BMC Pulmonary Medicine

RESEARCH

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The association between the use of angiotensin-converting enzyme inhibitors /angiotensin receptor blockers and the development of ventilator-associated pneumonia in the intensive care unit: a retrospective cohort study

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Abstract

Background This study was to examine the association between treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and the risk of developing ventilator-associated pneumonia (VAP) among patients receiving mechanical ventilation (MV) in the intensive care unit (ICU).

Methods Utilizing a retrospective cohort approach, the data were extracted from the Medical Information Mart for Intensive Care IV database. VAP diagnoses were ascertained through the international classification of disease codes recorded in the database. Both univariate and multivariable logistic regression analyses were conducted to assess the association between ACEI or ARB use and VAP. Subgroup analyses were performed to evaluate the impact of comorbidities (AKI, renal failure, diabetes, hypertension, and sepsis), simplified acute physiology score II (SAPS II), as well as the use of vasopressors and antibiotics on this association. Odds ratios (ORs) with 95% confidence intervals (CIs) were used as the evaluation metrics.

Results The study comprised 8,888 patients, with 897 (10.09%) experiencing VAP. The analysis revealed that patients on ACEI or ARB therapy had a lower risk of developing VAP (OR: 0.79, 95% CI: 0.62–0.99, $P=0.047$). Subgroup analyses revealed that the protective effect was observed in patients with AKI (OR: 0.70, 95% CI: 0.52–0.94, $P=0.020$), renal failure (OR: 0.14, 95% CI: 0.02–0.84, $P=0.032$), and diabetes (OR: 0.64, 95% CI: 0.43–0.94, $P=0.024$), as well as in those receiving vasopressors (OR: 0.67, 95% CI: 0.49–0.92, $P=0.012$), and antibiotics (OR: 0.74, 95% CI: 0.57–0.96, $P=0.021$). No significant difference in VAP development was observed between patients treated with ACEI versus ARB (OR: 0.84, 95% CI: 0.49–1.47, $P=0.547$).

Conclusion This study's findings suggest a substantial association between the use of ACEIs or ARBs and reduced development of VAP, particularly among patients with specific comorbidities and those on vasopressor and antibiotic

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therapy. This study may educate the ICU team on the potential benefits of ACEIs and ARBs in preventing VAP, emphasizing the importance of considering these medications in the overall treatment plan.

Keywords Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, Ventilator-associated pneumonia, Intensive care unit, MIMIC database

Background

The application of mechanical ventilation (MV) in the intensive care unit (ICU) for critically ill patients represents a standard therapeutic intervention [1, 2]. However, ventilator-associated pneumonia (VAP) is one of the most prevalent healthcare-acquired infections in the ICU environment [3, 4], defined as pneumonia that develops in ICU patients who have been mechanically ventilated for at least 48 h [5]. The reported incidence of VAP is around 55.3% [6]. VAP leads to prolonged stays in the ICU and increased hospitalization costs, and it is a significant cause of mortality among critically ill patients [7]. Therefore, exploring the factors associated with the risk of developing VAP in the ICU is critical for prevention, early diagnosis, and effective treatment.

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used antihypertensive drugs that play a crucial role in the management of hypertension [8]. Beyond blood pressure-lowering effects, ACEI and ARBs have also improved short-term outcomes in hospitalized and ICU patients [9–12]. Previous studies have indicated that the use of ACEI and ARBs was associated with a reduced risk of community-acquired pneumonia (CAP) occurrence [13] and hospitalization [14, 15]. In a study conducted among patients with chronic obstructive pulmonary disease (COPD), compared to ACEI, the utilization of ARBs was associated with a lower risk of pneumonia and severe pneumonia occurrence [16]. The potential mechanisms by which ACEI and ARBs reduce the risk of pneumonia may involve the modulation of immune responses [17] and attenuation of lung injury [18]. By inhibiting the effects of angiotensin II, both ACEIs and ARBs can reduce the production of pro-inflammatory cytokines [19], which are key mediators in the inflammatory response and have been implicated in the pathogenesis of pneumonia. Although the benefits of ACEI and ARB in the treatment of several diseases are widely recognized, studies on whether these drugs have an impact on the risk of developing VAP remain relatively limited.

Therefore, this study aims to investigate the association between ACEI or ARB use and the risk of VAP in patients with MV in the ICU. This study may provide clinicians with guidelines on the use of ACEI/ARB in ICU patients, as well as directions for future research aimed at improving strategies for the prevention and management of VAP.

Methods

Study design and selection of patients

The study was a retrospective cohort design, and collected data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database from the period 2008 to 2019: https://mimic.mit.edu/docs/iv/. The MIMIC database is a collaborative effort published by the Computational Physiology Laboratory at the Massachusetts Institute of Technology (MIT, Cambridge, MA, USA), Beth Israel Deaconess Medical Center (BIDMC, Boston, MA, USA), and Philips Medical. This database compiles and organizes clinical diagnosis and treatment information from over 40,000 actual patients, in the ICU at BIDMC, since the year 2001. The inclusion criteria were: (1) Patients aged $\geq$ 18 years old; (2) Patients who have undergone continuous MV for a duration exceeding 48 h; (3) Information for usage of ACEI or ARB at admission. Exclusion criteria included patients who were not evaluated for VAP. All patient information within the database was stripped of identifiers to ensure privacy protection. As a result, the requirement for obtaining informed consent was waived. Utilization of the MIMIC database for this study was approval by the review boards of MIT and the BIDMC. Consequently, it was determined that there was no requirement to seek supplementary ethical approval from the People's Hospital, Yanliang District.

Data collection

The dataset extracted from the MIMIC database encompassed a range of information, including (1) Baseline characteristics:age (years), gender, race, comorbidities [diabetes, hypertension, trauma, liver failure, renal failure, sepsis, and acute kidney injury (AKI)]; (2) Vital signs: heart rate (bpm), temperature (Deg.C), mean blood pressure (MBP, mmHg), respiratory rate (bpm); (3) Laboratory value: peripheral capillary oxygen saturation (SpO_2, %), hematocrit (%), white blood cell (WBC, K/uL), platelet (K/uL), red cell distribution width (RDW, %), creatinine (mg/dL), glucose (mg/dL), blood urea nitrogen (BUN, mg/dL), phosphate (mg/dL), anion gap (mEq/L), urine output mL); (4) Scoring systems: simplified acute physiology score II (SAPS II); (5) Intervention: MV duration (hours), antibiotics, Propofol, Midazolam, Dexmedetomidine, and vasopressor use.

Definitions and measurements

In the MIMIC-IV database, patients diagnosed with VAP were identified using the following classification codes: international classification of diseases (ICD)-9 codes 4957 and 99,731, as well as the ICD-10 code J95851. The use of ACEI (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, monopril, quinapril, ramipril, trandolapril) and ARB (irbesartan, valsartan, candesartan, losartan, irbesartan, olmesartan, and valsartan, telmisartan) was identified by keywords in the database, with the period from admission to the ICU until the first 48 h of continuous MV (baseline). The definitions and measurements of other potential covariates are shown in Supplementary File 1.

Statistical analysis

Continuous data that were normally distributed were described using the mean (standard deviation) [Mean ± SD], and comparisons between groups were checked using the independent samples t-test. Non-normally distributed continuous data were presented as the median and interquartile range [M (Q1, Q3)], with group comparisons performed using the Mann–Whitney U test. Categorical data were expressed as the number of cases and the proportion [N (%)], and comparisons between groups were conducted using the chi-square test. Rank data were compared by the rank sum test. To address missing data in the variables, multiple imputation techniques were applied (Supplementary Table 1). Subsequent sensitivity analyses (Supplementary Table 2) were carried out to evaluate the consistency of the outcomes pre- and post-imputation, thereby determining the influence of the imputation process on the research results.

For the selection of covariates for the association between the use of ACEI or ARBs and the risk of VAP, a univariate logistic regression model was employed to identify variables that could potentially influence the risk of VAP. The variables with $P<0.05$ were considered as the covariates including age, gender, race, ventilation duration, antibiotics, Propofol, Midazolam, Dexmedetomidine, vasopressor use, SAPSII, Trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output. Subsequently, the cohort was narrowed down by excluding patients who did not receive ACEI or ARB. Another round of univariate logistic regression was conducted to select covariates for the outcome of the comparative analysis of association with VAP in patients using ACEI and ARB.. The variables with $P<0.05$ were included as covariates, which involved age, ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and platelet count. Additionally, considering the clinical significance of gender and race, these variables were also included as covariates. The univariate (adjusted for none) and multivariable (adjusted for covariates) logistic regression models were employed to explore the association between the use of ACEI or ARBs and the risk of VAP. To ensure the reliability of our multivariable models, we employed the variance inflation factor (VIF) to test for multicollinearity among the variables. A VIF threshold of 10 was used to identify variables that may be collinear and to guide decisions on variable retention in the model (Supplementary Table 3). Subgroup analyses were conducted based on whether the patients suffered from AKI, renal failure, diabetes, hypertension, sepsis, or SAPSII, and based on whether the patients used vasopressors and antibiotics. The likelihood ratio (LR), Wald test, and score test were employed to evaluate the statistical significance of the models, with their respective *P*-values reported in Supplementary Table 4. These tests demonstrated statistical significance, affirming the model's validity. Additionally, the area under the curve (AUC) value of 0.784 (Supplementary Fig. 1) provided an indication of the model's discriminative power. In addition, patients were matched on the calculated propensity scores using a 1:1 ratio. Evaluation indexes were reported as odds ratios (ORs) with 95% confidence intervals (CIs). All statistical tests were two-tailed, with a significance level set at $\alpha=0.05$. Data cleaning, handling of missing values, and statistical analysis of the models were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Population selection process and characteristics of included populations

A total of 53,538 records of patients at ICU admission were identified from the MIMIC IV database. After exclusions, the final sample was 8,888. Figure 1 illustrates the patients' selection process. Among the 8,888 individuals included, 897 (10.09%) developed VAP. In the group not receiving either ACEI or ARB, 800 out of 7,486 patients (10.69%) developed VAP. In the group receiving either ACEI or ARB, 97 out of 1,402 patients (6.92%) developed VAP. Table 1 presents a comparative analysis of various indicators based on the grouping of patients who did not use either ACEI or ARBs in conjunction with those who used ACEI or ARBs. The mean age was 65.05 ± 16.33 years. The sample comprised 3,946 females (44.40%) and 4,942 males (55.60%). Within the group not receiving either ACEI or ARBs, there were 3,359 females (44.87%) and 4,127 males (55.13%). In the group receiving ACEI or ARBs, the count was 587 females (41.87%) and 815 males (58.13%). For the overall sample, the median ventilation duration was 70.05 (57.00, 99.00) hours. Out

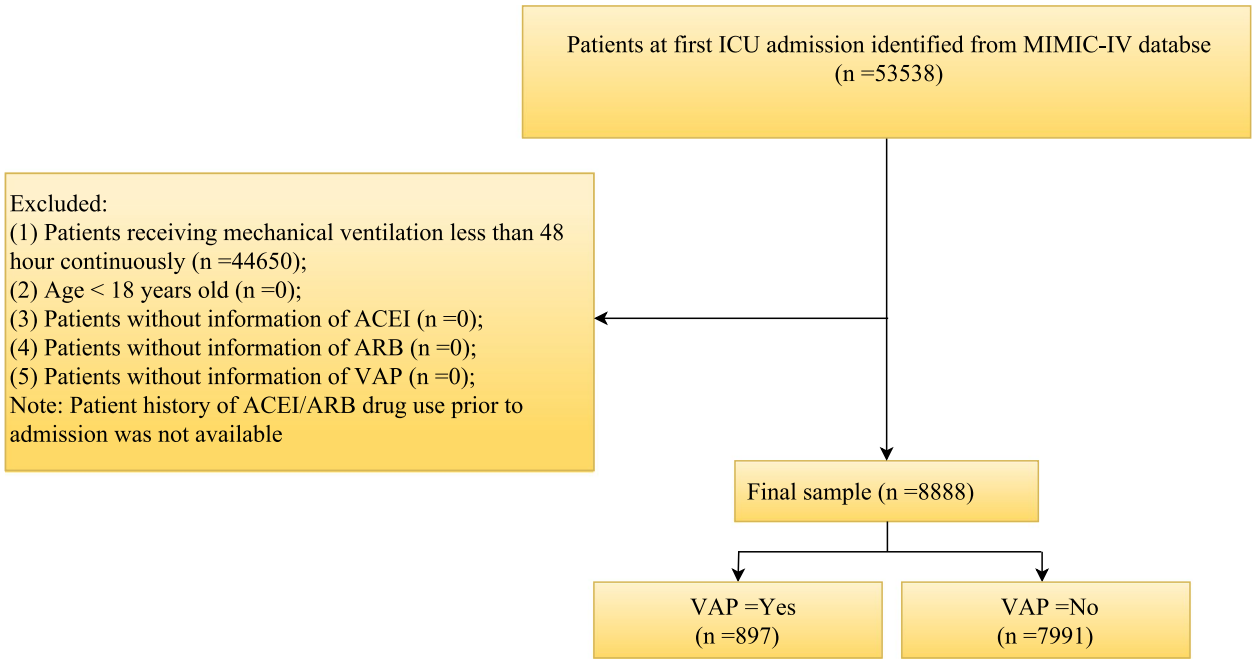

Fig. 1 The flow diagram of the patient's selection process

of the total patient population, 1,749 (19.68%) did not receive antibiotics, while a substantial majority, 7,139 patients (80.32%), were treated with antibiotics. There were significant differences between patients who used ACEI or ARBs and patients who did not use either ACEI or ARB in age, gender, race, ventilation duration, antibiotics use, Midazolam use, vasopressor use, VAP risk, SAPSII, diabetes, hypertension, trauma, liver failure, sepsis, heart rate, temperature, MBP, respiratory rate, WBC, platelet, RDW, phosphate, anion gap, and urine output (each $P<0.05$). The characteristics of included populations after propensity score matching (PSM) are shown in Supplementary Table 5. Supplementary Fig. 2 illustrates the distribution of the Logit of Propensity Score in the treatment and control groups with respect to patients with the use of ACEI or ARB and patients without the use of ACEI or ARB before and after PSM. Supplementary Fig. 3 shows the distribution of the Logit of Propensity Score in the treatment and control groups that compared the use of ACEI and ARB.

Analysis of the association between the use of ACEI or ARBs and the development of VAP

Table 2 presents the analysis of the association between the use of ACEI or ARB, and the development of VAP. For patients using either ACEI or ARB, model 1 showed a significantly reduced risk of VAP compared to the reference group (patients not using either ACEI or ARB) (OR: 0.62, 95% CI: 0.50–0.77, $P<0.001$). After adjusting for covariates (model 2), the results also showed that the use of ACEI or ARB was associated with a decreased risk of VAP development (OR: 0.79, 95% CI: 0.62–0.99, $P=0.047$). After PSM, the results were consistent (Supplementary Table 6).

Subgroup analyses of the association between the use of ACEI or ARBs and the development of VAP

The subgroup analyses indicated that in patients with AKI (OR: 0.70, 95% CI: 0.52–0.94, $P=0.020$), in patients with renal failure (OR: 0.14, 95% CI: 0.02–0.84, $P=0.032$), in patients with diabetes (OR: 0.64, 95% CI: 0.43–0.94, $P=0.024$), in patients used vasopressor (OR: 0.67, 95% CI: 0.49–0.92, $P=0.012$), and antibiotics (OR: 0.74, 95% CI: 0.57–0.96, $P=0.021$), the use of ACEI/ARB was associated with a reduced risk of VAP. Subgroup analyses of the association between the use of ACEI or ARBs and the risk of VAP are presented in Table 3.

Comparison analysis of association with VAP development in patients using ACEI and ARB

The result showed that there was no statistical difference in the risk of VAP development between patients who used ACEI and ARB (OR: 0.84, 95% CI: 0.49–1.47, $P=0.547$) (Table 4). The findings from the subgroup analyses also indicated no significant difference in the risk of VAP development among patients treated with ACEI compared to those treated with ARBs (Table 5).

Table 1 Basic characteristics of included patients

Variables	Total (*n* = 8888)	ACEI = No and ARB = No (*n* = 7486)	ACEI = Yes or ARB = Yes (*n* = 1402)	Statistic	*P*
Age, ages, Mean ± SD	65.05 ± 16.33	64.08 ± 16.77	70.24 ± 12.55	t = -15.91	< 0.001
Gender, n (%)				χ^2 = 4.310	0.038
Female	3946 (44.40)	3359 (44.87)	587 (41.87)		
Male	4942 (55.60)	4127 (55.13)	815 (58.13)		
Race, n (%)				χ^2 = 40.010	< 0.001
Black	647 (7.28)	534 (7.13)	113 (8.06)		
White	5874 (66.09)	4870 (65.05)	1004 (71.61)		
Other	919 (10.34)	787 (10.51)	132 (9.42)		
Unknown	1448 (16.29)	1295 (17.30)	153 (10.91)		
Ventilation duration, hours, M (Q_1, Q_3)	70.05 (57.00, 99.00)	71.21 (57.57, 101.28)	66.50 (56.00, 90.00)	Z = -6.030	< 0.001
Antibiotics, n (%)				χ^2 = 26.337	< 0.001
No	1749 (19.68)	1403 (18.74)	346 (24.68)		
Yes	7139 (80.32)	6083 (81.26)	1056 (75.32)		
Propofol, n (%)				χ^2 = 0.087	0.768
No	3880 (43.65)	3273 (43.72)	607 (43.30)		
Yes	5008 (56.35)	4213 (56.28)	795 (56.70)		
Midazolam, n (%)				χ^2 = 74.744	< 0.001
No	6169 (69.41)	5059 (67.58)	1110 (79.17)		
Yes	2719 (30.59)	2427 (32.42)	292 (20.83)		
Dexmedetomidine, n (%)				χ^2 = 2.234	0.135
No	7748 (87.17)	6543 (87.40)	1205 (85.95)		
Yes	1140 (12.83)	943 (12.60)	197 (14.05)		
Vasopressor use, n (%)				χ^2 = 35.138	< 0.001
No	3917 (44.07)	3198 (42.72)	719 (51.28)		
Yes	4971 (55.93)	4288 (57.28)	683 (48.72)		
VAP, n (%)				χ^2 = 18.476	< 0.001
No	7991 (89.91)	6686 (89.31)	1305 (93.08)		
Yes	897 (10.09)	800 (10.69)	97 (6.92)		
SAPSII, M (Q_1, Q_3)	44.00 (34.00, 56.00)	44.00 (34.00, 56.00)	42.00 (33.00, 52.00)	Z = -4.929	< 0.001
Diabetes, n (%)				χ^2 = 122.243	< 0.001
No	6316 (71.06)	5492 (73.36)	824 (58.77)		
Yes	2572 (28.94)	1994 (26.64)	578 (41.23)		
Hypertension, n (%)				χ^2 = 193.898	< 0.001
No	5119 (57.59)	4548 (60.75)	571 (40.73)		
Yes	3769 (42.41)	2938 (39.25)	831 (59.27)		
Trauma, n (%)				χ^2 = 18.395	< 0.001
No	7482 (84.18)	6248 (83.46)	1234 (88.02)		
Yes	1406 (15.82)	1238 (16.54)	168 (11.98)		
Liver failure, n (%)				χ^2 = 68.905	< 0.001
No	8120 (91.36)	6759 (90.29)	1361 (97.08)		
Yes	768 (8.64)	727 (9.71)	41 (2.92)		
Renal failure, n (%)				χ^2 = 0.094	0.759
No	8539 (96.07)	7190 (96.05)	1349 (96.22)		
Yes	349 (3.93)	296 (3.95)	53 (3.78)		
Sepsis, n (%)				χ^2 = 34.145	< 0.001
No	7574 (85.22)	6308 (84.26)	1266 (90.30)		
Yes	1314 (14.78)	1178 (15.74)	136 (9.70)		
AKI, n (%)				χ^2 = 1.261	0.261

Table 1 (continued)

Variables	Total (*n* = 8888)	ACEI = No and ARB = No (*n* = 7486)	ACEI = Yes or ARB = Yes (*n* = 1402)	Statistic	*P*
No	3129 (35.20)	2617 (34.96)	512 (36.52)		
Yes	5759 (64.80)	4869 (65.04)	890 (63.48)		
Heart rate, bpm Mean ± SD	91.15 ± 20.53	92.01 ± 20.83	86.52 ± 18.22	t = 10.12	< 0.001
Temperature, Deg.C, Mean ± SD	36.79 ± 1.89	36.78 ± 1.99	36.87 ± 1.20	t = -2.30	0.021
MBP, mmHg, Mean ± SD	82.89 ± 17.02	82.70 ± 16.99	83.88 ± 17.16	t = -2.39	0.017
Respiratory rate, bpm, M (Q_1, Q_3)	19.00 (15.00, 23.00)	19.00 (15.00, 23.00)	20.00 (16.00, 24.00)	Z = 3.706	< 0.001
SpO_2,%, Mean ± SD	96.42 ± 10.06	96.45 ± 10.86	96.27 ± 3.54	t = 1.14	0.255
Hematocrit, %, Mean ± SD	31.71 ± 6.38	31.73 ± 6.47	31.59 ± 5.83	t = 0.82	0.411
WBC, K/uL, M (Q_1, Q_3)	11.80 (8.60, 15.90)	11.90 (8.50, 16.20)	11.50 (8.80, 14.60)	Z = -3.369	< 0.001
Platelet, K/uL, M (Q_1, Q_3)	183.00 (127.00, 256.00)	182.00 (125.00, 254.00)	190.00 (135.00, 264.00)	Z = 3.591	< 0.001
RDW, %, Mean ± SD	15.26 ± 2.30	15.32 ± 2.38	14.94 ± 1.80	t = 6.94	< 0.001
Creatinine, mg/dL, M (Q_1, Q_3)	1.00 (0.70, 1.70)	1.00 (0.70, 1.70)	1.00 (0.80, 1.40)	Z = -1.498	0.134
Glucose, mg/dL, M (Q_1, Q_3)	131.00 (108.00, 165.00)	131.00 (108.00, 166.00)	131.50 (110.00, 163.00)	Z = -0.057	0.954
BUN, mg/dL, M (Q_1, Q_3)	21.00 (14.00, 36.00)	21.00 (14.00, 36.00)	22.00 (15.00, 33.00)	Z = 0.815	0.415
Phosphate, mg/dL, M (Q_1, Q_3)	3.50 (2.80, 4.40)	3.50 (2.80, 4.50)	3.40 (2.80, 4.10)	Z = -3.521	< 0.001
Anion gap, mEq/L, Mean ± SD	14.66 ± 4.31	14.82 ± 4.43	13.80 ± 3.49	t = 9.58	< 0.001
Urine output, mL, M (Q_1, Q_3)	1600.00 (930.00, 2488.50)	1555.00 (897.00, 2465.00)	1770.50 (1145.00, 2625.00)	Z = 6.561	< 0.001

Notes: *ACEI* Angiotensin-converting enzyme inhibitors, *ARB* Angiotensin receptor blocker, *VAP* Ventilator-associated pneumonia, *SAPSII* Simplified acute physiology score II, *AKI* Acute kidney injury, *MBP* Mean blood pressure, *SpO2* Peripheral capillary oxygen saturation, *WBC* White blood cell, *RDW* Red cell distribution width, *BUN* Blood urea nitrogen

Table 2 Association between the use of ACEI or ARB and the risk of VAP

Indicators	Model I		Model II	
	OR (95% CI)	*P*	OR (95% CI)	*P*
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	0.62 (0.50–0.77)	< 0.001	0.79 (0.62–0.99)	0.047

Notes: *ACEI* Angiotensin-converting enzyme inhibitors, *ARB* Angiotensin receptor blocker, *VAP* Ventilator-associated pneumonia, *OR* Odds ratio, *CI* Confidence interval; Model I was an unadjusted model; Model II adjusted for age, gender, race, ventilation duration, antibiotics, Propofol, Midazolam, Dexmedetomidine, vasopressor use, SAPSII, trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output

Discussion

In this study, we focused on exploring the association between the utilization of ACEI or ARBs and the risk of developing VAP among patients who were in the ICU. The use of ACEI/ARB was found to be associated with a reduced risk of VAP, specifically in patients with AKI, renal failure, and diabetes. Additionally, the association between ACEI/ARB use and decreased VAP risk was observed in patients receiving vasopressor support and those treated with antibiotics. The comparison analysis of the association between the use of ACEI and ARB and the risk of VAP development did not reach statistical significance.

Previous studies have confirmed the association between ACEI/ARB and pneumonia. A case-crossover study conducted using the Taiwan National Health Insurance Research Database (NHIRD) revealed a significant protective effect of ACEI use on pneumonia hospitalization in stroke patients, exhibiting a dose–response relationship [20]. In a study evaluating patients aged fifty years or older, initially diagnosed with Parkinson's disease (PD) and comorbid hypertension, the use of ACEI was associated with a reduced risk of pneumonia [21]. A systematic review suggests that ACEI may be beneficial in reducing the incidence of CAP in the elderly [22]. A retrospective cohort study conducted in Taiwan found that the use of both ACEI and ARB was associated with a reduced risk of CAP infection [13]. A cohort study also found that, compared to non-users of ACEI, users of ACEI had a lower likelihood of developing pneumonia [14]. This study was the first study revealing the association between the use of ACEI/ARB and a reduced risk of VAP in the ICU. This association, not previously reported, opens up new avenues for further research into the potential protective effects of these medications beyond their established cardiovascular benefits. Our findings may also have implications for clinical practice, guiding the consideration of ACEI/ARB use in the ICU setting

Table 3 Subgroup analyses of the association between the use of ACEI or ARB and the risk of VAP

Indicators	OR (95% CI)	*P*	OR (95% CI)	*P*
Subgroup I: AKI	No		Yes	
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	0.98 (0.66–1.45)	0.922	0.70 (0.52–0.94)	0.020
Subgroup II: Renal failure	No		Yes	
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	0.82 (0.64–1.04)	0.094	0.14 (0.02–0.84)	0.032
Subgroup III: Vasopressor use	No		Yes	
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	1.10 (0.77–1.57)	0.612	0.67 (0.49–0.92)	0.012
Subgroup IV: Antibiotics	No		Yes	
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	1.19 (0.65–2.20)	0.572	0.74 (0.57–0.96)	0.021
Subgroup V: Diabetes	No		Yes	
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	0.90 (0.67–1.21)	0.473	0.64 (0.43–0.94)	0.024
Subgroup VI: Hypertension	No		Yes	
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	0.63 (0.42–0.93)	0.020	0.85 (0.63–1.15)	0.295
Subgroup VII: Sepsis	No	Yes	No	Yes
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	0.81 (0.63–1.04)	0.103	0.65 (0.34–1.24)	0.191
Subgroup VIII: SAPSII	< 34 (Q1)		> = 34 (Q1)	
ACEI = NO and ARB = NO	Ref		Ref	
ACEI = YES or ARB = YES	0.94 (0.44–2.02)	0.876	0.79 (0.62–1.00)	0.054

Notes: *ACEI* Angiotensin-converting enzyme inhibitors, *ARB* Angiotensin receptor blocker, *VAP* Ventilator-associated pneumonia, *OR* Odds ratio, *CI* Confidence interval, *AKI* Acute kidney injury, *SAPSII* Simplified Acute Physiology Score II; Subgroup I of AKI adjusted for age, gender, race, ventilation duration, antibiotics, Propofol, Midazolam, Dexmedetomidine, Vasopressor use, SAPSII, trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output; Subgroup II of renal failure adjusted for age, gender, race, ventilation duration, antibiotics, Propofol, Midazolam, Dexmedetomidine, vasopressor use, SAPSII, trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output. Subgroup III of vasopressor use adjusted for age, gender, race, ventilation duration, antibiotics, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output; Subgroup IV of antibiotics adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, vasopressor use, SAPSII, trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output; Subgroup V of diabetes adjusted for age, gender, race, ventilation duration, antibiotics, Propofol, Midazolam, Dexmedetomidine, vasopressor use, SAPSII, trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output; Subgroup VI of hypertension adjusted for age, gender, race, ventilation duration, antibiotics, propofol, midazolam, dexmedetomidine, vasopressor use, SAPSII, trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output; Subgroup VII of sepsis adjusted for age, gender, race, ventilation duration, antibiotics, Propofol, Midazolam, Dexmedetomidine, vasopressor use, SAPSII, trauma, liver failure, MBP, respiratory rate, glucose, anion gap, and urine output; Subgroup VIII of SAPSII adjusted for age, gender, race, ventilation duration, antibiotics, Propofol, Midazolam, Dexmedetomidine, vasopressor use, trauma, liver failure, sepsis, MBP, respiratory rate, glucose, anion gap, and urine output; SAPS II values were divided at the first quartile (Q1) of the study population's distribution

Table 4 Comparison analysis of the association with VAP risk in patients using ACEI and ARB

Indicators	Model I		Model II	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Drug type				
ACEI	Ref		Ref	
ARB	0.80 (0.48–1.32)	0.379	0.84 (0.49–1.47)	0.547

Notes: *ACEI* Angiotensin-converting enzyme inhibitors, *ARB* Angiotensin receptor blocker, *VAP* Ventilator-associated pneumonia, *OR* Odds ratio, *CI* Confidence interval; Model I was an unadjusted model; Model II adjusted for Age, Gender, Race, Ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and platelet

for patients who could benefit from a reduced risk of VAP. The potential mechanisms by which ACEI and ARBs may be associated with a reduced risk of VAP are multifaceted and not yet fully elucidated. However, several hypotheses can be proposed based on current understanding. ACEI and ARBs are known to modulate the renin–angiotensin–aldosterone system (RAAS), which plays a role in immune function [23]. By inhibiting the production of angiotensin II, ACEI and ARBs may reduce inflammation and enhance the immune response to pathogens, potentially decreasing the risk of pneumonia [24]. The use of ACEI and ARBs may improve pulmonary vascular integrity by reducing endothelial dysfunction and inflammation [25], which could limit the spread of infection within the lungs.

The findings from the study indicate that the association between the use of ACEI or ARBs and a reduced risk of VAP was significant in patients with comorbidities such as AKI, renal failure, and diabetes, as well as in patients who are receiving vasopressors and antibiotics. However, in patients without these comorbidities and those not receiving vasopressors or antibiotics, the use of ACEI/ARB does not show a statistically significant association with a reduced risk of VAP. Further research is needed to elucidate the underlying mechanisms and to determine whether the observed associations are due to the direct effects of ACEI/ARBs on VAP risk or if they are related to other factors associated with the complex care of patients with multiple comorbidities in the ICU. These results highlight the importance of considering patient-specific factors and treatment regimens when evaluating the potential benefits of ACEI/ARB use in the ICU.

Previous research has compared the association between the use of ACEI and ARBs with the risk of pneumonia. A systematic review and meta-analysis indicated that ACEI (but not ARBs) have a presumed protective effect on the risk of pneumonia [26]. A study that recruited patients with COPD who had

Table 5 Subgroup of the comparison analysis of the association with VAP risk in patients using ACEI and ARB

Indicators	OR (95%CI)	*P*	OR (95%CI)	*P*
Subgroup I:AKI	No		Yes	
ACEI	Ref		Ref	
ARB	1.03 (0.41–2.59)	0.956	0.83 (0.40–1.72)	0.618
Subgroup II: Renal failure	No		Yes	
ACEI	Ref		Ref	
ARB	0.84 (0.48–1.48)	0.556	-	-
Subgroup III: Vasopressor use	No		Yes	
ACEI	Ref		Ref	
ARB	0.57 (0.22–1.47)	0.244	1.11 (0.54–2.29)	0.777
Subgroup IV: Antibiotics	No		Yes	
ACEI	Ref		Ref	
ARB	0.26 (0.03–2.21)	0.217	1.01 (0.56–1.84)	0.968
Subgroup V: Diabetes	No		Yes	
ACEI	Ref		Ref	
ARB	0.94 (0.47–1.89)	0.863	0.75 (0.28–2.01)	0.565
Subgroup VI: Hypertension	No		Yes	
ACEI	Ref		Ref	
ARB	0.93 (0.39–2.22)	0.875	0.81 (0.38–1.70)	0.570
Subgroup VII: Sepsis	No		Yes	
ACEI	Ref		Ref	
ARB	0.88 (0.49–1.60)	0.679	0.35 (0.04–3.16)	0.352
Subgroup VIII: SAPSII	< 34 (Q1)		< 34 (Q1)	
ACEI	Ref		Ref	
ARB	0.77 (0.07–8.89)	0.836	0.91 (0.52–1.59)	0.740

Notes: *ACEI* Angiotensin-converting enzyme inhibitors, *ARB* Angiotensin receptor blocker, *VAP* Ventilator-associated pneumonia, *OR* Odds ratio, *CI* Confidence interval, *AKI* Acute kidney injury, *SAPSII* Simplified Acute Physiology Score II; Subgroup I of AKI adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and platelet; Subgroup II of the renal failure adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and platelet; Subgroup III of the vasopressor use adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and platelet; Subgroup IV of the antibiotics adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and Platelet; Subgroup V of diabetes adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and platelet; Subgroup VI of hypertension adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and platelet; Subgroup VII of sepsis adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, SAPSII, trauma, liver failure, temperature, MBP, and Platelet; Subgroup VIII of SAPSII adjusted for age, gender, race, ventilation duration, Propofol, Midazolam, Dexmedetomidine, trauma, liver failure, temperature, MBP, and platelet

used ACEI and ARBs for more than 90 days between 2000 and 2005 found an association between the use of ARBs and pneumonia, including severe pneumonia, in patients with COPD when compared to ACEI use [16]. A nationwide cohort study within the Taiwan National Health Insurance database found no association between ACEI treatment and a reduced risk of pneumonia incidence compared to losartan (an ARB with similar indications) [16]. Our study discovered no statistically significant difference in the association between the use of ACEI and ARBs with the risk of VAP. The results indicate that, within the confines of our research and the parameters examined, the impact of ACEI and ARBs on the incidence of VAP is comparable, with neither class demonstrating a distinct advantage in terms of risk reduction. Further investigation may be required to check other factors that could influence VAP outcomes among ICU patients.

The clinical significance of our study encompasses several key aspects. First, our findings may guide intensivists in considering the use of ACEI or ARBs as adjunctive therapy in patients requiring MV, with the aim of reducing the risk of VAP. Second, given that VAP treatment often necessitates additional antibiotic use and prolonged MV, this could lead to increased healthcare resource utilization. A reduction in VAP risk may consequently help to mitigate the associated medical costs. Third, the results of this study underscore the potential benefits of using ACEI/ARBs in patients with specific comorbidities, supporting the concept of personalized medicine that tailors treatment plans according to the individual patient's conditions. Fourth, our findings may stimulate further research into the role of ACEI/ARBs in preventing other complications in the ICU, as well as a broader assessment of the safety and efficacy of these medications in critically ill patients.

This study is the first to explore the relationship between the use of ACEI or ARBs and the risk of VAP in mechanically ventilated patients in the ICU, providing a basis for drug decision-making aimed at reducing VAP risk in this patient population. The large sample size ensures adequate power to detect significant associations, and the study comprehensively considers various factors, including comorbidities and laboratory indicators, that could influence outcomes within the ICU setting.

However, this study still has limitations. First, the retrospective cohort design of the study is subject to inherent biases characteristic of this type of research. Second, the data was collected from the MIMIC-IV database, which is a single medical center, potentially limiting the generalizability of the findings. Large-scale, multicenter studies are needed to validate the results. Third, due to database limitations, pre-admission medication use could not be included in the analysis, which may affect the comprehensiveness of the study's conclusions. Fourth, one of the primary constraints of this research is the inability to differentiate between patients who were newly prescribed ACEIs or ARBs and those who were already on these

medications prior to their ICU admission. This limitation stems from the constraints inherent in the available database, which does not provide comprehensive medication histories for all patients. The absence of detailed pre-ICU admission medication data may obscure the nuances in patient responses to ACEIs and ARBs, as the effects of de novo therapy could differ significantly from those of chronic use. Given that some medications require an accumulation period to achieve therapeutic efficacy, the timing of initiation relative to ICU admission could be a pivotal factor influencing the study outcomes. Furthermore, this limitation underscores the need for caution when interpreting the results, as the observed associations may not be generalizable to all patients receiving ACEIs or ARBs, particularly those who have been on these medications for an extended period prior to ICU admission. Fifth, the reduced sample sizes within certain subgroups may impact the robustness of our model, particularly in terms of variable selection and significance. While we performed rigorous statistical testing to select covariates, smaller subgroup sizes may limit the power to detect associations, potentially introducing variability in the model outcomes. Future studies with larger sample sizes are needed to validate these findings and enhance generalizability.

Conclusion

While the findings from this study suggest a significant association between the use of ACEIs or ARBs and a lower risk of VAP in the ICU setting, it is crucial to consider the limitations regarding medication usage. The incomplete data on certain medications may introduce variability that affects the precision of our estimates. Therefore, these results should be interpreted with caution and serve as a foundation for further investigation. Future research with more comprehensive medication data is needed to confirm these findings and to fully assess the potential benefits of incorporating ACEIs or ARBs into clinical strategies aimed at improving patient outcomes in the ICU.

Abbreviations

MV	Mechanical ventilation;
ICU	Intensive care unit
VAP	Ventilator-associated pneumonia
ACEIs	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
CAP	Community-acquired pneumonia
COPD	Chronic obstructive pulmonary disease
MIMIC-IV	Medical Information Mart for Intensive Care IV
MIT	Massachusetts Institute of Technology
BIDMC	Beth Israel Deaconess Medical Center
AKI	Acute kidney injury
MBP	Mean blood pressure
WBC	White blood cell
RDW	Red cell distribution width
ICD	International classification of diseases
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03386-y.

Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.
Supplementary Material 5.
Supplementary Material 6.
Supplementary Material 7.
Supplementary Material 8.
Supplementary Material 9.
Supplementary Material 10.

Acknowledgements

Not applicable.

Authors' contributions

HC designed the study and wrote the manuscript. HS and XC collected, analyzed, and interpreted the data. HC critically reviewed, edited, and approved the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Data availability

The datasets generated and/or analyzed during the current study are available in the MIMIC-IV database, https://mimic.mit.edu/docs/iv/.

Declarations

Ethics approval and consent to participate

The requirement of ethical approval for this was waived by the Institutional Review Board of People's Hospital, Yanliang District, because the data was accessed from MIMIC-IV (a publicly available database). The need for written informed consent was waived by the Institutional Review Board of People's Hospital, Yanliang District due to retrospective nature of the study. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 16 April 2024 Accepted: 6 November 2024
Published online: 21 November 2024

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