Journal of Translational Medicine

RESEARCH

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Comparison of rhythm and rate control medications for new-onset atrial fibrillation in septic patients: MIMIC-IV database analysis

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Abstract

Background The optimal management strategy for new-onset atrial fibrillation (NOAF) in patients with sepsis remains unclear. This study aimed to investigate and compare the associations of rhythm control medications versus rate control medications with mortality outcomes in septic patients with NOAF.

Methods This propensity score-matched cohort study utilized data from the Medical Information Mart in Intensive Care-IV database. Adult septic patients with NOAF were categorized into two groups based on initial medications (rhythm or rate control). The primary outcome was 28-day mortality, with secondary outcomes including intensive care unit(ICU),1-year mortality.

Results A total of 586 patients were included in the prematched cohort, with 277 patients remaining after propensity score matching. In the matched cohort, the primary outcome of 28-day mortality rate was 49.7% (85/171) in the rate control group and 46.2% (49/106) in the rhythm control group, with no significant difference between the groups (HR 0.97; 95% CI 0.68-1.37,$P=0.849$). Secondary outcomes showed that rhythm control medications were not associated with increased ICU mortality (HR 1.03, 95% CI 0.60–1.78, $P=0.906$) or 1-year mortality (HR 0.84, 95% CI 0.61–1.16, $P=0.299$).However, the rhythm control group had higher successful cardioversion rates compared to the rate control group at 6 h (68.9% vs. 49.1%, $P=0.001$), 12 h (71.1% vs. 52.4%, $P=0.002$), and 24 h (72.7% vs. 53.2%, $P=0.002$).

Conclusions In septic patients with NOAF, rhythm control and rate control medications showed no difference in 28-day, ICU, or 1-year mortality.However, rhythm control may provide transient hemodynamic stabilization through rapid cardioversion, potentially beneficial during acute critical illness.

Keywords Rhythm control, Rate control, New-onset atrial fibrillation, Sepsis

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Introduction

New-onset atrial fibrillation(NOAF), defined as atrial fibrillation (AF) occurring in patients without a prior AF history is the most prevalent arrhythmia affecting patients with sepsis. Sepsis increases AF risk six-fold [1], with the incidence of NOAF ranging from 5 to 15% in patients with sepsis [2, 3]. The incidence of NOAF has been shown to rise with the increasing severity of sepsis, with a cumulative risk of 10%, 22%, and 40% in patients with sepsis, severe sepsis, and septic shock, respectively [4]. NOAF typically emerges within three days of hospitalization, lasting a median of five hours (interquartile range [IQR], 2–11 h) [5].

Sepsis-induced inflammation, autonomic dysfunction, and cardiovascular instability [6] create an atrial substrate for AF, potentially reducing cardiac output and organ perfusion. NOAF is linked to prolonged intensive care unit (ICU) stay [3, 7], increased mortality [4, 8–11] and a higher risk of ischemic stroke [12, 13].

Given these adverse clinical consequences, the management of NOAF in septic patients is of paramount importance. Current AF guidelines, primarily based on the general population, may not fully apply to sepsis-related NOAF [5]. According to the latest European Society of Cardiology (ESC) guidelines for stroke prevention, NOAF in the context of sepsis is recognized as a clinically significant yet unresolved challenge [5]. In hemodynamically stable septic patients, either rhythm or rate control medications might be considered the initial pharmacologic interventions.Rhythm control is favored when atrial contraction loss contributes to symptoms, while rate control is preferred for tachycardia [14, 15]. However, studies report conflicting outcomes: some suggest rhythm control reduces mortality [16, 17], while others find no significant difference [18–20], often due to small sample sizes and confounding factors.This study utilizes the Medical Information Mart in Intensive Care-IV (MIMIC-IV) database to compare the effects of rhythm control and rate control medications on mortality in septic patients with NOAF.

Methods

Study design and population

The present study was a retrospective analysis of the MIMIC-IV database. The MIMIC-IV is a free, publicly accessible database that includes data on ICU stays for more than 50,000 unique patients from Beth Israel Deaconess Medical Center between 2008 and 2019 (Boston, Massachusetts). The database was approved for research use by the review committee of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The requirement for written informed consent was waived because patients were not identifiable by their health information in the database.

Sepsis was determined based on the International Classification of Disease-9th Revision (ICD-9) or International Classification of Disease-10th Revision (ICD-10). Newborn patients with sepsis and puerperal sepsis were excluded. The total of 50920 unique patients were included in the MIMIC-IV from 2008 to 2019. Among them, 7460 patients with sepsis were selected based on the diagnosis record of ICD-9 or ICD-10. Subsequently, patients who met the following criteria were included in the study: 1). Patients aged 18 years or older; 2). AF was first recorded after ICU admission, defined by heart rate status recorded at the nurse's bedside; 3). Patients who were administered rate control medicine or rhythm control medicine to treat AF within 24 h of the onset of AF. Patients were excluded if they met any of the following criteria: 1) Preexisting AF prior to ICU admission; 2) Administration of both rate control and rhythm control medicines;3) Multiple ICU admissions, only ICU admission records from the patient's first admission were included.

Exposure and outcomes

Eligible patients were divided into 2 groups: the rate control medicine group and the rhythm control medicine group. Patients who were administered digoxin, diltiazem, verapamil, or beta-blockers (BBs) other than sotalol were identified as the rate control group. Patients who were administered amiodarone, dronedarone, dofetilide, flecainide, propafenone, ibutilide, or sotalol were identified as the rhythm control group. The primary outcome was 28-day all-cause mortality from the onset of NOAF. The secondary outcomes were ICU mortality and 1-year mortality.

Data collection

Demographics, laboratory results, comorbidity, medications, cardiac surgery procedures, 28-day mortality from onset of NOAF, ICU mortality, and 1-year mortality and scores were extracted from the MIMIC-IV database using the pgAdmin PostgreSQL tools. The following data were obtained: (1) demographic data, including age, and, sex; (2) laboratory data, including blood urea nitrogen (BUN), creatinine, sodium, chloride, calcium, glucose, potassium, and magnesium levels, inflammatory markers (white blood cell, neutrophil percentage), and lactate levels; (3) Severity of disease included Sequential Organ Failure Assessment (SOFA) score; (4) comorbidities: heart failure, hypertension, renal failure, respiratory failure, and coronary artery disease (CAD); (5) treatment at baseline: need for renal replacement therapy(CRRT), need for mechanical ventilation, need for vasopressors; (6) cardioversion rate, defined as the rate of patients whose rhythm return to sinus rhythm 6 h, 12 h, 24 h hour after administrated medicine.

Statistical analysis

The missing data for each variable is presented in Table S1. Multivariate imputation was used for imputing missing data for each variable.The remaining missing values in the covariates were multiple imputed using chained equations by generated five datasets with 10 iterations each, assuming data were missing at random. Continuous variables are expressed as the mean and standard deviation (SD) or the median and interquartile range (IQR). Continuous variables were evaluated with Student's t test or a nonparametric test, as appropriate. Categorical variables are expressed as counts and percentages in each category. Categorical variables were evaluated with the χ^2 test or Fisher's exact test, as appropriate. Cox proportional hazard models were used to generate hazard ratios (HRs) with 95% confidence intervals (CIs) for the outcomes. The screening criteria of confounders: (1) the outcome variables might be affected by some factors based on clinical experience; and (2) the variables with p value less than 0.05 in univariable analysis. The multivariable analysis was adjusted for age, gender, SOFA score, heart failure, hypertension, renal failure, respiratory failure, coronary artery disease, need for renal replacement therapy, need for mechanical ventilation, need for vasopressors, systolic blood pressure, blood urea nitrogen (BUN), creatinine, sodium, chloride, potassium, calcium, glucose, potassium, magnesium, levels inflammatory markers (white blood cell, neutrophil percentage), lactate.The cumulative incidence of mortality was analyzed with the Kaplan–Meier (KM) method and evaluated by the log-rank test.

Propensity score matching

To reduce the impact of potential confounders, we employed propensity score matching (PSM) to adjust for covariates when modeling the association between the use of rhythm control or rate control medicine to treat NOAF and 28-day mortality. We used propensity score matching to adjust covariates in modeling the association between use of rhythm or rate medication control and NOAF. We fitted multivariable logistic regression models to estimate propensity score as the probability of use of rhythm or rate medication control based on prespecified covariates, included baseline demographics (age, gender), comorbidities (cardiac surgery, heart failure, renal failure, respiratory failure), intervention-related factors [vasopressors (dobutamine, epinephrine, milrinone, phenylephrine, dopamine, norepinephrine), CRRT, invasive ventilation, systolic blood pressure], and organ dysfunction markers (SOFA score, creatinine, lactate levels). Treatment group (rhythm vs. rate control) groups were matched using 1:2 nearest-neighbor matching based on propensity score, with a caliper width of 0.1 SDs or less to ensure high-quality matches, reducing bias by ensuring similarity in observed characteristics between groups [21]. We assessed the covariate balance before and after matching using absolute standardized mean differences (SMDs) and specified an SMD greater than 0.1 as a relevant imbalance [22].

Subgroup analyses

Subgroup analyses for 28-day mortality in the matched cohort were based on age, sex, SOFA score, cardiac surgery, creatinine levels, heart failure, renal failure, respiratory failure, the need for CRRT, the need for vasopressors, the need for invasive ventilation, systolic blood pressure, and lactate levels.

Sensitivity analysis

To test the robustness of the findings obtained in the matched cohort, sensitivity analyses were performed on the entire cohort. A multivariable Cox proportional hazard model was used to analyze the effects of covariates on 28-day mortality, ICU mortality, and 1-year mortality.

All the statistical analyses were performed with R version 4.2.3 and STATA version 17.0. A two-sided $\alpha < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

The process of patient enrollment in this study is presented in Fig. 1. A total of 586 patients were included in the entire cohort, 459 in the rate control group and 127 in the rhythm control group: After PSM, 277 patients remained: 106 patients in the rhythm control group and 171 patients in the rate control group. Baseline characteristics before and after matching are shown in Table 1. In the entire cohort, patients in the rate control group were older, more likely to be female, had lower SOFA scores and fewer comorbidities (e.g., renal and respiratory failure). Fewer patients in this group required cardiac surgery, CRRT, and invasive ventilation, or vasopressors. Matching improved variable balance, with an absolute SMD < 0.10 (Table S2, Figure S1). Distributional balance before and after propensity score matching is shown in Figure S2.

In the matched cohort, 75.4%, 19.7%, and 9.9% of patients in the rate control group received BBs, diltiazem, or digoxin respectively (Table S3). In the rhythm control group,98.1% used amiodarone (median dose 150 mg/day, max 1200 mg/day) (Table S3). The median dose of metoprolol tartrate was 10 mg per day, and the highest dose was 400 mg per day in the rate control group. No excess doses of these drugs were recorded. In the matched cohort, successful cardioversion to sinus rhythm was higher in the rhythm control group (68.9% vs. 49.1% at 6 h, 71.1% vs. 52.4% at 12 h, and 72.7% vs. 53.2% at 24 h Table S4).

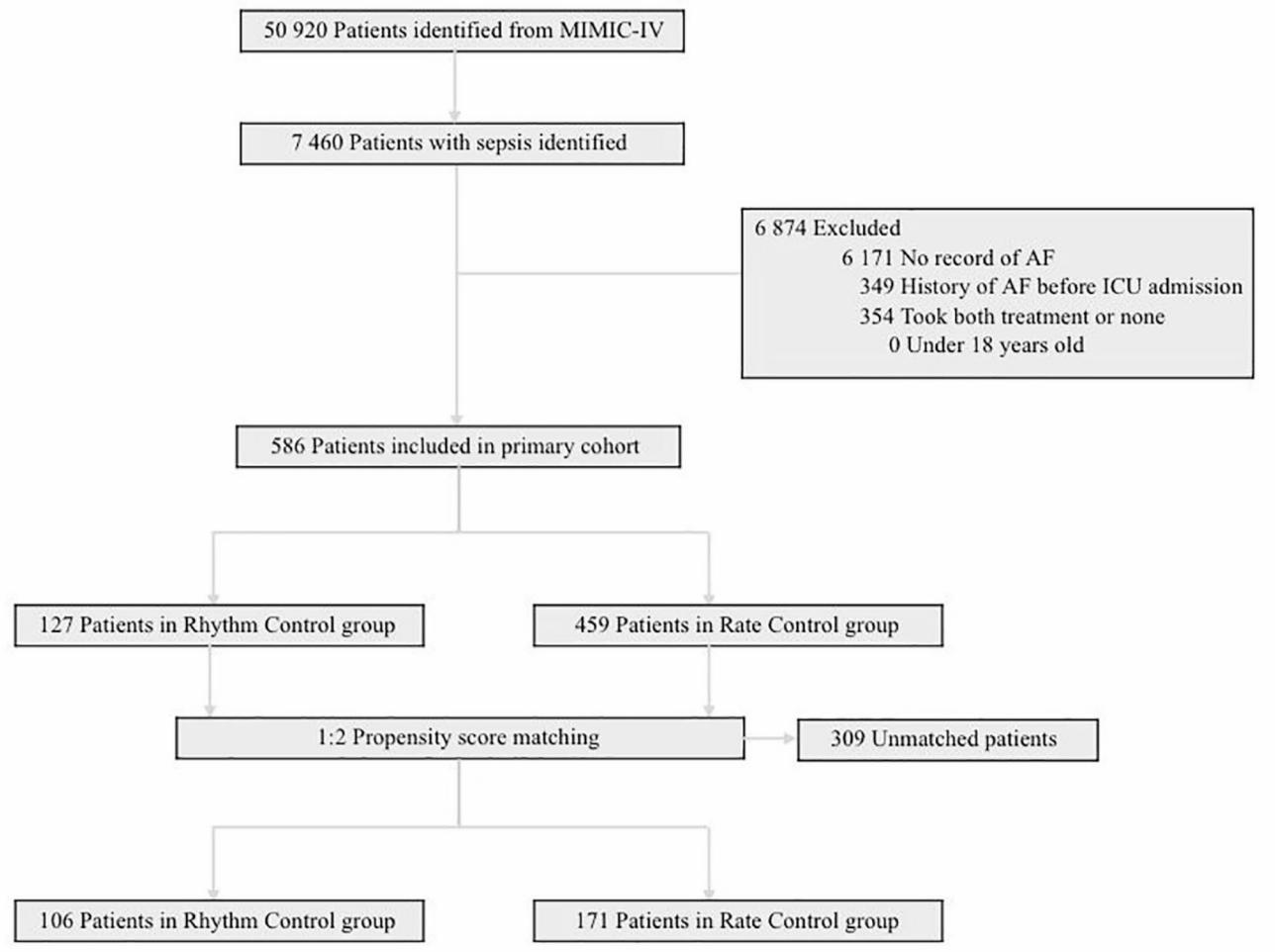


Fig. 1 Flowchart of patient inclusion. MIMIC-IV, medical information mart in intensive care-IV; ICU, intensive care unit; AF, atrial fibrillation

Primary outcome

In the matched cohort, the 28-day mortality rate was 49.7% (85/171) in the rate control group and 46.2% (49/106) in the rhythm control group. No significant difference in 28-day mortality was observed between the two groups (HR 0.97, 95% CI 0.68–1.37, $P = 0.849$; Fig. 2), which was also confirmed by multivariable analysis (HR 0.84, 95% CI 0.58–1.22, $P = 0.359$;Table 2).

Subgroup analyses

Subgroup analyses for 28-day mortality showed no significant differences across across various subgroups of matched patients (Fig. 3).

Sensitivity analyses

In the entire cohort, the 28-day mortality rate was 38.8% (178/459) in the rate control group and 49.6% (63/127) in the rhythm control group (Table 3). Kaplan-Meier curves for 28-day mortality by NOAF treatment strategy are shown for the entire cohort (Figure S3).In univariable analysis, rhythm control medication was associated with higher 28-day mortality (HR 1.51,95% CI 1.14–2.02, $P = 0.004$). However, this association became non-significant after multivariable adjustment (HR 0.96, 95% CI 0.70–1.32, $P = 0.799$).

Secondary outcomes

In the matched cohort, ICU mortality was 36.8% (63/171) in the rate control group and 41.5% (44/106) in the rhythm control group. One-year mortality was 63.2% (108/171) in the rate control group and 63.2% (67/106) in the rhythm control group, respectively. There was no significant difference between the two groups for ICU mortality and 1-year mortality rate (unadjusted HR 1.22,95% CI 0.74-2.00, $P = 0.438$, unadjusted HR 1.02,95% CI 0.75-1.38, $P = 0.899$, respectively) and (adjusted HR 1.03, 95% CI0.60 -1.78,$P = 0.906$, adjusted HR 0.84,95% CI 0.61–1.16, $P = 0.299$, respectively, Table 2).Kaplan-Meier curves for the 1-year mortality rate based on the NOAF treatment medications are presented for the matched cohort (Figure S4).

Table 1 Baseline characteristics before and after propensity score matching

Characteristic	Unmatched			matched		
	Rate Control *N* = 459	Rhythm Control *N* = 127	*P*	Rate Control *N* = 171	Rhythm Control *N* = 106	*P*
Age	77 ± 12	72 ± 12	< 0.001	73 ± 13	73 ± 12	0.969
Gender			0.042			0.209
Male	250 (54.5%)	82 (64.6%)		95 (55.6%)	67 (63.2%)	
Female	209 (45.5%)	45 (35.4%)		76 (44.4%)	39 (36.8%)	
Smoker			0.359			0.755
NO	433 (94.3%)	117 (92.1%)		158 (92.4%)	99 (93.4%)	
YES	26 (5.7%)	10 (7.9%)		13 (7.6%)	7 (6.6%)	
Cardiac Surgery			0.017			0.678
NO	452 (98.5%)	120 (94.5%)		168 (98.2%)	103 (97.2%)	
YES	7 (1.5%)	7 (5.5%)		3 (1.8%)	3 (2.8%)	
Heart Failure			0.021			0.643
YES	145 (31.6%)	54 (42.5%)		108 (63.2%)	64 (60.4%)	
NO	314 (68.4%)	73 (57.5%)		63 (36.8%)	42 (39.6%)	
Hypertension			0.765			0.623
NO	210 (45.8%)	60 (47.2%)		81 (47.4%)	47 (44.3%)	
YES	249 (54.2%)	67 (52.8%)		90 (52.6%)	59 (55.7%)	
Renal Failure			< 0.001			0.773
NO	170 (37.0%)	23 (18.1%)		38 (22.2%)	22 (20.8%)	
YES	289 (63.0%)	104 (81.9%)		133 (77.8%)	84 (79.2%)	
Respiratory Failure			< 0.001			0.514
NO	239 (52.1%)	45 (35.4%)		68 (39.8%)	38 (35.8%)	
YES	220 (47.9%)	82 (64.6%)		103 (60.2%)	68 (64.2%)	
CAD			0.102			0.331
NO	354 (77.1%)	89 (70.1%)		130 (76.0%)	75 (70.8%)	
YES	105 (22.9%)	38 (29.9%)		41 (24.0%)	31 (29.2%)	
CRRT			< 0.001			0.359
NO	442 (96.3%)	111 (87.4%)		160 (93.6%)	96 (90.6%)	
YES	17 (3.7%)	16 (12.6%)		11 (6.4%)	10 (9.4%)	
Need of invasive ventilation			< 0.001			0.382
NO	302 (65.8%)	36 (28.3%)		67 (39.2%)	36 (34.0%)	
YES	157 (34.2%)	91 (71.7%)		104 (60.8%)	70 (66.0%)	
Need for vasopressors			< 0.001			0.996
None	191 (41.6%)	11 (8.7%)		20 (11.7%)	11 (10.4%)	
Dopamine	8 (1.7%)	8 (6.3%)		6 (3.5%)	5 (4.7%)	
Phenylephrine	87 (19.0%)	18 (14.2%)		33 (19.3%)	18 (17.0%)	
Norepinephrine	154 (33.6%)	68 (53.5%)		94 (55.0%)	59 (55.7%)	
Vasopressin	14 (3.1%)	15 (11.8%)		13 (7.6%)	9 (8.5%)	
Dobutamine	3 (0.7%)	4 (3.1%)		3 (1.8%)	2 (1.9%)	
Epinephrine	1 (0.2%)	1 (0.8%)		1 (0.6%)	1 (0.9%)	
Milrinone	1 (0.2%)	2 (1.6%)		1 (0.6%)	1 (0.9%)	
SOFA	6.6 ± 3.7	10.1 ± 3.8	< 0.001	8.8 ± 3.9	9.5 ± 3.7	0.155
BUN (mg/dL)	33 ± 21	40 ± 22	0.003	37 ± 22	39 ± 23	0.385
Calcium (mg/dL)	8.24 ± 0.70	8.12 ± 0.76	0.093	8.26 ± 0.76	8.14 ± 0.74	0.216
Chloride (mmol/L)	104 ± 5	103 ± 6	0.088	104 ± 6	103 ± 6	0.490
Creatinine (mg/dL)	1.42 ± 0.94	1.87 ± 1.11	< 0.001	1.58 ± 1.01	1.75 ± 1.06	0.178
Glucose (mg/dL)	137 ± 49	144 ± 53	0.161	144 ± 54	143 ± 53	0.880
Sodium (mmol/L)	139.0 ± 4.5	138.3 ± 4.8	0.098	139.2 ± 4.5	138.3 ± 4.7	0.148
Potassium (mmol/L)	4.06 ± 0.59	4.20 ± 0.63	0.054	4.07 ± 0.59	4.15 ± 0.62	0.258
Magnesium (mg/dL)	2.00 ± 0.32	2.04 ± 0.34	0.347	2.04 ± 0.33	2.03 ± 0.35	0.765
Systolic Blood Pressure (mmHg)	119 ± 23	110 ± 21	< 0.001	112 ± 23	112 ± 20	0.915
White blood cell (10^9/L)	14 ± 8	16 ± 9	0.056	15 ± 8	16 ± 8	0.454

Table 1 (continued)

Characteristic	Unmatched			matched		
	Rate Control *N* = 459	Rhythm Control *N* = 127	*P*	Rate Control *N* = 171	Rhythm Control *N* = 106	*P*
Neutrophil percentage (%)	81 ± 13	79 ± 13	0.063	80 ± 13	79 ± 13	0.500
Lactate (mmol/L)	2.05 ± 1.23	2.61 ± 1.64	< 0.001	2.23 ± 1.45	2.45 ± 1.54	0.236

Abbreviations: CAD, coronary artery disease; CRRT, continuous renal replacement therapy; SOFA, sequential organ failure assessment; BUN, blood urea nitrogen

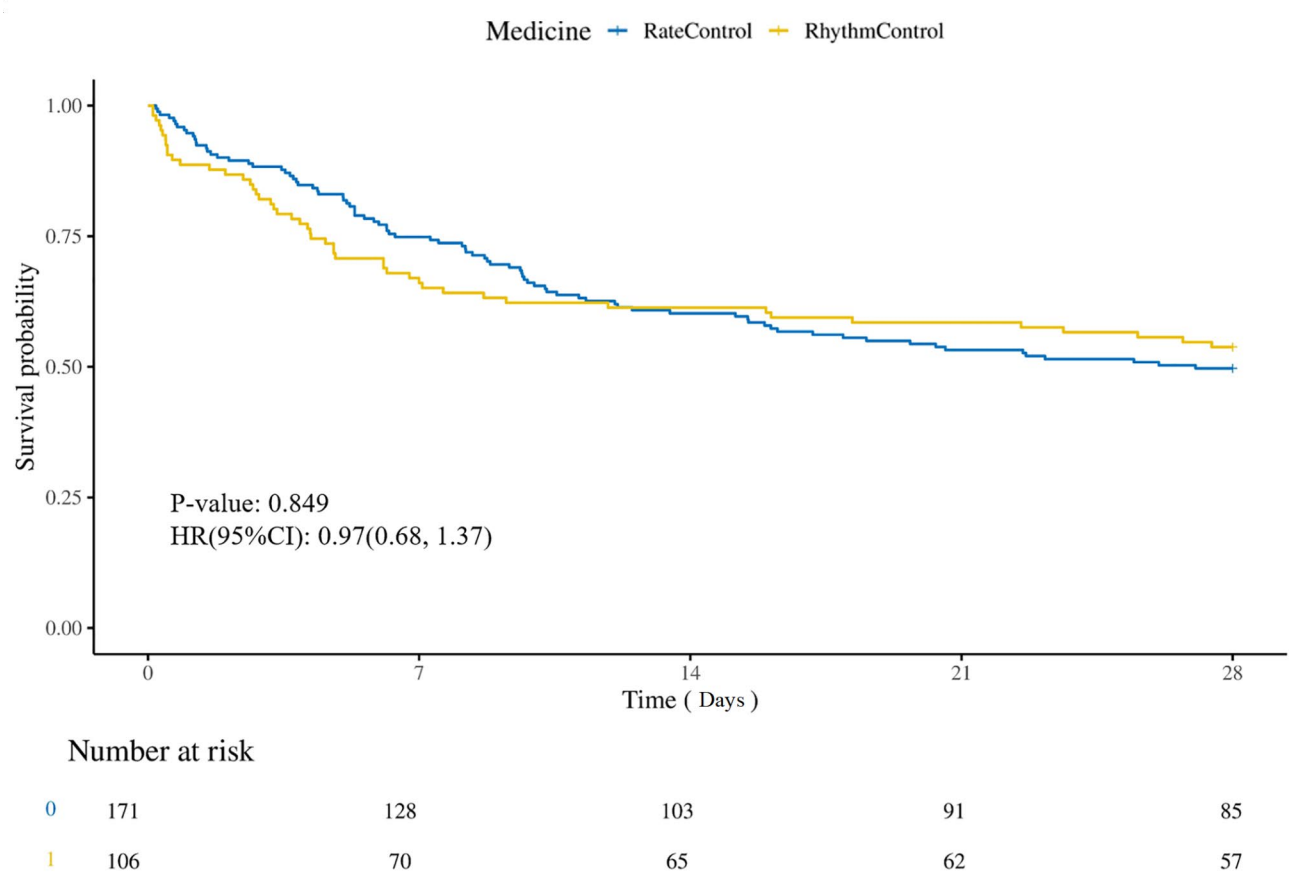


Fig. 2 Kaplan–Meier curve for 28-day all-cause mortality according to the use of NOAF treatment medications in the matched cohort. HR, hazard ratio

Table 2 The association of NOAF treatment medications with outcomes in the matched cohort

Outcome	Rate Control (*n* = 171)	Rhythm Control (*n* = 106)	Univariable analysis HR/OR (95%CI)	*P*-value	Multivariable analysis HR/OR (95%CI)	*P*-value
28-day mortality *n*(%)	85 (49.7)	49 (46.2)	HR 0.97 (0.68, 1.37)	0.849	HR 0.84 (0.58, 1.22)	0.359
ICU mortality *n*(%)	63 (36.8)	44(41.5)	OR 1.22 (0.74, 2.00)	0.438	OR 1.03 (0.60, 1.78)	0.906
1-year mortality *n*(%)	108 (63.2)	67 (63.2)	HR 1.02 (0.75, 1.38)	0.899	HR 0.84 (0.61, 1.16)	0.299

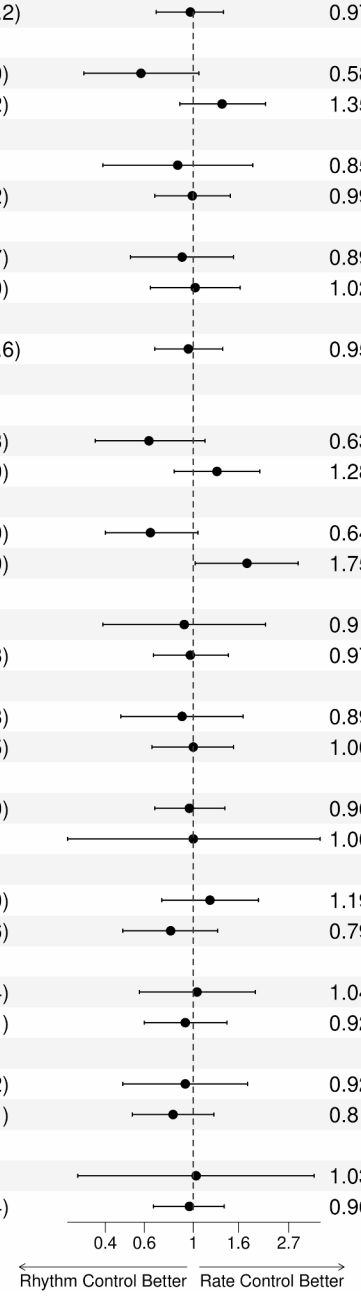
Multivariable analysis adjusted for age, gender, Sequential Organ Failure Assessment score, heart failure, hypertension, renal failure, respiratory failure, coronary artery disease, need for renal replacement therapy, need for mechanical ventilation, need for vasopressors, blood urea nitrogen (BUN), creatinine, sodium, chloride, calcium, glucose, potassium, magnesium levels inflammatory markers (white blood cell, neutrophil percentage)

HR hazard ratio, OR Odds Ratio, CI confidential interval

Discussion

The present study found no difference in 28-day mortality between critically ill septic patients with NOAF treated with rhythm control versus rate control medications.These findings remained consistent across subgroup analyses and sensitivity analyses, reinforcing the robustness of the results. Similarly, ICU mortality and 1-year mortality did not differ between the two treatment strategies. However, in the matched cohort, the rhythm control group exhibited a higher rate of successful cardioversion to sinus rhythm at 6 h, 12 h, and 24 h compared to the rate control group.

Subgroup	RateControl*	RhythmControl*	HR (95% CI)	P value	P for interaction
Overall	85/171 (49.7)	49/106 (46.2)	0.97 (0.68, 1.37)	0.85	
Gender					0.024
Female	42/76 (55.3)	14/39 (35.9)	0.58 (0.32, 1.06)	0.076	
Male	43/95 (45.3)	35/67 (52.2)	1.35 (0.87, 2.12)	0.183	
Age					0.746
< 65	21/43 (48.8)	9/23 (39.1)	0.85 (0.39, 1.86)	0.689	
≥ 65	64/128 (50.0)	40/83 (48.2)	0.99 (0.67, 1.47)	0.97	
SOFA					0.726
< 9	39/85 (45.9)	20/48 (41.7)	0.89 (0.52, 1.52)	0.661	
≥ 9	46/86 (53.5)	29/58 (50.0)	1.02 (0.64, 1.63)	0.93	
Cardiac Surgery					0.994
NO	85/168 (50.6)	48/103 (46.6)	0.95 (0.67, 1.36)	0.79	
YES	0/3 (0.0)	1/3 (33.3)			
Creatinine					0.068
< 1.3	40/82 (48.8)	16/48 (33.3)	0.63 (0.36, 1.13)	0.124	
≥ 1.3	45/89 (50.6)	33/58 (56.9)	1.28 (0.82, 2.00)	0.285	
Heart Failure					0.006
NO	57/108 (52.8)	23/64 (35.9)	0.64 (0.40, 1.05)	0.076	
YES	28/63 (44.4)	26/42 (61.9)	1.75 (1.02, 2.98)	0.041	
Renal Failure					0.863
NO	16/38 (42.1)	8/22 (36.4)	0.91 (0.39, 2.12)	0.825	
YES	69/133 (51.9)	41/84 (48.8)	0.97 (0.66, 1.44)	0.897	
Respiratory Failure					0.721
NO	29/68 (42.6)	14/38 (36.8)	0.89 (0.47, 1.68)	0.714	
YES	56/103 (54.4)	35/68 (51.5)	1.00 (0.65, 1.52)	0.987	
CRRT					0.888
NO	80/160 (50.0)	45/96 (46.9)	0.96 (0.67, 1.39)	0.839	
YES	5/11 (45.5)	4/10 (40.0)	1.00 (0.27, 3.75)	0.995	
Systolic Blood Pressure					0.247
< 109	39/87 (44.8)	25/51 (49.0)	1.19 (0.72, 1.97)	0.498	
≥ 109	46/84 (54.8)	24/55 (43.6)	0.79 (0.48, 1.29)	0.341	
Invasive Ventilation					0.747
NO	30/67 (44.8)	16/36 (44.4)	1.04 (0.57, 1.91)	0.893	
YES	55/104 (52.9)	33/70 (47.1)	0.92 (0.60, 1.42)	0.705	
Lactate					0.717
< 1.8	31/91 (34.1)	13/43 (30.2)	0.92 (0.48, 1.76)	0.806	
≥ 1.8	54/80 (67.5)	36/63 (57.1)	0.81 (0.53, 1.24)	0.337	
Vasoactive Agent					0.914
NO	7/20 (35.0)	4/11 (36.4)	1.03 (0.30, 3.52)	0.963	
YES	78/151 (51.7)	45/95 (47.4)	0.96 (0.66, 1.38)	0.818	



*no. of events / total no. (%)

Fig. 3 Subgroup analyses for 28-day all-cause mortality in the matched cohort. BMI, body mass index

Table 3 The association of NOAF treatment medications with outcomes in the prematch cohort

Outcome	Rate Control (*n* = 459)	Rhythm Control (*n* = 127)	Univariable analysis HR/OR (95%CI)	*P*-value	Multivariable analysis HR/OR (95%CI)	*P*-value
28-day mortality *n*(%)	178 (38.8)	63 (49.6)	HR 1.51 (1.14, 2.02)	0.004	HR 0.96 (0.70, 1.32)	0.799
ICU mortality *n*(%)	111 (24.2)	58(45.7)	OR 2.64 (1.75, 3.97)	< 0.001	OR 1.12 (0.67, 1.88)	0.664
1-year mortality *n*(%)	254 (55.3)	82 (64.5)	HR 1.40 (1.09, 1.79)	0.008	HR 0.96 (0.73, 1.26)	0.747

Multivariable analysis adjusted for age, gender, Sequential Organ Failure Assessment score, heart failure, hypertension, renal failure, respiratory failure, coronary artery disease, need for renal replacement therapy, need for mechanical ventilation, need for vasopressors, blood urea nitrogen (BUN), creatinine, sodium, chloride, calcium, glucose, potassium, magnesium levels inflammatory markers (white blood cell, neutrophil percentage)

HR hazard ratio, OR Odds Ratio, CI confidential interval

Sepsis frequently induces atrial fibrillation (AF), with NOAF occurring in patients without prior cardiac disease, suggesting a distinct pathophysiology [1, 5, 10, 12]. NOAF is triggered by systemic inflammation, catecholamine surges, inflammatory mediators (PAMPs, DAMPs), electrolyte imbalances, and fluid overload [5, 12, 23]. These factors exacerbate mitochondrial dysfunction, oxidative stress, and myocardial injury, increasing cardiac excitability and promoting atrial remodeling [24, 25]. The resulting structural and electrical changes facilitate reentrant circuits, sustaining AF and impairing atrial function [26, 27]. AF is a frequent and serious sepsis complication, elevating both short- and long-term mortality [28]. NOAF compromises hemodynamics, reducing cardiac output and blood pressure, thereby prolonging ICU stay, doubling ICU mortality, and increasing daily mortality risk by 50% [27]. Additionally, it elevates 28-day and 1-year mortality [1] and increases stroke risk [2]. Given its impact on outcomes, NOAF represents a critical complication in sepsis requiring optimized management.

Managing NOAF in critically ill septic patients remains a clinical challenge at present, with treatment focused on optimizing ventricular filling, cardiac output, and hemodynamic stability while minimizing organ dysfunction [29]. Rate and rhythm control are the primary strategies, withβ-blockers (BBs), nondihydropyridine calcium channel blockers (CCBs), and digoxin commonly used for rate control, offering a safer alternative to antiarrhythmic drugs.Amiodarone is the preferred rhythm control agent, facilitating sinus rhythm restoration, improving functional capacity, and reducing thromboembolic risk [30–32]. However, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial suggested a potential, though not statistically significant, trend toward higher mortality in the rhythm control group (HR 1.15, 95% CI: 0.99–1.34; $P=0.08$) [30, 33], highlighting the ongoing debate over the optimal approach.

The optimal initial medication for treating NOAF in septic patients remains controversial, with studies reporting conflicting results. Bosch NA et al. compared amiodarone, CCBs, digoxin, and BBs in 666 patients with AF during sepsis in a mixed ICU population [18]. Unlike our study, they included patients with preexisting AF, and rapid ventricular response (RVR, HR > 110 beats/min).While BBs achieved faster RVR resolution (1 h), all agents resulted in similar heart rate control by 6 h, with no significant difference in hospital mortality [amiodarone, adjusted odds ratio (OR)1.23,95% CI 0.61–2.51, $P=0.56$; CCBs, adjusted OR 0.63, 95% CI 0.30–1.34, $P=0.23$; digoxin, adjusted OR 0.33, 95% CI 0.09–1.22, $P=0.10$] [18]. Balik et al. showed that no difference in 28-day or ICU mortality between amiodarone and metoprolol (49.6% vs. 21.4% and 40.4% vs. 21.4%, respectively) during septic shock [19]. Our results were consistent with that study. However, the metoprolol group had only 14 patients, causing statistical asymmetry. Moskowitz A et al. also observed no mortality differences among 1,646 critically ill patients receiving diltiazem, amiodarone, and metoprolol [20]. Our results were consistent, but differences in AF mechanisms between septic patients and general ICU populations may affect drug efficacy and mortality outcomes [18]. Walkey JA et al. reported lower mortality in BB-treated patients compared to those receiving amiodarone (RR 0.67, 95% CI 0.59–0.77,$P<0.001$) during sepsis [17]. However, only 60% of patients were in the ICU, so the study results may not apply to all ICUs and could be biased due to confounding factors [31]. The physiologic variables used for propensity scores came from admission day, not the time of atrial fibrillation onset. Our study, focusing on ICU patients without prior AF and treated within 24 h of NOAF onset, found no significant difference in 28-day, ICU, or 1-year mortality between rhythm and rate control medications. These results were consistent with those from propensity-matched cohorts.The unadjusted association between rhythm control medications and higher mortality may reflect bias by indication, as rhythm control patients initially had higher SOFA scores, lower SBP, and greater need for invasive ventilation, vasoactive agents, and CRRT.The higher unadjusted mortality in the rhythm control group may not indicate a real treatment effect but could be due to a greater severity of illness. After matching, there were no significant differences in 28-day, ICU, or 1-year mortality between the rhythm control and rate control groups.

In our study, BBs were the most commonly used rate control medication for sepsis-related NOAF. BBs theoretically reduce atrioventricular node conduction and counteract catecholamine-induced myocardial stress by antagonizing β-1 receptors [32, 34, 14]. Small, single-center trials suggest that BBs may facilitate sinus rhythm conversion in patients with new-onset AF [27, 34], possibly by improving hemodynamics and mitigating catecholamine surges [33]. In our study, patients in rhythm control group were predominantly treated with amiodarone. Amiodarone possesses both rhythm- and rate-controlling properties, prolonging AV node conduction and promoting cardioversion [18, 35]. Our study found that rhythm control medications were associated with a higher rate of successful cardioversion at 6, 12, and 24 h compared to rate control agents.However, no significant differences in mortality were observed between the rhythm control and the rate control groups.This did not translate into a significant mortality difference between the two treatment strategies, highlighting the need for individualized management approaches.

In septic shock, previously reported mortality rates range from 25 to 30%, while in sepsis without shock, the 30-day mortality ranges from 15 to 28%. However, the 28-day mortality in our study was higher than previously reported rates for both conditions. Bernadette Corica et al. found that sepsis patients with NOAF had a 1.69-fold higher risk of in-hospital mortality and a 2.12-fold greater risk of ICU mortality compared to those without NOAF (RR 1.69, 95% CI1.47-1.96; RR 2.12,95% CI 1.86–2.43) [36]. These findings reinforce that NOAF in sepsis is associated with significantly increased ICU and hospital mortality, underscoring its prognostic importance.

The strengths of our study include a relatively large sample size and a robust propensity score weighting analysis. Septic ICU patients enrolled in our study had no history of AF.However, several limitations must be acknowledged. First, this was a retrospective observational study. Although the variables likely influencing treatment choice were well represented in this study, and we employed propensity score matching, multivariable analyses, and subgroup analyses, residual bias and unmeasured confounders may still have affected the results. Second,,data on the rate of successful cardioversion to sinus rhythm were only collected during the first 24 h, limiting our ability to analyze long-term changes in successful cardioversion rates. Moreover, there is a significant amount of missing data regarding subsequent time of conversion in the MIMIC database, making it difficult to conduct accurate analysis. Future studies could further investigate this through clinical trials.Third the safety of the rate control and rhythm control medications was not evaluated in this study. Fourth, the MIMIC database lacks explicit indications for medication use, introducing potential bias, it is possible that some of these medications were administered due to other underlying conditions or complications rather than solely for the management of AF. This ambiguity in medication indication introduces a potential bias, as the association between medication use and atrial fibrillation outcomes may be confounded by these unmeasured factors.Fifth, this was a retrospective study, and large-scale, multicenter, randomized controlled trials are needed to verify these retrospective findings in the future.

Conclusions

In critically ill patients with sepsis and NOAF, rhythm control and rate control medications showed no significant differences in 28-day mortality, ICU, or 1-year mortality. However, the superior early cardioversion rates (6–24 h) with rhythm control suggest its potential role in acute hemodynamic stabilization, particularly for patients requiring rapid rhythm restoration.This underscores the need for personalized treatment decisions, balancing immediate hemodynamic benefits with long-term safety. Future research should prioritize long-term outcomes beyond the one-year mark, delve into the mechanisms that connect rapid cardioversion to hemodynamic stability, and assess the effects of rhythm control on non-mortality outcomes, such as vasopressor dependence, cardiac function recovery, long-term arrhythmia recurrence, quality of life, and complications in septic patients.

Abbreviations

NOAF	New-onset atrial fibrillation
AF	Atrial fibrillation
ICU	Intensive care unit
MIMIC-IV	Medical information mart in intensive care-IV
ICD-9	International classification of disease-9th
Revision or ICD-10	International classification of disease-10th revision
BBs	Beta-blockers
BUN	Blood urea nitrogen
SOFA	Sequential organ failure assessment
CAD	Coronary artery disease
CRRT	Need for renal replacement therapy
SD	Standard deviation or the median
IQR	Interquartile range
HRs	Hazard ratios
CIs	Confidence intervals
KM	Kaplan–Meier
PSM	Propensity score matching
SMDs	Standardized mean differences

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06380-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Acknowledgements

No.

Author contributions

CW, JL, XZ, and QL conceived and designed the study. CW, MZ, and JL collected the data. CW, CZ, TJ, LJ, XZ, and HF performed the data analysis and interpretation. The initial draft of the manuscript was prepared by CW, XZ, and HF. All authors reviewed, contributed to, and approved the final version of the article. The corresponding author ultimately submitted the manuscript for publication.

Funding

This work was supported by the Natural Science Foundation of Fujian Province (Grant Number: 2020J011095), the Fujian Provincial Health Technology Project (Grant Number: 2023GGA003), and the Sailing Fund of Fujian Medical University (Grant Number: 2022QH1309). Joint Funds for the innovation of science and Technology,Fujian province(Grant Number:2024Y9011)

Data availability

Data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The MIMIC-IV database has received ethical approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA). All the data were identified in this database, patient identity information was removed, and the requirement for individual patient consent was not met.

Consent for publication
Not applicable.

Conflict of interest
The authors declare that they have no conflicts of interest to disclose.

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Received: 30 September 2024 / Accepted: 13 March 2025
Published online: 07 May 2025

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