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Impact of Angiotensin Receptor Blockers Use on In-Hospital Mortality in Community-Acquired Pneumonia Patients with Hypertension

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Keywords
Angiotensin receptor blockers · Mortality · Community-acquired pneumonia · Hypertension

Abstract
Introduction: This study aimed to explore the association of angiotensin receptor blockers (ARBs) use with in-hospital mortality among Chinese patients with hypertension hospitalized with community-acquired pneumonia (CAP). ***Methods:*** This study was conducted from January 2014 to January 2017, and data from patients with hypertension hospitalized with CAP were analyzed retrospectively. Multivariable logistic regression and propensity score matching (PSM) were used to investigate any association. ***Results:*** 1,510 patients were included in this study. The crude in-hospital mortality was significantly lower in patients with ARBs use (4.2% vs. 12.5%, $p < 0.001$). In the extended multivariable logistic models, the odds ratios (ORs) of ARBs use were consistently significant in all six models (OR range 0.27–0.48, $p < 0.05$ for all). After subgroup analysis, ARBs use remained a potentially protective factor against in-hospital mortality, and no interaction was detected. After PSM, the in-hospital mortality remained significantly lower in the ARBs use group (4.2% vs. 10.9%, $p = 0.002$). In the univariate analysis, using ARBs was associated with in-hospital mortality (PSM OR, 0.36; 95% CI, 0.19–0.68; $p = 0.002$). Additionally, compared with the control group, ARBs use did not significantly increase the risk of acute kidney injury (12.4% vs. 10.9%, $p = 0.628$), renal replacement therapy (0.6% vs. 0.3%, $p = 1.000$), and hyperkalemia (1.8% vs. 2.1%, $p = 1.000$). ***Conclusion:*** Although residual confounding cannot be excluded, the use of ARBs was associated with lower in-hospital mortality in Chinese patients with hypertension hospitalized with CAP.

Introduction

Community-acquired pneumonia (CAP) is one of the most prevalent infectious diseases and causes high morbidity and mortality [1]. It is also a costly illness due to its mortality and long-term morbidity [2, 3]. Hypertension is the most important modifiable risk factor for all-cause morbidity and mortality worldwide [4]. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs), two of renin-angiotensin-aldosterone system blockades, are the first-line antihypertensive drugs [5]. Previous studies revealed that ACEIs were associated with improved pneumonia-related outcomes [6–12]. In the literature, ACEIs might mediate an anti-inflammatory effect and alleviate acute lung injury [13]. Similarly, ARBs suppress the downstream immune responses and ameliorate acute lung injury [14]. In recent

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years, in spite of the extensive literature available on the effect of ACEIs/ARBs on COVID-19 outcomes, the evidence remains controversial [15]. However, among Chinese patients with hypertension hospitalized with CAP before 2019, the association of ARBs use with in-hospital mortality is also unknown well. Therefore, this study aimed to explore the association between ARBs use and in-hospital mortality in this population.

Materials and Methods

Study Design and Patients

This retrospective study included patients aged 18 years or older who were hospitalized with CAP at the Nanjing First Hospital in Nanjing, China, from January 2014 to January 2017. All patients in this study were diagnosed with CAP. Pneumonia was defined by a new pulmonary infiltrate on chest radiograph accompanied with at least one of the following signs [16, 17]: (a) the presence of cough, sputum production, and dyspnea; (b) core body temperature >38.0°C; (c) peripheral white blood cell counts $>10 \times 10^9$/L or $<4 \times 10^9$/L. CAP was defined as patients who acquired pneumonia in the community, rather than in a healthcare setting. The research was performed without patient or public involvement.

The flowchart of patient selection is shown in Figure 1. Finally, 1,510 patients who were diagnosed with CAP and had a history of hypertension were selected for analysis. All patients enrolled in this study were divided into the ARBs group and the control group. The control group was defined as patients who did not use ARBs before hospitalization and after admission. The ARBs group was defined as patients who had used ARBs before hospitalization and continued using ARBs after admission. For each patient, we identified a history of prior ARBs use and all prescriptions for inpatient ARBs use, and ARBs included irbesartan, valsartan, losartan, and telmisartan. After propensity score matching (PSM), 330 patients from the ARBs use group and the control group were well matched (shown in Fig. 1).

Variables

The following variables were collected from the medical records: gender, age, comorbid conditions (diabetes, coronary artery disease, cardiac dysfunction, atrial fibrillation, chronic obstructive pulmonary disease [COPD], pulmonary arterial hypertension, chronic cor pulmonale, cerebrovascular disease, tumor, and rheumatic disease), complication (acute respiratory failure [18]) on admission, laboratory investigations (hemoglobin, white blood cell count, platelet count, and serum creatinine) within 48 h on admission, and severity of pneumonia (confusion, urea >7 mmol/L, respiratory rate >30/min, blood pressure systolic <90 mm Hg or diastolic 60< mm Hg, and age >65 years at the time of presentation to hospital [CURB-65]) [19] on admission.

In-Hospital Outcomes

The primary endpoint was set as in-hospital mortality. The secondary endpoints were set as acute kidney injury (AKI), renal replacement therapy (RRT), hyperkalemia, intensive care unit (ICU) admission, length of ICU stay, and duration of hospitalization.

AKI was defined as a serum creatinine change that met the 2012 Kidney Disease Improving Global Outcomes criteria: an increase in the serum creatinine level by ≥0.3 mg/dL within 48 h or ≥1.5-fold from the baseline within 7 days [20]. The baseline level of serum creatinine was defined as the serum creatinine on admission. Due to the lack of data concerning urine output, urine output standards were not considered in this study.

Statistical Analysis

For categorical variables, the data were shown as percentages. For continuous variables, data were presented as mean ± SD or median values (25th–75th percentile) as appropriate. Comparison between two groups for categorical variables was made using the χ^2 test and the Fisher's exact test where appropriate. An unpaired Student's *t*-test was used to compare mean values between the two groups. The Mann-Whitney U test was employed to compare median values.

An extended logistic model approach was used for covariate adjustment (gender, age, comorbid conditions, complication, laboratory investigations, and CURB-65) to explore the association between ARBs use and in-hospital mortality. Furthermore, we conducted stratification analyses to examine whether the effect of ARBs use differed across various subgroups classified by age, gender, comorbidities (diabetes, coronary artery disease, cardiac dysfunction, and cerebrovascular disease), complication (acute respiratory failure), laboratory investigations (hemoglobin, white blood cell count, platelet count, and serum creatinine), and CURB-65 score. Stratification analyses and interaction analyses were adjusted for all the above factors except the stratification factor itself.

To verify our results further, a sensitivity analysis was performed using 1:1 PSM based on the patient's age, gender, comorbid conditions (diabetes, coronary artery disease, cardiac dysfunction, atrial fibrillation, COPD, pulmonary arterial hypertension, chronic cor pulmonale, cerebrovascular disease, tumor, and rheumatic disease), complication (acute respiratory failure), laboratory investigations (hemoglobin, white blood cell count, platelet count, and serum creatinine), and CURB-65 score. The nearest-neighbor matching method was used, and the maximum difference between propensity probabilities for matching was set at 0.01. After applying the PSM adjustment, a standardized mean difference (SMD) for each covariate was examined. SMDs of 10% or less were considered suggestive of covariate balance [21]. After matching, patient characteristics and clinical outcomes were compared again between the two groups. In the PSM subsample, univariate logistic regression analysis was performed to estimate the matched odds ratio (OR) of in-hospital mortality. All the statistical tests were two-sided, and the p value <0.05 was considered statistically significant. All the statistical analysis was performed using SPSS v22.0 (IBM Corporation, Armonk, NY, USA), the EmpowerStats (www.empowerstats.net, X&Y solutions, Inc. Boston MA), and R version 3.6.1 (http://www.r-project.org).

Results

Patient Characteristics

1,510 patients were enrolled. Most (62.0%) patients were male. The mean age of the overall cohort was 76.0 years (SD: 11.0). The comparisons of the baseline characteristics and clinical outcomes between the ARBs

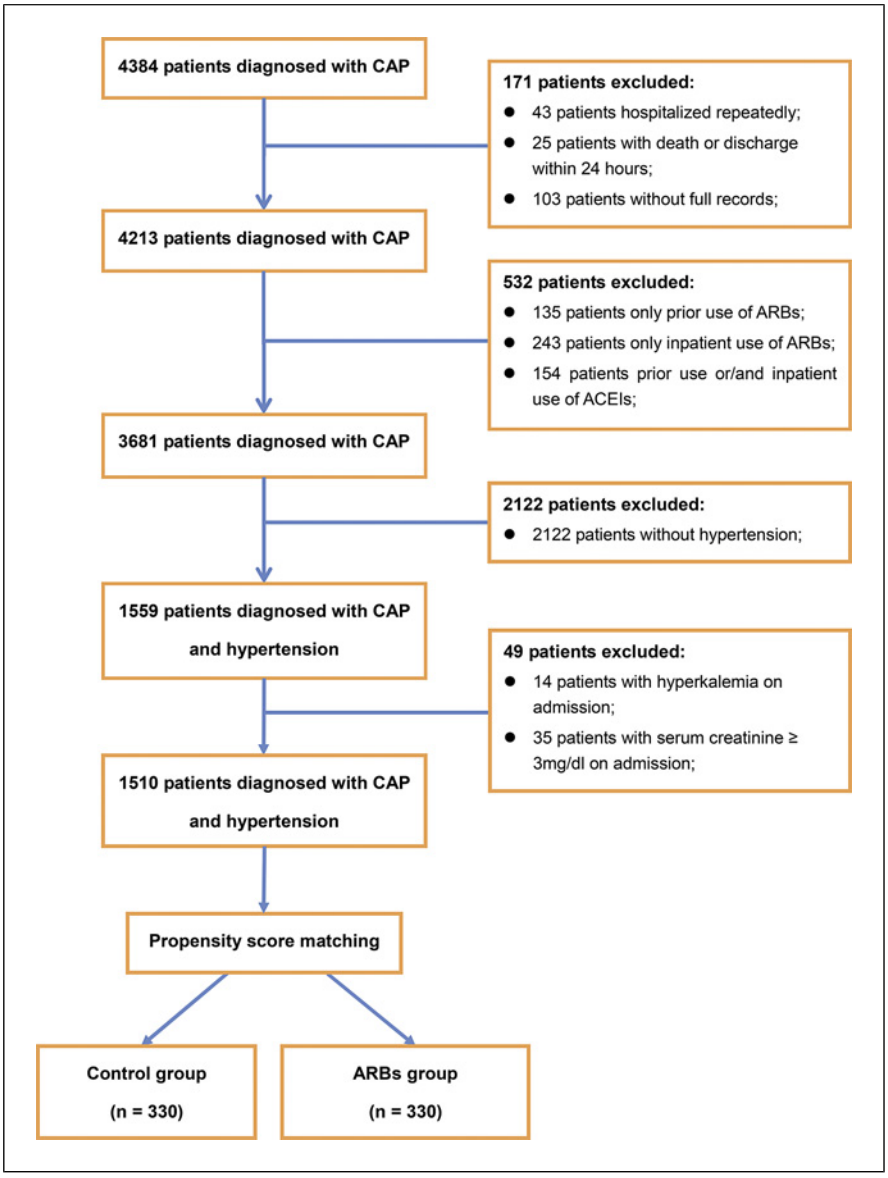

Fig. 1. Flowchart for patient selection. CAP, community-acquired pneumonia; ARBs, angiotensin receptor blockers.

use group and the control group are listed in Table 1. There were no significant differences in age and gender between the ARBs use group and the control group. Patients using ARBs were more likely to have diabetes (34.2% vs. 23.7%, $p < 0.001$), coronary artery disease (46.8% vs. 35.0%, $p < 0.001$), and tumor (11.7% vs. 8.1%, $p = 0.039$) and less likely to have acute respiratory failure (10.2% vs. 20.8%, $p < 0.001$) and CURB-65 score ≥3 (6.9% vs. 15.2%, $p < 0.001$). Nevertheless, comparison of the prevalence of various comorbidities between the two groups revealed approximately equal proportions of cardiac dysfunction, atrial fibrillation, COPD, pulmonary arterial hypertension, chronic cor pulmonale, cerebrovascular disease, and rheumatic disease. In addition, serum creatinine was higher in the ARBs use group, while hemoglobin was higher in the control group.

Outcomes before PSM

Overall, the overall in-hospital mortality was 10.7% (161/1,510). The in-hospital mortality (4.2% vs. 12.5%, $p < 0.001$) and ICU admission (9.9% vs. 23.0%, $p < 0.001$) were significantly lower in the ARBs use group, and the duration of hospitalization (10 days vs. 11 days, $p = 0.038$) was also shorter in the ARBs use group. However, there were no significances in AKI, RRT, hyperkalemia, and duration of ICU between the two groups (Table 2).

Table 1. Comparison of the baseline characteristics between patients with and without ARBs use before propensity score-matched analysis

Variables	Control group (n = 1,177)	ARBs group (n = 333)	p value
Age, years	76.1±10.9	75.9±11.4	0.826
Male, n (%)	727 (61.8)	209 (62.8)	0.897
Comorbid conditions, n (%)			
Diabetes	279 (23.7)	114 (34.2)	<0.001
Coronary artery disease	412 (35.0)	156 (46.8)	<0.001
Cardiac dysfunction	306 (26.0)	93 (27.9)	0.481
Atrial fibrillation	139 (11.8)	51 (15.3)	0.089
COPD	152 (12.9)	48 (14.4)	0.476
Pulmonary arterial hypertension	40 (3.4)	7 (2.1)	0.229
Chronic cor pulmonale	34 (2.9)	12 (3.6)	0.503
Cerebrovascular disease	519 (44.1)	148 (44.4)	0.910
Tumor	95 (8.1)	39 (11.7)	0.039
Rheumatic disease	26 (2.2)	10 (3.0)	0.402
Complication, n (%)			
[a]Acute respiratory failure	245 (20.8)	34 (10.2)	<0.001
Laboratory investigations			
[b]Hemoglobin, g/L	116.1±21.8	119.9±18.9	0.005
[b]White blood cell count, 10^9/L	8.7±5.1	8.2±4.0	0.085
[b]Platelet count, 10^9/L	203.8±89.3	208.9±79.0	0.347
[b]Serum creatinine, μmol/L	86.8±41.0	89.7±36.6	0.018
Severity of pneumonia			
[c]CURB-65 score, n (%)			
[c]CURB-65 score <3	998 (84.8)	310 (93.1)	<0.001
[c]CURB-65 score ≥3	179 (15.2)	23 (6.9)	

ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; CURB-65, confusion, urea >7 mmol/L, respiratory rate >30/min, blood pressure systolic <90 mm Hg or diastolic 60< mm Hg, and age >65 years at the time of presentation to hospital. [a]Acute respiratory failure on admission. [b]Laboratory indexes (hemoglobin, white blood cell count, platelet count, and serum creatinine) within 48 h on admission. [c]CURB-65 score on admission.

Association between ARBs Use and In-Hospital Mortality

In the extended multivariable logistic models (Table 3), we observed that the ORs of ARBs use were consistently significant in all six models (OR range: 0.27–0.48, p < 0.05, for all). In the subgroup analyses, the association between the ARBs use and the risk of in-hospital mortality was similar for all subgroups (age, gender, diabetes, coronary artery disease, cardiac dysfunction, cerebrovascular disease, acute respiratory failure, hemoglobin, white blood cell count, platelet count, serum creatinine, and CURB-65 score), and no significant interaction was observed (p = 0.050–0.946) (Fig. 2).

Outcomes after PSM

On the basis of the propensity score, 330 patients who received ARBs were successfully matched to 330 patients who did not have the ARBs treatment. The quality of PSM was considered balanced (all SMDs <10%). After PSM, no statistically significant baseline characteristics between the ARBs use group and the control group were found (Table 4). Cohort analysis revealed that the rate of in-hospital death (4.2% vs. 10.9%, p = 0.002) was lower in the ARBs use group. In the univariate analysis, the ARBs use was associated with in-hospital mortality (PSM OR, 0.36; 95% CI, 0.19–0.68; p = 0.002). In addition, ICU admission was significantly lower in the ARBs use group (15.5% vs. 10.0%, p = 0.047). However, no statistically significant differences in AKI, RRT, hyperkalemia, length of ICU stay, and duration of hospitalization were found between the control group and the ARBs use group (p > 0.05 for all) (Table 2).

Discussion

In this study, we investigated the association of ARBs use with in-hospital mortality among Chinese patients with hypertension hospitalized with CAP. The present

Table 2. Comparison of outcomes between patients with and without ARBs use before and after propensity score-matched analysis

Outcomes	Before PSM			After PSM		
	control group (n = 1,177)	ARBs group (n = 333)	p value	control group (n = 330)	ARBs group (n = 330)	p value
AKI, n (%)	154 (13.1)	36 (10.8)	0.269	41 (12.4)	36 (10.9)	0.628
RRT, n (%)	15 (1.3)	1 (0.3)	0.125	2 (0.6)	1 (0.3)	1.000
Hyperkalemia, n (%)	39 (3.3)	7 (2.1)	0.256	6 (1.8)	7 (2.1)	1.000
ICU admission, n (%)	271 (23.0)	33 (9.9)	<0.001	51 (15.5)	33 (10.0)	0.047
Duration of ICU (IQR), days	12 (6–21)	8 (5–17)	0.085	13 (6–25)	8 (5–17)	0.108
In-hospital mortality, n (%)	147 (12.5)	14 (4.2)	<0.001	36 (10.9)	14 (4.2)	0.002
Duration of hospitalization (IQR), days	11 (8–16)	10 (8–14)	0.038	11 (8–16)	10 (8–14)	0.179

ARBs, angiotensin receptor blockers; AKI, acute kidney injury; RRT, renal replacement therapy; ICU, intensive care unit; IQR, interquartile ratio.

Table 3. Association between ARBs use and in-hospital mortality using an extended model approach

Models	OR of ARBs use	95% confidence interval	p value
Model 1	0.31	0.18–0.54	<0.001
Model 2	0.30	0.17–0.52	<0.001
Model 3	0.27	0.15–0.49	<0.001
Model 4	0.37	0.20–0.67	0.001
Model 5	0.43	0.24–0.79	0.007
Model 6	0.48	0.26–0.89	0.019

Adjusted covariates: model 1: ARBs use; model 2: model 1 + gender + age; model 3: model 2 + comorbid conditions (diabetes, coronary artery disease, cardiac dysfunction, atrial fibrillation, COPD, pulmonary arterial hypertension, chronic cor pulmonale, cerebrovascular disease, and tumor); model 4: model 3 + complication (acute respiratory failure); model 5: model 4 + laboratory investigations (hemoglobin, white blood cell count, platelet count, and serum creatinine); model 6: model 5 + severity of pneumonia (CURB-65 score). ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease.

study demonstrated that the use of ARBs was associated with significantly decreased in-hospital mortality in patients with hypertension coexisting with CAP. This result was robust in the extended logistic model and remained consistent in the PSM analysis after adjustment for covariates. In addition, compared with the control group, ARBs use did not significantly increase the risk of AKI, RRT, and hyperkalemia in CAP patients with hypertension. Therefore, our findings suggested a possible beneficial role for the use of ARBs in patients with hypertension coexisting with CAP, which has not been previously demonstrated.

In this study, we found that use of ARBs in patients with hypertension coexisting with CAP was associated with the lower in-hospital mortality (PSM OR, 0.36; 95% CI, 0.19–0.68; p = 0.002). Mortensen et al. [7] found that the inpatient ARBs use of patients hospitalized with pneumonia was associated with significantly lower 30-day mortality (OR 0.47, 95% CI, 0.30–0.72). Wu and his colleagues conducted a retrospective study on male patients aged ≥65 years hospitalized with pneumonia and who did not have preexisting cardiac disease. They found that ARBs (OR 0.58, 95% CI, 0.44–0.77) were associated with decreased 90-day mortality [21].

Since only few research studies had been performed to explore the potential mechanisms of ARBs on reducing pneumonia-related mortality, the mechanisms are not clear. A previous study reported that ARBs were associated with improved survival and reduced adverse cardiovascular events [22]. However, it was interesting that Wu and his colleagues found that ARBs treatment was also associated with lower mortality in patients hospitalized with pneumonia, but there was no significant association between ARBs use and lower cardiovascular events. Therefore, they thought that the beneficial effects of ARBs on mortality in patients admitted with pneumonia may not be due to the prevention of future cardiac events but other mechanisms [23]. In the literature, ARBs had been confirmed to have anti-inflammatory effect in various extents by blocking the AT1 receptor [24], which could protect against acute lung injury [25]. In addition, angiotensin-converting enzyme 2 (ACE2) was found primarily in epithelial cells in the lung [26], and the ACE2/angiotensin-(1–7)/Mas axis directly regulated epithelial cell survival [27]. In patients, the increased level of ACE2 was associated with severe

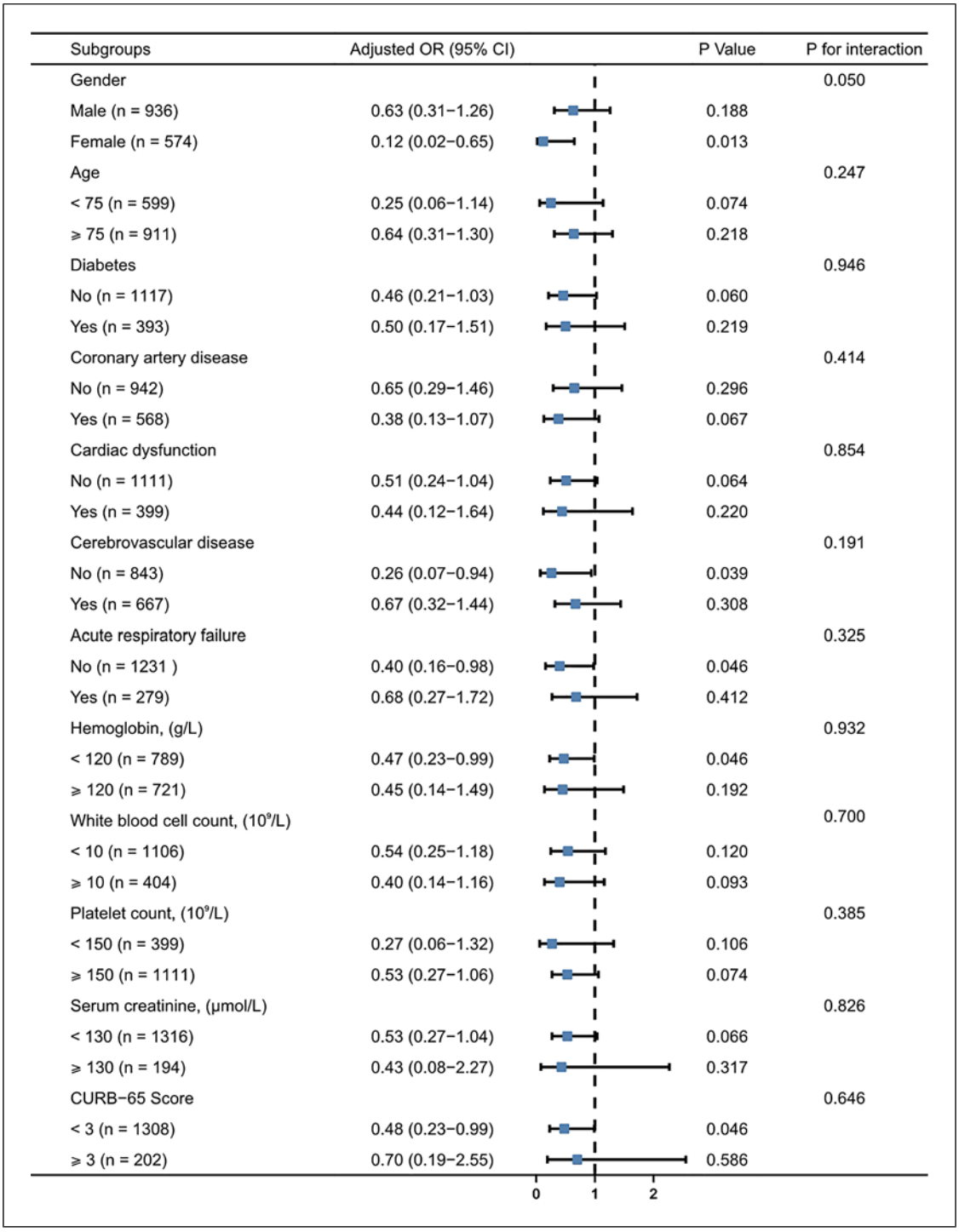

Fig. 2. Subgroup analysis of the association between ARBs use and in-hospital mortality. ARBs, angiotensin receptor blockers; CURB-65, confusion, urea >7 mmol/L, respiratory rate >30/min, blood pressure systolic <90 mm Hg or diastolic 60< mm Hg, and age >65 years at the time of presentation to hospital.

disease [28, 29]. In mice, ACE2 was a mediator of the acute lung injury caused by influenza A H5N1 and H7N9 virus infection [28], and treatment with ARB (losartan) at a dose clinically equivalent to human significantly improved the survival rate in H5N1 virus-infected mice by ameliorating acute lung injury [14].

Table 4. Comparison of the baseline characteristics between patients with and without ARBs use after propensity score-matched analysis

Variables	Control group (n = 330)	ARBs group (n = 330)	SMD	p value
Age, years	75.7±11.0	75.9±11.4	0.014	0.86
Gender, *n* (%)				
Male	207 (62.7)	207 (62.7)	<0.001	1.00
Female	123 (37.3)	123 (37.3)		
Comorbid conditions, *n* (%)				
Diabetes				
No	221 (67)	219 (66.4)	0.013	0.93
Yes	109 (33)	111 (33.6)		
Coronary artery disease				
No	183 (55.5)	177 (53.6)	0.037	0.70
Yes	147 (44.5)	153 (46.4)		
Cardiac dysfunction				
No	237 (71.8)	238 (72.1)	0.007	1.00
Yes	93 (28.2)	92 (27.9)		
Atrial fibrillation				
No	287 (87.0)	281 (85.2)	0.053	0.57
Yes	43 (13.0)	49 (14.8)		
COPD				
No	290 (87.9)	283 (85.8)	0.063	0.49
Yes	40 (12.1)	47 (14.2)		
Pulmonary arterial hypertension				
No	320 (97.0)	323 (97.9)	0.057	0.62
Yes	10 (3.0)	7 (2.1)		
Chronic cor pulmonale				
No	317 (96.1)	318 (96.4)	0.016	1.00
Yes	13 (3.9)	12 (3.6)		
Cerebrovascular disease				
No	179 (54.2)	183 (55.5)	0.024	0.81
Yes	151 (45.8)	147 (44.5)		
Tumor				
No	296 (89.7)	293 (88.8)	0.019	0.90
Yes	34 (10.3)	37 (11.2)		
Rheumatic disease				
No	320 (97.0)	320 (97.0)	<0.001	1.00
Yes	10 (3.0)	10 (3.0)		
Complication, *n* (%)				
[a]Acute respiratory failure				
No	89 (87.6)	296 (89.7)	0.067	0.46
Yes	41 (12.4)	34 (10.3)		
Laboratory indexes				
[b]Hemoglobin, g/L	119.0±20.8	119.3±19.6	0.016	0.84
[b]White blood cell count, 10^9/L	8.2±4.8	8.2±3.9	0.004	0.96
[b]Platelet count, 10^9/L	206.2±92.5	208.5±79.7	0.027	0.73
[b]Serum creatinine, μmol/L	92.0±54.5	92.6±43.4	0.013	0.87
Severity of pneumonia				
[c]CURB-65 score, *n* (%)				
[c]CURB-65 score <3	304 (92.1)	307 (93.0)	0.035	0.77
[c]CURB-65 score ≥3	26 (7.9)	23 (7.0)		

ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; CURB-65, confusion, urea >7 mmol/L, respiratory rate >30/min, blood pressure systolic <90 mm Hg or diastolic 60< mm Hg, and age >65 years at the time of presentation to hospital; SMD, standardized mean difference. [a]Acute respiratory failure on admission. [b]Laboratory indexes (hemoglobin, white blood cell count, platelet count, and serum creatinine) within 48 h on admission. [c]CURB-65 score on admission.

Hyperkalemia and AKI are common adverse drug events of ARBs in some clinical scenarios [30–32]. However, our results showed no significant differences in AKI, RRT, and hyperkalemia between the control group and the ARBs group. It suggested that ARBs use did not significantly increase the risk of AKI, RRT, and hyperkalemia.

There are several limitations in this study. First, our study is a retrospective, single-center study, making it prone to bias. Further prospective randomized controlled trials with large sample sizes and multicenter are warranted to confirm the protective role of ARBs in CAP patients with hypertension. Second, we do not discriminate pneumonia due to bacterial or viral pathogens. In the further, studies could be conducted to explore the impact of ARBs use on the mortality of patients with pneumonia due to bacterial or viral pathogens, respectively. Third, AKI was defined by serum creatinine and urine output levels according to KDIGO criteria [19]. However, we did not obtain urine output data. Therefore, our analysis did not include the urine output standard of AKI. Fourth, for the ARBs use group, we did not distinguish the single dose or multiple doses of ARBs drugs. Fifth, due to the limited numbers of patients of only prior use of ARBs, only inpatient use of ARBs, and use of ACEIs, the effect of ARBs use on in-hospital mortality was not compared between the group who used ARBs before hospitalization and continued use after admission and the groups with only prior use of ARBs, only inpatient use of ARBs, and use of ACEIs, respectively. Sixth, as this was a retrospective study, we lacked some parameters (such as baseline proteinuria, C-reactive protein, procalcitonin, smoking status, and frailty). Most importantly, as a retrospective observational study, we can only report associations and cannot prove that the use of ARBs causes improvement of in-hospital mortality for these patients.

In conclusion, although residual confounding could not be excluded, ARBs use was associated with lower in-hospital mortality in CAP patients with hypertension. In addition, compared with the control group, ARBs treatment did not significantly increase the risk of AKI, RRT, and hyperkalemia.

Statement of Ethics

This study was conducted according to the principles stated in the Declaration of Helsinki and was approved by the Regional Human Research Ethics Committee of Nanjing First Hospital, approval number (KY20181102-03). Due to the retrospective analysis, individual patient consent was waived on the condition that all patient data were deidentified before analysis.

Conflict of Interest Statement

All the authors declare that there is no conflict of interest.

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Author Contributions

Dawei Chen and Xin Wan conceived the study. Dawei Chen, Yan Tan, and Xin Wan participated in data preparation and analyses. Dawei Chen, Yan Tan, and Xin Wan contributed toward drafting and critically revising the paper and agreed to be accountable for all aspects of the work. Dawei Chen, Yan Tan, and Xin Wan reviewed and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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