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The Association of Renin-Angiotensin System Blockades and Mortality in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease and Acute Respiratory Failure: A Retrospective Cohort Study

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Background: Acute respiratory failure (ARF) is a common cause of admission to the intensive care unit (ICU) for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). There is still a lack of effective interventions and treatments. ACE inhibitors (ACEI)/ angiotensin II receptor blockers (ARB) were effective in COPD patients. We aimed to study the effect of ACEI/ ARB use on AECOPD combined with ARF and evaluate the effect of in-hospital continuation of medication.

Methods: We included patients with AECOPD and ARF from the Medical Information Bank for Intensive Care (MIMIC-III) database. MIMIC III is a large cohort database from Boston, USA. Patients were divided into two groups according to the use of ACEI/ARB before admission. Propensity score matching (PSM) was used to reduce potential bias between the two groups. Cox regression and Kaplan-Meier curves compared 30-day mortality in ACEI/ARB users and non-users. We also defined and analyzed the use of in-hospital ACEI/ARB. Multiple models were used to ensure the robustness of the findings. Subgroup analysis was used to analyze the variability between groups.

Results: A total of 544 patients were included in the original study. After PSM, 256 patients were included in the matched cohort. Multivariate Cox regression showed 30-day mortality was significantly lower in ACEI/ARB users compared with controls (HR = 0.50, 95% CI: 0.29–0.86, p= 0.013). In PSM and inverse probability-weighted models, the results are stable Continued in-hospital use of ACEI/ARB remains effective (HR 0.40, 95% CI 0.22–0.74, p = 0.003). Kaplan-Meier showed a significant difference in survival between the two groups.

Conclusion: This study found that pre-hospital ACEI/ARB use was associated with reduced mortality in patients with AECOPD and ARF.

Keywords: chronic obstructive pulmonary disease, acute respiratory failure, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, mortality

Background

In the intensive care unit (ICU), acute respiratory failure (ARF) is one of the most frequent complications in patients with acute exacerbations chronic obstructive pulmonary disease (AECOPD).[1,2] Effective treatment options remain limited, and it is necessary to explore appropriate methods to anti-inflammatory and protect against acute lung injury.

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor antagonists (ARB), an inhibitor of the renin-angiotensin-aldosterone system, have been widely used in cardiovascular diseases. Previous studies have shown

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a protective effect of ACEI/AEB in the prognosis of patients with COPD. Mancini reported that the use of ACEI/ARB reduced morbidity and mortality in COPD patients, suggesting its potential dual cardioprotective properties.[3] Subsequently, Mortensen found that patients with AECOPD using ACEI/ARB were associated with lower mortality.[4] There is a lack of studies on ACEI/ARB use in COPD combined with ARF patients admitted to the ICU, and it is unclear whether these patients should continue with ACEI/ARB. We hypothesized that ACEI/ARB would benefit patients with AECOPD and ARF. Hence, we decided to conduct a retrospective study to ascertain the association between ACEI/ARB use and mortality in these patients.

Methods

Study Design and Data Source

This study used a retrospective cohort study. Data were extracted from the Medical Information Bank for Intensive Care (MIMIC)-III (v 1.4). MIMIC-III covered 53423 adult patients hospitalized at the Beth Israel Deaconess Medical Center in Boston from June 2001 to October 2012.[5] One author Zhishen Ruan gained access to the database by completing the online course and passing the National Institutes of "Protecting Human Research Participants Exam" (certification number 43453324). The Institutional Review Board of Beth Israel Deaconess Medical Center and MIT affiliates approved the database.[6] Our findings were reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[7]

Inclusion and Exclusion Criteria

We extracted patients with AECOPD and ARF diagnoses from MIMIC III based on SQL language. The diagnostic criteria were derived from the International Classification of Diseases, Ninth Revision. Unfortunately, the lung function test was lacking in the database to confirm COPD diagnosis. We considered patients with COPD and AECOPD diagnoses in the ICD-9 codes to reduce diagnostic errors as AECOPD patients. Patients with missing vital information, comorbid asthma, or admission time less than 24 hours were excluded from our cohort.

Diagnostic Criteria and Drug Use

Primary diagnosis of COPD consistent with (ICD-9-CM codes: 490.x, 491.xx, 492.xx and 496.xx); secondary AECOPD diagnosis (ICD-9-CM codes: 491.21,491.22); primary diagnosis of acute respiratory failure (ICD-9-CM codes: 518.81, 518.82, 518.84 or 799.1).[8] The diagnosis of other diseases is shown in Table S1. The ACEI/ARB use was defined as a record of using ACEI or ARB in "Medications on admission" in MIMIC-III.[4] Medications classified as ACEIs were benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, and ramipril, and ARBs included candesartan, irbesartan, losartan, telmisartan and valsartan.[9] We included ARB in the ACEI category for the analysis in this study due to the small number of subjects using this class of medications. Other medications are also taken from "Medications on admission". The specific drugs are presented in Table S2.

Demographic Characteristics

We extracted the following outcome variables: age, gender, ethnicity, smoking history, comorbidities (diabetes, hypertension, hyperlipidemia, coronary artery disease, congestive heart failure, stroke, pulmonary circulatory disease, peripheral vascular disease, pneumonia, sepsis, renal failure, cancer), mechanical ventilation, Acute Physiology Score III (APS III), quick sequential organ failure assessment score (qSOFA), acute physiology II (SAPSII), Oxford acute severity of illness score (OASIS), respiratory medication use (LABA: Long-acting β2 agonists, LAMA: long-acting muscarinic antagonist, inhaled and oral corticosteroid), Cardiovascular and other medications use (beta-blockers, calcium-channel blockers, diuretics, antiplatelet, nitrates, Anti-glycemic drugs, statins), arterial blood gases results, and length of hospital stay.

Primary Outcome

Our primary outcome, 30-day mortality, was evaluated against a database developed and maintained by the MIT Computational Physiology Laboratory.[5]

Statistical Analysis

We used propensity score matching (PSM) based on the 40 covariates described above to minimize potential bias in the treatment of allocation and confounding factors.[10] Variable matching follows a 1:1 nearest neighbor matching algorithm with a caliper width of 0.02. To assess the validity of the PSM, we compared the balance of covariates between the original and matched cohorts using standardized mean differences (SMD). SMD<0.1 is considered an acceptable result.[9]

Data were described as mean ± standard deviation, median (25th-75th percentile), or number (percentage), depending on the type and distribution of the variable. Kruskal Wallis and Chi-square (or Fisher's exact) tests were used to compare among the categorical covariates. Cox proportional risk models were used to calculate the risk ratios (HRs) and 95% ci of patients applying ACEI/ARB with 30-day mortality levels. The cumulative rates of death were compared over 30-day using the Kaplan-Meier curves. To further analyze the impact of in-hospital ACEI/ARB use, we defined ACEI/ARB use records within 24 hours of the first admission as in-hospital ACEI/ARB use. We divided them into four groups for analysis based on pre-hospital and in-hospital use of ACEI/ARB.

We performed a series of sensitivity analyses to verify the robustness of the results. A Cox regression was then performed on the weighted cohort to obtain the results. Three association inference models were used: an inverse probability weighting model, a propensity score-based patient-matching model, and a Cox regression-based multivariate analysis model. Cox proportional hazards regression was performed to adjust for the population before and after the propensity score. In addition, sensitivity analysis was used to analyze the differences between the subgroups.

The analyses were performed with the statistical software packages R v3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software versions (1.4).

Results

Flow Chart

A total of 646 patients with AECOPD combined with ARF were extracted from the MIMIC-III. After excluding patients diagnosed with asthma and those hospitalized for less than 24 hours, 544 patients were included in the original cohort. (Figure 1)

Characters of Patients

Population baseline information for all patients was presented in Table 1. 199 (36.6%) patients used ACEI/ARB in the original cohort. Patients in the ACEI/ARB group had more comorbidities: diabetes 74 (37.2) vs 76 (22.0), hypertension 35 (17.6) vs 31(9.0), CAD 62 (31.2) vs 64 (18.6). We used PSM to balance the variation between the two groups to reduce this potential bias. After PSM, 256 patients were included in the matched cohort. The mean ages of these patients were 71.7 ± 11.9, females accounted for 45.7%, 198 (77.3%) were whites, and 58 (22.7%) were non-whites.

Clinical Outcomes

Multivariate Cox regression (Table 2) shows a protective effect of ACEI/ARB use on 30-day death in patients with AECOPD combined with ARF (HR = 0.51, 95% CI = 0.32–0.81, $p = 0.005$). Compared to the group not in and pre-hospital ACEI/ARB use, the HRs of the other three groups were (in-hospital use: HR 0.51, 95% CI 0.24–1.07, $p = 0.073$; pre-hospital use: HR 0.45, 95% 0.21–0.96, $p = 0.039$; in and pre-hospital use: HR 0.40, 95% CI 0.22–0.74, $p = 0.003$). K-M survival curves (Figure 2) revealed that the ACEI/ARB group had higher survival times and significantly lower mortality rates than patients in non-ACEI/ARB group. ($p < 0.001$).

Sensitivity Analysis

In the original cohort (N = 544), ACEI/ARB users remained protective for 30-day mortality in the model I (HR 0.50, 95% CI 0.29–0.86, $p = 0.013$) after adjusting for various covariates, such as age, sex, comorbidities, pre-hospital medication, Severity scale, and ABG values. After PSM, the HR in model II (HR 0.56, 95% CI 0.34–0.94, $p = 0.028$) and model III (HR 0.55, 95% CI 0.34–0.89, $p = 0.014$) were similar to those before adjustment (Table 3). Table 4 shows the

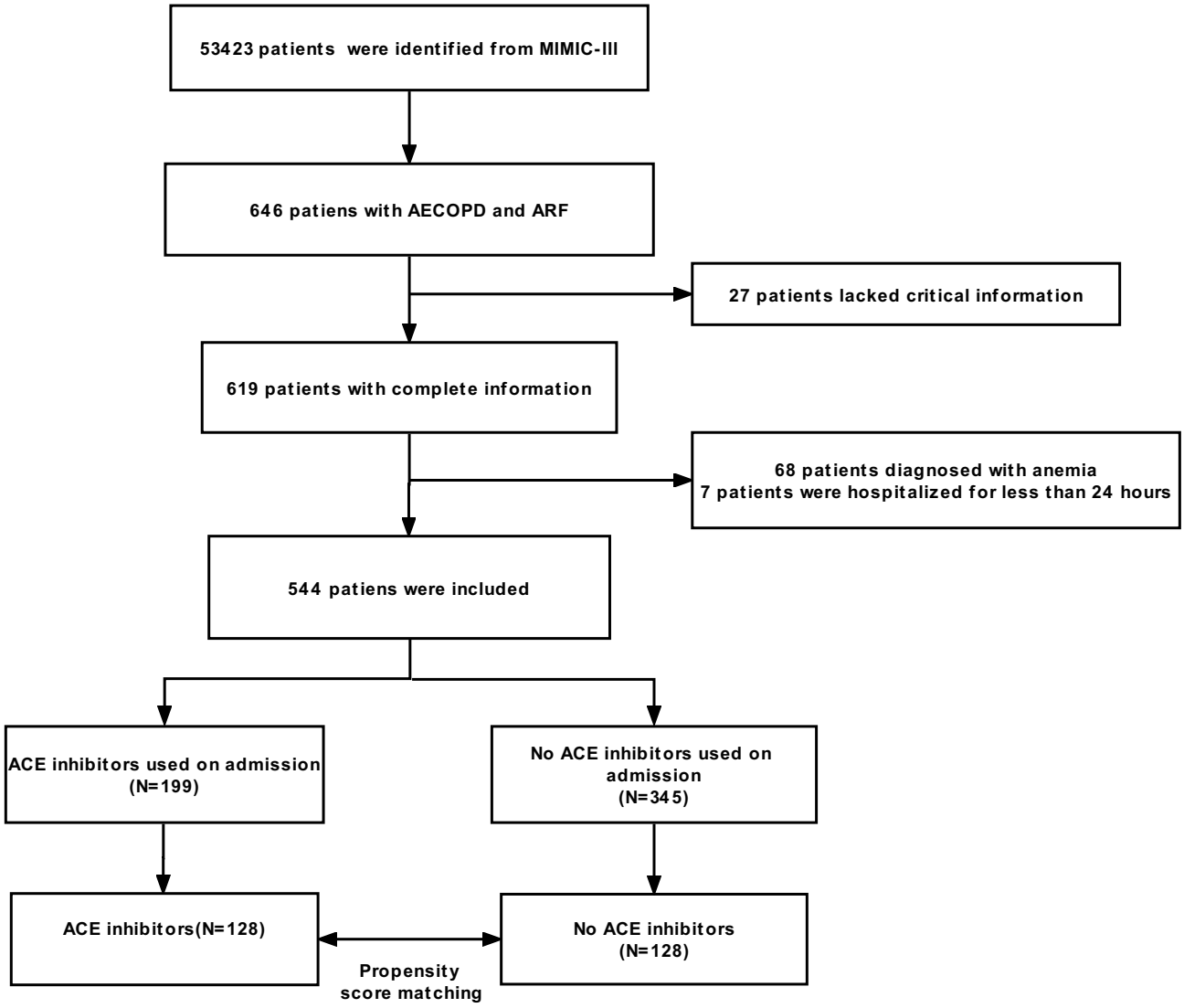

Figure 1 The flow chart of study.

results of the subgroup analysis. Table S3 is the subgroup analysis of in-hospital and pre-hospital use of ACEI/ARB. The HRs assessed by baseline risk factors were less than 1.0 for all subgroups.

Discussion

In this study, ACEI/ARB pre-hospital users with AECOPD and ARF had lower 30-day mortality than non-ACEI/ARB users. This association is reliable in three models after PSM. Bidulka found that discontinuation of AECI/ARB increased mortality in patients with kidney injury.[11] We further analyzed the prognosis of in-hospital use of ACEI/ARB in patients with AECOPD. Our results found that continued in-hospital use of ACEI/ARB was associated with lower mortality in patients with AECOPD and ARF.

In our study, 36.6% (199/544) of patients received ACEI or ARB, which was higher than the results of previous studies. Mortensen said that 32.0% of patients with AECOPD on ACEI/ARB and Tejwani in the COPD gene cohort study reported 28.0% of COPD patients using ACEI/ARB.[4,12] The higher rate of medication use may be related to the higher number of cardiovascular comorbidities in critically ill patients. In addition, the definition of ACEI/ARB use may have led to this discrepancy. ACEI/ARB exposure was a recent history of ACEI/ARB use in mimic-III. In contrast, Mortensen and Tejwani, in their cohorts, described ACEI/ARB exposure as ACEI/ARB use in the 90 days before hospital admission or continued ACEI/ARB use.

Table 1 Baseline Characteristics of Participants

Variables	Original Cohort			SMD	Matched Cohort			SMD
	All Patients (n= 544)	No ACEI/ARB (n=345)	ACEI/ARB (n=199)		All Patients (n= 256)	No ACEI/ARB (n=128)	ACEI/ARB (n=128)	
Sex, Female	258 (47.4)	162 (47.0)	96 (48.2)	0.03	117 (45.7)	58 (45.3)	59 (46.1)	0.02
Age, y	71.0 ± 11.6	70.3 ± 11.7	72.0 ± 11.3	0.15	71.7 ± 11.9	71.9 ± 12.0	71.4 ± 11.8	0.04
Ethnicity, white	410 (75.4)	258 (74.8)	152 (76.4)	0.04	198 (77.3)	99 (77.3)	99 (77.3)	<0.001
Smoker	438 (80.5)	288 (83.5)	150 (75.4)	0.20	197 (77.0)	101 (78.9)	96 (75.0)	0.09
Comorbidities								
Diabetes	150 (27.6)	76 (22.0)	74 (37.2)	0.34	86 (33.6)	44 (34.4)	42 (32.8)	0.03
Hypertension	66 (12.1)	31 (9.0)	35 (17.6)	0.26	37 (14.5)	21 (16.4)	16 (12.5)	0.11
Hyperlipidemia	141 (25.9)	74 (21.4)	67 (33.7)	0.28	76 (29.7)	37 (28.9)	39 (30.5)	0.03
CAD	126 (23.2)	64 (18.6)	62 (31.2)	0.30	73 (28.5)	36 (28.1)	37 (28.9)	0.02
CHF	217 (39.9)	134 (38.8)	83 (41.7)	0.06	106 (41.4)	53 (41.4)	53 (41.4)	<0.001
Stroke	26 (4.8)	18 (5.2)	8 (4.0)	0.06	11 (4.3)	5 (3.9)	6 (4.7)	0.04
PC	44 (8.1)	23 (6.7)	21 (10.6)	0.14	22 (8.6)	13 (10.2)	9 (7.0)	0.11
PVD	53 (9.7)	29 (8.4)	24 (12.1)	0.12	21 (8.2)	11 (8.6)	10 (7.8)	0.03
Pneumonia	334 (61.4)	205 (59.4)	129 (64.8)	0.11	158 (61.7)	78 (60.9)	80 (62.5)	0.03
Sepsis	91 (16.7)	58 (16.8)	33 (16.6)	0.01	46 (18.0)	24 (18.8)	22 (17.2)	0.04
Renal failure	83 (15.3)	45 (13.0)	38 (19.1)	0.17	39 (15.2)	22 (17.2)	17 (13.3)	0.11
Cancer	62 (10.1)	29 (8.4)	12 (6.0)	0.09	18 (7.0)	9 (7.0)	9 (7.0)	<0.001
Mechanical ventilation	420 (68.1)	217 (62.9)	123 (61.8)	0.02	158 (61.7)	80 (62.5)	78 (60.9)	0.03
Severity scales								
APSIII	44.6 ± 17.4	44.8 ± 17.5	44.1 ± 17.2	0.04	44.5 ± 17.7	44.5 ± 17.2	44.5 ± 18.3	0.01
qSOFA	1.7 ± 0.8	1.7±0.8	1. 7 ±0.7	0.08	1.7 ± 0.8	1.7±0.9	1.7±0.7	0.03
SAPSII	38.0 ± 12.6	38.0 ± 13.2	38.0 ± 11.5	0.01	37.6 ± 13.0	37.4 ± 13.7	37.8 ± 12.3	0.03
OASIS	35.0 ± 9.2	35.5 ± 9.1	34.0 ± 9.3	0.16	34.8 ± 9.6	35.0 ± 9.8	34.6 ± 9.3	0.04
Respiratory medications use								
LABA	166 (30.5)	107 (31.0)	59 (29.6)	0.03	81 (31.6)	43 (33.6)	38 (29.7)	0.08
LAMA	122 (22.4)	75 (21.7)	47 (23.6)	0.05	63 (24.6)	31 (24.2)	32 (25.0)	0.02
Inhaled corticosteroid	230 (42.3)	155 (44.9)	75 (37.7)	0.15	99 (38.7)	53 (41.4)	46 (35.9)	0.11
Oral corticosteroid	144 (26.5)	106 (30.7)	38 (19.1)	0.27	62 (24.2)	29 (22.7)	33 (25.8)	0.07
Cardiovascular and other medications								
Beta-blockers	180 (33.1)	103 (29.9)	77 (38.7)	0.19	117 (40.9)	46 (35.9)	43 (33.6)	0.05
Calcium-channel blocker	136 (25.0)	80 (23.2)	56 (28.1)	0.11	64 (22.4)	35 (27.3)	33 (25.8)	0.04
Diuretics	53 (9.7)	111 (32.2)	87 (43.7)	0.24	120 (42.0)	60 (46.9)	53 (41.4)	0.11
Antiplatelet	235 (38.1)	113 (32.8)	95 (47.7)	0.31	123 (43.0)	56 (43.8)	60 (46.9)	0.06
Nitrates	55 (8.9)	24 (7.0)	29 (14.6)	0.25	28 (9.8)	17 (13.3)	18 (14.1)	0.02
Anti-glycemic drugs	57 (10.5)	23 (6.7)	34 (17.1)	0.33	30 (10.5)	15 (11.7)	16 (12.5)	0.02
Statins	196 (36.0)	90 (26.1)	106 (53.3)	0.58	104 (40.6)	51 (39.8)	53 (41.4)	0.03
ABG values on the admission								
$PaCO_2$	56.0 ± 17.6	56.0 ± 17.8	55.9 ± 17.5	0.01	56.2 ± 17.8	57.1 ± 19.3	55.3 ± 16.2	0.10
PH	7.32±0.11	7.35 (0.09)	7.34 (0.08)	0.09	7.34 ± 0.08	7.34 ±0.09	7.35±0.07	0.01
PaO_2/FiO_2	212 (130, 251)	214 (130, 255)	207 (133, 239)	0.09	217 (137, 255)	217 (141, 251)	215 (133, 257)	0.02
Time in hospital	11.6 ± 9.1	11.3±9.1	12.2 ±9.1	0.09	11.6 ± 9.5	11. 9±9.7	11.6±8.9	0.04
Time in ICU	6.4 ± 7.1	6.0±6.8	7.1±7.6	0.16	7.6 ± 8.9	7.0±8.8	6.4±6.4	0.08

Abbreviations: CAD, Coronary artery disease; CHF, Congestive heart failure; PC, Pulmonary circulation disease; PVD, Peripheral vascular disease; APS III, Acute Physiology Score III; qSOFA, quick sequential organ failure assessment score; SAPSII, acute physiology II; OASIS, Oxford acute severity of illness score; LABA, Long-acting β2 agonists; LAMA, long-acting muscarinic antagonist; SMD, standardized mean difference.

As far back as 2006, Mancini identified a protective effect of ACEI/ARB use in COPD.[3] After that, Mortensen placed this effect and found that patients ≥65 years with AECOPD treated with ACE inhibitors were associated with lower 90-day all-cause mortality (OR 0.55, 95% CI 0.45–0.66).[4] However, they only studied older male patients, which

Table 2 Univariate and Multivariate Cox Hazard Analysis of Risk Factors for 30-Day Mortality in AECOPD and ARF

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Sex, Female	1.46 (0.97–2.19)	0.068		
Age, y	1.06 (1.04–1.08)	<0.001	1.06 (1.02–1.09)	0.001
Ethnicity, white	1.34 (0.81–2.21)	0.255		
Smoker	1.22 (0.71–2.09)	0.466		
Medications				
ACEI/ARB	0.50 (0.32–0.81)	0.004	0.50 (0.29,0.86)	0.013
No ACEI/ARB use	1 (ref)		1 (ref)	
In-hospital ACEI/ARB use	0.53 (0.26–1.06)	0.074	0.51 (0.24–1.07)	0.073
Pre-hospital ACEI/ARB use	0.48 (0.27–0.85)	0.011	0.45 (0.21–0.96)	0.039
In and pre-hospital use	0.41 (0.20–0.86)	0.018	0.40 (0.22–0.74)	0.003
Comorbidities				
Diabetes	0.91 (0.58–1.44)	0.683		
Hypertension	1.06 (0.58–1.94)	0.846		
CAD	0.69 (0.41–1.16)	0.162		
CHF	1.7 (1.14–2.54)	0.01		
Stroke	1.16 (0.47–2.85)	0.749		
PC	1.07 (0.52–2.21)	0.855		
PVD	1.11 (0.57–2.13)	0.761		
Pneumonia	0.98 (0.65–1.48)	0.927		
Sepsis	2.38 (1.54–3.68)	<0.001	1.97 (1.11–3.47)	0.02
Renal failure	1.45 (0.88–2.4)	0.145		
Cancer	2.59 (1.49–4.49)	0.001	3.7 (1.78–7.68)	<0.001
Mechanical ventilation	0.99 (0.65–1.5)	0.963		

Abbreviations: LABA, Long-acting β2 agonists; LAMA, long-acting muscarinic antagonist; CAD, Coronary artery disease; CHF, Congestive heart failure; PC, Pulmonary circulation disease; PVD, Peripheral vascular disease.

may lead to potential bias. Our cohort focused on patients with AECOPD combined with ARF, adjusting for various confounding factors such as age, gender, comorbidities, arterial blood gas analysis, and preadmission medications. Thus, our study provides further evidence that ACEI/ARB use is associated with lower mortality in patients with AECOPD and ARF.

Over the past few years, there has been a proliferation of studies on ACEI/ARB and COPD. In COPD combined with pneumonia, Kim found that ACEI/ARB use reduced the incidence of pneumonia in COPD patients.[13] To differentiate the effect of ACEI and ARB, Lai conducted a study founding that ARB use was superior to the use of ACEI in COPD patients regarding the incidence of pneumonia and mortality.[14] Recently, several studies have found a potential therapeutic benefit of ACEI/ARB use in stable COPD patients. It plays a vital role in delaying the progression of emphysema and decline in lung function, improving lung compliance, decreasing peak response to exercise training, improving exercise capacity, and enhancing pulmonary rehabilitation.[12,15–18] These studies responded that ACEI/ARB could reduce the rate of lung function deterioration in COPD patients and reduce the risk of pneumonia, thereby reducing mortality in AECOPD combined with ARF.

Renin-Angiotensin System blockages are effective in acute respiratory distress syndrome (ARDS). Kim found that ARDS patients' mortality from ACEI/ARB during ICU admission was lower than no-ACEI/ARB users.[19] However, there was some bias in selecting medication use at entrance, with patients who survived longer being more opportunistic to take AECI/ARB. Thus, for patients with acute viral respiratory illness (AVRI), Jeffery found a reduced probability of ARDS in AVRI patients on outpatient ARB and reduced 30-day mortality in patients on AECI.[20]

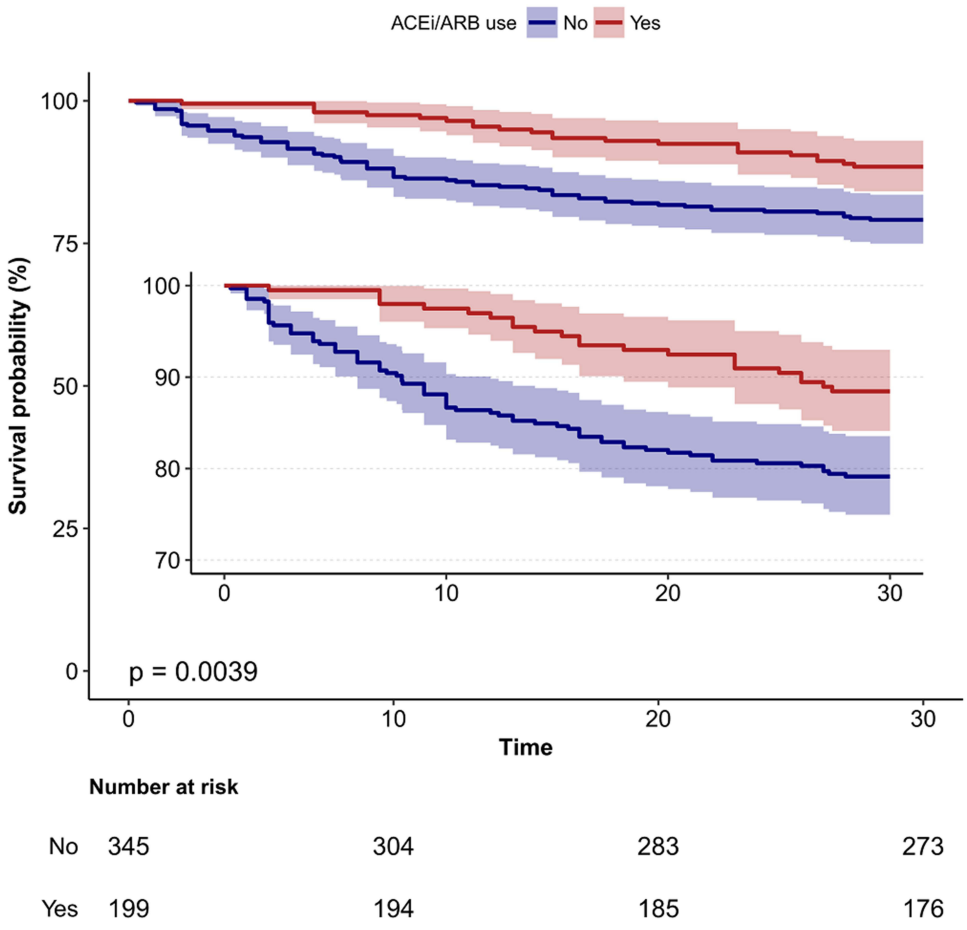

Figure 2 Kaplan-Meier survival curves for 30-day of AECOPD patients with ARF.

We can propose several explanations to analyze the association between ACEI/ARB use and lower mortality in patients with AECOPD combined with ARF.

First, the angiotensin-converting enzyme (ACE) is highly abundant in the lungs. When AECOPD combined with ARF occurs, acute alveolar hypoxia activates ACE, increasing the production of angiotensin II (Ang II).[21,22] In addition

Table 3 Associations Between ACE Inhibitors Use and the 30-Day Mortality

	30-Day Mortality (%)	
Original cohort		
No ACE inhibitors	72/345 (20.86)	
ACE inhibitors	23/199 (11.55)	
Matched cohort		
No ACE inhibitors	29/128 (22.66)	
ACE inhibitors	12/128 (9.38)	
30-day mortality	**HR (95% CI)**	**P value**
Crude analysis	0.51 (0.32,0.81)	0.005
Multivariable analysis[a]	0.50 (0.29,0.86)	0.013
Adjusted for propensity score[b]	0.56 (0.34,0.94)	0.028
With inverse probability weighting[c]	0.55 (0.34,0.89)	0.014

Notes: [a]Shown is a multivariable Cox regression model of 544 patients by adjusting all covariates in Table 1. [b]Shown is a multivariable Cox regression model adjusted for all covariates after propensity score matching. [c]Shown is a multivariable Cox regression model adjusted for inverse probability-weighted covariates after propensity score matching.

Table 4 Subgroup Analysis Between ACE Inhibitors Use and the 30-Day Mortality

Subgroup	No. Event_%	HR 95% CI	*P*	P for Interaction
Age				0.384
< 70	5/76 (6.6)	0.66 (0.24–1.80)	0.416	
≥70	18/123 (14.6)	0.39 (0.23–0.67)	0.001	
Gender				0.390
Female	8/103 (7.8)	0.34 (0.16–0.74)	0.007	
Male	15/96 (15.6)	0.51 (0.28–0.93)	0.029	
Sepsis				
No	16/159 (10.1)	0.44 (0.25–0.78)	0.004	0.944
Yes	7/40 (17.5)	0.47 (0.2–1.11)	0.085	
Pneumonia				
No	9/70 (12.9)	0.5 (0.24–1.07)	0.075	0.643
Yes	14/129 (10.9)	0.42 (0.23–0.77)	0.005	
CAD				0.134
No	20/137 (14.6)	0.54 (0.33–0.90)	0.019	
Yes	3/62 (4.8)	0.21 (0.06–0.73)	0.014	
CHF				0.218
No	13/116 (11.2)	0.57 (0.30–1.09)	0.092	
Yes	10/83 (12.0)	0.32 (0.16–0.65)	0.001	
Renal failure				0.578
No	17/161 (10.6)	0.40 (0.22–0.72)	0.002	
Yes	6/38 (15.8)	0.08 (0.01–0.92)	0.043	
Hypertension				0.705
No	18/164 (11.0)	0.43 (0.26–0.73)	0.002	
Yes	5/35 (14.3)	0.58 (0.17–1.95)	0.380	
Diabetes				0.449
No	17/125 (13.6)	0.50 (0.29–0.88)	0.016	
Yes	6/74 (8.1)	0.33 (0.13–0.84)	0.019	

Abbreviations: CAD, Coronary artery disease; CHF, Congestive heart failure.

to being a potent vasoconstrictor, Ang II appears to be an essential mediator of lung injury and apoptosis. It can modulate the inflammatory response by interfering with cytokine production, inflammatory cell migration, epithelial apoptosis, oxidative stress, activation of tissue mast cells, and lung fibrosis.[23–28] Ang II also can induce bronchoconstriction, leading to the deterioration of lung function.[29,30] Like ACE inhibitors, ACEI/ARB has significant immunomodulatory effects.[31,32] We believe that ACEI/ARB may alleviate acute lung injury and reduce the deterioration of lung function through the above channels.

Second, angiotensin-converting enzyme II (ACE2), a crucial active biopeptide, is produced through the ACE/ Ang II axis and plays a vital role in preventing lung disease.[33,34] Ferrario was the first to find that ACE inhibitor administration increased ACE2 expression in an animal model.[35] Furthermore, Kriszta reviewed 27 animal studies and found that most of these papers reported increased ACE2 levels after ACEI/ARB treatment.[36] ACE2 can reduce the severity of acute lung injury (ALI) by antagonizing the ACE/Ang II pathway and reducing ALI-induced apoptosis of lung endothelial cells.[37–39] Ye found that ACEI and ARB treatment could attenuate lipopolysaccharide-induced lung injury by increasing ACE2 expression.[40] From both perspectives, we can suggest that the protective effects of AECI/ARB on the lung are associated with increased ACE2 expression and inhibition of the RAS system by reducing Ang II effects. We plan to test our hypothesis through basic experiments in the next step.

There are some limitations to our study. First, estimating ACEI/ARB use based solely on the use of "admission medications" in discharge records may have biased our analysis. Nevertheless, ACEI/ARB is a very sticky drug, and the likelihood of drug deficiency in this study was minimal. To add credibility to our results, we stratified the patients who continued medication in the hospital. Second, this is a retrospective study, and there may be residual confounding factors.

However, we adjusted for variables associated with ARF risk and balanced the cohort by matching propensity scores. Then, we investigated all-cause mortality because we could not obtain the specific cause of death of the patients. Finally, because pulmonary function tests and annual frequency of exacerbations were not available for this dataset, we could not assess the severity of COPD. However, to our best knowledge, most patients admitted to the ICU with combined ARF were more severe.

Conclusions

In conclusion, our study found that pre-hospital ACEI/ARB use was associated with reduced mortality in patients with AECOPD combined with ARF. We further found that in-hospital continuation of ACEI/ARB was more protective than patients who discontinued it. Therefore, for patients with AECOPD admitted to the ICU, pre-admission ACEI/ARB use should be continued. Further randomized controlled trials are needed to confirm our results.

Abbreviations

COPD, Chronic obstructive pulmonary disease; ARF, Acute respiratory failure; ICU, intensive care unit; ACEI, ACE inhibitors; ARB, Angiotensin II receptor blockers; HR, Hazard ratio; SMD, Standardized mean difference; CAD, Coronary artery disease; CHF, Congestive heart failure; PC, Pulmonary circulation disease; PVD, Peripheral vascular disease; APS III, Acute Physiology Score III; OASIS, Oxford acute severity of illness score; qSOFA, quick sequential organ failure assessment score; SIRS, systemic inflammatory response syndrome; LABA, Long-acting β2 agonists; LAMA, long-acting muscarinic antagonist; ARDS, Acute respiratory distress syndrome; ACE, Angiotensin-converting enzyme; ACE2, Angiotensin-converting enzyme II; ALI, Acute lung injury.

Data Sharing Statement

Data in the article can be obtained from the MIMIC-III database (https://mimic.physionet.org/).

Ethics Approval and Consent to Participate

The project was approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center and was granted a waiver of informed consent. As all data were de-labeled, the Ethics Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine exempted our ethical review with the acceptance number 2022–0007.

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Zhishen Ruan and Dan Li are co-first authors for this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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