

Atrial fibrillation of new onset during acute illness: prevalence of, and risk factors for, persistence after hospital discharge

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Background: Atrial fibrillation (AF) of new onset during acute illness (AFNOAI) has a variable incidence of 1%–44% in hospitalized patients. This study assesses the risk factors for persistence of AFNOAI in the 5 years after hospital discharge for critically ill patients.

Methods: This was a retrospective cohort study. All patients ≥18 years old admitted to the medical intensive care unit (MICU) of a tertiary care hospital from January 1, 2012, to October 31, 2015, were screened. Those designated with AF for the first time during the hospital admission were included. Risk factors for persistent AFNOAI were assessed using a Cox's proportional hazards model.

Results: Two-hundred and fifty-one (1.8%) of 13,983 unique MICU admissions had AFNOAI. After exclusions, 108 patients remained. Forty-one patients (38%) had persistence of AFNOAI. Age (hazard ratio [HR], 1.05; 95% confidence interval [CI], 1.01–1.08), hyperlipidemia (HR, 2.27; 95% CI, 1.02–5.05) and immunosuppression (HR, 2.29; 95% CI, 1.02–5.16) were associated with AFNOAI persistence. Diastolic dysfunction (HR, 1.46; 95% CI, 0.71–3.00) and mitral regurgitation (HR, 2.00; 95% CI, 0.91–4.37) also showed a trend towards association with AFNOAI persistence.

Conclusions: Our study showed that AFNOAI has a high rate of persistence after discharge and that certain comorbid and cardiac factors may increase the risk of persistence. Anticoagulation should be considered, based on a patient's individual AFNOAI persistence risk.

Key Words: atrial fibrillation; paroxysmal atrial fibrillation; persistent atrial fibrillation

INTRODUCTION

First-time atrial fibrillation (AF) in otherwise medically ill patients without a history of AF has a variable incidence of 1%–44% in hospitalized patients [1,2]. However, it is unclear whether the arrhythmia is transient in this setting, or rather the harbinger of persistent AF in years to come [1]. Here we will refer to this phenomenon as AF of new onset during acute illness (AFNOAI). Risk factors for the long-term persistence of AFNOAI are unknown. Identification of these factors might help guide decisions around initiation of anticoagulation for higher risk individuals. This study assesses the risk factors for persistence of AFNOAI in the 5 years after hospital discharge for critically ill patients.

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MATERIALS AND METHODS

Study Design

This was a retrospective cohort study. All patients ≥ 18 years old admitted to the medical intensive care unit (MICU) of a tertiary care hospital from January 1, 2012, to October 31, 2015, were screened for inclusion. Those designated with AF for the first time during the hospital admission, using a diagnostic code or electrocardiogram (EKG), were included. Patients with pre-existing AF were excluded. AF was verified by analyzing EKG and/or clinical notes. The study was approved by the local Institutional Review Board of the Cleveland Clinic (IRB No. 20-690); informed consent was waived.

Data Acquisition

Relevant demographic, clinical and echocardiographic variables were compiled manually using the electronic medical record. Comorbidities were counted if present on admission. Persistence of AFNOAI or occurrence of stroke/transient ischemic attack was determined via EKG and/or clinical documentation in the 5 years after hospital discharge. Persistent AFNOAI was coded as present if a patient had an AF diagnosis recorded in any clinical documentation in the 5 years following the hospital admission, or an EKG demonstrating AF during this period.

Variable Definitions

For referral status, a referred patient was one who did not present initially to the main tertiary care hospital or one of its in-state regional branches. Chronic kidney disease included stages I-V kidney disease. Malignancy was defined as any active hematologic malignancy or solid tumor. Immunosuppression was defined as the extended use of steroids, steroid-sparing agents, biologics or history of human immunodeficiency virus (HIV). Ischemic heart disease was defined as a history of angina, acute coronary syndrome, coronary artery disease, coronary artery bypass graft or cardiac stents. Hyperlipidemia included elevated triglyceride and/or cholesterol levels. Tobacco smoking was defined as regular tobacco smoking within 1 year of admission. Alcohol excess was defined as regular excess alcohol ingestion within 1 year of admission.

Echocardiographic variables were extracted from an echocardiogram performed within a year of admission. Mitral stenosis and regurgitation included mild, moderate or severe forms. Other valvular heart disease was a history of 3–4+ stenosis or regurgitation of any of the pulmonic, tricuspid or

KEY MESSAGES

- Atrial fibrillation of new onset during acute illness (AFNOAI) has a high rate of persistence after hospital discharge and is associated with a high in-hospital and 5-year mortality.
- Age, hyperlipidemia, immunosuppression, mitral regurgitation, and diastolic dysfunction may increase the risk of long-term persistence of AFNOAI.

aortic valves. Left atrial dilatation included mild, moderate or severe dilatation. Diastolic dysfunction included grades I–IV dysfunction.

The admission Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) score was used. Hypotension was defined as blood pressure persistently $< 90/60$ mm Hg at any time during admission. Renal failure was defined as new dialysis dependence. Respiratory failure was defined as the need for non-invasive ventilation or intubation. Neurologic failure was defined as altered mental status compared to baseline. Metabolic abnormality included any electrolyte disturbance. Need for transfusion was defined as the need for red blood cell transfusion. Vasopressor use included use of vasopressors at any point during admission.

Statistical Analysis

Baseline variables were expressed as means and standard deviations (continuous variables), or frequencies and percentages (categorical variables). In the first stage of analysis, characteristics of patients with and without AFNOAI persistence were compared using analysis of variance (continuous variables), or Pearson chi-square and Fisher's exact tests (categorical variables). In the second stage, clinically relevant variables, or those with statistically significant univariable associations (P-value of less than 0.05), were included in a multivariable Cox's proportional hazards model to assess risk factors for persistent AFNOAI. Hazard ratios and 95% confidence intervals were reported. Fully conditional specification was used for multiple imputation of missing data. There was no evidence of multicollinearity using variance inflation factors. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

RESULTS

Two-hundred and fifty-one (1.8%) of 13,983 unique MICU

Table 1. Baseline characteristics of patients with and without persistence of AFNOAI in the 5 years after discharge

Variable	AFNOAI persistence	No AFNOAI persistence	P-value
Patient	41 (38.0)	67 (62.0)	-
Demographics			
Age (yr)	70 (57–83) ^a	62 (50–74) ^a	<0.05 ^a
Male	29 (70.7)	45 (67.2)	0.70
Referred patients	14 (34.1) ^a	38 (56.7) ^a	0.02 ^a
Race			
White	24 (63.2)	46 (70.8)	0.54
Black	13 (34.2)	16 (24.6)	
Comorbidity			
Diabetes mellitus	18 (43.9)	23 (34.3)	0.32
Liver cirrhosis	4 (9.8)	6 (9.0)	0.89
COPD	8 (19.5)	16 (23.9)	0.60
Malignancy	9 (22.0)	22 (32.8)	0.22
Immunosuppression	12 (29.3)	12 (17.9)	0.17
Hypertension	29 (70.7)	38 (56.7)	0.15
Ischemic heart disease	10 (24.4)	20 (29.9)	0.54
Peripheral vascular disease	5 (12.2)	3 (4.5)	0.25
Prior stroke or TIA	6 (14.6)	8 (11.9)	0.69
Hyperlipidemia	23 (56.1) ^a	14 (20.9) ^a	<0.001 ^a
OSA	4 (9.8)	6 (9.0)	0.89
Hypothyroidism	8 (19.5)	9 (13.4)	0.40
Chronic kidney disease	13 (31.7) ^a	9 (13.4) ^a	0.02 ^a
Obesity (BMI >30 kg/m ²)	18 (47.4)	31 (47.0)	0.97
Tobacco smoking	8 (20.0)	21 (32.3)	0.17
Alcohol excess	5 (12.8)	3 (4.9)	0.26
Echocardiographic variable			
Mitral stenosis	1 (2.6)	0	0.39
Mitral regurgitation	11 (28.2)	10 (16.4)	0.16
Other valvular disease	5 (12.8)	4 (6.6)	0.29
Left atrial dilatation	19 (51.4)	19 (31.7)	0.05
Diastolic dysfunction	21 (56.8) ^a	20 (33.9) ^a	0.03 ^a
EF <40	5 (12.8)	9 (15.0)	0.76
Admission diagnosis			
Sepsis	12 (29.2)	18 (26.9)	0.87
Pulmonary disease	10 (24.4)	21 (31.3)	
Gastrointestinal bleed	4 (9.8)	6 (9.0)	
Renal failure	4 (9.8)	3 (4.5)	
Cardiac arrest	2 (4.9)	4 (6.0)	
Other	9 (22.0)	15 (22.4)	
ICU course			
APACHE score	82 (60–104)	76 (49–103)	0.28
Hypotension	23 (56.1)	30 (44.8)	0.25
Vasopressor use	16 (39.0)	24 (35.8)	0.74
Respiratory failure	24 (58.5)	42 (62.7)	0.67
Renal failure	9 (22.0)	16 (23.9)	0.82
Altered mental status	14 (34.1)	23 (34.3)	0.98
Metabolic abnormalities	24 (58.5)	29 (43.3)	0.12
Need for transfusion	22 (53.7)	25 (37.3)	0.10
Outcome variable			
Occurrence of new stroke/TIA	4 (9.8)	1 (1.5)	0.07
Death in 5 years post-discharge	25 (61.0)	34 (50.7)	0.30

Values are presented as number (%) or mean (interquartile range).

AFNOAI: atrial fibrillation of new onset during acute illness; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack; OSA: obstructive sleep apnea; BMI: body mass index; EF: ejection fraction; ICU: intensive care unit; APACHE: Acute Physiologic Assessment and Chronic Health Evaluation.

^aStatistically significant.

admissions had AFNOAI. One-hundred and twenty-six (50%) were excluded due to in-hospital death and 17 (7%) were excluded due to absence of clinical documentation after discharge. One-hundred and eight patients were included. Median follow-up time was 26.0 months (interquartile range [IQR], 6.1–60.0 months).

Table 1 compares characteristics of patients with and without persistence of AFNOAI in the 5 years after discharge. The mean age overall was 65 years (IQR, 52–78 years); 69% were male. Thirty (28%) were admitted for sepsis, 31 (29%) for pulmonary disease, 10 (9%) for gastrointestinal bleed, 6 (6%) for cardiac arrest, 7 (6%) for renal failure, and 24 (22%) for other causes. Eighty percent had AF with rapid ventricular response.

Forty-one patients (38%) had persistence of AFNOAI, with a median time to first documented recurrent AF episode of 6.6 months (IQR, 1.0–29.5 months) after hospital discharge. Five patients (4.6%) had a stroke, of whom 4 had persistent AFNOAI. Fifty-nine (55%) patients died in the 5 years after discharge; median time to death was 9.6 months (IQR, 1.6–24.6 months).

Table 2 shows the results of the Cox's proportional hazards model, using select predictors. Age, hyperlipidemia and immunosuppression were associated with AFNOAI persistence. Diastolic dysfunction and mitral regurgitation (MR) also showed a trend towards association with AFNOAI persistence. Eight patients had no echocardiogram available within a year of admission and seven had incomplete echocardiogram data. Missing data was imputed.

DISCUSSION

Our study describes risk factors associated with the persistence of AFNOAI after critical illness. We found that age, hyperlip-

idemia and immunosuppression were linked with AFNOAI persistence in our cohort of patients. Diastolic dysfunction and MR may also predispose to persistence. By contrast, disease-associated variables, such as admission diagnosis and organ failure, bore no influence.

The importance of cardiac factors demonstrated in our study reinforces prior data in patients who had undergone non-cardiac surgery, which showed that hypertension and left atrial enlargement were associated with persistence of new onset AF [3]. The association with age likely mirrors the increasing prevalence of AF in the older population [4]. MR and diastolic dysfunction may increase the likelihood of AFNOAI persistence by creating a more arrhythmogenic atrial substrate [4,5]. However, the relationship with hyperlipidemia is ambiguous—other studies have demonstrated both increased and decreased AF risk with respect to hyperlipidemia [6]. Immunosuppression may increase susceptibility to intercurrent illness, including arrhythmias.

Of the five patients who had a stroke, four had persistence of AFNOAI, implying a causal link therein. Indeed, other studies have demonstrated an increased stroke risk in patients with AFNOAI and up to 47.5% of patients did not receive another AF diagnosis before their stroke, highlighting the importance of initiating anticoagulation in a timely fashion [3,7].

The epidemiology of AFNOAI in our study is consistent with previous data, lending credence to the generalizability of our results. AFNOAI was rare in our study (1.8%), but the AFNOAI persistence rate was high (38%), similar to prior research [1,3,7]. Half of patients with AFNOAI expired in hospital, and over half of hospital survivors died in the 5 years after discharge, again consistent with existing evidence of a high mortality rate in this cohort [7–10].

Our study is the first of its kind to look at a vast array of risk factors for persistence of AFNOAI. A limitation is the small sample size. Additionally, some episodes of AFNOAI may have been missed by our screening algorithm, while others may have been clinically silent—in one study only 16.4% of cases were clinically detected [9]. Due to the lack of timely EKGs in patient charts, it was not possible to determine the cardiac rhythm at the time of discharge for each patient—there is potentially a difference in AFNOAI persistence rates between those with sinus rhythm restored at the time of discharge versus those with AF on discharge. Moreover, since patients did not have continuous cardiac monitoring after discharge, it was impossible to tell precisely if and when they first reverted to AF during the 5-year follow-up period. The true AFNOAI

Table 2. Effect sizes for variables in Cox's proportional hazards model of time to first recurrent episode of AF after discharge

Variable	Hazard ratio	95% CI	P-value
Age	1.05 ^a	1.01–1.08 ^a	0.009 ^a
Hypertension	0.57	0.21–1.52	0.261
Hyperlipidemia	2.27 ^a	1.02–5.05 ^a	0.044 ^a
Immunosuppression	2.29 ^a	1.02–5.16 ^a	0.045 ^a
Chronic kidney disease	1.07	0.45–2.55	0.876
Diastolic dysfunction	1.46	0.71–3.00	0.308
Left atrial dilatation	1.22	0.57–2.63	0.612
Mitral regurgitation	2.00	0.91–4.37	0.084

AF: atrial fibrillation; CI: confidence interval.

^aStatistically significant.

persistence rate may be even higher, if we consider that only symptomatic AF, and AF recorded on EKG, was counted in our study during the follow-up period. Larger prospective studies with continuous cardiac monitoring on discharge are needed to confirm the risk factors for persistent AFNOAI, and whether anticoagulation confers benefit.

Our study showed that AFNOAI has a high persistence rate after discharge and that certain comorbid and cardiac factors may increase the risk of persistence. Stroke prophylaxis should be considered, based on a patient's individual AFNOAI persistence risk, though ultimately such discussion must be framed in the context of the guarded prognosis in this cohort.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: AR, DS, AD. Data curation: AR, JPP. Software: ML, XW. Formal analysis: ML, XW. Methodology: AR, DS, AD. Project administration: AR. Validation: AR. Investigation: AR, JPP. Visualization: AR. Resources: AD. Supervision: AD. Writing- original draft: AR. Writing-review & editing: AR, JPP, DS, AD.

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