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Impact of New-Onset Atrial Fibrillation on Mortality in Critically Ill Patients

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Background: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia in critically ill patients and significantly impacts mortality. This study sought to evaluate the impact of new-onset AF on mortality in a critically ill population.

Methods: This study identified 48018 adult patients admitted to the ICU from the Medical Information Mart for Intensive Care (MIMIC)-IV database. Patients were categorized as no AF, pre-existing AF, or new-onset AF. We analyzed mortality at 3 months, 6 months, and 1 year.

Results: Overall, 31,562 (65.73%) patients had no AF, 4877 (10.16%) had pre-existing AF, and 11,579 (24.11%) had new-onset AF. Median ages were 61.47 years (no AF), 76.12 years (pre-existing AF), and 75.26 years (new-onset AF). New-onset AF was associated with the highest mortality rates: 25.16% at 3 months, 29.23% at 6 months, and 34.04% at 1 year, compared to 17.94%, 22.55%, and 28.52% for pre-existing AF, and 14.54%, 17.25%, and 20.69% for no AF respectively ($p < 0.001$ for all). Multivariate Cox regression indicated that new-onset AF significantly increased the risk of 1-year mortality by 15.5% compared to no AF (HR: 1.155, 95% CI: 1.101–1.212; $p < 0.001$) and by 23.9% compared to pre-existing AF (HR: 1.239, 95% CI: 1.164–1.318; $p < 0.001$). Kaplan-Meier analysis confirmed lower survival probabilities for new-onset AF over one year compared to the other groups ($p < 0.001$).

Conclusion: In patients with critical illness, new-onset AF is associated with an increased risk of mortality compared with pre-existing AF or no AF.

Keywords: atrial fibrillation, mortality, intensive care unit

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice and is particularly prevalent among critically ill patients.[1–7] The incidence and implications of AF in the intensive care unit (ICU) setting present unique challenges, as it is associated with significant morbidity and mortality.[1,2,5–7] AF may be worsened or triggered in critically ill patients due to the presence of multiple comorbidities. The presence of AF can negatively affect heart function and worsen the severity of other life-threatening conditions, resulting in an intricate interaction of health problems that can greatly impact patient outcomes.[1,5,6] Prior studies have shown a correlation between AF and elevated mortality rates in the general public, but its specific influence on critically ill patients, who tend to face more adverse outcomes, is not well understood.[3,4]

Prophylactic strategies are crucial for reducing the incidence of new-onset AF and improving patient outcomes in the ICU. These strategies typically include rigorous management of electrolyte balances, with a particular focus on magnesium levels, due to its critical role in maintaining cardiac electrical stability.[8–10] Additionally, the early identification and management of sepsis, along with the appropriate treatment of underlying conditions such as heart failure and acute coronary syndromes, are vital components of AF prevention.[9] Despite these measures, a notable gap persists in the

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literature, particularly concerning robust data tailored to the unique needs of critically ill patients, underscoring the imperative for more targeted research to develop evidence-based practices.

This research leverages data from the Medical Information Mart for Intensive Care (MIMIC)-IV database, which provides a comprehensive overview of patient histories, treatment interventions, and outcomes across numerous hospitalizations at a major medical center.[11–13] By categorizing patients based on their AF status—no AF, pre-existing AF, and new-onset AF—this study aimed to elucidate the differential impacts of AF on patient outcomes in the ICU. The primary goal was to assess whether the presence of new-onset AF contributes to an increased risk of mortality and how these conditions influence survival rates over a one-year period post-ICU admission. Comprehension of these dynamics may elevate patient care strategies, directing more focused interventions and potentially enhancing prognostic outcomes for this susceptible patient population.

Methods

Data Source and Ethical Considerations

This study utilized the MIMIC-IV, version 2.2, a comprehensive critical care database encompassing hospitalized patients and ICU admissions between 2008 and 2019 at Beth Israel Deaconess Medical Center, Boston, Massachusetts.[11–13] The data accessed includes detailed patient records from emergency and ICU departments. Dr. Zhang HD, the primary investigator, secured access to this de-identified data set under certification number 57478823, ensuring compliance with privacy regulations. An Institutional Review Board exemption was granted by Fuwai Hospital for this study due to the use of de-identified data from a publicly available database, which negates the need for individual patient consent.

Cohort Selection and Data Extraction

The study encompassed adult critically ill patients admitted to the ICU, and the selection criteria are shown in Figure 1. The study focused exclusively on the first ICU admission of critically ill patients to avoid duplication in cases of multiple admissions. Patient diagnoses were categorized using the "diagnoses_icd" and "d_icd_diagnoses" tables of the MIMIC-IV database, adhering to the International Classification of Diseases criteria. Based on clinical notes and discharge diagnoses, specific attention was given to identifying patients with a history of AF and those who developed new-onset AF during their hospital stay. Comprehensive data extraction included demographics, vital signs at baseline, severity of illness scores, existing comorbidities, and administered treatments (Table 1). Patients with missing data for the above parameters were not included. It needs to be mentioned that body mass index, liver function tests, lipid profiles, and cardiac enzymes were excluded due to more than 20% data unavailability. The primary outcome assessed was the 1-year mortality post-admission. Other outcomes included ICU mortality, in-hospital mortality, 3-month and 6-month mortalities. Data extraction was performed using pgAdmin4 version 7.6.

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges (IQR), while categorical variables were reported as percentages. Comparative analyses between two groups were conducted using the Mann–Whitney *U*-test,

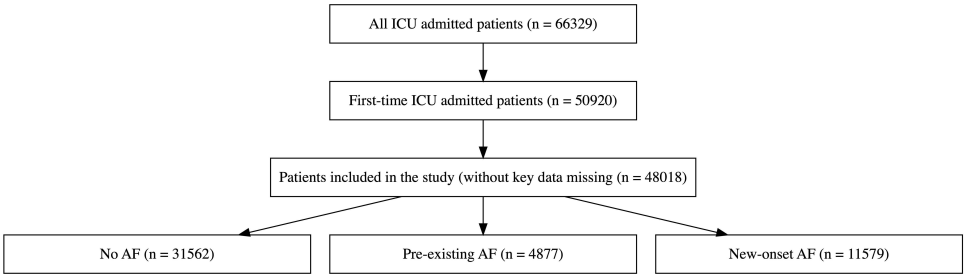

Figure 1 Flow chart for patient enrollment.
Abbreviations: ICU, intensive care unit; AF, atrial fibrillation.

Table 1 Demographic and Clinical Characteristics of Patients Stratified by AF Status

	Overall (n = 48018)	No AF (n = 31562)	Pre-existing AF (n = 4877)	New-onset AF (n = 11579)	P value*
Age, years	66.78 (54.58–78.24)	61.47 (49.46–72.78)	76.12 (66.40–84.28)	75.26 (66.21–83.54)	<0.001
Women, n (%)	21,409 (44.59%)	14,431 (45.72%)	2136 (43.80%)	4842 (41.82%)	<0.001
Ethnicity					<0.001
White, n (%)	32,202 (67.06%)	20,201 (64.00%)	3660 (75.05%)	8341 (72.04%)	
Black, n (%)	4440 (9.25%)	3300 (10.46%)	424 (8.69%)	716 (6.18%)	
Asian, n (%)	1425 (2.97%)	1015 (3.22%)	139 (2.85%)	271 (2.34%)	
Hispanic/Latino, n (%)	1638 (3.41%)	1290 (4.09%)	108 (2.21%)	240 (2.07%)	
Other/Unknown, n (%)	8313 (17.31%)	5756 (18.24%)	546 (11.20%)	2011 (17.37%)	
Marital status					<0.001
Married, n (%)	21,652 (45.09%)	13,725 (43.49%)	2322 (47.61%)	5605 (48.41%)	
Divorced, n (%)	3386 (7.05%)	2273 (7.20%)	341 (6.99%)	772 (6.67%)	
Single, n (%)	12,925 (26.92%)	9792 (31.02%)	989 (20.28%)	2144 (18.52%)	
Widowed, n (%)	5891 (12.27%)	2842 (9.00%)	994 (20.38%)	2055 (17.75%)	
Other/Unknown, n (%)	4164 (8.67%)	2930 (9.28%)	231 (4.74%)	1003 (8.66%)	
Insurance					<0.001
Medicare, n (%)	20,709 (43.13%)	11,099 (35.17%)	2993 (61.37%)	6617 (57.15%)	
Medicaid, n (%)	3442 (7.17%)	2893 (9.17%)	162 (3.32%)	387 (3.34%)	
Other, n (%)	23,867 (49.70%)	17,570 (55.67%)	1722 (35.31%)	4575 (39.51%)	
Admission type					<0.001
Emergency/urgency, n (%)	35,291 (73.50%)	23,338 (73.94%)	3714 (76.15%)	8239 (71.15%)	
Elective, n (%)	1708 (3.56%)	809 (2.56%)	236 (4.84%)	663 (5.73%)	
Other, n (%)	11,019 (22.95%)	7415 (23.49%)	927 (19.01%)	2677 (23.12%)	
Severity Scores					
SOFA	4.00 (2.00–6.00)	3.00 (1.00–6.00)	4.00 (2.00–7.00)	5.00 (2.00–7.00)	<0.001
LODS	4.00 (2.00–6.00)	3.00 (2.00–5.00)	5.00 (3.00–7.00)	5.00 (3.00–7.00)	<0.001
APS III	38.00 (29.00–52.00)	36.00 (27.00–48.00)	44.00 (34.00–57.00)	43.00 (32.00–58.50)	<0.001
OASIS	30.00 (24.00–36.00)	29.00 (23.00–35.00)	32.00 (26.00–38.00)	33.00 (27.00–39.00)	<0.001
SAPS II	34.00 (25.00–43.00)	31.00 (22.00–40.00)	38.00 (31.00–46.00)	39.00 (31.00–48.00)	<0.001
SIRS	3.00 (2.00–3.00)	3.00 (2.00–3.00)	3.00 (2.00–3.00)	3.00 (2.00–3.00)	<0.001
Vital signs					
Heart rate, bpm	85.08 (75.08–97.25)	84.69 (74.60–96.46)	86.99 (76.24–100.78)	85.42 (75.90–97.94)	<0.001
Systolic blood pressure, mmHg	119.06 (109.00–131.76)	120.04 (109.68–132.42)	119.05 (108.75–132.13)	116.63 (107.53–129.46)	<0.001
Diastolic blood pressure, mmHg	64.14 (57.24–72.36)	65.20 (58.15–73.39)	63.85 (56.88–71.61)	61.62 (55.23–69.50)	<0.001
Mean blood pressure, mmHg	79.08 (72.46–87.46)	80.08 (73.14–88.44)	78.41 (72.00–86.50)	76.96 (71.14–84.72)	<0.001
Respiratory rate, breaths per minute	19.00 (16.80–21.85)	18.64 (16.53–21.40)	20.00 (17.76–22.99)	19.55 (17.27–22.44)	<0.001
Oxygen saturation, (%)	97.36 (96.00–98.61)	97.32 (95.97–98.61)	97.46 (96.04–98.65)	97.43 (95.96–98.59)	0.006
Reason for Hospital Admission					< 0.001
Cardiac, n (%)	13,290 (27.68)	6679 (21.16)	1911 (39.18)	4700 (40.59)	
Non-cardiac, n (%)	34,728 (72.32)	24,883 (78.84)	2966 (60.82)	6879 (59.41)	
Comorbidities					
Hypertension, n (%)	20,963 (43.66%)	13,527 (42.86%)	2052 (42.08%)	5384 (46.50%)	<0.001
Coronary artery disease, n (%)	14,970 (31.18%)	7622 (24.15%)	2162 (44.33%)	5186 (44.79%)	<0.001
Myocardial infarction, n (%)	7662 (15.96%)	4099 (12.99%)	1049 (21.51%)	2514 (21.71%)	<0.001
Cardiomyopathy, n (%)	1440 (3.00%)	622 (1.97%)	292 (5.99%)	526 (4.54%)	<0.001
Heart failure, n (%)	11,070 (23.05%)	4263 (13.51%)	2450 (50.24%)	4357 (37.63%)	<0.001
Hyperlipidemia, n (%)	17,701 (36.86%)	10,141 (32.13%)	2237 (45.87%)	5323 (45.97%)	<0.001
Sleep apnea, n (%)	4327 (9.01%)	2552 (8.09%)	592 (12.14%)	1183 (10.22%)	<0.001
Peripheral vascular disease, n (%)	5276 (10.99%)	2807 (8.89%)	758 (15.54%)	1711 (14.78%)	<0.001
Cerebrovascular disease, n (%)	7908 (16.47%)	4932 (15.63%)	781 (16.01%)	2195 (18.96%)	<0.001
Dementia, n (%)	1749 (3.64%)	980 (3.10%)	223 (4.57%)	546 (4.72%)	<0.001
Chronic pulmonary disease, n (%)	11,334 (23.60%)	6560 (20.78%)	1523 (31.23%)	3251 (28.08%)	<0.001
Rheumatic disease, n (%)	1563 (3.26%)	897 (2.84%)	202 (4.14%)	464 (4.01%)	<0.001
Peptic ulcer, n (%)	1350 (2.81%)	884 (2.80%)	148 (3.03%)	318 (2.75%)	0.582

(*Continued*)

Table 1 (Continued).

	Overall (n = 48018)	No AF (n = 31562)	Pre-existing AF (n = 4877)	New-onset AF (n = 11579)	P value*
Liver disease, n (%)	5339 (11.12%)	3890 (12.32%)	404 (8.28%)	1045 (9.02%)	<0.001
Diabetes, n (%)	13,189 (27.47%)	7869 (24.93%)	1661 (34.06%)	3659 (31.60%)	<0.001
Paraplegia, n (%)	2528 (5.26%)	1569 (4.97%)	231 (4.74%)	728 (6.29%)	<0.001
Renal disease, n (%)	8620 (17.95%)	4156 (13.17%)	1563 (32.05%)	2901 (25.05%)	<0.001
Cancer, n (%)	6289 (13.10%)	4153 (13.16%)	600 (12.30%)	1536 (13.27%)	0.213
Aids, n (%)	264 (0.55%)	231 (0.73%)	11 (0.23%)	22 (0.19%)	<0.001
Laboratory data					
White blood cell, k/ul	10.50 (7.50–14.40)	10.40 (7.50–14.30)	10.20 (7.40–14.10)	10.80 (7.80–15.00)	<0.001
Hemoglobin, g/dl	10.90 (9.30–12.40)	11.10 (9.50–12.60)	10.50 (9.00–12.00)	10.40 (8.90–12.00)	<0.001
Hematocrit, %	32.80 (28.20–37.40)	33.40 (28.70–37.70)	32.00 (27.60–36.60)	31.60 (27.35–36.40)	<0.001
Platelet, k/ul	192.00 (140.00–253.00)	198.00 (146.00–259.00)	188.00 (137.00–247.00)	177.00 (130.00–238.00)	<0.001
Urea nitrogen, mg/dl	18.00 (12.00–28.00)	16.00 (11.00–24.00)	23.00 (16.00–38.00)	21.00 (15.00–33.00)	<0.001
Serum creatinine, mg/dl	0.90 (0.70–1.30)	0.90 (0.70–1.20)	1.10 (0.80–1.70)	1.00 (0.80–1.50)	<0.001
Glucose, mg/dl	124.00 (103.00–157.00)	123.00 (102.00–156.00)	125.00 (103.00–159.00)	126.00 (104.00–157.00)	<0.001
Sodium, mEq/L	139.00 (136.00–141.00)	139.00 (136.00–141.00)	139.00 (136.00–141.00)	139.00 (136.00–141.00)	0.028
Calcium, mg/dL	8.40 (7.90–8.80)	8.40 (7.90–8.90)	8.40 (8.00–8.90)	8.40 (7.90–8.80)	<0.001
Potassium, mEq/L	4.10 (3.70–4.50)	4.10 (3.70–4.50)	4.20 (3.80–4.60)	4.20 (3.80–4.60)	<0.001
Chloride, mEq/L	105.00 (101.00–108.00)	105.00 (101.00–108.00)	104.00 (100.00–108.00)	105.00 (101.00–109.00)	<0.001
Bicarbonate, mEq/L	23.00 (21.00–25.00)	23.00 (21.00–25.00)	24.00 (21.00–26.00)	23.00 (21.00–25.00)	<0.001
Aniongap, mEq/L	14.00 (12.00–16.00)	14.00 (12.00–16.00)	14.00 (12.00–17.00)	14.00 (12.00–17.00)	<0.001
Interventions					
Mechanical ventilation, n (%)	16,991 (35.38%)	10,518 (33.32%)	1558 (31.95%)	4915 (42.45%)	<0.001
CRRT, n (%)	1328 (2.77%)	601 (1.90%)	159 (3.26%)	568 (4.91%)	<0.001
Medications					
Antiplatelets, n (%)	22,474 (46.80%)	12,095 (38.32%)	3008 (61.68%)	7371 (63.66%)	<0.001
Lipid lowering drugs, n (%)	21,612 (45.01%)	11,933 (37.81%)	2961 (60.71%)	6718 (58.02%)	<0.001
Oral anticoagulants, n (%)	11,705 (24.38%)	4061 (12.87%)	2676 (54.87%)	4968 (42.91%)	<0.001
Beta-blockers, n (%)	29,027 (60.45%)	15,701 (49.75%)	3922 (80.42%)	9404 (81.22%)	<0.001
DHP CCB, n (%)	9863 (20.54%)	6438 (20.40%)	946 (19.40%)	2479 (21.41%)	0.008
Non-DHP CCB, n (%)	4510 (9.39%)	954 (3.02%)	1153 (23.64%)	2403 (20.75%)	<0.001
Class IC Antiarrhythmic drugs, n (%)	173 (0.36%)	23 (0.07%)	77 (1.58%)	73 (0.63%)	<0.001
Class III Antiarrhythmic drugs, n (%)	5620 (11.70%)	560 (1.77%)	1382 (28.34%)	3678 (31.76%)	<0.001
Digoxin, n (%)	2057 (4.28%)	151 (0.48%)	698 (14.31%)	1208 (10.43%)	<0.001
ACEI, n (%)	11,053 (23.02%)	6610 (20.94%)	1413 (28.97%)	3030 (26.17%)	<0.001
ARB, n (%)	3450 (7.18%)	1915 (6.07%)	494 (10.13%)	1041 (8.99%)	<0.001
ARNI, n (%)	49 (0.10%)	16 (0.05%)	14 (0.29%)	19 (0.16%)	<0.001
MRA, n (%)	2153 (4.48%)	1228 (3.89%)	390 (8.00%)	535 (4.62%)	<0.001
Loop diuretics, n (%)	22,833 (47.55%)	11,833 (37.49%)	3246 (66.56%)	7754 (66.97%)	<0.001
Thiazides/thiazide-like diuretics, n (%)	4415 (9.19%)	2491 (7.89%)	564 (11.56%)	1360 (11.75%)	<0.001
Oral glucose-lowering drugs, n (%)	2979 (6.20%)	1830 (5.80%)	291 (5.97%)	858 (7.41%)	<0.001
Insulin, n (%)	28,729 (59.83%)	17,746 (56.23%)	2958 (60.65%)	8025 (69.31%)	<0.001
PPIs, n (%)	23,193 (48.30%)	14,411 (45.66%)	2665 (54.64%)	6117 (52.83%)	<0.001
Inotropes and vasopressors, n (%)	18,692 (38.93%)	10,290 (32.60%)	2075 (42.55%)	6327 (54.64%)	<0.001

Note: *Comparisons among the three subgroups.

Abbreviations: AF, atrial fibrillation; APS III, Acute Physiologic Score III; LODS, Logistic Organ Dysfunction Score; OASIS, the Oxford Acute Severity of Illness Score; SAPS II, Simplified Acute Physiology Score II; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment; CRRT, continuous renal replacement therapy; DHP CCB, dihydropyridine calcium channel blocker; Non-DHP, non- dihydropyridine; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; PPI, proton pump inhibitors; ICU, intensive care unit.

whereas the Kruskal–Wallis test was applied for multiple group comparisons. Chi-square tests were employed for categorical data analysis. Survival differences by AF status were illustrated through Kaplan-Meier curves, with significance tested using log-rank p-values. Further, a multivariate Cox regression model was developed to quantify the risk of mortality associated with AF status, adjusting for clinically significant covariates, with hazard ratios (HRs) and 95%

confidence intervals (CIs) calculated. To ensure the assumption of proportional hazards was met, we utilized the cox.zph function in R, which performs a global test of the proportional hazards assumption as well as individual tests for each covariate included in the model. We maintained the integrity of continuous confounders by modelling them as continuous variables, avoiding categorization prior to model entry to prevent the loss of information and potential introduction of confounding. Our analysis utilized two main models to investigate the impacts of AF on mortality among critically ill patients. The basic model adjusted for age and gender, which are fundamental demographic factors known to significantly influence outcomes in our study population, serving as a baseline for more complex analyses. The multivariate model adjusted for additional parameters, including all demographics, comorbidities, vital signs, laboratory parameters, disease severity scores, and treatment information, as shown in Table 1. These variables were selected based on their clinical significance and their potential impact on patient outcomes, supported by existing literature and our preliminary analyses which identified them as relevant factors. Incomplete data records were excluded from the analysis, so no data imputation was necessary. Outliers were identified using graphical methods, such as box plots. After careful consideration, we decided to manually remove outliers that were clearly errors or anomalies unrelated to the clinical conditions under investigation. A p-value of less than 0.05 was deemed statistically significant. All data management and analysis were conducted using R software, version 4.3.2.

Results

Cohort Characteristics

The demographic and clinical characteristics of the study population, comprising 48,018 critically ill patients, are displayed based on the status of AF in Table 1. The overall median age was 66.78 years, with interquartile ranges from 54.58 to 78.24 years. Regarding sex distribution, 44.59% were female. Patients were categorized into three groups: no AF (n = 31,562), pre-existing AF (n = 4887), and new-onset AF (n = 11,579). The median age was significantly higher in patients with pre-existing and new-onset AF (76.12 years and 75.26 years, respectively) compared to those without AF (61.47 years, $p < 0.001$). Females comprised a lower percentage of the new-onset AF group (41.82%) compared to the no AF group (45.72%, $p < 0.001$). Ethnic diversity showed significant differences, with white patients being more prevalent in the pre-existing AF group (75.05%, $p < 0.001$).

Comorbidity profiles indicated higher prevalence rates of coronary artery disease, heart failure, and diabetes among patients with AF, particularly those with pre-existing AF ($p < 0.001$). Vital signs at admission, including heart rate and blood pressure, showed minor but statistically significant differences between the groups ($p < 0.001$). The severity of illness, assessed using scores like SOFA and SAPS II, was higher in the AF groups, especially in patients with new-onset AF ($p < 0.001$). Laboratory tests revealed differences in hemoglobin, platelet counts, and renal function markers between the groups, with generally worse values in the AF groups ($p < 0.001$). Mechanical ventilation use was highest in the new-onset AF group (48.40%, $p < 0.001$). Medication usage, including antiplatelets and lipid-lowering drugs, was significantly different across groups, with higher use in the AF groups ($p < 0.001$). Additionally, the administration of inotropes and vasopressors shows variation among the groups, with 32.60% in patients with no AF, 42.55% in those with pre-existing AF, and 54.64% in those with new-onset AF, underscoring the potential influence of these interventions as risk factors for the development of new-onset AF in critically ill patients.

Outcomes and Kaplan-Meier Survival Analysis

Outcome results are listed in Table 2. Mortality rates varied dramatically, with new-onset AF associated with the highest ICU mortality (10.37%), in-hospital mortality (15.12%), 3-month mortality (25.16%), 6-month mortality (29.23%), and 1-year mortality (34.04%, $p < 0.001$ for all). The length of stay in both the hospital and ICU was longest among those with new-onset AF, highlighting the strong association between AF and prolonged hospitalization for critically ill patients ($p < 0.001$ for both).

The Kaplan-Meier survival curve illustrates the one-year and short-term survival probabilities for critically ill patients categorized into three groups based on the status of AF (Figures 2 and 3). The results indicated significantly lower survival probabilities for patients with new-onset AF compared to those with no AF and pre-existing AF over a one-year period (Figure 2, $p < 0.001$). This pattern remained consistent in the 6-month and 3-month follow-up periods (Figure 3).

Table 2 Outcomes Stratified by AF Status

	Overall (n = 48018)	No AF (n = 31562)	Pre-existing AF (n = 4877)	New-onset AF (n = 11579)	P value*
Outcomes					
Length of ICU stay, days	1.94 (1.11–3.68)	1.82 (1.05–3.23)	2.13 (1.17–3.97)	2.31 (1.28–4.57)	<0.001
Length of hospital stay, days	6.68 (3.91–11.43)	6.03 (3.60–10.52)	7.69 (4.72–12.64)	7.79 (4.88–13.05)	<0.001
ICU mortality	3246 (6.76%)	1776 (5.63%)	269 (5.52%)	1201 (10.37%)	<0.001
In-Hospital mortality	4689 (9.77%)	2532 (8.02%)	406 (8.32%)	1751 (15.12%)	<0.001
3-month mortality	8378 (17.45%)	4590 (14.54%)	875 (17.94%)	2913 (25.16%)	<0.001
6-month mortality	9930 (20.68%)	5445 (17.25%)	1100 (22.55%)	3385 (29.23%)	<0.001
1-year mortality	11862 (24.70%)	6530 (20.69%)	1391 (28.52%)	3941 (34.04%)	<0.001

Note: *Comparisons among the three subgroups.
Abbreviation: ICU, intensive care unit.

COX Regression Analysis

Cox proportional hazard models were utilized to assess the impact of AF on mortality (Table 3). The unadjusted model revealed that new-onset AF patients had a 1.80 times higher risk of one-year mortality compared to those without AF (95% CI: 1.729, 1.872, $p < 0.001$). Even after adjustment for age and gender (the basic model), and further adjustments for demographics, comorbidities, and clinical variables (the multivariate model), the increased risk persisted though attenuated (HR 1.155, 95% CI: 1.101, 1.212, $p < 0.001$). When compared to pre-existing AF, new-onset AF also showed a significantly increased risk of 1-year mortality across all models, with the most comprehensive model showing an HR of 1.239 (95% CI: 1.164, 1.318, $p < 0.001$). Furthermore, across the short-term periods assessed—three months and six months—new-onset AF consistently showed a stronger association with higher mortality risk compared to no AF and pre-existing AF.

Discussion

AF is associated with increased comorbidity and mortality in both the general population and critically ill patients.[1,3–7] In this study, we investigated the impact of new-onset AF on the survival of critically ill patients. The results of our study support the notion that the new-onset of AF is a significant marker of a grim prognosis, linked to elevated one-year and

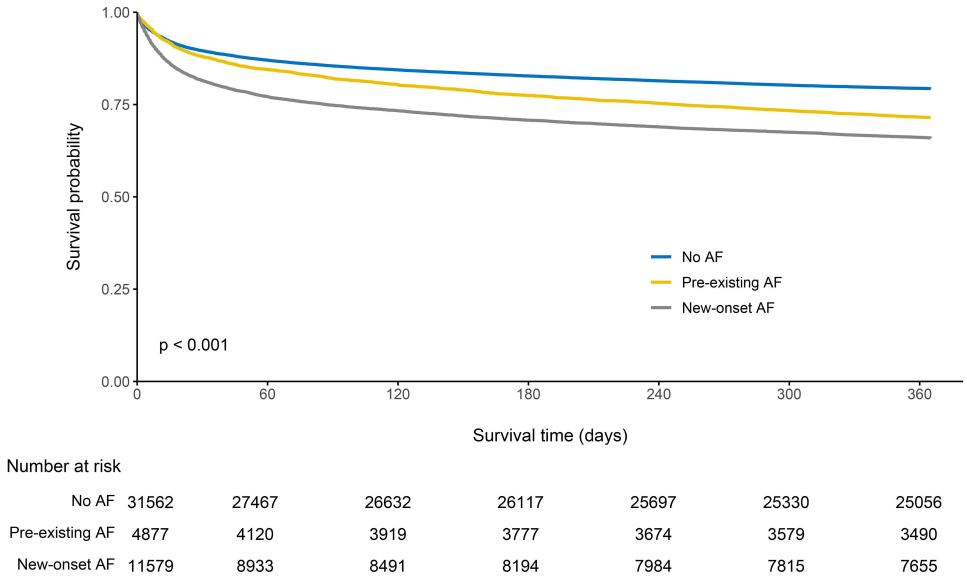

Figure 2 Kaplan-Meier curves of 1-year mortality stratified by AF status.
Abbreviation: AF, atrial fibrillation.

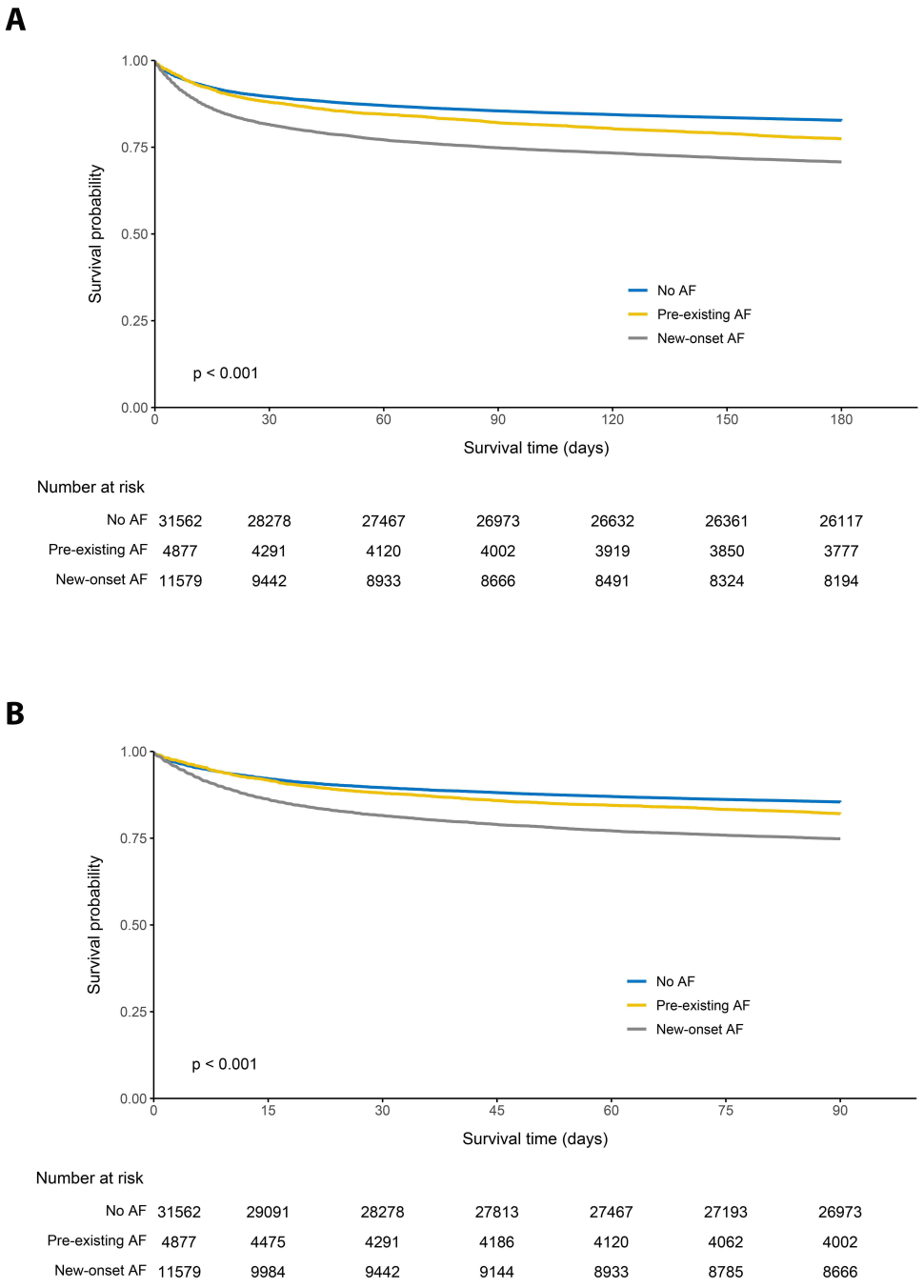

Figure 3 Kaplan-Meier curves of short-term mortality stratified by AF status. (**A**) 6-month mortality; (**B**) 3-month mortality.
Abbreviation: AF, atrial fibrillation.

short-term mortality rates in comparison to patients without AF or with pre-existing AF. The results of this study bring attention to the significant effect of AF on mortality in critically ill patients, especially underscoring the elevated risks associated with new-onset AF.

The incidence of new-onset AF in critically ill patients varies widely, reported as ranging from 1.7% to over 43.9% depending on the patient population.[6,7] This variability is impacted by factors such as the critical illness type, disease severity, patient demographics, and pre-existing health conditions.[6,14,15] An increase in incidence rates is noted in patients with septic shock, myocardial infarction, and those undergoing major surgeries, particularly cardiac and thoracic procedures.[16–18] In the present study, a comprehensive population of ICU patients was included, and new-onset AF was

Table 3 Association of AF Status and Mortality Evaluated by COX Regression Analysis

	Hazard Ratio (95% CI)					
	New-onset AF vs No AF			New-onset AF vs Pre-existing AF		
	No AF	New-onset AF	p-value	Pre-existing AF	New-onset AF	p-value
1-year mortality						
Unadjusted model	1 (Reference)	1.800 (1.729, 1.872)	< 0.001	1 (Reference)	1.271 (1.195, 1.351)	< 0.001
Basic model	1 (Reference)	1.241 (1.190, 1.293)	< 0.001	1 (Reference)	1.299 (1.222, 1.381)	< 0.001
Multivariate model	1 (Reference)	1.155 (1.101, 1.212)	< 0.001	1 (Reference)	1.239 (1.164, 1.318)	< 0.001
6-month mortality						
Unadjusted model	1 (Reference)	1.825 (1.748, 1.905)	< 0.001	1 (Reference)	1.374 (1.284, 1.471)	< 0.001
Basic model	1 (Reference)	1.260 (1.205, 1.318)	< 0.001	1 (Reference)	1.404 (1.312, 1.503)	< 0.001
Multivariate model	1 (Reference)	1.156 (1.098, 1.218)	< 0.001	1 (Reference)	1.262 (1.178, 1.353)	< 0.001
3-month mortality						
Unadjusted model	1 (Reference)	1.839 (1.756, 1.927)	< 0.001	1 (Reference)	1.477 (1.370, 1.593)	< 0.001
Basic model	1 (Reference)	1.280 (1.219, 1.344)	< 0.001	1 (Reference)	1.509 (1.399, 1.627)	< 0.001
Multivariate model	1 (Reference)	1.155 (1.091, 1.222)	< 0.001	1 (Reference)	1.271 (1.176, 1.373)	< 0.001

Notes: Basic model: adjustment for age and gender. Multivariate model: basic model plus adjustment for all demographics, comorbidities, vital signs, laboratory parameters, disease severity scores, and treatment.
Abbreviations: CI, confidence interval; AF, atrial fibrillation.

identified in 26.8% of the 43,141 patients without a history of AF. Age, severity of illness, inflammatory conditions, cardiac burden, electrolyte imbalances, and neurological issues are commonly linked to new-onset AF in critically ill individuals.[6,10,14,15,19] In critically ill patients, the systemic inflammatory response and release of stress hormones contribute to autonomic dysfunction and cardiovascular instability, which are potent triggers for AF. Additionally, organ dysfunction, particularly in the respiratory and renal systems, often leads to significant intravascular volume shifts and electrolyte disturbances, exacerbating the risk of AF. Pulmonary artery catheter use and the presence of a respiratory tract infection have also been identified as independent risk factors, highlighting the complex interplay of clinical interventions and disease processes in the development of AF in this patient population.[6,10,14,15,19] The prediction of new-onset AF is being investigated in an ongoing project and was not in the scope of this study.

This study examines the impact of new-onset AF on increased mortality among critically ill patients, a topic that has been subject to limited and varied conclusions in existing research.[9,20–22] Walkey et al reported that among patients with severe sepsis, patients with new-onset AF were at increased risk of in-hospital stroke and death compared with patients with no AF and patients with pre-existing AF.[21] Lancini et al indicated that new-onset AF was associated with long-term mortality in the univariate analysis.[20] While in another study new-onset AF was not associated with death or requiring discharge to long-term care among critically ill patients.[22] In our study, the high 1-year mortality rate in the new-onset AF group (34.04%) compared to those with pre-existing AF (28.52%) and no AF (20.69%) highlights the severity of new-onset AF as a comorbid condition in the ICU (Table 2). Kaplan-Meier survival analyses further demonstrated the worst survival outcomes in these patients (Figures 2 and 3). Patients with new-onset AF exhibited a more rapid decline in survival curves, indicating that the abrupt onset of AF during critical illness may signal heightened physiological stress and a greater disease load. The risk related to new-onset AF was examined more comprehensively by multivariate Cox regression models, taking into account a variety of demographic, clinical, and treatment-related variables. Even after these adjustments, new-onset AF remained significantly associated with a higher risk of death. The continual connection noted in diverse models suggests that the elevated risk of death is not exclusively linked to preexisting or concurrent conditions, but is significantly shaped by the presence of AF. The observation was notably alarming and underscored the need for a proactive approach in managing such patients to lessen the risks tied to the sudden emergence of AF.

The connection between new-onset AF and increased mortality in critically ill patients is intricate, involving both physiological responses to critical illness and the inherent risks of AF.[1,4,6] At the forefront of issues with AF is its significant impact on cardiac output, as the loss of atrial contraction and the irregular rapid ventricular rates commonly

seen in AF can decrease myocardial efficiency and stroke volume, ultimately affecting systemic circulation.[1,3,4] In patients with underlying health issues, the weakened cardiac function plays a vital role and could result in reduced organ blood flow, aggravating existing pathologies. Additionally, AF markedly increases the risk of thromboembolic events. These incidents greatly amplify the intricacy of patient care and can rapidly elevate the risk of patient mortality. Moreover, the task of managing fluid and hemodynamic stability becomes particularly challenging when AF is involved. The unpredictable heart rhythms not only interfere with controlling blood pressure but also upset the fine balance of retaining and expelling fluids. AF may be initiated by the stress of critical illness, as the body's reaction to stress can lead to elevated sympathetic nervous system activity and altered levels of electrolytes. As AF progresses, it can intensify the stress on the body, exacerbating the patient's condition in a vicious circle. This interaction between critical illness and AF creates a feedback loop that can significantly complicate clinical management strategies, making it difficult to stabilize the patient effectively.[1,6] The results bring to light the idea that new-onset AF is not just a major comorbidity but can also intensify pre-existing conditions, resulting in a swift decline in the patient's condition.

The higher mortality risk associated with new-onset AF in critically ill patients, in contrast to pre-existing AF, is a compelling discovery that requires thorough scrutiny. One study showed that pre-existing AF was not, but new-onset AF was associated with an increased risk for death in patients with heart failure.[23] In an analysis of the Framingham Heart Study, it was found that the presence of AF in individuals with heart failure did not contribute to mortality, but the development of new AF was associated with increased mortality.[24] Another study demonstrated that new-onset AF had an increased risk of in-hospital death than no AF and pre-existing AF in critically ill patients, which was consistent with our findings.[25] The differentiation between these two forms of AF has important implications for their perception and treatment in clinical settings, especially in ICU. The underlying reasons of the different impact on mortality of these two forms of AF are unknown. One could speculate that a possible explanation for the higher mortality rates in new-onset AF may be the pathophysiological conditions surrounding its development. AF that develops suddenly often happens during periods of acute stress, like sepsis, surgery, or acute myocardial infarction, when the body's normal balance is already significantly disturbed.[7,25] Conversely, pre-existing AF typically arises over an extended period, giving the body an opportunity to adjust to the irregular heart rhythm.[7,25] Patients who have been dealing with AF for an extended period may have had the chance to stabilize or control the hemodynamic effects of the rhythm, or they may be receiving chronic treatment regimens that alleviate some of the risks associated with AF. Severe illnesses can serve as powerful catalysts for the development of new AF by aggravating pre-existing vulnerabilities, including structural heart changes, inflammation, and stress-related sympathetic activation. These factors may lead to AF in patients with no history of arrhythmias, indicating a pronounced level of cardiac and systemic instability. The abrupt onset of AF in these scenarios points to an extra strain on a system that is already operating at its peak, leading to an increased risk of adverse outcomes like death.[7,25] In summary, the greater risk of death associated with new-onset AF in critically ill patients underscores the serious consequences of this arrhythmia in acute stress situations. This distinction calls for targeted clinical strategies and research efforts to better manage and understand new-onset AF in the ICU setting.

The findings of this study underscore the significant impact of new-onset AF on the mortality of critically ill patients and highlight potential intervention points for improving outcomes. Incorporating routine screening for AF risk factors such as electrolyte imbalances, cardiac stress, and inflammatory markers could facilitate earlier identification and management of patients at high risk for developing AF.[6,7,26,27] Ultimately, personalizing care based on individual risk profiles, could lead to more targeted therapies and better overall patient outcomes. Integrating these insights into clinical practice necessitates a multidisciplinary effort, fostering collaboration among cardiologists, intensivists, and clinical pharmacologists to refine and implement protocols that address the complex nature of AF in critically ill patients.[6,7,26,27]

Limitations

This study offers valuable insights into how new-onset and pre-existing AF influence mortality in critically ill patients, but it is important to recognize its limitations. First, the retrospective nature of the study limits our ability to establish causality between AF and increased mortality. Although we controlled for a variety of confounders in our multivariate models, there is a chance of residual confounding from unmeasured or poorly measured variables. Second, the study data were obtained from a singular center, potentially hindering the generalizability of the results to other settings. The

incidence and outcomes of AF may vary depending on the patient demographics, clinical practices, and care levels at different hospitals. Third, the inclusion criteria and the exclusion of patients with missing data might introduce selection bias. The excluded patient population could have different baseline characteristics and outcomes, potentially influencing the study's findings. Fourth, the diagnosis of new-onset AF was based on clinical notes and discharge diagnoses, which may not capture all cases of AF, especially those that are transient or asymptomatic. This reliance on documented medical records may lead to an underestimation of the true incidence and impact of AF. Fifth, the study did not take into account the duration of AF episodes or the specific management strategies employed, both of which could have a considerable impact on outcomes. Sixth, we did not report and evaluate the prognostic role of CHA_2DS_2-VASc score in the prognostic risk stratification, which may have an independent prognostic role not only in AF patients but also in non-AF patients.[28,29] Additionally, the reliance on existing medical records for data collection introduces the potential for information bias, particularly in the accuracy and completeness of the recorded data. This includes variability in how different clinicians might record diagnoses or treatment details.

Conclusions

This study provides compelling evidence that in patients with critical illness, new-onset AF is associated with an increased risk of mortality compared with pre-existing AF or no AF. The study's insights into the epidemiology of AF in critically ill patients point to the need for heightened surveillance, proactive management, and potentially the development of preventive measures aimed at reducing the incidence and impact of new-onset AF. Future research should focus on prospective studies to better understand the causal relationships and mechanisms underlying the association between new-onset AF and mortality in critically ill patients.

Abbreviation

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; APS III, Acute Physiologic Score III; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CI, confidence interval; CRRT, continuous renal replacement therapy; DHP CCB, dihydropyridine calcium channel blocker; HR, hazard ratio; IQR, interquartile range; ICU, intensive care unit; LODS, Logistic Organ Dysfunction Score; MIMIC, Medical Information Mart for Intensive Care; MRA, mineralocorticoid receptor antagonist; Non-DHP, non- dihydropyridine; OASIS, the Oxford Acute Severity of Illness Score; PPI, proton pump inhibitors; SAPS II, Simplified Acute Physiology Score II; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment.

Data Sharing Statement

The datasets presented in the current study are available in the MIMIC-IV database (https://physionet.org/content/mimiciv/2.2/).

Ethics Approval and Consent to Participate

This database was exempted from our institutional review board approval. As the data was completely deidentified, no patient-informed consent was required.

Consent to Publish

Not applicable; no individual participant's data are shown.

Author Contributions

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

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Disclosure

The authors report no conflicts of interest in this work.

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