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Atrial Fibrillation in Critical Illness: Innocent Bystander or Guilty Party?*

"There are no innocent bystanders … what are they doing there in the first place?"
–William Burroughs, Exterminator

Evin Yucel, MD
Steven Hollenberg, MD
Section of Cardiology
Cooper University Hospital
Camden, NJ

Atrial fibrillation (AF) is the most common arrhythmia seen in the ICU (1–4) and is an important cause of morbidity, both in (3, 5) and out (6) of the ICU. Several factors, including loss of atrial contraction, reduction in ventricular loading, and shortened filling time with tachycardia, can lead to a reduction in cardiac performance in patients with AF. In addition, increased myocardial oxygen demand with tachycardia along with decreased coronary artery diastolic filling time can predispose to myocardial ischemia (7, 8). Management of AF in the ICU can be challenging, particularly because many drugs used to control heart rate can worsen hypotension and decrease contractility. Given this, it is not surprising that patients with AF in the ICU have worse outcomes. Despite the high prevalence in ICU, the data about the mechanism, treatment, and stroke prevention are sparse.

Nonetheless, although previous studies showed increased mortality in patients with AF (5, 9), the degree to which AF is a marker of severe disease or contributes to morbidity and mortality is still not entirely clear. Previous studies (4, 10–12) were underpowered to show an independent association, a limitation addressed in this issue of *Critical Care Medicine* by Shaver et al (13). The authors performed a large retrospective analysis of 1,770 patients admitted to a medical or general surgical ICU. Seven percent of the patients had new-onset AF, and 6% had recurrent AF. As expected, AF was associated with male gender, increased age, cardiac disease, organ failures, and disease severity. Patients with AF had increased mortality, and AF was independently associated with death when controlled for severity of illness and other confounders.

AF is generally believed to require both a trigger and a receptive substrate. Many AF episodes are initiated by premature beats emanating from areas around the pulmonary veins (14), but the number of such premature beats vastly exceeds the incidence of AF—a permissive atrial substrate is necessary. In other words, AF is both an electrical and a structural disease. Potential triggers, such as ischemia, local or generalized inflammation, hypoxia, hypervolemia or sudden increase in afterload, are common in the ICU (15, 16). When combined with atrial structural abnormalities, abnormal activation patterns in the atria can result. To get at the mechanisms of AF in the ICU, the study examined the relationship between fluid balance and AF and found greater net positive fluid balance in patients with new onset (but not recurrent) AF. There are limitations in using this finding to argue that fluid balance is a mediator of AF in the ICU. The use of vasopressors was also associated with AF, and patients requiring vasopressors likely received fluid resuscitation beforehand. In addition, whether hypervolemia and the use of vasopressors are causative or a marker of disease severity is still an unanswered question. Finally, increased left atrial size, as expected, was associated with new-onset AF. Retrospective analysis are not ideal for sorting

***See also p. 2104.**

Key Words: arrhythmia; atrial fibrillation; critical care; outcomes

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out the contributions of individual factors to conditions, such as AF, with multifactorial etiologies and predispositions.

AF has been associated with inflammation and has been reported in up to 46% of patients with septic shock (17). AF has been associated with mortality in sepsis (9, 11, 17), a finding that was not replicated in this population. It seems likely that this study, as well as previous studies, was underpowered to show a specific association between sepsis and AF mortality. The previous limitations of using retrospective analyses to sort out correlations from causations apply to this issue as well.

The authors also cited recent genome-wide association studies that have identified single-nucleotide polymorphisms that are associated with susceptibility to AF, with the suggestion that such studies might be applied to critically ill patients. As promising as this sounds, the reader is wise to consider the tremendous difficulty of such an enterprise and the enormous challenge of using associations in retrospective analyses to guide personalized therapy guided by genetic susceptibilities. While there may well be genes that predispose to AF, its mechanisms almost certainly represent a sophisticated interaction between nature and nurture.

Nevertheless, it is clear that AF is an important problem in the ICU. Independent associations suggest that AF can have deleterious effects, worsening hemodynamics in critically ill patient. Management of AF in ICU is and will likely remain a challenge. The current study does not speak to how the patients with AF in this cohort were managed. AF is well studied in non-ICU patients, and multiple therapeutic options exist in this setting (18), but due to the lack of randomized clinical trials, there is no evidence on management of AF in the ICU (19, 20). Intensivists must rely on extrapolation of information gained from other patient populations along with pathophysiologic considerations and personal experience to manage critically ill patients. There are no current guidelines for AF in the ICU, but the ultimate goal is to restore hemodynamic stability with adequate organ perfusion, eliminating the possible causes and preventing thromboembolic events when possible. Many of these patients will likely need further treatment for AF downstream. A multidisciplinary approach, with attention to hemodynamic, thrombotic, pulmonary, and other consideration, and making sure to coordinate ICU, inpatient, and outpatient strategies, will produce the best clinical outcomes.

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Atrial Fibrillation Is an Independent Predictor of Mortality in Critically Ill Patients*

Ciara M. Shaver, MD, PhD[1]; Wei Chen, MD[2]; David R. Janz, MD, MSc[3]; Addison K. May, MD[4]; Dawood Darbar, MD[5]; Gordon R. Bernard, MD[1]; Julie A. Bastarache, MD[1]; Lorraine B. Ware, MD[1,6]

Objectives: Atrial fibrillation has been associated with increased mortality in critically ill patients. We sought to determine whether atrial fibrillation in the ICU is an independent risk factor for death. A secondary objective was to determine if patients with new-onset atrial fibrillation have different risk factors or outcomes compared with patients with a previous history of atrial fibrillation.

Design: Prospective observational cohort study.

Setting: Medical and general surgical ICUs in a tertiary academic medical center.

Patients: One thousand seven hundred seventy critically ill patients requiring at least 2 days in the ICU.

Interventions: None.

Measurements and Main Results: Demographics, medical history, development of atrial fibrillation, fluid balance, echocardiographic findings, medication administration, and hospital mortality were collected during the first 4 days of ICU admission. Atrial fibrillation occurred in 236 patients (13%) (Any AF). Of these, 123 patients (7%) had no prior atrial fibrillation (New-onset AF) while the remaining 113 (6%) had recurrent atrial fibrillation (Recurrent AF). Any AF was associated with male gender, Caucasian race, increased age, cardiac disease, organ failures, and disease severity. Patients with Any AF had increased mortality compared with those without atrial fibrillation (31% vs 17%; $p < 0.001$), and Any AF was independently associated with death (odds ratio, 1.62; 95% CI, 1.14–2.29; $p = 0.007$) in multivariable analysis controlling for severity of illness and other confounders. The association of atrial fibrillation with death was magnified in patients without sepsis (odds ratio, 2.92; 95% CI, 1.52–5.60; $p = 0.001$). Treatment for atrial fibrillation had no effect on hospital mortality. New-onset AF and Recurrent AF were each associated with increased mortality. New-onset AF, but not Recurrent AF, was associated with increased diastolic dysfunction and vasopressor use and a greater cumulative positive fluid balance.

Conclusions: Atrial fibrillation in critical illness, whether new-onset or recurrent, is independently associated with increased hospital mortality, especially in patients without sepsis. (*Crit Care Med* 2015; 43:2104–2111)

Key Words: atrial fibrillation; critical illness; fluid balance; intensive care unit; mortality; vasopressor

***See also p. 2254.**

[1]Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN.

[2]Division of Pulmonary and Critical Care Medicine, Chiayi Christian Hospital, Chiayi, Taiwan.

[3]Section of Pulmonary and Critical Care Medicine, Louisiana State University School of Medicine New Orleans, LA.

[4]Department of Surgery, Vanderbilt University School of Medicine, Nashville, TN.

[5]Division of Cardiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN.

[6]Department of Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN.

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For information regarding this article, E-mail: ciara.shaver@vanderbilt.edu

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Atrial fibrillation (AF) is the most common sustained arrhythmia in critically ill patients, affecting as many as 25% of patients admitted to noncardiac surgery ICUs (1–14). Several studies have identified risk factors associated with development of AF in these patients, but few have been large enough to test the independent contribution of AF to poor clinical outcomes. In addition, management of AF in this population is particularly challenging given that many patients have coincident hypotension that may limit use of both rate- and rhythm-controlling medications.

That the onset of AF during critical illness is associated with poor outcomes in a variety of patient populations is clear. Several previous reports have suggested that development of new-onset AF in the ICU portends increased mortality (1, 3–7, 9, 11–13, 15–17), particularly in patients with sepsis. Despite these reports, it remains unclear whether the association between mortality and AF in critical illness is due to AF itself or due to AF simply being a marker of greater severity of illness. Additionally, limited data are available to examine the strength of association of new-onset AF versus recurrent or preexisting AF with mortality. Finally, the effect of fluid management, vasopressor use, or therapeutic interventions for AF on its association with mortality has not been studied.

In order to address these uncertainties, we designed a large prospective cohort study of AF in critical illness that was done concurrently with a prospective study of biomarkers of acute lung injury. The primary goal of the AF study was to test the hypothesis that development of AF during critical illness is associated with increased mortality independent of underlying comorbidities and severity of illness. The secondary goal of this study was to determine whether new-onset AF and recurrent AF had similar risk factors and consequences in critically ill patients. We further hypothesized that a more positive fluid balance, greater requirement for vasopressors, and underlying cardiac disease would be associated with an increased risk of AF.

MATERIALS AND METHODS

Study Design

This study was a prospective observational cohort study of 1,770 critically ill adults (age ≥ 18 yr) admitted to the medical or general surgical ICUs at Vanderbilt University Medical Center who were prospectively enrolled in the Validating Acute Lung Injury Markers for Diagnosis (VALID) study within 24 hours of ICU admission. Patients in the cardiovascular/cardiothoracic surgical ICU and in the trauma ICU were excluded from the current study. Patients were excluded from VALID if they did not remain in the ICU beyond 24 hours, if they had cardiac arrest prior to enrollment, had medication overdose, or had chronic lung disease requiring home oxygen therapy (18). The study protocol was approved by the Vanderbilt University Institutional Review Board (IRB# 051065). Informed consent was obtained from the patient or their designee whenever possible; in cases where neither individual was able to give consent, a waiver of consent was approved. On enrollment, clinical data including patient demographics, medical history including history of AF, cardiac history, cardiac risk factors, medications, vital signs, and laboratory values were extracted from the medical record. Additional data including the Acute Physiology and Chronic Health Evaluation (APACHE) II score on enrollment (19), daily fluid balance, echocardiographic findings, vasopressor use, and evidence of organ failures according to Brussels definitions (20) were recorded for the first 3 days after enrollment in addition to the 24 hours before study enrollment, for a total of four study days. Development of AF was determined daily by documentation of any occurrence of the arrhythmia in a physician's progress note, electrocardiogram interpretation by a cardiologist, and nursing vital sign flowsheet records. Patients who had any AF during the first 4 days in the ICU were defined as Any AF and were compared with patients who did not have AF during the study period in the ICU (No AF). Within the Any AF group, new-onset AF was defined as development of AF in the ICU in a patient with no prior history of AF by patient history or review of available medical records. Recurrent AF was defined as AF in the ICU in a patient with any previous history of AF, without distinction between those with chronic persistent AF and those with paroxysmal AF. All treatments administered for AF were recorded daily and categorized as rate-controlling (β-blockers, calcium channel blockers) or rhythm-controlling (amiodarone, digoxin) agents. Outcome data, including hospital mortality, duration of mechanical ventilation, ICU length of stay, and hospital length of stay, were also recorded.

Statistical Analysis

The primary outcome was in-hospital mortality in relation to the presence of Any AF or No AF during the VALID study period. Secondary analyses compared New-onset AF with Recurrent AF in relation to in-hospital mortality. Univariate analyses for categorical data were conducted using chi-square test or Fisher exact test. For continuous variables, comparisons were performed using Mann-Whitney *U* tests. *p* values of less than or equal to 0.05 were considered significant. Multivariable logistic regression models including variables known to be associated with both AF and poor clinical outcomes were created using the a priori selected variables of age, history of congestive heart failure, hypertension, APACHE II score, shock, and sepsis to determine the association between AF and in-hospital mortality. Logistic regression analysis for New AF and Recurrent AF were each performed comparing to patients with No AF. All statistical analysis was performed with SPSS version 22 for Macintosh (IBM, Armonk, NY).

RESULTS

Study Population

The study population included 1,275 patients admitted to the medical ICU and 495 patients admitted to the general surgical ICU (**Fig. 1**). The patient demographics and clinical characteristics are shown in **Table 1**. Patients with Any AF were significantly older, more likely to be male, and had increased severity of illness as measured by higher APACHE II scores and more organ failures. Known risk factors for AF, including congestive heart failure, stroke, and hypertension, were more frequent in the Any AF group.

Frequency of AF in the ICU

Overall, 236 of 1,770 patients (13%) developed Any AF during the 4-day study period in the ICU (Fig. 1). The frequency of Any AF was 13% in medical ICU subjects and 15% in surgical ICU subjects. Of the 236 patients with Any AF, 123 had

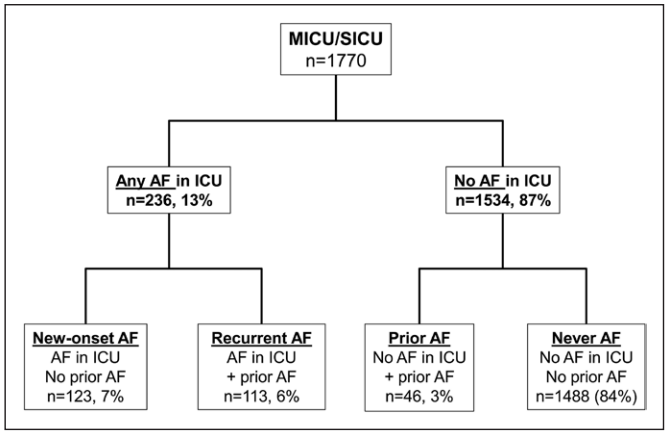

Figure 1. Study population. Patients at risk for acute lung injury were enrolled on the morning of ICU day 2 and separated into groups based on the occurrence of atrial fibrillation (AF) in the ICU and history of prior AF. MICU = medical ICU, SICU = surgical ICU.

New-onset AF (no prior history of AF) and 113 had Recurrent AF (prior history of AF). The majority of patients with a previous history of AF had recurrence in the ICU (113 of 159; 71%).

Any AF in the ICU Is Associated With Increased Mortality and Prolonged Duration of Illness

Of the patients who had Any AF during the 4-day study period, 30% died during hospitalization compared with 17% of patients with No AF ($p < 0.001$) (**Fig. 2**). Patients with Any AF also had increased lengths of stay in the ICU and in the hospital (**Table 2**). To determine whether the association between Any AF and hospital mortality was independent of differences in severity of illness and other potential confounders, we created a multivariable logistic regression model with in-hospital mortality as the outcome. We focused on variables that have been associated with increased risk for development of AF or with increased mortality. After controlling for these potential confounding factors, Any AF remained significantly associated with increased risk of mortality (odds ratio [OR], 1.62; 95% CI, 1.14–2.29; $p = 0.007$) (**Fig. 3**; **Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B355).

Comparison of New-Onset AF to Recurrent AF

A subgroup analysis was done to determine whether there were clinically important differences between patients who had

TABLE 1. Demographics and Baseline Clinical Characteristics of the Study Population

Characteristic	Any AF ($n = 236$)	No AF ($n = 1,534$)	p
Demographics			
Age, yr	68 (61–77)	56 (46–65)	< 0.001[a]
Male	154 (65%)	821 (54%)	0.001[b]
Caucasian	215 (91%)	1,287 (84%)	0.004[b]
Cardiac risk factors			
Current smoker	50 (21%)	495 (32%)	0.001[b]
Weight (kg)	83 (69–100)	77 (65–94)	0.001[a]
Dialysis	17 (7%)	96 (6%)	0.580[b]
Diabetes	84 (36%)	458 (30%)	0.075[b]
Myocardial infarction/angina	51 (22%)	165 (11%)	< 0.001[b]
Congestive heart failure	60 (25%)	159 (10%)	< 0.001[b]
Cerebrovascular accident	32 (14%)	116 (8%)	0.002[b]
Hypertension	177 (75%)	749 (49%)	< 0.001[b]
Hyperlipidemia	108 (46%)	368 (24%)	< 0.001[b]
ICU risk factors			
Acute Physiology and Chronic Health Evaluation II score	28 (22–33)	25 (20–31)	< 0.001[a]
Sepsis	154 (65%)	898 (59%)	0.051[b]
Total no. of organ failures	2 (1–2)	2 (1–2)	< 0.001[a]
Respiratory failure	164 (70%)	1,038 (68%)	0.576[b]
Shock	141 (60%)	663 (43%)	< 0.001[b]
Renal failure	124 (53%)	567 (37%)	< 0.001[b]

AF = atrial fibrillation.
[a]*p* values determined by Mann-Whitney *U* test.
[b]*p* values determined by chi-square test.
Data are presented as median (interquartile range) or *n* (%).

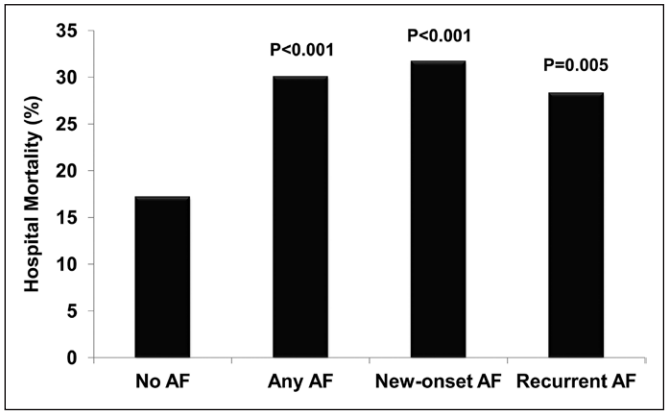

Figure 2. Atrial fibrillation (AF) during critical illness is associated with increased mortality. *p* values shown are compared to No AF.

TABLE 2. Clinical Outcomes of Patients With Any Atrial Fibrillation or No Atrial Fibrillation in the ICU

Outcome	Any AF ($n = 236$)	No AF ($n = 1,534$)	*p*
ICU LOS (d)	7 (4–13)	5 (2–11)	< 0.001[a]
Duration of mechanical ventilation (d)	3 (0–8)	2 (0–5)	0.062[a]
Hospital LOS (d)	14 (9–24)	11 (6–19)	0.001[a]
Hospital mortality, *n* (%)	71 (30)	264 (17)	< 0.001[b]

AF = atrial fibrillation, LOS = length of stay.
[a]*p* values determined by Mann-Whitney *U* test.
[b]*p* values determined by chi-square test.
Values are median (interquartile range) or *n* (%).

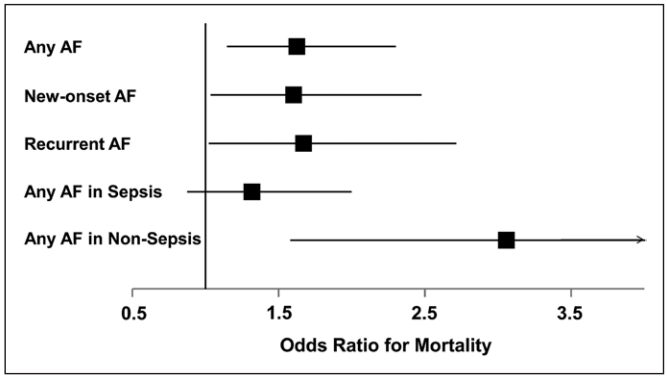

Figure 3. Odds ratios for mortality depending on atrial fibrillation (AF) group. Odds ratios for death were calculated by logistic regression controlling for age, congestive heart failure, hypertension, severity of illness, sepsis, and shock. *p* values shown are compared to No AF.

their first episode of AF in the ICU (New-onset AF) compared with those with a history of AF who developed AF in the ICU (Recurrent AF). The demographic and clinical characteristics of patients with New-onset AF and Recurrent AF are shown in **Table 3**. Compared with patients with New-onset AF, patients with Recurrent AF were older and more likely to have a history of congestive heart failure, hypertension, and hyperlipidemia. Patients with Recurrent AF had fewer organ failures and less shock than those with New-onset AF. Patients with Recurrent AF developed AF earlier during critical illness than those with New-onset AF, with 84% of Recurrent AF occurring within the first 2 study days compared with 51% of New-onset AF ($p < 0.001$). The majority (65%) of New-onset AF resolved in less than 48 hours with no additional episodes of AF during the study period. By contrast, only 29% of Recurrent AF resolved in the same interval ($p < 0.001$) and 52% of Recurrent AF persisted throughout the entire 4-day study period. Both New-onset AF and Recurrent AF were associated with increased hospital mortality (Fig. 2). Logistic regression confirmed that New-onset AF and Recurrent AF were each independently associated with increased mortality after controlling for known AF risk factors and potential confounders (New-onset AF: OR, 1.60; 95% CI, 1.03–2.48; $p = 0.036$; Recurrent AF: OR, 1.66; 95% CI, 1.02–2.71; $p = 0.042$) (Fig. 3; **Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/B356). Those with Recurrent AF had longer hospital length of stay but similar duration of mechanical ventilation and ICU length of stay compared with those with New-onset AF (**Table 4**).

Treatment of AF in the ICU

Overall, the majority of patients with Any AF (209 of 236; 85%) received at least one form of rate- or rhythm-control treatment for arrhythmia during the study period. Patients with New-onset AF were more likely to be treated with direct current cardioversion or amiodarone and less likely to receive the atrioventricular blocking agents digoxin or verapamil (**Table 5**). AF resolved during the study period in 39% of patients who received treatment for AF with a similar frequency of treatment success with rate-controlling or rhythm-controlling agents. Treatment of Any AF with either rate or rhythm control therapy was not associated with hospital mortality (untreated group, 34% mortality; treated group, 29% mortality; $p = 0.557$), although there was a nonsignificant trend toward improved outcomes with rhythm control agents (mortality 34% with rate control agent vs 25% with rhythm control agent; $p = 0.179$). AF-directed therapy did not affect the minimum daily heart rate or the frequency of bradycardia (**Supplemental** Table 3, Supplemental Digital Content 3, http://links.lww.com/CCM/B357). Patients receiving rhythm control agents had more severe hypotension on study days 2 and 3 compared with those receiving rate control agents.

Fluid Balance and Echocardiographic Features of Patients With and Without AF

We hypothesized that greater net positive fluid balance is a surrogate marker of distension of the left atrium and would be associated with an increased risk of New-onset AF and Recurrent AF. During the first day in the ICU, all groups of patients had equivalent fluid resuscitation as measured by the net positive fluid balance (**Fig. 4**). Through the 4-day study period, there were no differences in total fluid balance between Any AF and No AF (median total net fluid balance through entire

TABLE 3. Demographics and Clinical Characteristics of New-Onset Atrial Fibrillation and Recurrent Atrial Fibrillation

Characteristic	New-Onset AF (*n* = 123)	Recurrent AF (*n* = 113)	*p*
Demographics			
Age, yr	70 (63–78)	66 (59–74)	0.008[a]
Male	80 (65)	74 (66)	0.943[b]
Caucasian	112 (91)	103 (91)	0.980[b]
Cardiac risk factors (%)			
Current smoker	28 (23)	22 (20)	0.536[b]
Weight, kg (range)	83 (70–101)	83 (68–100)	0.762[a]
Dialysis	9 (7)	8 (7)	0.944[b]
Diabetes	44 (36)	40 (35)	0.952[b]
Myocardial infarction/angina	29 (24)	22 (20)	0.444[b]
Congestive heart failure	19 (15)	41 (36)	< 0.001[b]
Cerebrovascular accident	15 (12)	17 (15)	0.523[b]
Hypertension	78 (63)	99 (88)	< 0.001[b]
Hyperlipidemia	45 (37)	63 (56)	0.003[b]
ICU risk factors			
Acute Physiology and Chronic Health Evaluation II score	27 (21–33)	29 (22–34)	0.185[a]
Any sepsis	79 (64)	75 (66)	0.730[b]
Total no. of organ failures	2 (1–2)	2 (1–3)	0.006[a]
Respiratory failure	90 (73)	74 (66)	0.200[b]
Shock	85 (69)	56 (50)	0.002[b]
Renal failure	62 (50)	62 (55)	0.516[b]

AF = atrial fibrillation.
[a]*p* values determined by Mann-Whitney *U* test.
[b]*p* values determined by chi-square test.
Data are presented as median (interquartile range) or *n* (%).

TABLE 4. Clinical Outcomes of Patients With New-Onset Atrial Fibrillation or Recurrent Atrial Fibrillation

Outcome	New-Onset AF (*n* = 123)	Recurrent AF (*n* = 113)	*p*
ICU LOS (d)	6 (3–13)	7 (4–14)	0.067[a]
Duration of mechanical ventilation (d)	3 (0–7)	3 (0–9)	0.103[a]
Hospital LOS (d)	12 (7–22)	15 (9–26)	0.049[a]
Hospital mortality, *n* (%)	39 (32)	32 (28)	0.571[b]

AF = atrial fibrillation, LOS = length of stay.
[a]*p* values determined by Mann-Whitney *U* test.
[b]*p* values determined by chi-square test.
Values are median (interquartile range) or *n* (%).

study period of 4.93 L and 5.4 L, respectively; $p = 0.480$). However, patients with New-onset AF, but not those with Recurrent AF, had significantly greater net positive cumulative fluid balance compared with those with No AF (median New-onset AF, 6.1 L; $p = 0.036$ vs No AF, 5.4 L; Recurrent AF, 4.7 L; $p = 0.250$ vs No AF, 5.4 L).

In the subset of patients with Any AF who underwent echocardiography during the study hospitalization (143 of 236; 61%) (**Table 6**), the left atrium was larger in patients with New-onset AF and Recurrent AF compared with No AF, with significantly greater left atrial size in those with New-onset AF. Diastolic dysfunction was more frequent in those with New-onset AF and less frequent in those with Recurrent AF compared with No AF. Mitral regurgitation was more frequently present in patients with Recurrent AF. There were no significant differences in plasma levels of troponin-I or brain natriuretic peptide (BNP) among groups (data not shown).

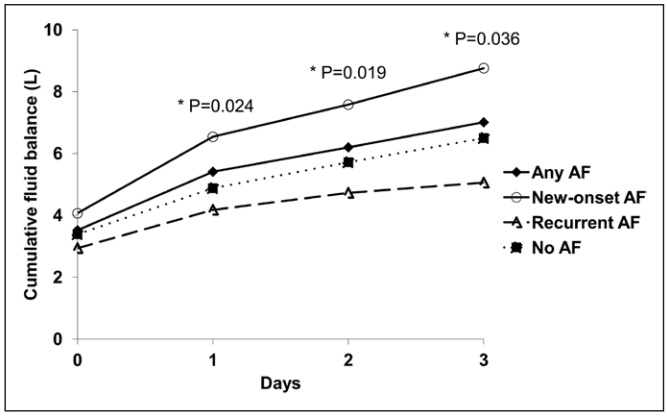

Figure 4. Cumulative fluid balance of patients with New-onset atrial fibrillation (AF), Recurrent AF, and No AF. *p* values shown are compared to No AF.

TABLE 5. Treatment Characteristics of New-Onset Atrial Fibrillation and Recurrent Atrial Fibrillation in the ICU

Treatment	New-Onset AF (*n* = 123) (%)	Recurrent AF (*n* = 113) (%)	*p*
Any treatment	105 (85)	96 (85)	0.929[a]
Cardioversion	20 (16)	3 (0.03)	< 0.001[a]
β-blockers	58 (47)	57 (50)	0.614[a]
Diltiazem	58 (47)	56 (50)	0.712[a]
Verapamil	0 (0)	6 (0.05)	0.011[b]
Amiodarone	49 (40)	27 (24)	0.009[a]
Digoxin	16 (13)	32 (28)	0.004[a]

AF = atrial fibrillation.
[a]*p* values determined by chi-square test.
[b]*p* values determined by Fisher exact test.
Values are *n* (%).

Patients With AF Required More Vasopressor and Inotropic Support

Because of the association of vasopressor use with development of atrial arrhythmias, the use of vasopressor and inotropic agents was assessed. More patients with Any AF were treated with vasopressors or inotropic agents compared with patients who did not develop AF in the ICU (59.7% vs 43.2%; $p < 0.001$). Compared with patients with Recurrent AF, patients with New-onset AF were more likely to be treated with vasoactive agents (69.1% vs 49.6%; $p = 0.002$) and were treated with vasopressors on more study days than those with Recurrent AF or No AF (1.7 ± 1.5 d in New-onset AF vs 1.3 ± 1.5 d in Recurrent AF vs 1.0 ± 1.3 d in No AF; $p < 0.001$ for New-onset AF vs No AF). Patients who developed New-onset AF on the 2nd study day were more likely to have received vasopressors on the previous day than those with Recurrent AF (55% vs 36%; $p = 0.018$). The specific vasoactive agent chosen by the clinicians differed between AF groups (**Table 7**). Specifically, norepinephrine was used more frequently in patients who developed New-onset AF compared with those with Recurrent AF.

TABLE 6. Echocardiographic Characteristics of a Subset of Patients With New-Onset Atrial Fibrillation or Recurrent Atrial Fibrillation in the ICU

Characteristic	New-Onset AF (*n* = 84)	Recurrent AF (*n* = 59)	*p*
Left atrial size (cm)	4.4 (3.8–5.0)	4.0 (3.6–4.5)	0.011[a]
Ejection fraction (%)	55 (40–55)	55 (45–55)	0.255[a]
Diastolic dysfunction	23 (27%)	10 (17%)	0.015[b]
Mitral regurgitation	53 (63%)	42 (71%)	0.025[b]

AF = atrial fibrillation.
[a]*p* values determined by chi-square test.
[b]*p* values determined by Fisher exact test.
Values are median (interquartile range) or *n* (%).

TABLE 7. Vasopressor and Inotrope Use in Patients With New-Onset Atrial Fibrillation or Recurrent Atrial Fibrillation

Treatment	New-Onset AF (*n* = 123) (%)	Recurrent AF (*n* = 113) (%)	*p*
Any vasopressor or inotrope treatment	85 (69)	56 (50)	0.002[a]
Norepinephrine	73 (59)	47 (42)	0.006[a]
Vasopressin	35 (29)	20 (18)	0.051[a]
Phenylephrine	21 (17)	17 (15)	0.672[a]
Epinephrine	1 (1)	1 (1)	1.000[b]
Dobutamine	1 (1)	3 (2)	0.352[b]
Dopamine	13 (11)	10 (9)	0.656[a]

AF = atrial fibrillation.
[a]*p* values determined by chi-square test.
[b]*p* values determined by Fisher exact test.
Values are presented as *n* (%).

Comparison of AF in Sepsis and Nonsepsis Patients

Because of presumed differences in proinflammatory stimuli in patients with sepsis compared with those without, we hypothesized that AF would be more common in patients with sepsis. Any AF occurred in 13% of patients with sepsis and 10% of those without sepsis ($p = 0.05$). Occurrence of Any AF was associated with increased mortality regardless of the presence of sepsis (sepsis: 33% mortality with Any AF vs 22% without AF; $p = 0.004$; nonsepsis: 24% mortality with AF vs 10% without AF; $p < 0.001$). The independent association between Any AF and mortality was magnified in the absence of sepsis. In nonsepsis patients, Any AF was associated with an OR for death of 2.92 (95% CI, 1.52–5.60; $p = 0.001$). By contrast, in patients with sepsis, Any AF was not significantly associated with death in the

multivariable analysis (OR, 1.29; 95% CI, 0.85–1.94; $p = 0.228$), although this analysis may be underpowered.

DISCUSSION

In this large prospective observational study of a diverse population of critically ill patients admitted to medical and surgical ICUs, AF during critical illness is associated with an increased risk of in-hospital mortality that is independent of the severity of critical illness, underlying cardiac risk factors, or presence of sepsis. These results are consistent with, and build upon, several previous reports that development of AF in the ICU is associated with increased mortality, which are summarized in **Supplemental Table 4** (Supplemental Digital Content 4, http://links.lww.com/CCM/B358) (1, 3–5, 7, 9, 11–13). Our study provides important new information compared with prior studies because the large cohort of patients with AF allowed us to determine that the association of AF with mortality in critical illness is not simply due to AF being a marker of increased disease severity. Furthermore, given the large sample size, we were able to compare the clinical characteristics and outcomes of New versus Recurrent AF in critical illness.

AF was consistently associated with higher mortality in the multivariable logistic regression analyses, regardless of whether the AF was new-onset or occurred in the setting of a prior history of AF. Overall, the development of Any AF during the first 4 days in the ICU was associated with a 62% increased risk of in-hospital mortality. This effect size for a common and potentially modifiable risk factor for death is clinically significant and intervention to reduce this risk could have clinical benefit. Because of its independent association with hospital mortality, development of AF in the ICU warrants close clinical attention, and further studies are needed to not only define the underlying pathophysiology of the arrhythmia but also to determine whether prevention or treatment of AF would improve clinical outcomes.

In addition to demonstrating the importance of AF during critical illness, we sought to determine whether there were differences between New-onset AF and Recurrent AF in the ICU. Although both New-onset AF and Recurrent AF were independently associated with increased mortality, to our knowledge, the association of Recurrent AF during critical illness with hospital mortality has not previously been reported, since most prior studies actually excluded patients with a history of prior AF. Patients with Recurrent AF, but not New-onset AF, were more likely to have underlying cardiac risk factors of congestive heart failure, hypertension, and hyperlipidemia. Despite having similar severity of illness, patients with New-onset AF more frequently had hypotension and had more organ failures compared with patients with Recurrent AF. New-onset AF was also more likely to be associated with positive fluid balance and antecedent vasopressor use. One interpretation of these differences could be that the development of New-onset AF occurs in the setting of prolonged hypotension and inadequate oxygen delivery while Recurrent AF is more likely related to underlying structural heart disease and traditional cardiac risk factors.

Our results demonstrate that a greater net positive fluid balance and increased vasopressor use were associated with development of New-onset AF or Any AF, suggesting that clinical management of critically ill patients may modulate the risk of developing AF in the ICU. Increased fluid administration and vasopressor use in patients with New-onset AF may have been in response to more frequent hypotension in this population. Conversely, patients with a history of AF may have received less fluid resuscitation due to the attendant risks of precipitating heart failure. One possible mechanism by which increased positive cumulative fluid balance may increase susceptibility to New-onset AF is by increasing atrial stretch acutely. This concept is supported by echocardiographic data showing that patients with AF had increased left atrial dimensions compared with those without AF. Vasoactive medications, particularly those with β-adrenergic activity, may also directly influence AF. A potential causal role for vasopressors in development of AF is supported by recent data showing an increased frequency of AF in patients with septic shock who had high blood pressure targets compared with those with low blood pressure targets (21).

As most previous studies of AF in the critically ill have focused specifically on patients with sepsis (7, 9, 11, 16), we tested whether the impact of AF differed in the presence or absence of sepsis. As anticipated, patients with sepsis were more likely to develop AF in the ICU than those without sepsis. AF during critical illness is associated with higher hospital mortality regardless of whether sepsis was present. Surprisingly, the association of Any AF with mortality was magnified in patients without sepsis (OR, 2.92 for nonsepsis patients vs 1.29 for sepsis patients), after controlling for other confounding variables, including age, disease severity, shock, heart failure, and hypertension. In sepsis patients, AF in the ICU did not carry an independent risk for death. These data point to the possibility that the etiology and consequences of AF may be modulated by the underlying pathophysiology of the acute illness.

It remains unclear why some patients in the ICU develop New-onset AF and others do not. One hypothesis is that some patients have an underlying susceptibility to atrial arrhythmias that is unmasked by the complex pathophysiology of critical illness. Such a predisposition for AF may be genetic or related to subclinical structural abnormalities in the heart. Recently, a "two-hit" model for development of ambulatory AF has been proposed (22). This model states that a genetic risk for AF in the setting of an acquired risk factor such as systemic inflammation that is common in critical illness together function as a trigger for AF. In support of this hypothesis, C-reactive protein levels have also been shown to increase prior to onset of arrhythmias in patients with sepsis in the ICU (9). A recent meta-analysis showed that the prophylactic use of the anti-inflammatory agent *N*-acetylcysteine in postoperative patients resulted in a decreased risk of developing New-onset AF (OR, 0.56) or death (OR, 0.40) (23). In addition, there are increasing data supporting genetic predisposition to development of New-onset AF that is not clinically apparent until an acute stressor occurs. Several genome wide association studies in the general population have identified common AF susceptibility alleles in genes encoding cardiac ion channels, cellular structure, intracellular

signaling proteins, and inflammation that are associated with development of AF (24–26). However, none of these have been studied in critical illness. A greater understanding of the underlying pathophysiology of AF during critical illness is warranted in order to identify novel therapeutic targets and direct therapy to underlying mechanisms (22).

This study has several strengths. First, to our knowledge, it is the largest prospective study of AF in critical illness and includes a broad group of both medical and surgical critically ill patients. The large study population with extensive prospective clinical data collection provided sufficient power for us to determine that the association of AF with mortality was not simply due to higher severity of illness in those with AF. Previous smaller studies have not addressed this question. Furthermore, the large patient cohort allowed analysis of differences between New-onset AF and Recurrent AF, which have not been previously explored. We were also able to compare patients with and without sepsis as an underlying diagnosis. There are also some limitations. In this prospective observational cohort study, we are unable to determine whether AF plays a causative role in increased mortality. There may also be additional unmeasured confounding variables that could influence risk for AF and for mortality, which were not included in our regression analysis. Determining the specific contribution of AF to clinical outcomes would be challenging, even in a prospective study. It is possible that the prior history of AF may be inaccurate as many patients have asymptomatic AF. Because we only studied AF during the first 4 ICU days, the implications of AF developing after ICU day 4 are unknown. Since the majority of patients with AF in this study received at least one medication or therapy aimed at rate or rhythm control, we were unable to detect a benefit of AF-directed therapy on mortality. However, the finding that treatment for AF did not worsen bradycardia may be valuable for designing a randomized trial of AF management in the critically ill.

In conclusion, AF in the ICU is associated with an increased mortality risk that is independent of other clinical risk factors such as severity of illness or preexisting cardiac disease and is strongest in patients without sepsis. Furthermore, Recurrent AF, which has not been previously studied, carries the same risk of mortality as New-onset AF during critical illness. Taken together with the existing literature, this study provides the framework for design of additional studies aimed at prevention and treatment of AF in critically ill patients with an ultimate goal to reduce patient mortality.

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