New-Onset Atrial Fibrillation in the Critically Ill

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Objective: To determine the association of new-onset atrial fibrillation with outcomes, including ICU length of stay and survival.

Design: Retrospective cohort of ICU admissions. We found atrial fibrillation using automated detection (≥ 90 s in 30 min) and classed as new-onset if there was no prior diagnosis of atrial fibrillation. We identified determinants of new-onset atrial fibrillation and, using propensity matching, characterized its impact on outcomes.

Setting: Tertiary care academic center.

Patients: A total of 8,356 consecutive adult admissions to either the medical or surgical/trauma/burn ICU with available continuous electrocardiogram data.

Interventions: None.

Measurements and Main Results: From 74 patient-years of every 15-minute observations, we detected atrial fibrillation in 1,610 admissions (19%), with median burden less than 2%. Most atrial fibrillation was paroxysmal; less than 2% of admissions were always in atrial fibrillation. New-onset atrial fibrillation was subclinical or went undocumented in 626, or 8% of all ICU admissions. Advanced age, acute respiratory failure, and sepsis were the strongest predictors of new-onset atrial fibrillation. In propensity-adjusted regression analyses, clinical new-onset atrial fibrillation was associated with increased hospital mortality (odds ratio, 1.63; 95% CI, 1.01–2.63) and longer length of stay (2.25 d; CI, 0.58–3.92). New-onset atrial fibrillation was not associated with survival after hospital discharge (hazard ratio, 0.99; 95% CI, 0.76–1.28 and hazard ratio, 1.11; 95% CI, 0.67–1.83, respectively, for subclinical and clinical new-onset atrial fibrillation).

Conclusions: Automated analysis of continuous electrocardiogram heart rate dynamics detects new-onset atrial fibrillation in many ICU patients. Though often transient and frequently unrecognized, new-onset atrial fibrillation is associated with poor hospital outcomes. (*Crit Care Med* 2017; XX:00–00)

Key Words: electrocardiography; intensive care unit; length of stay; mortality; survival

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Atrial fibrillation (AF) is an arrhythmia frequently found among the critically ill (1–3). Several acute and chronic comorbid conditions common to the ICU are substrates for its occurrence and potentiate its impact on prognosis (1–12). Although AF can be a debilitating illness with potentially catastrophic complications such as thromboembolic stroke and heart failure, these risks can be substantially mitigated by anticoagulation and by control of heart rate or rhythm (13). Thus, there is an imperative for detection of AF, even in patients without arrhythmia symptoms.

Despite widespread use of continuous electrocardiography (ECG) monitoring, methods for detection of AF in the ICU

are not standardized and transient episodes can go unrecognized (3). The commotion of patients, providers, and technology common to most modern ICUs results in ECG artifact that further obfuscates AF detection. Such short episodes in the context of other acute comorbid conditions are of unclear clinical consequence in the short and long terms (1, 13–19).

In this work, we detected AF using mathematical analyses of heart rate dynamics from continuous ECG rather than relying entirely on clinical recognition and chart documentation. The ECG-derived heartbeat interval time series is a robust signal, and we have demonstrated that measurements in its nonlinear domain can assist in the detection of arrhythmia and improve prognostication (20–24).

In 74 patient-years of ECG recording from 8,356 consecutive ICU patients, we examined the prevalence, incidence, and burden of AF (22, 23). We tested the hypothesis that new-onset AF, recognized or not, is associated with outcomes such as ICU length of stay (LOS), hospital mortality, and survival after hospital discharge.

METHODS

Study Population

We studied consecutive admissions to the surgical/trauma/burn ICU (SICU) and medical ICU (MICU) at the University of Virginia Health System from March 1, 2011, through July 26, 2015. Both ICUs used continuous ECG monitoring systems. An institutional electronic data warehouse archived the complete medical record from which we collected demographics, diagnosis codes, 12-lead ECG reports, and the attributes pertaining to all inpatient encounters including details such as LOS and hospital mortality. The University of Virginia Institutional Review Board approved this study with a waiver of informed consent.

Rhythm Classification

We analyzed 30-minute segments of the interbeat interval time series from the continuous ECG record using a previously validated rhythm classification methodology, and we labeled segments as AF if they contained a burden of more than or equal to 90 seconds (23). The external validation of the algorithm on 500 randomly selected 30-minute segments from our ICU study population found a sensitivity of 89% and a positive predictive value of greater than 99% (**Online Tables 1** and **2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C416). From the larger dataset, we excluded observations occurring within 12 hours prior to hospital mortality to guard against the possibility of analyzing terminal rhythms.

We categorized admissions as having prior AF if there was evidence of preexisting AF or atrial flutter (AFL) as determined by diagnosis code, 12-lead ECG report, or as the first detected rhythm from the ICU bedside monitor. In those without prior AF, if we subsequently detected AF or AFL during ICU monitoring, we categorized the admission as new-onset AF. We categorized all other admissions as without AF. We considered new-onset AF to be clinical or recognized if it was associated with a diagnosis code or confirmed by 12-lead ECG during the hospitalization. Although AF and AFL could not be more dissimilar in terms of dynamical properties of heart rate, we justify categorizing them together on the basis of related pathophysiology and similar clinical treatment (20).

Severity of Illness

To assess severity of illness, we calculated the Oxford Acute Severity of Illness Score (OASIS) for all admissions (5). OASIS is an abbreviated acute physiology score that has equivalent discrimination and calibration of the Acute Physiology, Age, and Chronic Health Evaluation (APACHE) IV system from which it was derived. OASIS scores the worst measurements from the first 24 hours of ICU admission and is comprised of pre-ICU LOS, age, Glasgow Coma Score, heart rate, mean arterial pressure, respiratory rate, temperature, urine output, mechanical ventilation status, and admission type. In admissions with multiple ICU stays, we calculated OASIS for the first.

Vasopressor Requirements

We collected the administrations of vasopressor agents used during ICU stays and calculated the number of different agents used during the first 24 hours of ICU monitoring. For regression analyses, we used an ordinal scale (0: no pressor requirements, 1: one agent, etc) and treated this as a continuous variable.

Statistical Analyses

For continuous variables, we calculated the medians and interquartile ranges (IQRs), and for categorical variables, the percents and counts. To test for differences in other physiologic measurements among groups, we regressed vital sign measurements on categorical groups and adjusted for repeated measures. To characterize the determinants of new-onset AF and its recognition, we regressed demographics, comorbid conditions, illness severity, and number of vasopressor required on an ordinal scale of no AF: 0; new-onset subclinical AF: 1; and new-onset clinical AF: 2. Cumulative incidence of AF during ICU monitoring and survival after hospital discharge were estimated using Kaplan-Meier methodology.

We used propensity score matching to balance patient characteristics between patient admissions with and without detection of AF by performing multiple logistic regression to predict the probability of any detected AF and controlling for admission characteristics, including demographics, comorbid conditions, severity of illness, number of vasopressors required, and postoperative state. To assess the association of new-onset AF on ICU LOS, we analyzed only the AF detected during the first 48 hours of ICU monitoring, matched on propensity score, and adjusted for common acute and chronic comorbidities as well as severity of illness and vasopressor requirement. To assess the association of new-onset AF on hospital mortality and postdischarge survival, we developed logistic and Cox proportional hazards regression models, respectively, matched on propensity score and adjusted for comorbidities, acuity of illness, and vasopressor requirement.

We allowed continuous variables such as age to have nonmonotonic association through use of restricted cubic splines (25). In all prespecified multiple regression analyses, our events per variable or degrees of freedom ratio exceeded 25 (26). We quantified predictive accuracy using a concordance index (*C*-statistic) or R^2

and validated these models internally using bootstrap resampling to estimate the performance on a new sample of observations from the same patient population (25). We performed all statistical analyses in R 3.2.0 (27). Additional information related to the study population, rhythm classification, and statistical analyses is provided in the **online supplement** (Supplemental Digital Content 1, http://links.lww.com/CCM/C416).

RESULTS

Prevalence

From 8,356 adult admissions to either the MICU or SICU and for whom continuous ECG data were available, we made 2,600,100 observations at 15-minute increments (74.2 patient-years; admissions to MICU, 3,441; SICU, 4,702; both units, 213). We classified 159,327 observations (6.1%) from 1,610 admissions (19.3%) as AF or AFL using our rhythm classification algorithm (for distribution of model output, see **Online Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C416). AF was more likely to occur in the MICU as compared to the SICU (7.3% vs 5.2% of all observations, respectively; $p < 0.0001$).

Incidence

We categorized 1,385 admissions (16.6%) as having prior AF, but detected its presence in only 861 of their ICU stays (62.2%). A portion of these (16.5%; $n = 228$) did not have a documented history of AF or AFL, but had it detected prior to or on arrival to the ICU. Of the remaining 6,971 admissions without prior AF, we detected its presence in an additional 749 (10.7%) or 46.5% of all admissions in which AF was detected (**Fig. 1**). Thus AF was detected in 1,610 patients, 861 with a prior diagnosis and 749 with new-onset AF. The median cumulative duration of new-onset AF was 60 minutes (IQR, 30–150), representing a median burden of 0.9% of total ICU monitoring time (IQR, 0.3–3.1%).

Recognition of New-Onset AF

Of those with new-onset AF occurring in the ICU, only 123 (16.4%) were recognized and confirmed or documented as clinical AF—we detected new-onset subclinical AF in 626 or 7.5% of all ICU admissions (Fig. 1). New-onset subclinical and clinical AF occurred at similar times during the ICU admission at a median of 35 hours from the time of initial monitoring (**Fig. 2**); however, the cumulative duration and burden were both higher in those with clinical AF (270 vs 45 min and 2.7% vs 0.7%, respectively). In follow-up, 12-lead ECG confirmed 67% of new-onset clinical AF a median of 1.5 days after we first detected its presence (**Online Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C416). Greater duration and burden of AF were both independently associated with increased recognition ($p < 0.001$).

During periods of AF, there were only subtle differences in vital sign measurement among the groups (**Online Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C416). AF was the cardiac rhythm at ICU discharge of 3%, 13%, and 18% of subclinical, clinical, and prior AF patients, respectively ($p < 0.0001$) (Online Table 3, Supplemental Digital Content 1, http://links.lww.com/CCM/C416).

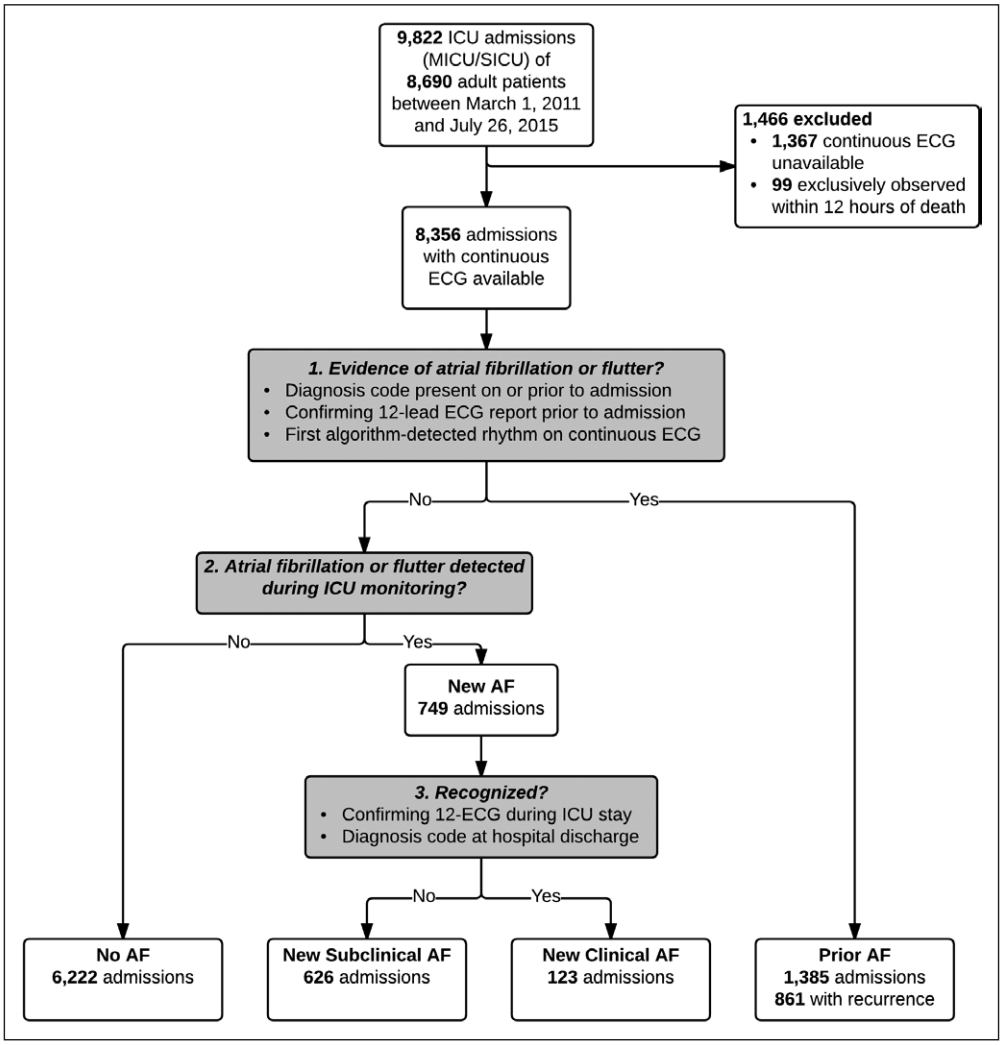

Figure 1. Flowchart of criteria for categorization of atrial fibrillation (AF) status. Flowchart of patient admissions analyzed and definitions of categorization according to AF status. ECG = electrocardiogram, MICU = medical ICU, SICU = surgical/trauma/burn ICU.

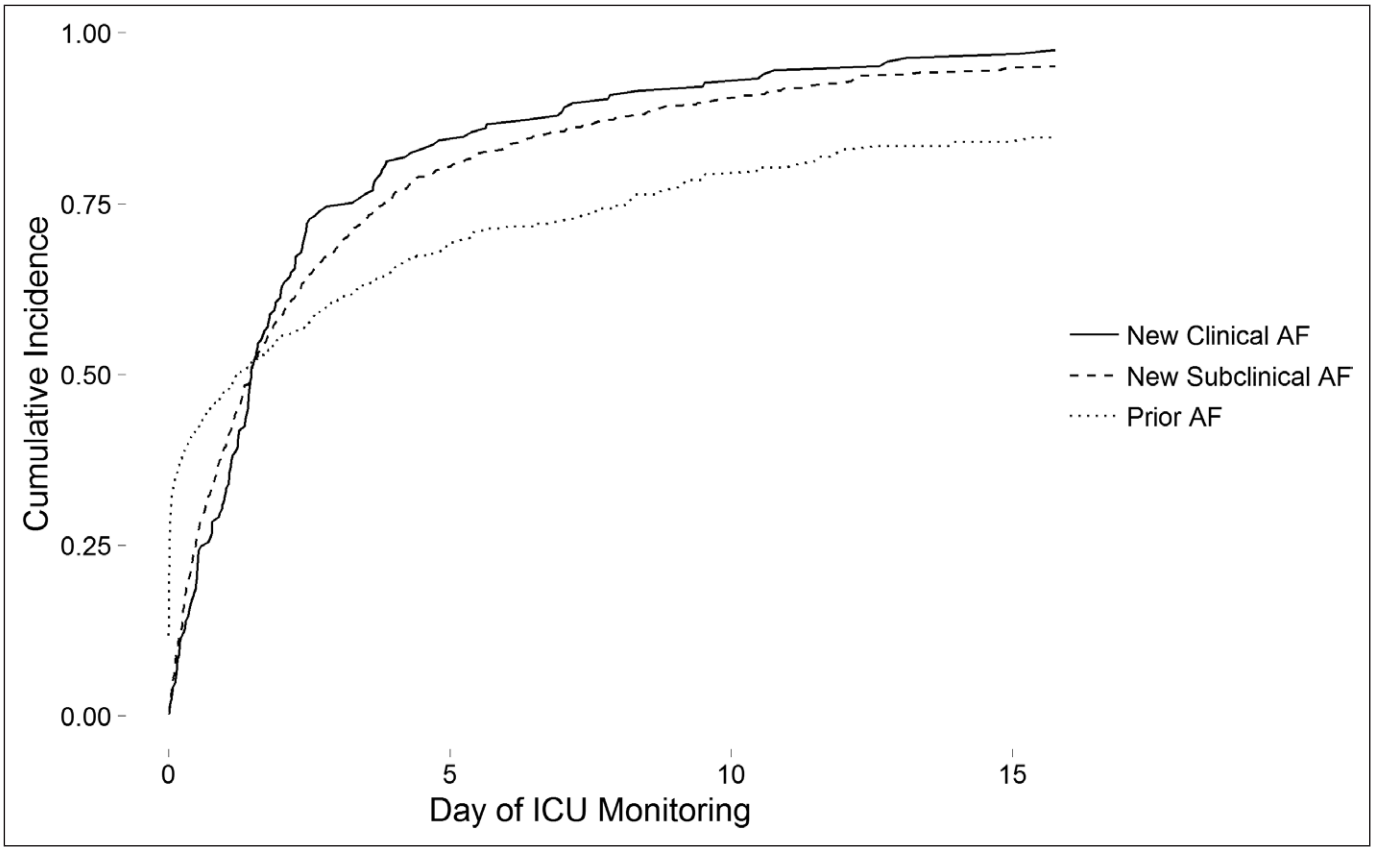

Figure 2. Cumulative incidence of atrial fibrillation (AF). Cumulative incidence of AF as a function of time monitored. There was no significant difference in the cumulative incidence of AF as a function of time monitored between the groups with AF ($p = 0.613$).

Determinants of New-Onset AF

Several patient admission characteristics were independent predictors of developing new-onset AF (*C*-statistic, 0.71; optimism, 0.02). The strongest associations were acute respiratory failure, advanced age (starting from 60 yr), and sepsis (**Fig. 3**, ***A*** and ***B***). We observed weaker but still significant associations for postoperative state, severity of illness, hemorrhage, vasopressor requirement, valvular heart disease, gender, and chronic pulmonary disease. Surprisingly, heart failure, kidney disease, and body mass index (BMI) were not significantly associated with new-onset AF. Consistent with existing knowledge, all these risk factors were strongly associated with prior AF in univariate analysis: valvular heart disease (odds ratio [OR], 4.42; CI, 4.05–4.83), renal failure (OR, 2.15; CI, 2.00–2.30), heart failure (OR, 6.45; CI, 6.04–6.89), and BMI (OR, 1.01; CI, 1.01–1.01). In sensitivity analysis, collapse of the ordinal scale to a binary outcome of any new-onset AF led to only minimal changes in the statistical significance of candidate predictors.

Impact on Outcomes

Compared to admissions without AF, the median ICU LOS was 2.5- and 4.1-fold longer in those with new-onset subclinical and clinical AF, respectively (Online Table 3, Supplemental Digital Content 1, http://links.lww.com/CCM/C416) ($p < 0.001$). In multiple regression analysis on the first 48 hours of ICU monitoring with propensity-matched controls and adjusting for patient demographics as well as acute and chronic comorbid conditions, both prior AF and new-onset clinical AF were independently associated with ICU LOS ($\beta = 1.29$; 95% CI, 0.62–1.97 and $\beta = 2.25$; 95% CI, 0.58–3.92, respectively) (**Fig. 4*A***).

Compared to admissions without AF, hospital mortality was two- and four-fold higher in those with new-onset subclinical and clinical AF, respectively (Online Table 3, Supplemental Digital Content 1, http://links.lww.com/CCM/C416) ($p < 0.001$). In logistic regression analysis with propensity-matched controls and adjusting for demographics, comorbid conditions, severity of illness, and vasopressor use, only new-onset clinical AF was associated with hospital mortality (OR, 1.63; 95% CI, 1.01–2.63) (**Fig. 4*B***).

Patients with new-onset clinical AF had worse outcomes than prior AF with a 2.6-fold increase in median ICU LOS and 1.8-fold higher hospital mortality (Online Table 3, Supplemental Digital Content 1, http://links.lww.com/CCM/C416). Interestingly, when adjusting for demographic and comorbid conditions including history of AF and AFL, the burden of AF as a proportion of total ICU ECG monitoring was not significantly associated with either ICU LOS or hospital mortality ($p = 0.301$ and $p = 0.088$, respectively).

For patients who survived to discharge, follow-up data were available for 99% with a median duration of 0.8 (IQR, 0.2–1.8; maximum, 4.4) years. In nonparametric survival analysis with propensity-matched controls, there were significant

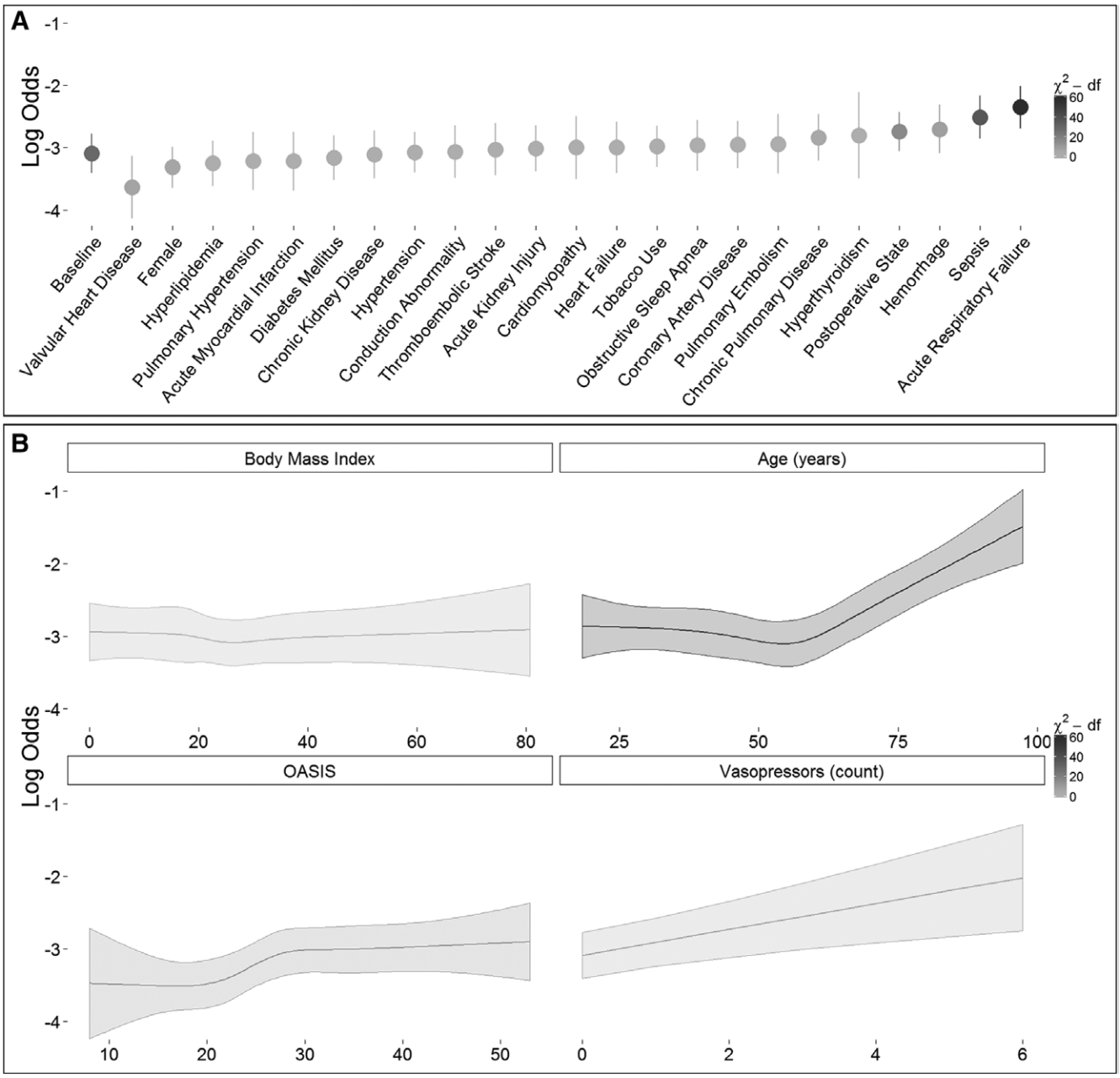

Figure 3. Determinants of atrial fibrillation, length of stay, and hospital mortality. Effect of each (**A**) categorical predictor or **(B)** continuous predictor across its range on the log odds of developing atrial fibrillation. SEs represented by line height or ribbon width, respectively. *Grayscale* is the relative proportion of variance accounted for by each term measured by Wald chi-square statistics (χ^2) minus the degrees of freedom (df). OASIS = Oxford Acute Severity of Illness Score.

differences between the groups in follow-up after hospital discharge (**Fig. 5*A***) ($p < 0.0001$). In adjusted Cox proportional hazards analysis with propensity-matched controls, however, new-onset AF was not associated with poorer survival (hazard ratio [HR], 0.99; 95% CI, 0.76–1.28 and HR, 1.11; 95% CI, 0.67–1.83, respectively, for new-onset subclinical and clinical AF), but prior AF was (HR, 1.55; 95% CI, 1.29–1.88).

DISCUSSION

We used automated analysis of continuous ECG to detect AF in a large, unselected ICU cohort. We found AF in nearly one of every five ICU admissions, nearly half of which was new. Our major findings are that new-onset clinically recognized AF is associated with both longer ICU LOS and increased hospital mortality. We found no significant association, though, of new-onset AF with survival following hospital discharge (Fig. 5*A*).

Though common, new-onset AF in the critically ill is a complex clinical challenge. There is no standardized method for detection and only scant evidence to guide treatment (13–16). Prior studies have relied on charted documentation, secondary administrative data, or been confined to specific subpopulations (4–7). Studies using continuous ECG have been small and with limited follow-up (3, 5–7).

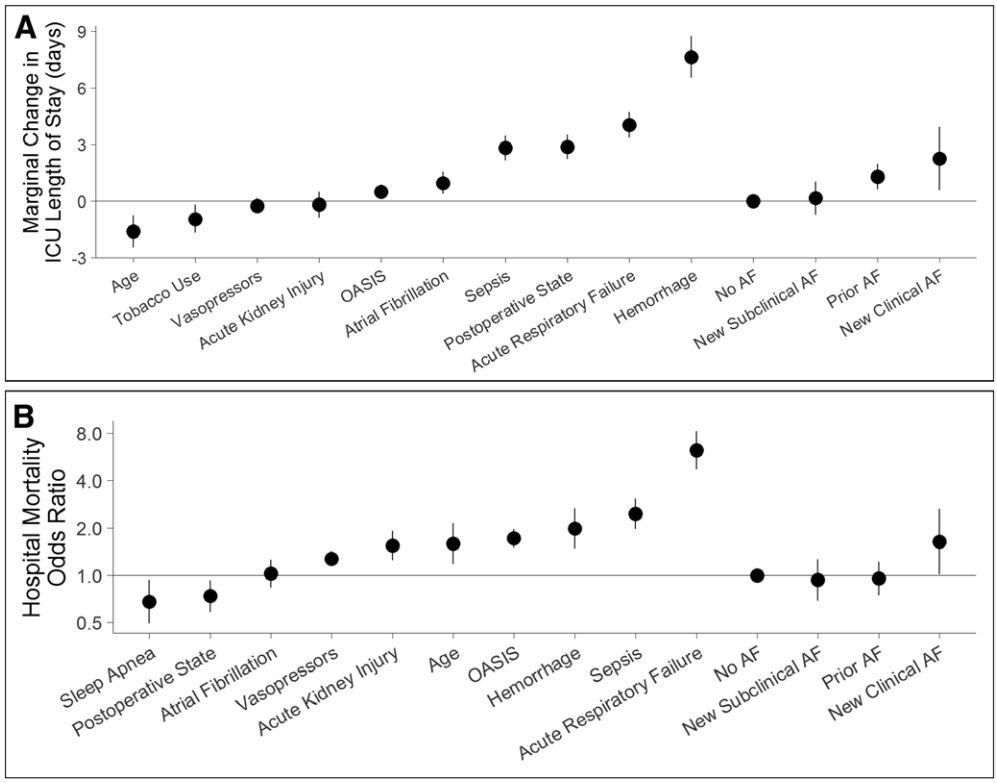

Figure 4. Determinants of ICU length of stay and hospital mortality. **A**, Estimated marginal effects on ICU length of stay of most significant predictors and atrial fibrillation (AF) status. For continuous predictors, we estimated the marginal effect between the interquartile range (75th percentile value vs 25th percentile value). B, Estimated odds ratio on hospital mortality of most significant predictors and AF status. For continuous predictors, we estimated the odds ratio between the interquartile range (75th percentile value vs 25th percentile value). OASIS = Oxford Acute Severity of Illness Score.

The incidence of new-onset AF in our study—10.7% of at-risk admissions—was similar to prior reports ranging from 4.5% to 29.5% (1, 28, 29). Episodes were often transient, and the overall burden was low. Like others, we found that new-onset AF was associated with acute respiratory failure, advanced age, sepsis, hemorrhage, or postoperative state (6, 8, 28–30). We have previously studied some of these potentially catastrophic conditions in subsets of this cohort and found that they profoundly affect outcomes (31). Though obesity is a risk factor for AF (32), we surprisingly found no such association in these ICU patients.

New-onset clinical AF was associated with longer ICU LOS and increased hospital mortality. Others have found a 2–3-fold increase in both the mean ICU LOS and hospital mortality in patients with new-onset AF (5–8, 28), similar to our observed 2.5- and 4.1-fold increase in the median ICU LOS and two- and four-fold increase in hospital mortality for new-onset subclinical and clinical AF, respectively. We suspect, but cannot demonstrate here, that transient hemodynamic derangement resulting from AF may be a tipping point for critically ill patients with limited physiologic reserve.

We found that only AF prior to ICU arrival was significantly associated with survival following hospital discharge. Other studies have found that new-onset AF portends poor long-term prognosis in select subpopulations (5, 30, 33). One particular study in patients with acute respiratory distress syndrome employed propensity matching on APACHE III scores, but failed to demonstrate any evidence that such matching resulted in balanced covariates (12). We replicated this finding in our unadjusted analysis, but found that it vanished with use of propensity-matched controls.

Why was new-onset AF unrecognized in nearly four of every five admissions? The transient nature of AF in the ICU is the most likely explanation. In cases when new-onset clinical AF was confirmed by 12-lead ECG, there was a median delay of 1.5 (0.1–3.1) days from first onset. The subtle differences in vital sign measurements between periods of recognized and unrecognized AF are unlikely to explain the low level of overall recognition. Similarly, the times of onset after admission were nearly identical. Consistent with prior findings, greater AF burden and greater illness severity led to clinical recognition (34).

We propose that new-onset AF in the critically ill exists as a spectrum such that once the burden is sufficient to attain clinical recognition, the arrhythmia is strongly associated with poor hospital outcomes (**Fig. 5*B***).

Would Improved AF Detection Lead to Better Outcomes?

A variety of continuous ECG monitoring technologies can now unveil otherwise silent paroxysmal AF, prompting earlier diagnosis and treatment (35). Silent AF occurs frequently in patients with implanted pacemakers and has been associated with increased risk of ischemic stroke (36). There are no guidelines about the minimum duration of silent or subclinical AF at which to consider therapy for stroke prevention, particularly in the context of acute noncardiovascular illness (13, 16).

We envision that algorithms to detect AF from ICU ECG monitoring might enable earlier recognition and potentially improve outcomes. Walkey et al (18, 37) proposed a systematic approach to identify and address reversible triggers and have shown that select interventions may indeed lead to better outcomes. As subclinical AF may have no direct

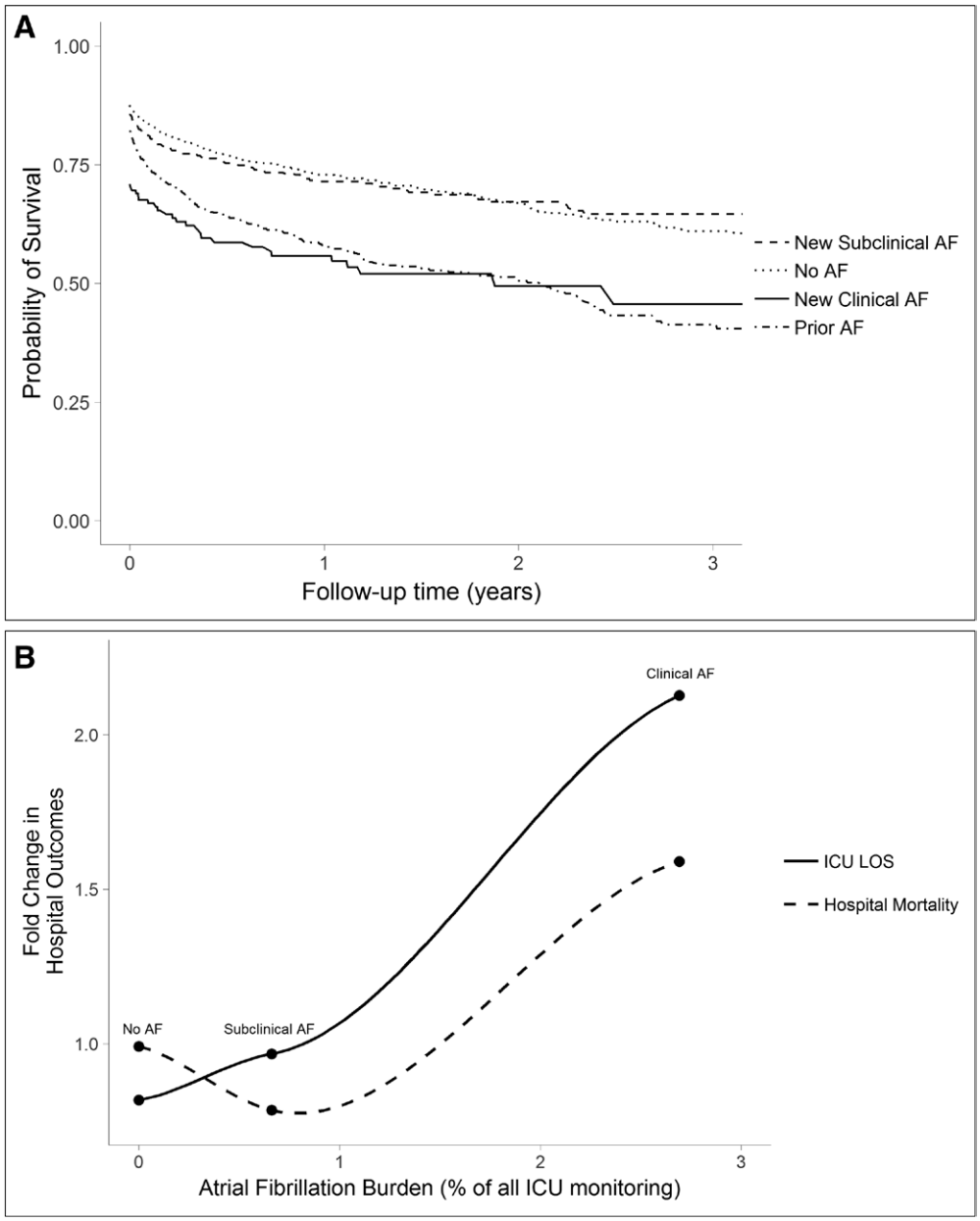

Figure 5. Impact of new-onset atrial fibrillation (AF) on outcomes. **A**, Probability of survival after hospital discharge according to AF status. Survival estimates at time zero reflect the differences in hospital mortality where admissions with new-onset clinical AF had by the poorest hospital mortality. **B**, Fold change in hospital outcomes—ICU length of stay (ICU LOS) and hospital mortality for new-onset subclinical and clinical AF as a function of the median AF burden, quantified as the percentage of all ICU monitoring, compared to propensity-matched controls without any AF.

impact on patient outcomes, its detection could result in additional diagnostic testing and treatments that would have no benefit. We agree with others about the need for randomized clinical trials to compare the effectiveness of various treatments currently in practice (38, 39). For example, Gillinov et al (39) recently showed no difference in rate control and rhythm control strategies in ICU patients after cardiac surgery. The study relied on clinical recognition of the arrhythmia, which cannot be standardized and may have differed among the centers. We propose that future studies be conducted using standardized methods of AF detection including analysis of the continuous ECG record.

Limitations

We conducted a single-center retrospective study in an unselected cohort from an academic, rural, tertiary care, academic medical center with a large catchment area. Other health systems might provide a greater portion of the preceding longitudinal care to their inpatients, which could result in more comprehensive documentation of chronic comorbidities, including AF.

We trained the AF detection algorithm on 30-minute segments of Holter monitors where AF was labeled for durations more than 90 seconds and taking atrial and ventricular ectopy into account (23). In the ICU, we can expect underdiagnosis of transient AF bursts and overdiagnosis when extreme burdens of ectopy, like multifocal atrial tachycardia, occur. The details of specific classes and dosages of vasopressors to which patients were exposed were not examined in our analyses and may represent another source of potential confounding.

LOS in clinical studies is challenging to predict and is confounded by nonclinical factors such as fluctuations in the availability of both floor beds and nurse staffing. As all admissions classed as new-onset AF had to survive to the point where AF was detected, our study may underestimate the magnitude of effect with respect to its association with hospital mortality. We note that the associations with outcome are not adequate to draw conclusions about causation (40). AF may yet be a surrogate of unmeasured characteristics; however, new-onset AF remained among the strongest predictors after propensity matching and adjusting for age, common comorbidities, severity of illness, and use of vasopressors.

CONCLUSIONS

Automated analysis of heart rate dynamics from ECG monitoring detects new-onset and otherwise subclinical AF in many ICU patients. Though often transient and frequently unrecognized, new-onset AF is associated with poor hospital outcomes.

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