 (45.7)	433 (40.2)	152 (62.6)	83 (58.0)	
Smoking status, n (%)					
Never	529 (36.2)	381 (35.4)	88 (36.2)	60 (42.0)	0.306
Ever	934 (63.8)	696 (64.6)	155 (63.8)	83 (58.0)	
Histology, n (%)					
NSCLC	1352 (92.4)	996 (92.5)	223 (91.8)	133 (93.0)	0.895
SCLC	111 (7.6)	81 (7.5)	20 (8.2)	10 (7.0)	
Tumor size, n (%)					
Mean (SD)	3.78 (1.93)	3.87 (1.99)	3.54 (1.71)	3.46 (1.71)	0.007
≤3 cm	688 (47.0)	487 (45.2)	118 (48.6)	83 (58.0)	0.014
>3 cm	775 (53.0)	590 (54.8)	125 (51.4)	60 (42.0)	
Lymph node metastasis, n (%)					
No	837 (57.2)	589 (54.7)	148 (60.9)	100 (69.9)	0.001
Yes	626 (42.8)	488 (45.3)	95 (39.1)	43 (30.1)	
Pathological grade, n (%)					
Well	212 (14.5)	150 (13.9)	39 (16.0)	23 (16.1)	0.577
Moderately	664 (45.4)	494 (45.9)	101 (41.6)	69 (48.3)	
Poorly	512 (35.0)	373 (34.6)	93 (38.3)	46 (32.2)	
Unknown	75 (5.1)	60 (5.6)	10 (4.1)	5 (3.5)	
Pathological stage, n (%)					
I	640 (43.7)	431 (40.0)	126 (51.9)	83 (58.0)	<0.001
II	390 (26.7)	310 (28.8)	56 (23.0)	24 (16.8)	
IIIa	433 (29.6)	336 (31.2)	61 (25.1)	36 (25.2)	

RASBs renin-angiotensin system blockers; SD standard deviation; NSCLC non-small cell lung cancer; SCLC small cell lung cancer.

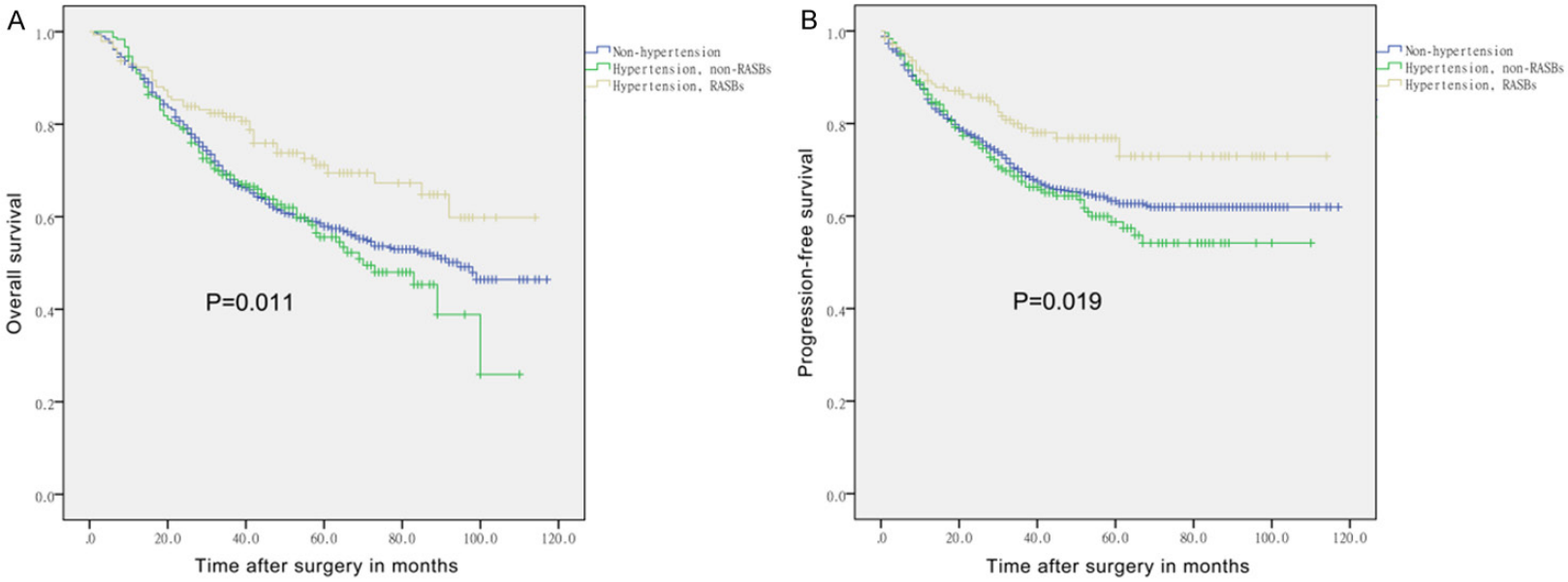
Results

Association of hypertension and RASBs with clinicopathological characteristics

Of the 1463 patients included, 386 (26.38%) had hypertension, among which 143 (9.77%) used RASBs. The patients' clinicopathological factors and their association with hypertension and RASBs use were shown in **Table 1**. In the "hypertension with RASBs" group, 108 patients took ACEIs and 30 patients took ARBs and 5 patients took both ACEIs and ARBs. The hypertension patients were more likely to be older than the non-hypertension patients (*P*<.001). Compared with the "non-hypertension" group and "hypertension without RASBs" group, the patients in the "hypertension with RASBs" group were more likely to have smaller tumor size (*P*=.01), to have no lymph node metastasis (*P*=.001), and to have earlier stage disease (*P*<.001). Other clinicopathological factors did not differ among the three groups.

Influence of hypertension and RASBs on survival of all patients

The mean follow-up was 45.97 months. Within the follow-up period, a total of 577 patients died. Kaplan-Meier survival curves for OS and PFS according to hypertension and RASBs use are provided in **Figure 1**. There was no signifi-



Pairwise comparisons (log rank)	P-value
Non-hypertension vs. Hypertension, non-RASBs	0.452
Non-hypertension vs. Hypertension, RASBs	0.005
Hypertension, non-RASBs vs. Hypertension, RASBs	0.002

Pairwise comparisons (log rank)	P-value
Non-hypertension vs. Hypertension, non-RASBs	0.341
Non-hypertension vs. Hypertension, RASBs	0.013
Hypertension, non-RASBs vs. Hypertension, RASBs	0.004

Figure 1. Kaplan-Meier curves depicting overall survival (A) and progression free survival (B) in 1463 patients with lung cancer according to hypertension and RASBs use.

Table 2. Univariable Cox regression analyses predicting OS and PFS in 1463 lung cancer patients

Characteristic	OS		PFS	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Gender, n (%)				
Male	1		1	
Female	0.73 (0.61, 0.88)	0.001	0.84 (0.69, 1.03)	0.093
Age, years				
≤60	1		1	
>60	1.23 (1.04, 1.44)	0.014	1.03 (0.86, 1.24)	0.737
Smoking history, n (%)				
Never	1		1	
Ever	1.40 (1.17, 1.67)	<0.001	1.08 (0.90, 1.31)	0.400
Histology, n (%)				
NSCLC	1		1	
SCLC	1.47 (1.12, 1.94)	0.006	1.18 (0.85, 1.64)	0.335
Tumor size, n (%)				
≤3 cm	1		1	
>3 cm	1.93 (1.63, 2.29)	<0.001	1.71 (1.42, 2.06)	<0.001
Lymph node metastasis, n (%)				
No	1		1	
Yes	2.81 (2.37, 3.33)	<0.001	2.23 (1.85, 2.68)	<0.001
Pathological grade, n (%)				
Well differentiated	1		1	
Moderately differentiated	2.52 (1.79, 3.55)	<0.001	1.94 (1.38, 2.74)	<0.001
Poorly differentiated	3.18 (2.25, 4.50)	<0.001	2.73 (1.94, 3.84)	<0.001
Unknown	1.30 (0.75, 2.26)	0.352	1.02 (0.55, 1.88)	0.948
Pathological stage, n (%)				
I	1		1	
II	2.59 (2.07, 3.25)	<0.001	1.99 (1.57, 2.53)	<0.001
III	4.39 (3.56, 5.41)	<0.001	3.00 (2.41, 3.74)	<0.001
Hypertension and RASBs status				
Non-Hypertension	1		1	
Hypertension, non-RASBs	1.09 (0.88, 1.35)	0.453	1.12 (0.89, 1.42)	0.344
Hypertension, RASBs	0.63 (0.46, 0.88)	0.006	0.64 (0.44, 0.91)	0.014

OS overall survival; PFS progression free survival; HR hazard ratio; CI confidence interval; RASBs renin-angiotensin system blockers; NSCLC non-small cell lung cancer; SCLC small cell lung cancer.

cant separation between "non-hypertension" group and "hypertension without RASBs" group in OS (*P*=.45) and PFS (*P*=.34). Compared with "non-hypertension" group and "hypertension without RASBs" group, the "hypertension with RASBs" group showed significant improved OS (*P*=.01) and PFS (*P*=.02). In univariable Cox regression analysis with the "non-hypertension" group as referent (**Table 2**), "hypertension without RASBs" group had no effect on OS (HR 1.09, 95% CI 0.88-1.35, *P*=.45) and PFS (HR 1.12, 95% CI 0.89-1.42, *P*=.34), whereas "hypertension with RASBs" group was associated with better OS (HR 0.63, 95% CI 0.46-0.88, *P*=.01) and PFS (HR 0.64, 95% CI 0.44-0.91, *P*=.01). In multivariable Cox regression analysis that adjusted for the effects of standard clinicopathological features (**Table 3**), "hypertension with RASBs" group remained associated with better OS (HR 0.74, 95% CI 0.53-1.02, *P*=.07) and PFS (HR 0.71, 95% CI 0.49-1.02, *P*=.07) compared with the "non-hypertension" group, whereas no significant differences were observed between the "hypertension without RASBs" group and the "non-hypertension" group.

Table 3. Multivariable Cox regression analyses predicting OS and PFS in 1463 lung cancer patients

Characteristic	OS		PFS	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Hypertension and RASBs status				
Non-Hypertension	1		1	
Hypertension, non-RASBs	1.14 (0.92, 1.42)	0.241	1.19 (0.94, 1.51)	0.155
Hypertension, RASBs	0.74 (0.53, 1.02)	0.067	0.71 (0.49, 1.02)	0.065

OS overall survival; PFS progression free survival; HR hazard ratio; CI confidence interval; RASBs renin-angiotensin system blockers. Multivariate Cox regression analyses of OS and PFS are adjusted for age, smoking history, histology, pathological grade and pathological stage.

Table 4. Univariable and multivariable Cox regression analyses predicting OS and PFS in NSCLC patients in relation to hypertension and RASBs use

Characteristic	OS		PFS	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Univariable analysis				
Non-hypertension	1		1	
Hypertension, non-RASBs	1.11 (0.88, 1.38)	0.379	1.11 (0.87, 1.41)	0.423
Hypertension, RASBs	0.60 (0.43, 0.85)	0.004	0.59 (0.40, 0.87)	0.008
Hypertension, ACEIs	0.56 (0.38, 0.83)	0.004	0.60 (0.39, 0.92)	0.019
Hypertension, ARBs	0.70 (0.33, 1.48)	0.350	0.57 (0.23, 1.37)	0.205
Multivariable analysis				
Non-hypertension	1		1	
Hypertension, non-RASBs	1.16 (0.92, 1.45)	0.210	1.16 (0.90, 1.49)	0.244
Hypertension, RASBs	0.71 (0.50, 1.01)	0.059	0.67 (0.45, 0.99)	0.043
Hypertension, ACEIs	0.69 (0.46, 1.03)	0.070	0.69 (0.45, 1.07)	0.096
Hypertension, ARBs	0.70 (0.33, 1.47)	0.341	0.57 (0.24, 1.38)	0.212

OS overall survival; PFS progression free survival; HR hazard ratio; CI confidence interval; RASBs renin-angiotensin system blockers; ACEIs angiotensin-converting enzyme inhibitors; ARBs angiotensin receptors 1 blockers; NSCLC non-small cell lung cancer. Multivariate Cox regression analyses of OS and PFS are adjusted for age, smoking history, pathological grade and pathological stage.

Influence of hypertension and RASBs on survival of NSCLC

Of the 1352 NSCLC patients, 356 had hypertension and 133 used RASBs. In univariable Cox regression analysis with the "non-hypertension" group as referent, "hypertension with RASBs" group was associated with better OS and PFS, whereas "hypertension without RASBs" group was observed to have no effect on OS and PFS (**Table 4**). After adjustment for standard clinicopathological features, the "hypertension with RASBs" group remained associated with better PFS compared with "non-hypertension" group, while the difference in OS between "hypertension with RASBs" group and "non-hypertension" group was not significant (**Table 4**). Furthermore, we subdivided the RASBs group into ACEIs and ARBs groups, and assessed the impact of ACEIs or ARBs on survival. In univariable Cox regression analysis, AECIs was associated with better OS and PFS, but ARBs was not. In multivariable Cox regression analysis, the effects of ACEIs and ARBs on survival of NSCLC were not statistically significant (**Table 4**).

Influence of hypertension and RASBs on survival of SCLC

Of the 111 SCLC patients, 30 had hypertension and 10 used RASBs. Within follow-up, 42 non-hypertension patients and 9 patients with hypertension without RASBs use and 5 patients with hypertension with RASBs use died. In uni- and multivariable Cox regression analyses hypertension and RASBs use were not associated with OS and PFS (**Table 5**). Due

Table 5. Univariable and multivariable Cox regression analyses predicting OS and PFS in SCLC patients in relation to hypertension and RASBs use

Characteristic	OS		PFS	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Univariable analysis				
Non-hypertension	1		1	
Hypertension, non-RASBs	0.90 (0.44, 1.84)	0.762	1.27 (0.57, 2.80)	0.557
Hypertension, RASBs	0.99 (0.39, 2.50)	0.979	1.20 (0.42, 3.45)	0.732
Multivariable analysis				
Non-hypertension	1		1	
Hypertension, non-RASBs	1.05 (0.50, 2.17)	0.904	1.59 (0.71, 3.58)	0.259
Hypertension, RASBs	1.00 (0.38, 2.58)	0.992	1.15 (0.39, 3.43)	0.800

OS overall survival; PFS progression free survival; HR hazard ratio; CI confidence interval; RASBs renin-angiotensin system blockers; SCLC small cell lung cancer. Multivariate Cox regression analyses of OS and PFS are adjusted for age, smoking history, pathological grade and pathological stage.

to the small number of only eleven RASBs recipients in the SCLC group, the analyses were only performed for the combined (ACEIs and ARBs) group.

Discussion

We found that patients with NSCLC and hypertension who took RASBs had a significantly better OS and PFS than their counterparts without hypertension or those with hypertension without taking RASBs, whereas the difference in survival between non-hypertension patients and those with hypertension without taking RASBs was not significant. Furthermore, hypertension with RASBs use was associated with smaller tumor size, reduced lymph node metastasis, and decreased pathological stage.

In the present study, hypertension seemed to have no impact on the outcomes of lung cancer. RASBs appeared to decrease tumor growth and inhibit lymph node metastasis, thereby influencing the survival of NSCLC. Although there were few articles reported the association between hypertension and lung cancer, the weak effect of hypertension on survival had some support in several other cancers [20-22]. In addition, this positive impact of RASBs on survival of NSCLC has been shown in several previous retrospective studies [23-25], but they mainly focused on the effect of RASBs in combination with standard chemotherapy on the advanced NSCLC patients. However, another retrospective study by Wang et al showed that ACEIs receipt increased the risk of local failure but had no effect on OS and disease-free survival of NSCLC [26]. The differences may come from different participants because Wang et al only chose the stage III NSCLC who had received radiotherapy. It seems that the protective effect of RASBs in combination with chemotherapy is more powerful than that in combination with radiotherapy. The difference between ACEIs and ARBs might be another reason because Wang et al used only ACEIs. Our study focused on the effect of RASBs on outcomes in early stage NSCLC and found that RASBs was associated with improved OS and DFS. The survival benefit of RASBs demonstrated in the univariable analysis but disappeared in the multivariable analysis, which might indicate that RASBs played a protective role through decreasing tumor stage. With inadequate subjects in the SCLC subgroup, we could not draw a convictive conclusion.

Although the mechanisms behind the impact of RASBs on cancer are not fully understood, certain *in vitro* and *in vivo* studies have reported that RASBs can suppress tumor cell growth and tumor metastasis in various cancers, including lung cancer, breast cancer and prostate cancer. AT1R signaling appears to be the main component of RAS involved in tumor proliferation and angiogenesis by promoting EGFR expression inducing VEGF generation and trans-activating multiple tyrosine kinases [9-11]. Both ACEIs and ARBs can reverse mitogenic and angiogenic effects of AT1R in cancer tissue [8]. Stimulation of AT2R also up-regulates VEGF and inhibition of the ACE leads to decreased levels of VEGF in animal studies. RASBs inhibit tumor growth as well as adminis-

tration of VEGFR-inhibitors [27]. *In vitro* studies also show an up-regulation of multiple adhesion molecules such as E-selection, P-selection, ICAM-1 and VCAM-1 by activation of the AT1R and inhibition of AT1R could decrease leukocyte adhesion and extravasation [28]. Inhibitors of the AT1R might similarly decrease tumor metastasis through reducing tumor cells movement. Whether these are the mechanisms through which RASBs work in NSCLC needs to be further investigated.

RASBs are widely used in cardiology because of moderate side effects and relatively low costs. Many NSCLC patients undergoing surgery also receive these drugs for arterial hypertension or other diseases. In the present study, patients receiving RASBs had smaller tumor size, reduced lymph node metastasis, decreased tumor stage and improved survival. As disease recurrence and metastasis are associated with severe mortality in NSCLC patients, interventions to reduce the risk of recurrence and metastasis are of utmost importance. In the patients with hypertension and operable NSCLC, it is considerable to put RASBs use as an important part during the treatmentprocess.

The present study has several limitations. Because this study was retrospective, some data may be missing or incomplete, such as the timing, dosage or duration of the RASBs. To decrease the loss of data about RASBs use, we collected all the data available from the patients' medical records and the prescription database. In this study, ACEIs were primarily used and captopril was the most commonly used ACEI, so the survival benefit may be attributable to ACEIs, especially to captopril. In this regard, drawing a conclusion that the survival benefit results from all RASB types and formulations is difficult. Despite the limitations, the present study is encouraging for further prospective researches.

In conclusion, this analysis demonstrated that the use of RASBs, particularly ACEIs, may significantly improve the survival of early stage NSCLC patients. Our results could support previous preclinical data that ACEIs/ARBs may have anti-proliferative and anti-metastasis effects on tumors. The impact of ACEIs/ARBs on lung cancer should be investigated in more comprehensive studies with larger population.

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Disclosure of conflict of interest

None.

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