

A propensity score-matching analysis of angiotensin-converting enzyme inhibitor and angiotensin receptor blocker exposure on in-hospital mortality in patients with acute respiratory failure

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Abstract

Study Objective: To explore the impact of pre-hospital ACEI and ARB exposure on the prognosis of ARF patients.

Design: A single-center retrospective cohort study.

Setting: Medical Information Mart for Intensive Care-III (MIMIC-III) database.

Patients: The patients meeting ICD-9 code of acute respiratory failure were enrolled.

Intervention: The primary exposure was the pre-hospital exposure of ACEI and ARB.

Measurement and main results: The primary outcome was in-hospital mortality. Multiple logistic regression analysis was conducted to determine the independent effect of ACEI/ARB exposure on mortality. Propensity score matching (PSM) method was adopted to reduce bias of the confounders. Subgroup analysis and sensitivity analysis were used to test the stability of the conclusion. 5335 adult ARF patients were enrolled. Mortality was significantly decreased in patients with ACEI/ARB exposure before and after PSM, and the adjusted odds ratio (OR) of ACEI/ARB exposure was 0.56 (95% CI 0.43–0.72). In the subgroup analysis, ACEI/ARB lost its protective effect in young subgroup, but no significant interaction was found between ACEI/ARB exposure and age ($p = 0.082$). The point estimation and lower 95% limit of E-value was 2.97 and 2.12. In sensitivity analysis, ACEI/ARB exposure showed similar effect in ARDS cohort, but no significantly difference was found in the MIMIC-IV database, which may be explained by small sample size of the ACEI/ARB group.

Conclusions: Among patients with acute respiratory failure, pre-hospital ACEI/ARB exposure was associated with better outcomes and acted as an independent factor. The relationship between ACEI/ARB and prognosis of ARF is worth investigating further.

KEYWORDS

acute respiratory distress syndrome, acute respiratory failure, angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, prognosis

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1 | INTRODUCTION

Acute respiratory failure (ARF) is responsible for significant morbidity and mortality within and outside the intensive care unit (ICU). As reported, the incidence of ARF is 77.6–137.1 hospitalizations per 100,000 and the in-hospital mortality rate is 35.9% in the United States.¹ ARF is a heterogeneous syndrome that occurs secondary to several kinds of diseases. In the acute hypoxemic failure subtype, cardiogenic pulmonary edema, pneumonia, trauma, and acute respiratory distress syndrome (ARDS) are the common causes.² ARDS is the main cause of severe hypoxemia, which is characterized by excessive inflammatory reaction, vascular hyperpermeability, pulmonary edema, and pulmonary fibrosis in the advanced stage.^{3,4} The mortality rate of severe ARDS is up to 42%.³ Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is the most common cause of the hypercapnic respiratory failure subtype. The in-hospital mortality and 1-year mortality were 2%–8% and 22%–43% of patients with AECOPD.⁵ The in-hospital mortality was up to 15% for those in ICU departments.⁵

Oxygen therapy and mechanical ventilation (MV) are the mainstays in the management of patients with ARF, aimed at buying time for the etiological therapy.² There is little evidence for medication use in the treatment of ARF. Recently, the roles of renin-angiotensin system (RAS) in the regulation of the respiratory system have received widespread attention, especially in patients with COVID-19 disease.⁶ Angiotensin-converting enzyme (ACE) and ACE2 (the homologue of ACE) play essential roles in the regulation of RAS, modulating the balance between vasoconstrictors and vasodilators. Angiotensin I (AngI) derived from angiotensinogen is converted to vasoconstricting angiotensin II (AngII) through cleavage of its C-terminal dipeptide catalyzed by ACE, while ACE2 converts AngII into vasodilating angiotensin-(1–7) (Ang[1–7]).⁷ Angiotensin II is a pro-inflammatory and vasoconstrictor protein, involved in the process of inflammatory reaction, oxidative stress, endothelial damage, and tissue fibrosis. Another subtype, Ang[1–7], plays an opposite role to AngII. The imbalance between AngII and Ang[1–7] relates to the damage of multiple organ systems including the lungs, heart, kidney, and liver. ACE2 plays important roles in the resolution of inflammation by regulating the balance of AngII and Ang[1–7].

ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB), the main classes of RAS-acting agents, are widely used for hypertension, heart failure, and to prevent remodeling after myocardial infarction. Moreover, they also provide remarkable target-organ protection by ameliorating inflammation, endothelial damage, fibrosis, and oxidative stress.⁸ However, there is little evidence supporting the protective effect of ACEI and ARB in patients with respiratory failure except for a small-sample retrospective study involving a total of 182 patients, which showed that ACEI exposure significantly improved the survival rates but prolonged the MV and ICU stay time in patients with ARDS.⁹ ACEI and ARB treatment could significantly elevate the expression level of ACE2 in different types of tissue, which might be a mechanism of inflammation treatment and organ protection.¹⁰

In the present study, we hypothesized that ACEI and ARB exposure might provide protective effects for patients with ARF. To this end, we conducted a retrospective observational study using a large, publicly available database aimed to investigate whether there is a difference in mortality rates in patients with ARF according to the pre-hospital exposure of ACEI and ARB.

The present manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines.¹¹

2 | METHODS

2.1 | Study design

Our study was a retrospective observational research, using publicly available data from a large, global database of Beth Israel Deaconess Medical Center (Boston, Massachusetts), named Medical Information Mart for Intensive Care III v1.4 (MIMIC-III v1.4).¹² The MIMIC-III v1.4 database collects hospitalization information from all patients admitted to the ICU of Beth Israel Deaconess Medical Center from 2001 to 2012. It contains 58,976 distinct hospital admissions of 46,520 patients. The author FYP, who was responsible for data extraction, gains free access to this database after passing the examination of the National Institutes of Health (NIH) web-based course and obtaining the certification (certification No. 43025968). PgAdmin4 and PostgreSQL (version 9.6) were used to extract data.

2.2 | Selection of patients

All patients with ARF aged 18 years or older were initially included in the study. ARF was identified using the International classification of diseases-9 (ICD-9) code “51881.” For patients readmitted to this hospital, only information from the first hospitalization with ARF diagnosis was retained. Fifty patients were excluded for lacking all laboratory indicators or disease severity score used in present study. Included patients were subdivided into two groups according to the pre-hospital usage of ACEI and ARB: the ACEI/ARB group and non-ACEI/ARB group.

2.3 | Variable extraction

Patients' baseline characteristics were directly obtained or indirectly calculated using the admission table and patients table. The differential value between the date of birth and the admission time was used to determine the age. Comorbidities including diabetes mellitus (DM), hypertension (HT), coronary heart disease (CHD), acute or chronic heart failure (HF), and chronic kidney disease (CKD) were identified using the recorded ICD-9 codes. The details of ICD-9 codes used to screen for comorbidities are shown in Table S1.

2.4 | Exposure of ACEI/ARB and outcome

The primary exposure was the pre-hospital exposure of ACEI and ARB. The entries in the prescription table of benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, monopril, quinapril, ramipril, trandolapril, irbesartan, valsartan, candesartan, losartan, irbesartan, olmesartan, and valsartan were collected as evidence of ACEI and ARB exposure. The start time of ACEI and ARB was compared with the admission time of the patients. When the start time was earlier than the admission time, the patients were considered to be an ACEI or ARB user and included in the ACEI/ARB group. The remaining patients were included in the non-ACEI/ARB group.

The primary outcome was in-hospital mortality. Secondary outcomes included 28-day mortality, 90-day mortality, length of hospital stay (hospital-LOS), sequential organ failure assessment (SOFA) score on admission, the maximum value of lactic acid, the maximum value of creatinine and blood urea nitrogen (BUN), the minimum of oxygen saturation (SpO_2), the ratio of ventilation on the first day and during hospitalization, the percentage of vasopressors used, and acute kidney injury (AKI). In-hospital death was defined as death (represented by date of death [DOD]) before discharge (represented by discharge time); 28-day mortality and 90-day mortality were defined as death within 28 and 90 days after admission (represented by admission time), respectively. Hospital-LOS was calculated from admission time and discharge time. Ventilation included oxygen, high flow, non-invasive mechanical ventilation (NIV), invasive mechanical ventilation (IMV), and tracheostomy. Vasopressors included dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin. The definition of AKI was based on the Kidney Disease Improving Global Outcomes (KDIGO) guideline using serum creatinine (SCr) criteria; urine output criteria were not considered.¹³

2.5 | Management of abnormal values and missing data

The age of patients who were recorded over 300 years old was replaced with 91. Other abnormal values were adjusted by the winsor2 command using threshold range from 1 to 99. The indicators with more than 20% missing values were removed in the present study. When missing data were <10%, we used mean or median to replace the missing value. The remaining data (10%–20% missing) were obtained with the multiple imputation method. The details of missing values are shown in Table S2.

2.6 | Statistical analysis

Continuous variables were presented as mean \pm standard deviation (SD) or median with first quartile to third quartile according to whether they conformed to normal distributions. Student's *t*-test and the Mann-Whitney *U* test were used in the continuous variables.

Categorical variables were expressed as number and proportion. Chi-square or Fishers exact test were used in categorical variables.

A directed acyclic graph (DAG) was used to explore the possible confounders.¹⁴ DAGitty was applied to construct and analyze the causal diagrams.¹⁵ The minimal sufficient adjustment set included age, HT, DM, CKD, CHD, and HF (showed in Figure S1). Multivariate modeling of the relationship between pre-hospital ACEI/ARB exposure and in-hospital mortality was determined using a logistic regression model. All possible confounders were included into the multivariate logistic regression model. The effect of ACEI/ARB exposure was expressed by odds ratio (OR) with 95% confidence interval (CI). Variance inflation factor (VIF) method was used to test the multicollinearity. Goodness-of-fit test was applied in the logistic regression model. *E*-value sensitivity analysis was used to further evaluate the minimum strength of the unmeasured confounding that needs to eliminate the observed associations.¹⁶ The value range of *E*-value is typically from 1 to infinity, where higher *E*-value indicates that a higher degree of unmeasured confounders are needed in order to negate the association between exposure (ACEI/ARB exposure) and outcome (mortality of patients with ARF).

Propensity score matching (PSM) method¹⁷ was applied to adjust the imbalanced confounders. A multivariate logistic regression model was performed to evaluate the scores of PSM for ACEI/ARB exposure of all the patients. PSM method was performed with replacement at a 5:1 matching ratio via nearest neighbor, and a caliper width of 0.02 was used in present analysis. All possible confounders were included in the PSM method. Outcomes were regenerated from the PSM cohort, constructed with 1401 and 363 patients in both groups.

Sensitivity analyses were constructed to demonstrate the robustness of our results by changing the research subject from ARF to ARDS and the database from MIMIC III to MIMIC IV. Our screening standards for patients with ARDS in the MIMIC III database were as previously reported.¹⁸ The same inclusion and exclusion criteria as MIMIC III database were used in the MIMIC IV database. Subgroup analyses were applied in our study according to the age, gender, and all possible confounders.

All statistical analyses were performed using Stata (version 15.0; StataCorp). A two-tailed test was performed, and $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline information and clinical outcomes

A total of 5335 adult patients with ARF were included in the final analysis, including 363 ACEI/ARB users (shown in Figure 1). The baseline information is shown in Table 1. The total in-hospital mortality was 31.90%. Patients in the ACEI/ARB group were older (72.04 ± 12.23 vs. 64.44 ± 17.37 years, $p < 0.001$) and had a lower percentage of emergency admissions than the non-ACEI/ARB group

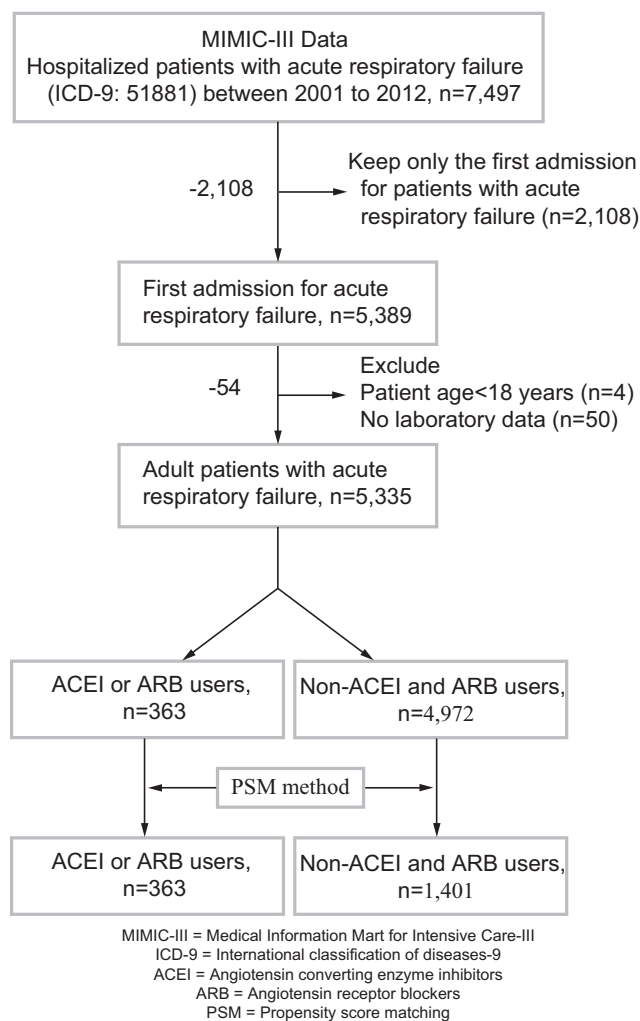


FIGURE 1 Flowchart of patient selection

(93.66% vs. 95.96%, $p = 0.035$). Patients with ACEI/ARB exposure had higher incidence of DM, HT, CHD, HF, and CKD (all $p < 0.001$).

Patients with ACEI/ARB exposure had significantly lower in-hospital mortality (22.31% vs. 32.60%, $p < 0.001$) compared with patients without ACEI/ARB exposure. Furthermore, 28- and 90-day mortality showed the same trend (both $p \leq 0.010$), with lower mortality in patients with ACEI/ARB exposure. Patients with pre-hospital ACEI/ARB exposure had longer hospital-LOS than patients without ACEI/ARB exposure did (11.4 (7.1, 20.3) days vs. 10.7 (5.6, 19.5) days, $p = 0.003$). The SOFA score on admission was slightly lower in the ACEI/ARB group than the non-ACEI/ARB exposure group (4 (3, 6) vs. 5 (3, 8), $p < 0.001$). The maximum value of serum lactate was significantly decreased in patients with ACEI/ARB exposure (2.2 (1.5, 3.3) mmol/L vs. 2.6 (1.7, 4.2) mmol/L, $p < 0.001$) compared with the non-exposure group. The minimum value of SpO₂ during hospitalization was similar between the ACEI/ARB exposure and non-ACEI/ARB exposure groups (92% (88, 94) vs. 92% (88, 95), $p = 0.270$). The percentage of ventilation on the first day and during hospitalization was lower in the ACEI/ARB exposure group (44.35% vs. 67.28%, $p < 0.001$; 85.67% vs. 89.10%, $p = 0.045$) compared with

the non-ACEI/ARB-exposure group, respectively. Patients in the ACEI/ARB group had lower percentage of vasopressor use (41.87% vs. 52.63%, $p < 0.001$), but higher percentage of AKI during hospitalization (59.78% vs. 49.72%, $p < 0.001$), compared with the non-ACEI/ARB group.

3.2 | Association between ACEI/ARB exposure and in-hospital mortality in patients with ARF

The OR of ACEI/ARB exposure was 0.59 (95% CI 0.46–0.77, $p < 0.001$) in multivariable logistic models (Table 2). After adjusting for possible confounders, the adjusted OR was 0.56 (95% CI 0.43–0.72, $p < 0.001$). The *E*-values of the point estimation and lower 95% confidence bound for the association between in-hospital mortality of ARF and pre-hospital ACEI/ARB exposure were 2.97 and 2.12, respectively (Figure 2). Subgroup analysis was performed according to age, gender, and all possible confounders (Figure 3). All the subgroup analyses supported that ACEI/ARB acted as protective factors for adult patients with ARF, except for the young patients' subgroup (<65 years). For young patients, the ACEI/ARB exposure did not affect the in-hospital mortality (OR 0.79, 95% CI 0.48–1.30, $n = 2494$, $p = 0.353$), whereas ACEI/ARB exposure significantly reduced the in-hospital mortality of elderly patients with ARF (OR 0.47, 95% CI 0.34–0.63, $n = 2841$, $p < 0.001$). However, no significant interacting effect was found between ACEI/ARB exposure and age (p for interaction = 0.082).

3.3 | Outcome after propensity score matching

After PSM, 1764 patients, including 363 ACEI/ARB users, were matched by 5:1 matching ratio (Table 3). The PSM method effectively reduced the bias of possible confounding factors (Table 3). No significant difference was found in all matched factors ($p > 0.05$) except for the percentage of patients with HF ($p = 0.040$). In the matched cohort, the in-hospital mortality (22.31% vs. 34.62%, $p < 0.001$), 28-day mortality (22.59% vs. 35.26%, $p < 0.001$), and 90-day mortality (33.88% vs. 44.47%, $p < 0.001$) were significantly lower in the ACEI/ARB exposure group compared with the non-ACEI/ARB exposure group, which was the same as with the original data. Both groups had similar hospital-LOS (11.4 days (7.1, 20.3) in the ACEI/ARB group vs. 11.2 days (6.1, 19.8) in the non-ACEI/ARB group, $p = 0.052$). The level of SOFA score on admission (4 (3, 6) vs. 6 (4, 8), $p < 0.001$) and the maximum lactate level (2.2 (1.5, 3.3) mmol/L vs. 2.5 (1.6, 4.0) mmol/L, $p = 0.006$) were both decreased in patients with ACEI/ARB exposure compared to those without ACEI/ARB exposure. Minimum SpO₂, proportion of ventilation on the first day of hospitalization, and vasopressor use during hospitalization in the matched cohort was similar to the original cohort. Notably, no significant differences in AKI ratio and ventilation percentage during hospitalization were found in the matched cohort ($p = 0.121$ and $p = 0.175$, respectively). Meanwhile, patients with ACEI/ARB exposure had lower serum

TABLE 1 Baseline information and outcomes of all patients with ARF

	All patients (n = 5335)	Non-ACEI/ARB (n = 4972)	ACEI/ARB (n = 363)	p-Value
Age, years	64.96 ± 17.18	64.44 ± 17.37	72.04 ± 12.23	<0.001
Male, %	2881 (54.00)	2695 (54.20)	186 (51.24)	0.274
Emergency admission, %	5111 (95.80)	4771 (95.96)	340 (93.66)	0.035
Comorbidities				
DM, %	1400 (26.24)	1246 (25.06)	154 (42.42)	<0.001
HT, %	1996 (37.41)	1813 (36.46)	183 (50.41)	<0.001
CHD, %	848 (15.90)	741 (14.90)	107 (29.48)	<0.001
HF, %	1884 (35.31)	1666 (33.51)	218 (60.06)	<0.001
CKD, %	732 (13.72)	658 (13.23)	74 (20.39)	<0.001
Clinical outcomes				
In-hospital mortality, %	1702 (31.90)	1621 (32.60)	81 (22.31)	<0.001
28-day mortality, %	1718 (32.20)	1636 (32.90)	82 (22.59)	<0.001
90-day mortality, %	2148 (40.26)	2025 (40.73)	123 (33.88)	0.010
Hospital-LOS, days	10.8 (5.7, 19.6)	10.7 (5.6, 19.5)	11.4 (7.1, 20.3)	0.003
SOFA score on admission	5 (3, 8)	5 (3, 8)	4 (3, 6)	<0.001
Minimum SpO ₂ , %	92 (88, 95)	92 (88, 95)	92 (88, 94)	0.270
Maximum creatinine, mg/dl	1.2 (0.8, 2.1)	1.2 (0.8, 2.1)	1.2 (0.9, 1.8)	0.493
Maximum BUN, mg/dl	27 (17, 45)	27 (17, 45)	26 (18, 44)	0.752
Maximum lactic acid, mmol/L	2.5 (1.6, 4.1)	2.6 (1.7, 4.2)	2.2 (1.5, 3.3)	<0.001
Ventilation on first day, %	3506 (65.72)	3345 (67.28)	161 (44.35)	<0.001
Ventilation during hospital, %	4741 (88.87)	4430 (89.10)	311 (85.67)	0.045
Vasopressors, %	2769 (51.90)	2617 (52.63)	152 (41.87)	<0.001
AKI, %	2689 (50.40)	2472 (49.72)	217 (59.78)	<0.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARB, angiotensin receptor blockers; BUN, blood urea nitrogen; CHD, coronary heart disease; CKD, chronic kidney disease; DM, diabetes mellitus; HF, acute or chronic heart failure; HT, hypertension; LOS, length of stay; SOFA, Sequential Organ Failure Assessment.

Data displayed as mean(SD), median(first quartile, third quartile) or n(%) as appropriate.

Bold $p < 0.05$ indicate statistical significance.

TABLE 2 Relationship between pre-hospital ACEI/ARB exposure and in-hospital mortality in patients with ARF using an extended model approach

	Odds ratio of ACEI exposure	95% confidence interval	p-Value
Model 1	0.59	0.46–0.77	<0.001
Model 2	0.56	0.43–0.72	<0.001

Note: Adjusted covariates: Model 1 = pre-hospital ACEI or ARB exposure. Model 2 = Model 1 + (age, diabetes, hypertension, coronary heart disease, acute or chronic heart failure, chronic kidney disease). The mean variance inflation factor was 1.72 and the p -value of the goodness-of-fit was 0.44 for Model 2.

creatinine and BUN levels in the matched cohort (1.2 (0.9, 1.8) mg/dl vs. 1.3 (0.9, 2.2) mg/dl, $p = 0.003$ and 26 (18, 44) mg/dl vs. 31 (20, 50) mg/dl, $p < 0.001$), respectively, which did not occur in the original cohort.

3.4 | Sensitivity analysis

Acute respiratory distress syndrome is a common clinical syndrome of respiratory failure. In order to test the robustness of our findings, we further evaluated the efficacy of ACEI/ARB in patients with ARDS from the MIMIC III database. In total, 4323 ARDS patients were screened out from the MIMIC III database, including 449 patients with ACEI/ARB exposure. In the original cohort, ACEI/ARB exposure significantly reduced the in-hospital, 28-day, and 90-day mortality ($p < 0.001$, <0.001 , and $=0.001$, respectively) (shown in Table S3). In the logistic regression model, ACEI/ARB showed efficient protective effect on ARDS after adjusting the confounders (OR 0.61, 95% CI 0.45–0.84, $p = 0.002$) (shown in Table S4). The effect on mortality of patients with ARDS was still robust in the PSM cohort (all $p < 0.05$) (shown in Table S5). It should be noted that the differences in SOFA score, creatinine, BUN, lactate, and vasopressors using percentage between ACEI/ARB exposure versus non-exposure groups found in

the ARF analysis did not occur in the ARDS cohort. However, patients with ARDS in the ACEI/ARB group were significantly more likely to develop AKI (67.19% vs. 55.24%, $p < 0.001$) compared with the non-ACEI/ARB exposure group, a finding that was not explored in the ARF cohort from MIMIC III database (shown in Table S5).

MIMIC IV (version 1.0) is an updated database of MIMIC III including critical care database from 2008 to 2019.¹⁹ There were 5955 patients with ARF in the MIMIC IV database, including 156 patients with ACEI/ARB exposure. Compared with patients in the non-ACEI/ARB group, patients with ACEI/ARB exposure had lower in-hospital, 28-day, and 90-day mortality, but no statistical difference was found in original cohorts (all $p > 0.05$) (shown in Table S6). In the logistic regression model, the point estimation of OR was 0.78, but no significant difference was found (95% CI 0.54–1.12, $p = 0.182$) (shown in Table S7). Similar result of mortality was obtained in the

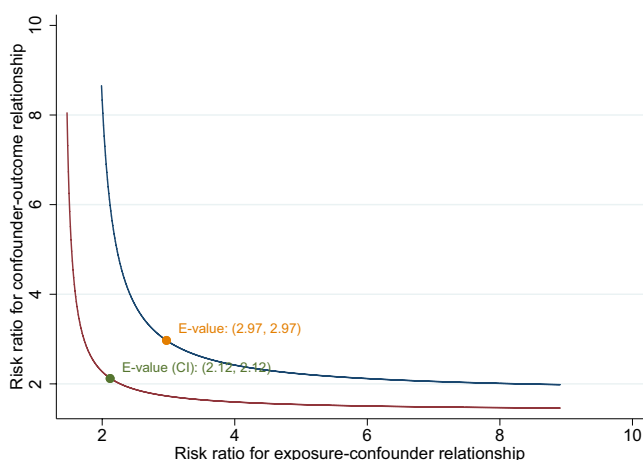


FIGURE 2 E-value for the lower 95% CI and point estimation in in-hospital mortality of patients with acute respiratory failure

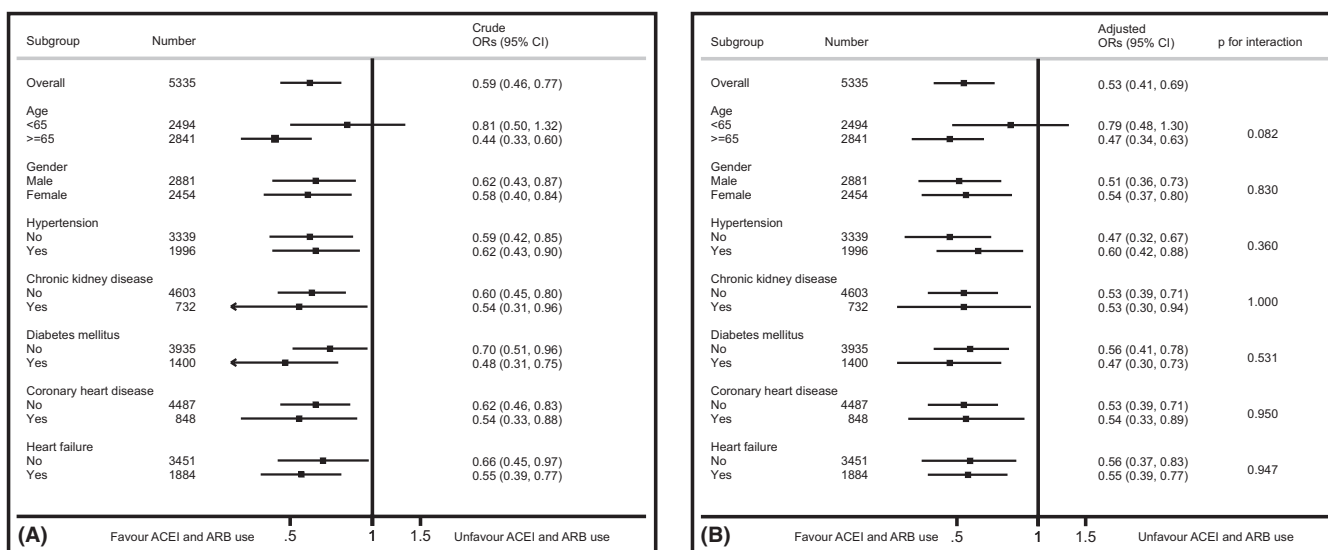
matched cohort (all $p > 0.05$) (shown in Table S8). Interestingly, patients with ACEI/ARB exposure had longer hospital-LOS compared to those without ACEI/ARB exposure (11.1 (7.0, 18.8) days vs. 10.0 (5.7, 16.0) days, $p = 0.015$); meanwhile, the difference of maximum lactic acid disappeared in the MIMIC-IV database ($p = 0.231$) (shown in Table S8).

3.5 | Is age a key factor affecting the protective effect of ACEI/ARB?: A post hoc analysis

The different effect of ACEI/ARB in the subgroup analysis of young and elderly patients (using 65 years as the cut-off point) attracted our attention, although no statistical interactive effect was found ($p = 0.082$; Figure 3). We further evaluated the effect of ACEI/ARB in young and elderly patients with ARF/ARDS, respectively (shown in Tables S9–S14). Notably, ACEI/ARB exposure reduced the in-hospital, 28-day, and 90-day mortality in elderly patients with ARF (shown in Table S10) and elderly patients with ARDS (shown in Table S12) from MIMIC-III database in both original and matched cohorts. In MIMIC-IV database, ACEI/ARB exposure significantly reduced 28-day mortality in elderly patients with ARF (shown in Table S14). Among all cohorts, ACEI/ARB lost its protective effect in young patients (all p of mortality > 0.05) (shown in Tables S9, S11, S13).

4 | DISCUSSION

In this large cohort of patients with ARF, the pre-hospital ACEI/ARB exposure was found to be associated with decreased in-hospital, 28-day, and 90-day mortality before and after removing the interference of possible confounding factors using PSM. Furthermore,



OR = Odds ratio; CI = Confidence interval; ACEI = Angiotensin converting enzyme inhibitors; ARB = Angiotensin receptor blockers

FIGURE 3 Subgroup analysis of the relationship between pre-hospital ACEI/ARB exposure and in-hospital mortality in patients with acute respiratory failure. (A) Indicates the crude ORs without adjusting, and (B) indicates the ORs adjusted by Model 2 mentioned in Table 3

subgroup analysis indicated that the use of ACEI/ARB could reduce the risk of death, except for patients younger than 65 years of age. The results were still robust in the ARDS cohort. Our findings suggested that pre-hospital exposure of ACEI and ARB plays a protective role in adult patients with ARF.

Acute respiratory failure is a serious and heterogeneous complication in hospitalized patients caused by different conditions such as pneumonia, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and ARDS. To date, oxygen therapy and IMV or NIV are still the mainstays of therapy for ARF, especially for patients with severe cases. Thus, the majority of therapeutic research on ARF focused on ventilation, whereas study of the effectiveness of drug intervention in ARF is limited.

Epidemiological studies indicate that infection is the leading cause of ARF, especially pneumonitis (23.7%),²⁰ and pneumonitis (59.4%) and extra-pulmonary sepsis (16.0%) are the most common risk factors for ARDS.³ Since inflammation and endothelial injury have been proven to be the key pathophysiological mechanisms of organ damage in infectious diseases,²¹ clinical studies have been performed to investigate the protective effects of several well-known anti-inflammatory agents including aspirin, statin, and heparin on ARF, but failed to show a significant improvement in survival and prognosis of patients with acute lung injury(ALI)/ARDS.²²⁻²⁴

Notably, ACEI and ARB have recently been shown to provide protection against chronic lung injuries by inhibiting pulmonary fibrosis in end-stage ARDS and Idiopathic Pulmonary Fibrosis (IPF).^{25,26} In addition, a prospective study suggested that 6 months of ACEI exposure could effectively improve lung function indexes through the enhancement of respiratory muscle strength in patients with heart failure.²⁷ In this study, we demonstrated that pre-hospital ACEI or ARB exposure was related to lower in-hospital, 28-day, and 90-day mortality of patients with ARF in both unmatched and matched cohort using PSM. Subgroup analysis and sensitivity analysis demonstrated that our results were robust. Our finding was consistent with a previous clinical study, which included 182 adult patients with ARDS.⁹ However, our study has a much larger sample size, and subgroup analysis, sensitivity analysis, and PSM method matching of multiple confounding factors were used to improve the validity of the conclusions. A retrospective cohort study conducted in the United States evaluated the relationship between different kinds of antihypertensive medications and prognosis of acute viral respiratory illness (AVRI).²⁸ Outpatient use of ACEI and ARB was associated with lower mortality (OR 0.78 (95% CI 0.74–0.83) with ACEI and OR 0.64 (95% CI 0.61–0.68) with ARB) compared with other antihypertensive medications.

Prior studies attempted to investigate the mechanisms of protective effect of ACEI and ARB on ARF. Data from recent pre-clinical research showed that ACEI treatment improved lung pathological injury via reducing oxidative stress and inflammatory reaction in a pre-clinical sepsis model.²⁹ In an oleic acid-induced ARF model, captopril prevented severe acute lung injury via inhibiting NF- κ B and protecting intercellular adhesion.³⁰ Besides ACEI treatment could reduce endothelial cell damage in a hypoxia environment via

inhibiting apoptosis.³¹ The effect of ACEI/ARB on the ACE2 expression level is worthy of attention. Both ACEI and ARB have been proven to increase ACE2 expression in pre-clinical study.¹⁰ ACE2 protein was highly expressed in lung alveolar epithelial cells as well as the vascular endothelial cells of lung tissue.³² The long-term use of ACEI/ARB could increase the expression level of ACE2 in lung tissue.^{33,34} Since ACE2 plays an important role in the degradation of AngII, an effective pro-inflammatory factor, patients with ACEI/ARB exposure would have the greater ability to fight against lung inflammation during ARF. Further studies are needed to unveil the molecular mechanism of this process.

Intriguingly, the protective effect of ACEI and ARB in patients with ARF was different between young and elderly patients. Although there was no interactive effect of age, the positive effect of ACEI/ARB disappeared in young patients among all cohorts. This difference may be related to the lower proportion of ACEI and ARB exposure in young patients than that in elderly, which would affect the power of the statistical analysis. In addition, the elderly may be exposed to ACEI and ARB for a longer time due to the greater proportion of patients with chronic diseases, which may result in a higher level of ACE2 expression and the better protective effect.³³⁻³⁵ Further studies are needed to explore whether age is a direct influencing factor of the protective effects of ACEI/ARB therapy.

One major concern of the study was that confounding factors, such as HT and severe kidney disease, the major indications and contraindications for ACEI and ARB, might affect the results. To balance the distribution of confounding factors, PSM method was used and conclusions were still robust. In subgroup analysis, the data supported the application of ACEI and ARB in patients with ARF both in hypertension positive and negative subgroups, which indicated that the protective effect of ACEI or ARB may not be mediated by blood pressure control. As we know, ACEIs inhibit the conversion of Ang I to Ang II, reducing production of Ang II, an inflammatory molecule, thereby ameliorate inflammation, oxidative stress, and endothelial damage. ARBs are the AT1R-specific blocking drugs and can block the binding of Ang II to AT1R, thereby blocking the RAS system.^{36,37} This further supported our speculation that the contribution of ACEI/ARB exposure to the improvement of survival might involve anti-inflammatory actions and effects on endothelium protection rather than blood pressure control. Meanwhile, ACEI and ARB exposure was significantly associated with decreased mortality in both CKD positive and negative groups. However, it cannot be ignored that CKD is a contraindication to both ACEI and ARB therapy, and kidney dysfunction may lead to the deregulation of the hormone levels of the RAS.³⁸ Whether ACEI/ARB is suitable for patients with CKD still needs to be decided according to the actual situation of individual patients. The interpretations of the CKD subgroup analysis should be made more cautiously due to the small sample size.

Acute respiratory distress syndrome is defined as a subtype of ARF. In recent years, more and more studies have moved toward the Berlin definition of ARDS published in 2012.³⁹ In contrast to ARF, ARDS caught more attention and we think that using ARDS for investigation may make more sense than using ARF. However,

	All patients (n = 1764)	Non-ACEI/ARB (n = 1401)	ACEI/ARB (n = 363)	p-Value
Confounders				
Age, years	71.54 ± 12.81	71.41 ± 12.96	72.04 ± 12.23	0.400
DM, %	696 (39.46)	542 (38.69)	154 (42.42)	0.194
HT, %	903 (51.19)	720 (51.39)	183 (50.41)	0.740
CHD, %	489 (27.72)	382 (27.27)	107 (29.48)	0.402
HF, %	975 (55.27)	757 (54.03)	218 (60.06)	0.040
CKD, %	344 (19.50)	270 (19.27)	74 (20.39)	0.633
Clinical outcomes				
In-hospital mortality, %	566 (32.09)	485 (34.62)	81 (22.31)	<0.001
28-day mortality, %	576 (32.65)	494 (35.26)	82 (22.59)	<0.001
90-day mortality, %	746 (42.29)	623 (44.47)	123 (33.88)	<0.001
Hospital-LOS, days	11.3 (6.3, 20.0)	11.2 (6.1, 19.8)	11.4 (7.1, 20.3)	0.052
SOFA score on admission	5 (3, 8)	6 (4, 8)	4 (3, 6)	<0.001
Minimum SpO ₂ , %	92 (88, 94)	92 (88, 94)	92 (88, 94)	0.712
Maximum creatinine, mg/dl	1.3 (0.9, 2.2)	1.3 (0.9, 2.2)	1.2 (0.9, 1.8)	0.003
Maximum BUN, mg/dl	30 (20, 49)	31 (20, 50)	26 (18, 44)	<0.001
Maximum lactic acid, mmol/L	2.4 (1.6, 3.8)	2.5 (1.6, 4.0)	2.2 (1.5, 3.3)	0.006
Ventilation on first day, %	1062 (60.20)	901 (64.31)	161 (44.35)	<0.001
Ventilation during hospital, %	1548 (87.76)	1237 (88.29)	311 (85.67)	0.175
Vasopressors, %	936 (53.06)	777 (55.46)	152 (41.87)	<0.001
AKI, %	991 (56.18)	774 (55.25)	217 (59.78)	0.121

TABLE 3 The baseline information and outcomes after propensity score matching in patients with ARF

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARB, angiotensin receptor blockers; BUN, blood urea nitrogen; CHD, coronary heart disease; CKD, chronic kidney disease; DM, diabetes mellitus; HF, acute or chronic heart failure; HT, hypertension; LOS, length of stay; SOFA, Sequential Organ Failure Assessment.

Data displayed as mean(SD), median(first quartile, third quartile) or n(%) as appropriate.

Age, DM, HT, CHD, HF and CKD were considered as the covariates and included in present propensity score matching (PSM) method. A multivariate logistic regression model was used to estimate the patient's propensity scores. A 5:1 nearest neighbor match was applied with a caliper width of 0.02.

Bold $p < 0.05$ indicate statistical significance.

the ICD9 codes used in MIMICIII database for disease diagnoses still lack a code for ARDS. Moreover, most ARF cases in the database lacked FiO₂ data, which makes it impossible to diagnose ARDS according to the Berlin definition.

Several recent studies investigating ARDS using the MIMICIII database attracted our attention,^{18,40-45} especially their screening criteria for ARDS patients. There were two mainstream screening strategies, based on ICD-9 code and the Berlin definition. ICD-9 = "518.82" or ICD-9 = "518.5" was regarded as the diagnostic standard for ARDS.⁴⁰ However, these codes representing pulmonary insufficiency and respiratory failure are not in agreement with the definition of ARDS. Berlin definition was more widely

used than ICD-9 code in these studies.^{18,41-45} Unfortunately, the large number of missing information for oxygen concentration (itemid = "50816") or oxygen flow (itemid = "50815") in the MIMICIII database, 362,668/490,629 (73.92%) of oxygen concentration and 478,321/490,629 (97.49%) of oxygen flow (Table S15), make it difficult to calculate the PaO₂/FiO₂ ratio which is the core factor of Berlin definition. We recognized that using the nearest FiO₂ to replace the missing values might be a good alternative.¹⁸ However, the frequent modulation of oxygen concentration may lead to a huge deviation between the actual value and the nearest one. What's more, MIMICIII database does not provide information about triggers and acute onset, which are important for ARDS diagnosis according to

Berlin definition. For these reasons, we used ICD-9 code for ARF screening to ensure rigor and high level of accuracy of our target population. In the present study, patients with ARDS were included in the sensitivity analysis to improve credibility of our conclusion. Due to the lack of ICD-9 code for ARDS, we screened for patients with ARDS according to a previous study,¹⁸ which resulted in the identification of a higher number of patients with ARDS than total number of patients with ARF. In short, the general conclusion of patients with ARDS was similar with what we found in the ARF cohort. Pre-hospital ACEI and ARB exposure reduced mortality in patients with ARDS or ARF. We also need to pay more attention to whether the pre-hospital use of ACEI/ARB was really related to the AKI occurrence in patients with ARDS that we found in sensitivity analysis.

As a retrospective database study, the conclusions of our study need to be interpreted cautiously and the generalizability of the conclusion is limited. Although we found that the exposure of ACEI and ARB might effectively reduce the mortality of patients with ARF in this specific cohort, ARF is not an adaptive condition for the use of ACEI or ARB so far. Taking medicine according to the indications and contraindications is an essential principle of pharmacotherapy. Moreover, whether taking ACEI or ARB in the acute phase of ARF reduces mortality is unclear because we focused on the ACEI and ARB exposure in the pre-hospital situation rather than ACEI and ARB use during the hospitalization. Perhaps for patients who are at risk of respiratory failure, ACEI and ARB could be given priority when the patients meet the indications for treatment and have no contraindications.

The limitations of this study need to be acknowledged. The influence of confounding factors on the outcome is an annoying problem. Although we used PSM to minimize the bias as much as possible, it still cannot be completely eliminated. In addition, the causal relationship between ACEI/ARB exposure and mortality could not be confirmed in the present study through PSM method, subgroup analyses, and sensitivity analysis due to the retrospective nature of the study. What's more, the completeness of the data is also an important issue that should not be ignored. It would be ideal to know whether the database used in the present study includes the pre-hospital drug record of all patients with ARF and whether the patients in the non-ACEI/ARB group really have no history of ACEI/ARB exposure. Unfortunately, since MIMIC-III/IV is a public database rather than the cohort constructed with our own patients, it is hard to draw any qualitative conclusion on the protective effect of ACEI/ARB in patients with ARF using only this database. However, our findings suggested that the relationship between ACEI/ARB and prognosis of ARF is worthy of further investigation. A strictly designed randomized controlled trial should be the only way to solve the above two problems.

5 | CONCLUSION

Pre-hospital ACEI and ARB exposure were associated with reduced mortality in adult patients with ARF. A high-quality randomized controlled trial is needed to further confirm our findings.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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