New-onset Atrial Fibrillation in the Critically Ill

Atrial Fibrillation in the Critically Ill

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Online Data Supplement

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Methods

Study Population

From the bedside monitors, we observed the canonical vital signs—heart rate, respiratory rate, blood pressure, and oxygen saturation.

From the electronic data warehouse, we collected demographics, diagnosis codes, 12-lead ECG reports, procedures performed in the operating room, red blood cell transfusions, and the attributes pertaining to all outpatient and inpatient encounters including details such as clinic type, length of stay, and hospital mortality. We defined hemorrhage as three units of red blood cells transfused within a 24-hour period with no red blood cell transfusion in the preceding 24 hours.

The UVa Clinical Data Repository (CDR) regularly collects information from the Virginia Department of Health’s Division of Vital Records and Division of Health Statistics. From the CDR, we collected survival status and date of last known follow-up or death. The UVa Institutional Review Board approved this study with a waiver of informed consent.

Rhythm Classification

From the continuous ECG we made observations every 15 minutes of the preceding 30 minutes and calculated the mean interbeat or RR interval and the standard deviation or heart rate variability (HRV). We also calculated nonlinear dynamics of heart rate, namely, the coefficient of sample entropy (COSEn, a measure of irregularity), the local dynamics score (LDs, a measure of reduced variability with interspersed ectopy), and detrended fluctuation analysis (DFA, a measure of short-term correlations or ectopy). As each measure is ECG-derived, failure to detect RR intervals led to a connected pattern of missing observations for all five measures (10.4%). Using only these five measures (mean RR, HRV, COSEn, LDs, DFA), we evaluated a previously validated rhythm classification methodology, developed from a large data set of 24-hour Holter studies.

Model Development

We studied 2,804 consecutive 24-hour Holter recordings collected by the University of Virginia Health System (UVa), an academic, tertiary-care center from December 2004 to October 2010. We previously reported the demographic and clinical characteristics of these patients and also described the
development and validation of rhythm classification algorithms in this and publicly available data sets to
distinguish atrial fibrillation from sinus rhythm and sinus rhythm with ectopy using measurements of the
linear and nonlinear domains of interbeat interval time series.\textsuperscript{2-4} We subdivided the interbeat interval time
series into 377,285 10-minute segments and classified them into one of two mutually exclusive categories:
(1) \textit{AF} if the burden of AF or atrial flutter (AFL) was greater than 5\% (i.e. \geq 30 \text{ seconds}) or (2) \textit{not AF},
which was primarily comprised of sinus rhythm with varying degrees of ectopy. The heart rate metrics for
each 10-minute segment included the means, standard deviations, COSEn, DFA, and LDs. We then
developed a random forest model to detect AF using only these ECG-derived measurements. We report the
performance of a forest containing 100 trees that had maximal performance as tested on a random sample
(20\%) held out from the original development data set.

\textit{External Validation}

We performed external validation of the model in our intensive care unit (ICU) data set on 500
randomly sampled segments of ECG tracings, each of 30 minutes duration. We annotated each for the
presence of AF or AFL, including both the time of onset and duration. We evaluated the algorithm on
segments consisting of \geq 10 minutes of continuous rhythm, consistent with the data structure used in model
development.\textsuperscript{3}

\textit{Propensity Score Matching}

Propensity score matching enables parametric models for causal inference to work better by
selecting well-matched subsets of the original case and control groups.\textsuperscript{5} We constructed a propensity score
to balance patient characteristics between groups of patients with and without AF during their ICU stay by
fashioning a multiple logistic regression model to predict the probability of any AF during ICU monitoring
controlling for all listed covariates, including demographics, acute and chronic comorbidities, and
postoperative status as listed in \textbf{Online Table 5}. We then matched each patient admission with AF to one
without using a nearest neighbor method without replacement. Admissions with scores above the
maximum or below the minimum of the comparator group were discarded (33 controls, 11 cases).
Results

AF Detection Algorithm Performance

In the testing subset held out from the development data set, the model demonstrated excellent performance with a sensitivity of 96% and PPV of 99% (Online Table 1). In the validation set of 500 randomly sampled segments from ICU admissions, the model also performed well with a sensitivity of 89% and PPV of >99% (Online Table 2).

Propensity Score Matching

Of the 1610 admissions with AF, 1594 (99%) were successfully matched to admissions without AF. The matching resulted in greater balance in covariates between the two groups (Online Table 5).
### Tables

#### Online Table 1: Confusion Matrix of Model Evaluated on Test Set from

**Holter dataset**

| Reference | AF  | Other |
|-----------|-----|-------|
| **Prediction** |     |       |
| AF        | 5,698 | 41   |
| Other     | 251   | 69,463 |

N=75,456 observations of 10 minute electrocardiography segments randomly selected from 2,801 unique 24-hour Holter studies; Accuracy: 99.6% (95% CI: 99.6-99.7%); Sensitivity: 95.7%; Specificity: 99.9%; Positive Predictive Value: 99.3%; Negative Predictive Value: 99.6%; Prevalence: 7.9%; Detection Rate: 7.6%. AF: atrial fibrillation or atrial flutter; Other: all other cardiac rhythms.

#### Online Table 2: Confusion Matrix of Model Externally Validated on Sample from ICU dataset

| Reference | AF  | Other |
|-----------|-----|-------|
| **Prediction** |     |       |
| AF        | 46   | 0     |
| Other     | 6    | 415   |

N=495 observations of individually verified 10-30 minute electrocardiography segments, randomly selected from both the medical and surgical intensive care units (while 500 segments were randomly selected, not all contained ≥ 10 minutes of continuous cardiac rhythm due to artifact or missing data). Accuracy: 98.7% (95% CI: 97.2-99.5%); Sensitivity: 89%; Specificity: >99%; Positive Predictive Value: >99%; Negative Predictive Value: 98.6%; Prevalence: 11.1%; Detection Rate: 9.9%. AF: atrial fibrillation or atrial flutter; Other: all other cardiac rhythms.
### Online Table 3: Baseline characteristics and outcomes by category

| Online Table 3: Baseline characteristics and outcomes by category | No AF (6,222) | New Subclinical AF (626) | New Clinical AF (123) | Prior AF (1,385) |
|---|---|---|---|---|
| **Percentage (n)** | 74 | 7 | 1 | 17 |

**Demographics**

| | No AF | New Subclinical AF | New Clinical AF | Prior AF |
|---|---|---|---|---|
| **Age, years** | 56 (45-67) | 59 (46-72) | 69 (61-78) | 72 (63-80) |
| **Male** | 55 (3,440) | 61 (381) | 50 (61) | 60 (835) |
| **Body mass index** | 27 (22-33) | 27 (22-33) | 28 (24-33) | 28 (23-34) |
| **Number of prior office visits** | 0 (0-1) | 0 (0-1) | 0 (0-1) | 1 (0-6) |
| **Number of recent office visits** | 0 (0-1) | 0 (0-1) | 0 (0-1) | 0 (0-4) |
| **Number of prior 12-lead ECGs** | 1 (0-3) | 1 (0-3) | 2 (0-10) | 1 (0-3) |

**Severity of Illness**

| | No AF | New Subclinical AF | New Clinical AF | Prior AF |
|---|---|---|---|---|
| **OASIS** | 26 (21-32) | 30 (24-36) | 32 (28-38) | 30 (24-36) |
| **Number of vaspressors required in first 24 hours** | 0 (0-0) | 0 (0-1) | 0 (0-1) | 0 (0-1) |

**Atrial Fibrillation**

| | No AF | New Subclinical AF | New Clinical AF | Prior AF |
|---|---|---|---|---|
| **ICU monitoring data, days** | 1.3 (0.7-2.6) | 3.7 (1.7-8.8) | 6.0 (3.2-12.3) | 2.2 (1.0-4.7) |
| **Detected during ICU stay** | 0 (0) | 100 (626) | 100 (123) | 62 (861) |
| **Time to onset from start of ICU monitoring, hours** | 0 (0-0) | 35 (11-93) | 35 (14-87) | 5.5 (0-36) |
| **Cumulative duration, minutes** | 0 (0-0) | 45 (30-105) | 270 (75-728) | 90 (0-1095) |
| **Burden as percentage** | 0 (0-0) | 0.7 (0.3-2.2) | 2.7 (0.9-12.7) | 1.8 (0-50.0) |

**New atrial fibrillation diagnosis code at hospital discharge**

| | No AF | New Subclinical AF | New Clinical AF | Prior AF |
|---|---|---|---|---|
| **New atrial fibrillation code at hospital discharge** | 2 (107) | 0 (0) | 73 (90) | 9 (120) |
|                                | 0 (0) | 7 (44) | 67 (83) | 5 (76) |
|--------------------------------|-------|--------|---------|--------|
| **Days to 12-lead ECG**        |       |        |         |        |
| confirmation of new AF/AFL     | 0 (0) | 143.5 (31.7-423.3) | 1.5 (0.1-3.1) | 2.3 (0.2-13.7) |
| **Final ICU rhythm AF/AFL**    | 0 (0) | 3 (20) | 13 (16) | 18 (213) |
| **CHA\textsubscript{2}DS\textsubscript{2}-VASc** | 2 (1-3) | 2 (1-4) | 4 (2-5) | 4 (3-5) |
| **CHA\textsubscript{2}DS\textsubscript{2}-VASc ≥ 2** | 60 (3,715) | 66 (414) | 85 (105) | 92 (1,277) |

**Comorbid conditions**

| Condition                        | 0 (0) | 7 (44) | 67 (83) | 5 (76) |
|----------------------------------|-------|--------|---------|--------|
| Acute kidney injury              | 15 (960) | 23 (142) | 27 (33) | 28 (390) |
| Acute myocardial infarction      | 5 (287) | 8 (48) | 13 (16) | 13 (180) |
| Acute respiratory failure        | 26 (1,640) | 50 (316) | 69 (85) | 45 (630) |
| Coronary artery disease          | 22 (1,399) | 29 (181) | 40 (49) | 52 (725) |
| Chronic kidney disease           | 19 (1,161) | 23 (147) | 22 (27) | 38 (523) |
| Cardiomyopathy                   | 4 (230) | 5 (31) | 7 (8) | 15 (206) |
| Conduction disorder              | 8 (473) | 9 (56) | 12 (15) | 22 (307) |
| Ischemic stroke                  | 9 (532) | 11 (71) | 12 (15) | 16 (218) |
| Diabetes mellitus                | 30 (1,865) | 31 (195) | 36 (44) | 47 (651) |
| History of atrial fibrillation   | 0 (0) | 0 (0) | 0 (0) | 81 (1128) |
| History of atrial flutter        | 0 (0) | 0 (0) | 0 (0) | 11 (150) |
| Heart failure                    | 13 (805) | 18 (115) | 24 (29) | 49 (678) |
| Hemorrhage                       | 7 (440) | 14 (87) | 15 (18) | 8 (116) |
| Hyperlipidemia                   | 38 (2,349) | 40 (248) | 43 (53) | 61 (844) |
| Hypertension                     | 60 (3,719) | 64 (401) | 77 (95) | 85 (1,175) |
| Hyperthyroidism                  | 1 (84) | 2 (12) | 2 (2) | 2 (34) |
| Obstructive sleep apnea          | 12 (749) | 15 (94) | 9 (11) | 23 (314) |
| Pulmonary embolism               | 4 (219) | 5 (30) | 7 (9) | 3 (45) |
| Pulmonary hypertension           | 5 (338) | 7 (43) | 9 (11) | 20 (282) |
| Post-operative state             | 40 (2,458) | 42 (265) | 53 (65) | 31 (435) |
| Condition                        | Count (Total) | Count (Total) | Count (Total) | Count (Total) |
|---------------------------------|---------------|---------------|---------------|---------------|
| Chronic pulmonary disease       | 17 (1,066)    | 27 (168)      | 24 (30)       | 33 (461)      |
| Sepsis                          | 21 (1,304)    | 40 (251)      | 50 (61)       | 40 (563)      |
| History of tobacco use          | 34 (2,109)    | 35 (217)      | 30 (37)       | 22 (310)      |
| Valvular heart disease          | 5 (330)       | 4 (27)        | 7 (8)         | 20 (275)      |

**Hospital Outcomes**

| Outcome                          | Median (IQR) | Median (IQR) | Median (IQR) | Median (IQR) |
|----------------------------------|--------------|--------------|--------------|--------------|
| Hospital LOS, days               | 7 (4-12)     | 11 (6-21)    | 16 (10-25)   | 8 (5-16)     |
| ICU LOS, days                    | 1.8 (1.0-3.4)| 4.5 (2.1-10.1)| 7.4 (3.9-14.5)| 2.8 (1.4-5.7)|
| Hospital mortality               | 8 (468)      | 16 (98)      | 32 (39)      | 18 (253)     |

Values are percentage (counts) or median (interquartile range). ICU: intensive care unit; ECGs: electrocardiograms; OASIS: Oxford Acute Severity of Illness Score; LOS: length of stay.
Online Table 4: Physiological measurements during periods of atrial fibrillation by category

|                         | New Subclinical AF | New Clinical AF | Prior AF | p-value |
|-------------------------|--------------------|-----------------|----------|---------|
| Heart rate              | 94 (82-107)        | 102 (90-116)    | 98 (86-111) | <0.001  |
| Respiratory rate        | 21 (17-26)         | 22 (19-26)      | 21 (17-26) | <0.001  |
| Oxygen Saturation       | 97 (95-99)         | 97 (95-98)      | 97 (96-99) | <0.001  |
| Systolic Blood Pressure | 119 (104-139)      | 113 (101-127)   | 113 (100-129) | <0.001  |
| Diastolic Blood Pressure| 65 (57-74)         | 62 (54-72)      | 64 (57-73) | <0.001  |

Heart rate in beats per minute; respiratory rate in breaths per minute; oxygen saturation in percent from pulse oximetry; systolic and diastolic blood pressures in millimeters of mercury.
Online Table 5: Summary of covariates before and after propensity score matching

| Before Matching | After Matching |
|-----------------|---------------|
|                 | Any AF (n: 1610) | No AF (n: 6746) | Std. Mean Diff. | Any AF (n: 1594) | No AF (n: 1594) | Std. Mean Diff. |
| Distance        | 0.307 | 0.165 | 0.816 | 0.304 | 0.298 | 0.030 |
| Age (years)     | 66.2  | 56.1  | 0.610 | 66.1  | 65.3  | 0.047 |
| Female          | 0.404 | 0.443 | -0.079 | 0.407 | 0.415 | -0.017 |
| Body Mass Index | 28.2  | 27.3  | 0.066 | 28.2  | 28.3  | 0.001 |
| Acute Kidney Injury | 0.276 | 0.160 | 0.258 | 0.272 | 0.275 | -0.004 |
| Acute Myocardial Infarction | 0.117 | 0.051 | 0.207 | 0.118 | 0.112 | 0.018 |
| Acute Respiratory Failure | 0.521 | 0.272 | 0.498 | 0.517 | 0.533 | -0.031 |
| Coronary Artery Disease | 0.414 | 0.250 | 0.332 | 0.411 | 0.403 | 0.017 |
| Chronic Kidney Disease | 0.306 | 0.202 | 0.225 | 0.305 | 0.310 | -0.011 |
| Cardiomyopathy  | 0.087 | 0.050 | 0.132 | 0.087 | 0.083 | 0.016 |
| Conduction Abnormality | 0.139 | 0.093 | 0.133 | 0.140 | 0.133 | 0.012 |
| Ischemic Stroke | 0.135 | 0.092 | 0.128 | 0.135 | 0.138 | -0.011 |
| Diabetes Mellitus | 0.394 | 0.314 | 0.164 | 0.393 | 0.402 | -0.018 |
| Heart Failure   | 0.353 | 0.157 | 0.410 | 0.348 | 0.337 | 0.024 |
| Hyperlipidemia  | 0.506 | 0.397 | 0.217 | 0.504 | 0.503 | 0.001 |
| Hypertension    | 0.760 | 0.618 | 0.334 | 0.760 | 0.747 | 0.031 |
| Hyperthyroidism | 0.021 | 0.015 | 0.041 | 0.021 | 0.019 | 0.009 |
| Obstructive Sleep Apnea | 0.174 | 0.132 | 0.112 | 0.173 | 0.171 | 0.007 |
| Pulmonary Embolism | 0.041 | 0.035 | 0.030 | 0.041 | 0.043 | -0.006 |
| Pulmonary Hypertension | 0.143 | 0.066 | 0.220 | 0.140 | 0.132 | 0.023 |
| Postoperative State | 0.390 | 0.385 | 0.011 | 0.390 | 0.372 | 0.036 |
| Condition                  | Value 1  | Value 2  | Value 3  | Value 4  | Value 5  | Value 6 |
|----------------------------|---------|---------|---------|---------|---------|---------|
| Chronic Pulmonary Disease  | 0.301   | 0.184   | 0.254   | 0.299   | 0.298   | 0.001   |
| Sepsis                     | 0.445   | 0.217   | 0.458   | 0.441   | 0.451   | -0.020  |
| Tobacco Use                | 0.262   | 0.334   | -0.163  | 0.262   | 0.268   | -0.013  |
| Valvular Heart Disease     | 0.125   | 0.065   | 0.181   | 0.121   | 0.114   | 0.023   |
| Hemorrhage                 | 0.122   | 0.069   | 0.162   | 0.119   | 0.126   | -0.023  |
| OASIS                      | 31.4    | 27.2    | 0.489   | 31.3    | 31.4    | -0.013  |
| Vasopressors               | 0.476   | 0.209   | 0.303   | 0.458   | 0.450   | 0.009   |

Values are proportion or standardized mean difference (Std. Mean Diff.) unless otherwise noted. AF: atrial fibrillation.
Online Figure 1. Distribution of estimated probability of atrial fibrillation as determined by rhythm classification model.
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