New-onset atrial fibrillation incidence and associated outcomes in the medical intensive care unit

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Abstract

Background: In patients with critical medical illness, data regarding new-onset atrial fibrillation (NOAF) is relatively sparse. This study examines the incidence, associated risk factors, and associated outcomes of NOAF in patients in the medical intensive care unit (MICU).

Methods: This single-center retrospective observational cohort study included 2234 patients with MICU stays in 2018. An automated extraction process using ICD-10 codes, validated by a 196-patient manual chart review, was used for data collection. Demographics, medications, and risk factors were collected. Multiple risk scores were calculated for each patient, and AF recurrence was also manually extracted. Length of stay, mortality, and new stroke were primary recorded outcomes.

Results: Two hundred and forty one patients of the 2234 patient cohort (11.4%) developed NOAF during their MICU stay. NOAF was associated with greater length of stay in the MICU (5.84 vs. 3.52 days, \( p < .001 \)) and in the hospital (15.7 vs. 10.9 days, \( p < .001 \)). Patients with NOAF had greater odds of hospital mortality (odds ratio (OR) = 1.92, 95% confidence interval (CI) 1.34–2.71, \( p < .001 \)) and 1-year mortality (OR = 1.37, 95% CI 1.02–1.82, \( p = .03 \)). CHARGE-AF scores performed best in predicting NOAF (area under the curve (AUC) 0.691, \( p < .001 \)).

Conclusions: The incidence of NOAF in this MICU cohort was 11.4%, and NOAF was associated with a significant increase in hospital LOS and mortality. Furthermore, the CHARGE-AF score performed best in predicting NOAF.

KEYWORDS
CHARGE-AF, medical intensive care unit, New-onset atrial fibrillation, New-onset atrial flutter

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1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting one in four patients over the age of 65, and is associated with significant morbidity and mortality. Patients with AF are at increased risk for complications including rapid ventricular response, decreased cardiac output, cardiogenic shock, and death. MICU patients who develop NOAF are a particularly susceptible population with increased risk for developing life-threatening sequelae. However, NOAF in specifically MICU patients has been understudied relative to NOAF in surgical patients. The risk of stroke associated with AF is well established, with AF patients at a 4 to 5-fold greater risk of ischemic stroke. Annual stroke risk in patients with AF is most commonly estimated using the CHA2DS2-VASc score to identify patients who will benefit from oral anticoagulation. However, data regarding the optimal long-term anticoagulation strategy for NOAF in MICU patients, especially those with only one or more brief episodes of AF, is relatively limited. Given the associated negative consequences, an improved way to stratify MICU patients based on their risk for developing NOAF may be helpful from a monitoring and prevention standpoint. The predictive value of previously existing risk scores (such as CHA2DS2-VASc, C2HEST, ESCARVAL, and CHARGE-AF scores) for NOAF in various settings has been previously assessed. In one study of post-coronary artery bypass graft (CABG) patients, CHARGE-AF was found to outperform CHA2DS2-VASc and age alone for prediction of NOAF. However, our literature review did not reveal any prior studies examining the predictive value of CHARGE-AF in the MICU population. While the majority of research on NOAF has been in post-cardiothoracic and non-cardiac surgery patients, this study focuses on patients treated in the MICU setting. Further characterization of the associated conditions and risk factors for NOAF in the MICU will aid in clarifying NOAF pathophysiology and risk stratification, potentially spurring the development of prevention strategies in the critically ill.

2 | METHODS

This single-center retrospective observational cohort study included all patients with one or more MICU encounters in 2018 at an over 800-bed tertiary/quaternary care academic medical center. If a patient had more than one MICU encounter in 2018, only the first MICU encounter was included in the final analysis. The patient population was identified using i2b2, the institutional translational data warehouse platform for research, to compile a list of all patients with MICU stays in 2018. The case group was composed of patients with NOAF during the MICU encounter or the overall associated hospital stay. NOAF was defined as AF or atrial flutter (AFL) detected during a hospital stay by telemetry or ECG in patients with no prior history of either. This definition is similar to that used in prior studies. The control group included all other adult patients with a MICU stay in 2018. Postoperative patients, patients less than 18 years of age, and patients with pre-existing AF or AFL were excluded. Postoperative patients were defined as those who underwent a surgical procedure during the same hospital encounter as their MICU stay. AF or AFL was considered pre-existing if it was diagnosed before January 1, 2018. This study was approved by the Institutional Review Board at Wake Forest School of Medicine (IRB 00059350).

Patient demographic, diagnostic, clinical, and outcome data were obtained from the electronic health record (EHR). Basic demographic information was collected, including age, sex, and race. Ambulatory data, including height, weight, and average blood pressure, was collected from prior to a patient’s hospital stay. Risk factors and specific metrics for AF were compiled including hypertension, coronary artery disease, congestive heart failure, obesity, diabetes, stroke, transient ischemic attack, thromboembolism, and smoking history. Automated data extraction was used to identify NOAF and to compile data for each patient primarily based on ICD-10 codes available through the EHR data warehouse. The automated extraction rules were validated by a manual data extraction of 196 patients, 90 with NOAF and 106 from the control group. The results of the manual and automated data extractions were found to be largely concordant. The final number of discordants between the automated extraction and manual extraction was 12 out of 196. Of these, five subjects were falsely negative for NOAF, and seven were falsely positive for NOAF by the automated extraction rules.

Outcomes of interest included in-hospital mortality, mortality at 1 year, length of stay (LOS) in the MICU and hospital, and new stroke in the year following the MICU stay. CHA2DS2-VASc was calculated for prediction of NOAF. However, our literature review did not reveal any prior studies examining the predictive value of CHARGE-AF in the MICU population. While the majority of research on NOAF has been in post-cardiothoracic and non-cardiac surgery patients, this study focuses on patients treated in the MICU setting. Further characterization of the associated conditions and risk factors for NOAF in the MICU will aid in clarifying NOAF pathophysiology and risk stratification, potentially spurring the development of prevention strategies in the critically ill.
including stroke and mortality within 1 year. Patients who died before discharge were censored. We also assessed associations of AF recurrence and medications prescribed at discharge with the primary outcomes of stroke and mortality. Statistical significance was defined as \( p < .05 \) for all analyses. All data was analyzed using R 3.6.1 statistical software.

### 3 | RESULTS

A total of 241 patients of the 2234 total cohort developed NOAF during their MICU stay, a NOAF incidence of 11.4%. The NOAF group was compared with a control group of 1993 MICU encounters. Patients with NOAF were significantly more likely to be older (67.5 years vs. 57.0 years), white (83.4% vs. 70.6%), on antihypertensive therapy (73.4% vs. 61.9%), have congestive heart failure (51.5% vs. 36.7%), and have diabetes (52.7% vs. 44.2%) compared to the control group. The demographic differences between the two groups are illustrated by Table 1.

NOAF was associated with greater LOS in the MICU (5.84 vs. 3.52 days, \( p < .001 \)) and in the hospital (15.7 vs. 10.9 days, \( p < .001 \)). After adjustment for age, sex, and race, patient’s with NOAF had significantly greater MICU LOS by 2.43 days (95% CI 1.84–3.02, \( p < .001 \)) and significantly greater hospital LOS by 5.02 days (95% CI 3.07–6.98, \( p < .001 \)). Patients with NOAF also had greater odds of hospital mortality (OR = 1.92, 95% CI 1.34–2.71, \( p < .001 \)) and 1-year mortality (OR = 1.37, 95% CI 1.02–1.82, \( p = .03 \)). NOAF was associated with a greater risk of stroke after 1-year, but this result was not significant (OR = 1.43, 95% CI 0.81–2.41, \( p = .19 \)). These outcomes are summarized in Table 2.

In our assessment of clinical risk scores for the prediction of NOAF, CHARGE-AF performed better than CHA\(^2\)DS\(_2\)-VASc (AUC 0.691 vs.
Table 2. Outcomes

|                      | NOAF (n = 241) | Control (n = 1993) | p-value |
|----------------------|----------------|--------------------|---------|
| MICU LOS, days       | 5.84 ± 6.09    | 3.52 ± 4.04        | < .001  |
| Hospital LOS, days   | 15.7 ± 18.7    | 10.9 ± 13.7        | < .001  |
| Hospital mortality   | 51 (21.2%)     | 206 (10.3%)        | < .001  |
| 1-year mortality     | 92 (38.2%)     | 515 (25.8%)        | < .001  |
| Stroke at 1 year     | 18 (7.5%)      | 88 (4.4%)          | .0517   |
| Beta blocker prescribed at discharge | 120 (49.8%) | 438 (22.0%)        | < .001  |
| Calcium channel blocker prescribed at discharge | 53 (22.0%) | 266 (13.3%)        | < .001  |
| Antiarrhythmic prescribed at discharge | 30 (12.4%) | 11 (0.6%)          | < .001  |
| Anticoagulation prescribed at discharge | 87 (36.1%) | 210 (10.5%)        | < .001  |
| CHARGE-AF score      | 14.5 ± 15.9    | 13.4 ± 2.01        | < .001  |
| CHARGE-AF score (imputed) | 14.6 ± 1.51    | 13.3 ± 2.00        | < .001  |
| CHA2DS2-VASc score   | 3.73 ± 1.81    | 3.13 ± 1.99        | < .001  |
| C2HEST score         | 1.95 ± 1.61    | 1.32 ± 1.44        | < .001  |
| ESCARVAL-RISK score  | 7.00 ± 2.99    | 5.56 ± 3.21        | < .001  |

Abbreviations: LOS, Length Of Stay; MICU, Medical Intensive Care Unit; NOAF, New-Onset Atrial Fibrillation.

Figure 1. ROC Curves

AUC 0.595, p < .001, and C2HEST (AUC 0.691 vs. 0.617, p < 0.001). Within the subpopulation associated with the ESCARVAL-RISK score (hypertensive patients aged 40–94), no significant difference in AUCs was found between CHARGE-AF and ESCARVAL-RISK (0.63 vs. 0.60, p = .05). These ROC curves are illustrated in Figure 1.

Of the NOAF group, 69 patients (28.6%) were found to have AF or AFL within 24 hours of discharge. Only 36 patients (15.0%) were found to have AF or AFL at follow-up within 1 year of discharge. In the subgroup analysis of the NOAF group, adjusting for age and sex, AF recurrence (defined as AF or AFL on day of discharge and/or at follow-up) was associated with a trend toward greater 1-year mortality (Hazard ratio = 1.84, 95% CI: 0.98–3.47, p = .06). Figure 2 is a graphical representation of this survival analysis. Recurrence of AF was associated with an increased stroke risk in the following year (Hazard Ratio = 1.69, 95% CI: 0.60–4.81, p = .32). Neither of these results were statistically significant. Regarding treatment strategies, 121 patients (50.2%) were placed on rate control medication alone versus 27 patients (11.2%) treated with a rhythm control strategy. The remaining 38.6% of patients did not receive any rate or rhythm control medications. Only 79 patients (32.8%) were prescribed anticoagulation. In our NOAF subgroup analysis of treatment strategies, which are summarized in Table 3, the only significant finding was that NOAF patients who were prescribed rate control medications were more likely to experience a stroke outcome (p = .034). However, this association was not significant after adjusting for age and sex (p = .062).
4 | DISCUSSION

We retrospectively analyzed a cohort of non-postoperative MICU patients diagnosed with NOAF to examine the incidence, predictive factors, and outcomes associated with this common condition. Overall, NOAF occurred in 11.4% of MICU patients. After adjustment for demographic factors, patients with NOAF were found to have significantly longer MICU and hospital stays as well as greater odds of hospital and 1-year mortality compared to the control group. The CHARGE-AF score was found to be more predictive for NOAF than the CHA2DS2-VASc score.

Our finding that patients with NOAF had a longer hospital LOS is supported by previous literature.\(^2,3,5,17,18,19\) This relationship between NOAF and LOS is not surprising given that NOAF appears to be a marker for more severe illness in the ICU setting.\(^20,21\) Unfortunately, our analysis does not elucidate causality of this association. NOAF may directly be responsible for longer LOS, longer LOS may allow for more time to detect NOAF, or patients who develop NOAF may tend to have more severe chronic illnesses at baseline, leading to longer ICU stays. These factors are all likely contributing to some degree. Regardless, longer ICU and hospital stays seen in this population increase healthcare costs and may contribute to worse patient outcomes.

We found a strong association between NOAF and in-hospital mortality as well as 1-year mortality. Previous studies have largely shown a similar positive relationship between NOAF and mortality.\(^2,4,22\) However, fewer studies have assessed mortality after discharge, and one prior large study did not find any significant difference in post-discharge survival among patients with NOAF.\(^2\) The present body of evidence regarding NOAF among MICU patients is heterogeneous, and we suspect measurable outcomes are highly variable in this population due to inter-study differences in exclusion criteria, patient age, and other demographic variables.\(^8\) Perhaps, with early detection and interventions for NOAF, mortality associated with AF-related complications (e.g., cerebrovascular accident) can be effectively mitigated among the critically ill.

We also examined AF recurrence and its effect on the primary outcomes of stroke and mortality. Prior research has demonstrated an association increased AF burden and these outcomes.\(^23\) A positive relationship existed between AF recurrence and both these clinical outcomes, but neither was significant. While our study has a large total population, there is a relatively small number (241) of patients with NOAF. Furthermore, this critically ill study population inherently leads to suboptimal follow-up, most commonly due to the high rates of mortality, including during the MICU stay itself. This relatively small sample size limited our statistical power. Likely for similar reasons, we did not observe any significant differences in treatments strategies used for NOAF and clinical outcomes. This is consistently an area in the literature that has been difficult to study.\(^8\) Regarding the association of beta blockers and stroke, while ultimately not a significant finding, perhaps this represents a reverse causation bias. Patients with higher AF burden, and therefore at higher risk of stroke, may have been more likely to be prescribed beta blockers.

In our cohort, we found that the CHARGE-AF score had the greatest predictive value for NOAF. Similar differences in predictive validity have been demonstrated in post-CABG patients\(^16\) and in various community-based and racially diverse cohorts.\(^11,24\) In our review of current literature, we did not find any previous studies assessing the predictive value of CHARGE-AF or any of the other examined clinical risk scores in the MICU population. Nonetheless, further study is needed to examine the utility of CHARGE-AF in evaluating MICU patient risk for NOAF.

The strengths of this study include a large sample size of patients with MICU stays over the course of an entire calendar year. By analyzing a full calendar year of data, we were able to assess a patient sample more representative of the range of pathologies requiring MICU stays that may vary based on the time of year. Our focus on MICU patients is a strength as this population is relatively understudied compared to postoperative patients. Additionally, a consistent automated data extraction process was used. This automated process was verified with a manual data extraction of 196 patients. This study further
corroborates the findings of other studies while also addressing some novel areas of interest such as the predictive value of CHARGE-AF in the NOAF population.

There were several limitations we encountered in our study. While we controlled for demographics in our measured outcomes, it is possible that either group had different degrees of illness severity that confounded our results. Due to limitations in the data available for automated extraction, we were unable to obtain useful information regarding the reason for MICU admissions. Furthermore, the Acute Physiology and Chronic Health Evaluation II score or a similar prognostic scoring system could have helped us control for this, however, automating retrieval of the values necessary to calculate such a score was limited by the data readily available in the EHR. Additionally, our automated data extraction was unable to pull all the data points required to calculate CHARGE-AF scores in 29% of the control and 45% of the NOAF cohorts, almost completely due to missing ambulatory weight and blood pressure data. The inclusion of data only prior to hospital stays likely led to the majority of this missingness. However, we felt this limitation was acceptable because the alternative of including data after hospital encounters would introduce a confounding factor of increased data missingness stemming from subjects who expired. Furthermore, the data was intended for the calculation of a predictive risk score and therefore should ideally employ data prior to the event of interest. To address this issue and include all available data from our cohort, we imputed a median value to supply the missing ambulatory data for each group. The AUC for this imputed CHARGE-AF score was quite close to the original CHARGE-AF score AUC.

5 | CONCLUSION

NOAF was common in this cohort of non-postoperative critical care patients, with an incidence of 11.4%. Compared to the control group, NOAF was associated with longer MICU and hospital LOS as well as greater risk of mortality. CHARGE-AF scores had the greatest predictive value for NOAF in our cohort. Future directions of research may focus on risk stratification of this patient population to potentially optimize prevention of NOAF, possibly with empiric antiarrhythmic drug use. There is also a need for stronger evidence to guide the treatment strategies for these patients. With such advancements, we can hope to mitigate both the negative patient outcomes and large healthcare costs associated with NOAF.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest or funding to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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