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CLINICAL RESEARCH

Critical illness associated new onset atrial fibrillation: subsequent atrial fibrillation diagnoses and other adverse outcomes

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Aims Amongst patients with critical illness associated new onset AF (CI-NOAF), the risk of subsequent atrial fibrillation (AF) diagnoses and other adverse outcomes is unknown, and the role for long-term anticoagulation is unclear. This study sought to determine the factors associated with subsequent AF diagnoses and other adverse outcomes in this cohort.

Methods and results Admissions to a tertiary general intensive care unit (ICU) between December 2015 and September 2018 were screened for AF episodes through hourly analysis of continuous ECG monitoring. Patients with a prior history of AF were excluded. AF burden was defined as the percentage of monitored ICU hours in AF. The primary endpoint was subsequent AF diagnoses, as collated from the statewide electronic medical records. Secondary endpoints included mortality, embolic events, MACE and subsequent anticoagulation.

Results Of 7030 admissions with 509 303 h of monitoring data, 309 patients with CI-NOAF were identified, and 235 survived to discharge. Subsequent AF diagnoses were identified in 75 (31.9%) patients after a median of 413 days. Increased AF burden had the strongest independent association with AF recurrence (OR = 15.03, $P = 0.002$), followed by increased left atrial area (OR = 1.12, $P = 0.01$). Only 128 (54.5%) patients had their AF diagnosis acknowledged at ICU discharge, and 50 (21.3%) received anticoagulation at hospital discharge.

Conclusion CI-NOAF is often under-recognized, and subsequent AF diagnoses are common post-discharge. AF burden during ICU admission has a strong independent association with subsequent AF diagnoses. Left atrial size is also independently associated with subsequent AF.

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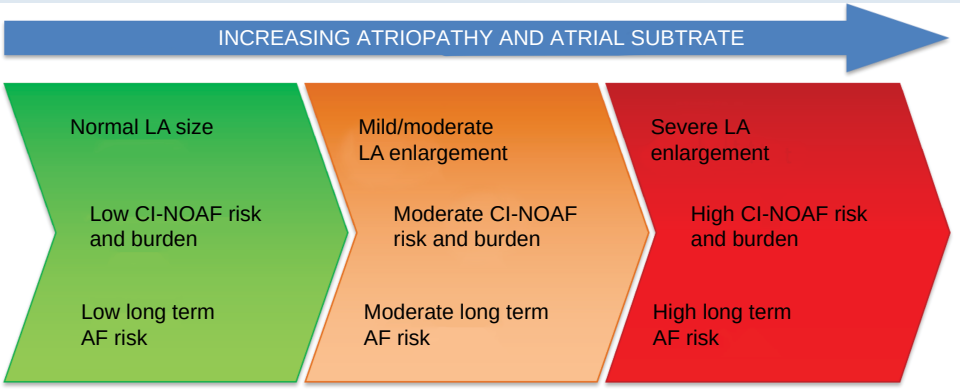
Graphical Abstract



Amongst **critically ill** patients in ICU with **new onset AF** (CI-NOAF):

- **One third** had **subsequent AF diagnoses** post discharge during follow up
- **AF burden** in ICU and **left atrial size** are **independent predictors** of **subsequent AF**
- **Subsequent AF** seen in **63% of patients with AF burden >25%** of ICU stay
- **21% of patients** with CI-NOAF received **anticoagulation at hospital discharge**

Keywords Atrial fibrillation • Critical illness • Atrial fibrillation burden • Atriopathy

What's new?

Amongst patients with critical illness associated new onset atrial fibrillation (CI-NOAF):

- Subsequent AF diagnoses are common, occurring in one third of patients during a median follow-up of 413 days.
- AF burden during intensive care unit (ICU) stay and left atrial size are independently associated with subsequent AF.
- Subsequent AF diagnoses were identified in 63% of patients with AF burden > 25% of ICU stay.
- Twenty-one percent of patients with CI-NOAF received anticoagulation at hospital discharge.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in the intensive care unit (ICU) setting.[1] Reported incidence rates of new onset AF (NOAF) generally range from 5–15% in the context of undifferentiated critical illness, with rates up to 46% in the highest risk subgroups, such as septic shock.[2]

Critical illness related NOAF (CI-NOAF) has been associated with adverse outcomes including mortality, length of ICU/hospital stay, and cerebrovascular events.[2,3] However, it is contentious whether NOAF independently contributes to these outcomes, or simply represents a marker of disease severity and poor prognosis. It is also currently unclear whether CI-NOAF can be regarded as an isolated event, or predicts subsequent AF episodes long-term. Existing data primarily arise from selected critically ill subgroups, such as surgical cohorts[4–6] or patients with sepsis,[7] with no identified studies performed amongst an unselected critically unwell population.

There is increasing evidence that AF burden can predict adverse outcomes in the ambulatory setting, including heart failure, cerebrovascular events, and mortality.[8] However, there is minimal evidence regarding the role of AF burden in predicting outcomes amongst patients with CI-NOAF.[9–11]

This study sought to evaluate the risk of subsequent AF and other adverse outcomes amongst unselected critically ill patients with new onset AF, and investigate the role of AF burden in predicting outcomes through evaluation of continuous ECG monitoring data. We hypothesized that AF burden would be associated with the risk of AF diagnoses at subsequent clinical encounters.

Methods

This was a single-centre observational study of all admissions to an Australian general ICU between December 2015 and September 2018, which participates in all tertiary level medical and surgical care, other than cardiac surgery (except in the instance of trauma-related cardiac surgery). Standard clinical care involved continuous ECG monitoring, with hourly rhythm interpretations routinely recorded in the ICU electronic medical records system (Metavision™, Tel Aviv-Yafo, Israel). Patients with an AF rhythm recorded at any point during ICU admission were identified, and those with a documented history of AF prior to the onset of critical illness were excluded from the NOAF cohort. In the event of multiple ICU admissions during the study period, the first admission where AF was identified was used as the index admission.

Clinical parameters collected from the ICU electronic medical records included age, gender, comorbidities, requirement for renal replacement therapy, invasive ventilation or inotropes/vasopressors. CHA_2DS_2VASc, Simplified Acute Physiology Score 2 (SAPS2) and Sequential Organ Failure Assessment (SOFA) scoring metrics were calculated as per published definitions.[12–14]

Echocardiographic data were extracted when studies were performed for clinical indications. Where multiple studies were available, the study most proximal to ICU admission date was used. All studies were performed by trained and certified cardiac sonographers, and echocardiographic reports were validated by an accredited echocardiologist. Left ventricular ejection fraction (LVEF) was either calculated by Simpson's biplane method

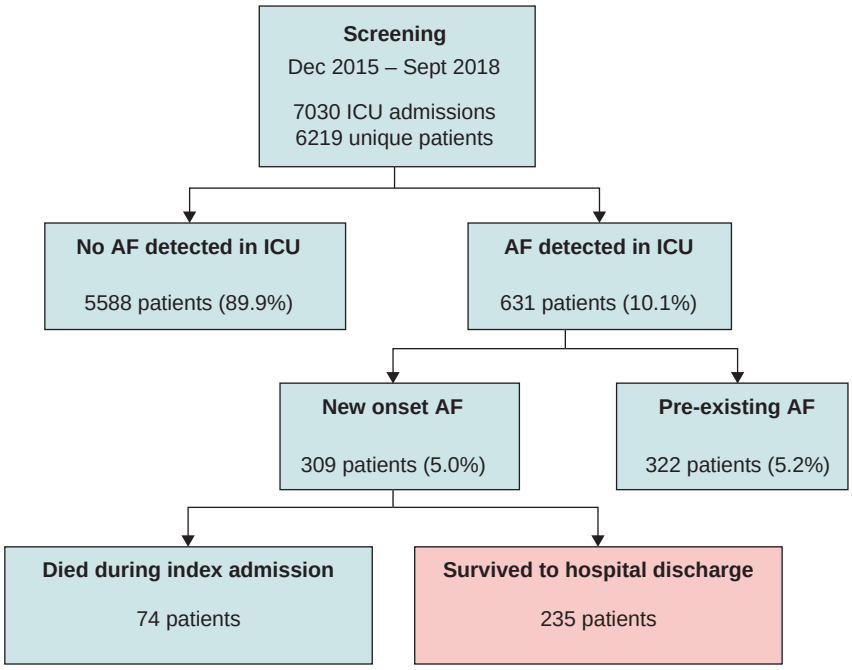


Figure 1 Flowchart of study screening and recruitment process.

of disks using apical four chamber and apical two chamber views, or a visual estimation by the reporting cardiologist. Left atrial area (LAA) was obtained using planimetry from the apical 4 chamber view at ventricular end-systole just prior to mitral valve opening. Right ventricular systolic pressure (RVSP) was calculated from tricuspid regurgitation (TR) velocity using the Bernoulli's equation.

AF burden was calculated as the number of hourly rhythm assessments in AF as a percentage of monitored hours of ICU stay, as follows:

AF burden = (hours of AF rhythm)/(hours in ICU with ECG monitoring)

AF burden was used as a continuous parameter in analyses of associations with subsequent AF. For binary analysis of other outcomes, the median AF burden was used to divide the study population into 'Low AF burden' and 'High AF burden' groups. 'AF acknowledgement' was defined as the documentation of AF episodes in the ICU discharge summary to the ward medical team providing ongoing care.

Outcomes data were obtained through interrogation of the statewide electronic medical records (including discharge summaries, clinic letters, and deceased information) by study investigators blinded to index admission data (including AF burden). 'Subsequent AF' was defined as an AF diagnosis being recorded in any clinical encounter subsequent to the index admission. Major adverse cardiac events (MACE) were defined as the composite outcome of death, myocardial infarction, revascularization including coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), cerebrovascular accident (CVA) or admission with heart failure.

The IBM SPSS Statistics package (v26) was used for all statistical analyses. Univariate analyses were performed using Pearson's chi squared analysis for categorical data, Student's T test for continuous data, and Mann–Whitney U test for non-parametric data. Multivariable analysis with binary logistic regression was used to identify independent associations with adverse outcomes (including subsequent AF diagnoses).

Ethical approval was received from the hospital's human research ethics committee, including a waiver of consent as per the National Health and Medical Research Council (NHMRC) guidelines (HREC/15/QRBW/510).

Results

NOAF cohort

During the study period, 7 030 patients were admitted to ICU, comprising 509 303 h of cardiac monitoring. From this cohort, 6219 unique patients were identified, of which 631 (10.1%) developed AF (see *Figure 1*). 322 patients (5.2%) had pre-existing AF diagnoses, with 309 patients having NOAF (5.0%). Of the CI-NOAF cohort, 235 patients with survived to hospital discharge, comprising the final study cohort. The mean duration of ICU monitoring was 192 h in this group. Echocardiography was performed on 169 (72%) of the cohort, with a median time from ICU admission to echocardiography of 3 days.

Amongst CI-NOAF patients who survived to hospital discharge, the median AF burden was 7.1% (IQR: 2.4–24.7%). The occurrence of NOAF was acknowledged in 54.5% of ICU discharge summaries, with increased recognition in the high AF burden group (69.7% vs. 38.8%, $P < 0.001$).

Subsequent AF diagnoses

Seventy-five (31.9%) patients of the final study cohort were subsequently diagnosed with AF over a median follow-up of 413 days (IQR: 119–763 days). The risk of subsequent AF was strongly associated with AF burden during ICU stay (see *Table 1*), with sequentially higher rates of subsequent AF across the quartiles of AF burden (see *Figure 2A*), ranging from 12% in the lowest quartile to 63% in the highest quartile. The area under the curve (AUC) of the receiver operating characteristic curve was 0.735 (see *Figure 2B*). The maximal Youden index (0.379) occurred at an AF burden threshold of 20%, with sensitivity = 0.562 and specificity = 0.819.

Other clinical factors associated with subsequent AF diagnoses included coronary artery disease, diabetes mellitus (DM), peripheral vascular disease, chronic kidney disease, renal replacement therapy, increased body mass index (BMI), CHA_2DS_2VASc score, SAPS2 score, and serum creatinine. Echocardiographic parameters associated with subsequent AF included decreased LVEF and increased LAA (See *Table 2*).

Table 1 Clinical characteristics of patients with critical illness associated new onset AF surviving to hospital discharge, subdivided by subsequent AF diagnosis post-hospital discharge

Parameter		Total cohort (*N* = 235)	No subsequent AF (*N* = 160)	Subsequent AF (*N* = 75)	*P*-value
Demographics	Age	66.9 ± 11.4	66.1 ± 11.2	68.5 ± 11.7	0.143
	Male gender	148 (63.0%)	99 (61.9%)	49 (65.3%)	0.609
	Body mass index (kg/m^2)	29.4 ± 8.2	28.4 ± 6.8	31.6 ± 10.4	0.017
Past medical history	Coronary artery disease	43 (18.3%)	22 (13.8%)	21 (28.0%)	0.008
	Hypertension	129 (54.9%)	82 (51.2%)	47 (62.7%)	0.101
	Heart failure	8 (3.4%)	4 (2.5%)	4 (5.3%)	0.264
	Diabetes mellitus	53 (22.6%)	30 (18.8%)	23 (30.7%)	0.042
	COPD/emphysema	45 (19.1%)	26 (16.3%)	19 (25.3%)	0.099
	Obstructive sleep apnoea	19 (8.1%)	11 (6.9%)	8 (10.7%)	0.320
	Dyslipidaemia	66 (28.1%)	44 (27.5%)	22 (29.3%)	0.771
	CVA/TIA	18 (7.7%)	11 (6.9%)	7 (9.3%)	0.509
	Peripheral vascular disease	22 (9.4%)	10 (6.3%)	12 (16.0%)	0.017
	Chronic kidney disease	19 (8.1%)	8 (5.0%)	11 (14.7%)	0.011
	Venous thromboembolism	17 (7.2%)	11 (6.9%)	6 (8.0%)	0.756
	Smoking	129 (54.9%)	88 (55.0%)	41 (54.7%)	0.962
	Alcohol excess	30 (12.8%)	25 (15.6%)	5 (6.7%)	0.055
	CHA_2DS_2VASC	2.6 ± 1.5	2.4 ± 1.5	3.1 ± 1.6	<0.001
Previous medications	Beta blocker	60 (25.5%)	35 (21.9%)	25 (33.3%)	0.060
	Calcium channel blocker	34 (14.5%)	20 (12.5%)	14 (18.7%)	0.210
	ACEi/ARB	93 (39.6%)	60 (37.5%)	33 (44.0%)	0.342
	Diuretic	34 (14.5%)	20 (12.5%)	14 (18.7%)	0.210
ICU admission	SOFA	4.6 ± 2.7	4.5 ± 2.8	4.9 ± 2.4	0.264
	SAPS2	39.8 ± 15.1	38.3 ± 15.1	42.8 ± 14.8	0.034
	Operation	176 (74.9%)	120 (75.0%)	56 (74.7%)	0.956
	Ventilation	137 (58.3%)	91 (56.9%)	46 (61.3%)	0.518
	Renal replacement therapy	31 (13.2%)	16 (10.0%)	15 (20.0%)	0.035
	Inotropes/vasopressors	137 (58.3%)	91 (56.9%)	46 (61.3%)	0.518
New onset AF	AF Burden (%)	21.1 ± 29.6	12.8 ± 20.0	38.7 ± 37.9	<0.001
	AF acknowledgement	128 (54.5%)	70 (43.8%)	58 (77.3%)	<0.001
Laboratory	Haemoglobin (g/L)	104.6 ± 22.3	103.0 ± 21.8	107.9 ± 23.0	0.123
	White cell count (x 10^9/L)	11.9 ± 7.7	11.4 ± 6.4	13.0 ± 9.9	0.202
	Creatinine (μmol/L)	135.3 ± 151.2	119.0 ± 142.2	170.1 ± 164.3	0.022
	Potassium (mmol/L)	4.2 ± 0.5	4.2 ± 0.4	4.3 ± 0.6	0.101
	Magnesium (mmol/L)	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.2	0.835
	Calcium (mmol/L)	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	0.561

Data are expressed as *n* (%) for binary data and mean ± standard deviation for continuous data. COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, TIA = transient ischaemic attack, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, SAPS2 = simplified acute physiology score 2, SOFA = sequential organ failure assessment, LV = left ventricular, RVSP = right ventricular systolic pressure.

On multivariable analysis using binary logistic regression incorporating significant univariate clinical and echocardiographic predictors (see *Table 3*), increased AF burden was strongly associated with subsequent AF (OR = 15.03, *P*-value = 0.002). LAA was the only other parameter to demonstrate a significant independent association with subsequent AF (OR = 1.12, *P* = 0.010).

When AF acknowledgement was additionally introduced to the logistic regression, it was not found to be independently associated with subsequent AF ($P > 0.05$), whilst increased AF burden ($P = 0.022$) and left atrial area ($P = 0.016$) retained significance. When the significance threshold for inclusion in the multivariable analysis was increased to $P < 0.2$, increased AF burden and LAA remained the only independently associated parameters.

In sensitivity analyses, increased AF burden remained associated with subsequent AF in the sub-cohort of 176 patients who underwent operative intervention ($P < 0.001$), as well the 59 patients who did not ($P < 0.001$). Amongst the 174 patients with CHA_2DS_2VASc score of 2 or more, 65 (37.4%) were diagnosed with subsequent AF, with increased AF burden remaining associated with the risk of subsequent AF ($P < 0.001$).

Alternative AF burden metrics

Alternative metrics of AF burden associated with subsequent AF diagnoses included total h of AF during ICU stay (40.3 vs. 13.6 h, *P* = 0.001), as well as longest continuous AF episode duration (26.7 vs. 9.4 h,

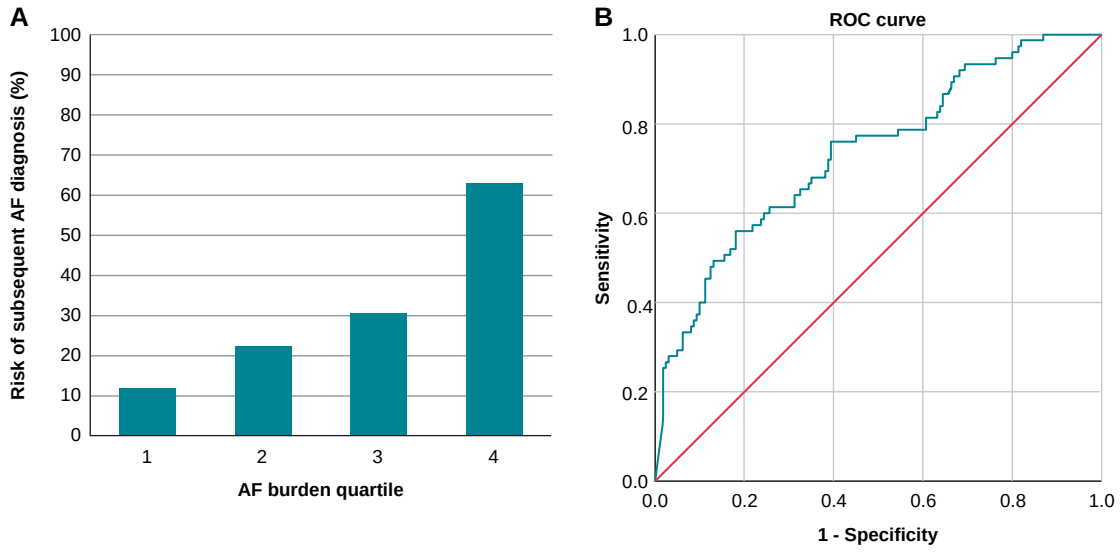


Figure 2 (*A*) Risk of subsequent AF diagnosis by AF burden quartile. Quartile ranges: Q1 = 0.1–2.4%, Q2 = 2.4–7.0%, Q3 = 7.1–23.9%, Q4 = 24.7–100%. (*B*) Receiver operating characteristic (ROC) curve of AF burden predicting subsequent AF diagnoses. AUC = 0.735.

$P < 0.001$). The number of AF episodes was not associated with subsequent AF ($P = 0.278$). Increased AF burden and LAA consistently remained the only parameters independently associated with subsequent AF diagnosis in alternative logistic regression models additionally incorporating (i) longest AF episode duration, (ii) total hours of AF, and (iii) the duration of ICU stay.

Mortality and other adverse outcomes

Patients with high AF burden had higher rates of mortality (28.8% vs. 12.8%, $P = 0.003$), and MACE (35.6% vs. 21.4%, $P = 0.016$) post-discharge (see *Table 4*). Neither of these associations were significant on multivariable analysis (data not shown). There were insufficient numbers of individual MACE components to undertake valid statistical analysis; however CVA/embolic events were numerically higher in the high AF burden group compared with the low AF burden group (6 vs. 1 event).

Subsequent anticoagulation

The rates of anticoagulation on follow-up were significantly higher than at hospital discharge (27.2% vs. 21.3%, $P < 0.001$), with the highest rate of anticoagulation in the high AF burden group (33.9% vs. 20.5%, $P = 0.021$). Other factors associated with long-term anticoagulation included increased BMI ($P = 0.010$), DM ($P = 0.021$), obstructive sleep apnoea ($P = 0.009$), AF acknowledgement ($P < 0.001$), and increased LAA ($P = 0.003$).

On multivariable analysis, increased AF burden (OR: 5.40, $P = 0.023$) and LAA (OR: 1.10, $P = 0.023$) were independently associated with subsequent anticoagulation. AF acknowledgement was not independently associated ($P = 0.782$). When subsequent AF was added as a covariate in the multivariable analysis, it was the only parameter independently associated of subsequent anticoagulation (OR = 15.48, $P < 0.001$).

Discussion

Key findings

Our study demonstrates patients with CI-NOAF are at high risk for subsequent AF diagnoses post-discharge, occurring in 32% of patients who survived to hospital discharge at a median follow-up of 413 days. It also identifies the novel finding that increased AF burden (derived from hourly analysis of routine continuous ECG monitoring during ICU admission) is strongly associated with subsequent AF diagnoses post-discharge, with 63% of patients in the highest quartile of AF burden (> 25% of ICU stay) receiving a subsequent AF diagnosis. Increased LAA was also independently associated with subsequent AF. CI-NOAF is frequently under-recognised and under-reported, with only 55% patients having their AF episode communicated to the ward medical team on discharge from ICU.

Adverse outcomes following CI-NOAF

Whether detected by continuous ECG monitoring, *ad hoc* clinician reporting or coding data, multiple previous studies have found CI-NOAF to be associated with adverse long-term outcomes such as mortality and length of stay, although independent associations are inconsistent.[1,3] Some studies have reported an association with ischaemic CVA,[3,10] although data are limited. A recent analysis of the combined Perioperative Ischemic Evaluation (POISE)-1 and POISE-2 trial datasets suggested that perioperative NOAF following non-cardiac surgery was independently associated with stroke, mortality and myocardial infarction at 1 year.[15]

However, the risk of subsequent AF diagnosis following CI-NOAF was previously unknown, with only a few, small studies involving selected post-surgical cohorts.[4–6] Amongst post-cardiac surgical patients, Ahlsson *et al.* found NOAF to be associated with an 8-fold increase (25.4% vs. 3.6%) in subsequent AF diagnosis at a median follow-up of 5.3 years,[5] and Park-Hansen reported a 9-fold increase (43.8% vs. 7.2%) at 3.7 years.[6] In a broader post-operative NOAF population, AF recurrence rates were reported at 12.5% after mean follow-up of 943 days, with no difference between cardiac and non-cardiac surgical groups.[4] No identified previous studies had evaluated the long-term risk of subsequent AF in unselected or non-surgical critically ill populations with NOAF. Understanding the risk of AF recurrence following CI-NOAF is of clinical significance, due to the well-recognized AF-related stroke risk even in asymptomatic individuals.

CI-NOAF burden is associated with adverse outcomes

Although data are limited, CI-NOAF burden has been associated with adverse in-hospital outcomes, including increased ICU stay, CVA, and

Table 2 Key echocardiographic metrics of study cohort, subdivided by subsequent AF diagnosis

	Total cohort ($n = 169$)		No subsequent AF ($n = 107$)		Subsequent AF ($n = 62$)		*P*-value
	n	Mean ± SD	*n*	Mean ± SD	*n*	Mean ± SD	
LVEF (%)	169	54.7 ± 14.0	107	56.5 ± 13.1	62	51.6 ± 15.0	0.036
LAA (cm^2)	138	22.8 ± 6.5	90	21.2 ± 5.1	48	25.9 ± 7.8	<0.001
RVSP (mmHg)	107	40.2 ± 11.4	65	39.7 ± 11.3	42	40.9 ± 11.7	0.626

P-values represent univariate statistical analyses for differences between groups. SD = standard deviation, LVEF = left ventricular ejection fraction, LAA = left atrial area, RVSP = right ventricular systolic pressure.

Table 3 Multivariable binary logistic regression of factors associated with subsequent AF diagnosis.

Parameter	Odds ratio (95% CI)	*P*-value
AF burden	15.03 (2.76–81.70)	0.002
Left atrial area (cm^2)	1.12 (1.03–1.23)	0.010
Creatinine (μmol/L)	1.00 (0.99–1.01)	0.093
Body mass index (kg/m^2)	1.05 (0.99–1.12)	0.109
CHA_2DS_2VASc score	1.32 (0.90–1.93)	0.163
Coronary artery disease	0.61 (0.16–2.30)	0.469
Renal replacement therapy	1.67 (0.38–7.37)	0.500
Diabetes	0.73 (0.22–2.39)	0.598
Chronic kidney disease	1.42 (0.28–7.32)	0.674
SAPS2 score	1.00 (0.96–1.03)	0.838
LV ejection fraction (%)	1.00 (0.98–1.04)	0.906
Peripheral vascular disease	1.00 (0.20–5.07)	0.995

SAPS2 = simplified acute physiology score 2, LV = left ventricular.

mortality.[9–11] No previous studies have investigated the incidence of subsequent AF diagnoses, or identified an independent association between CI-NOAF burden and long-term outcomes. In addition to a strong independent association between CI-NOAF burden and subsequent AF diagnoses, our study found that CI-NOAF burden was associated with both long-term mortality and MACE on univariate analysis. However, it remains unclear whether AF burden itself has a causal role in these findings.

AF burden has received increasing recognition as being associated with adverse outcomes (including heart failure, CVA, and mortality) in ambulatory patients.[16] However, the data are contentious, the optimal definition of AF burden in unclear, and at present there is insufficient evidence to use AF burden to guide anticoagulation.[14]

Anticoagulation following CI-NOAF

In our study, only 21.3% of patients were anticoagulated on discharge from hospital, despite 74% of patients having a CHA_2DS_2VASc score of 2 or higher. Factors contributing to this relatively low rate of anticoagulation include (i) nearly half of patients with CI-NOAF did not have this finding communicated to the ward team in the ICU discharge summary, (ii) limited published data regarding risk of long-term AF and embolic events following CI-NOAF, and (iii) bleeding risks associated with anticoagulation, particularly in the critically ill. Amongst patients receiving anticoagulation for AF whilst hospitalized with severe sepsis, Darwish *et al.*[17] found the incidence of anticoagulation-related complications (including bleeding and heparin-induced thrombocytopaenia) to be 8.6%, without any difference in survival or stroke.

Post-discharge, the rate of anticoagulation in the study cohort increased to 27.2%. The increment in anticoagulation uptake was greatest in the high AF burden cohort, in whom anticoagulation increased from 25.4% to 33.9%, with 46.6% of this group having subsequent AF diagnoses. Whilst AF burden was strongly associated with rates of subsequent anticoagulation, it was not independently associated when correcting for subsequent AF diagnosis in multivariable analysis, suggesting that the increment in anticoagulation rates was driven by subsequent AF diagnoses. Furthermore, AF acknowledgement in ICU discharge summaries was not independently associated with subsequent anticoagulation, suggesting information bias was not a primary explanation for this finding, although the potential for unmeasured confounding cannot be excluded.

At present there is minimal evidence to guide the long-term management or monitoring of patients following an episode of CI-NOAF. The 2020 European Society of Cardiology (ESC) guidelines suggest that anticoagulation can be considered for post-operative NOAF (although note the lack of evidence), but do not comment on management of CI-NOAF in non-surgical cohorts.[14] The 2014 American Heart Association (AHA) AF guidelines (and subsequent 2019 focussed update) acknowledge that the role of long-term anticoagulation for NOAF in the context of acute non-cardiac illness is unclear.[18]

It is therefore unsurprising that substantial practice variation exists in the management of CI-NOAF. A 2017 survey of UK-based intensivists found that most do not routinely use stroke risk scores or anticoagulate ICU patients with NOAF.[19] However, our study demonstrates that a significant proportion of patients with CI-NOAF are diagnosed with AF subsequent to hospital discharge and are ultimately anticoagulated. Randomised interventional trials are clearly needed to inform the role of anticoagulation in patients with CI-NOAF. Further data on the role for management of AF risk factors and cardiovascular comorbidities in this cohort would also be of value.

Pathophysiological considerations

The incidence of subsequent AF following CI-NOAF can be rationalized by either of the following: (i) critical illness unmasks a pre-existing intrinsic susceptibility to AF or (ii) CI-NOAF inducing a susceptibility to subsequent AF, by establishing structural and electrophysiological maladaptations that disrupt organized atrial activity ('AF begets AF'). The former hypothesis is supported by the association with LAA in a present study (as a surrogate for AF substrate). *Figure 3* outlines a proposed schematic for this relationship, whereby CI-NOAF burden and risk of subsequent AF are consequential to the degree of underlying atriopathy (of which left atrial size is a marker).

Table 4 Outcomes of patients with critical illness associated new onset atrial fibrillation (AF) surviving to hospital discharge, subdivided by AF burden relative to the median burden (7.1%).

Outcome		Total cohort ($n = 235$)	Low AF burden ($n = 117$)	High AF burden ($n = 118$)	*P*-value
Follow-up duration (days)		413 (116–765)	457 (105–834)	401 (143–728)	0.821
Subsequent AF		75 (31.9%)	20 (17.1%)	55 (46.6%)	<0.001
Mortality	Long-term mortality	49 (20.9%)	15 (12.8%)	34 (28.8%)	0.003
	Time to death	284 (136–511)	204 (149–637)	266 (138–360)	0.233
Adverse outcomes	CVA event	5 (2.1%)	1 (0.9%)	4 (3.4%)	[a]
	Non-CVA embolic event	2 (0.9%)	0 (0%)	2 (1.7%)	[a]
	Myocardial infarction	7 (3.0%)	3 (2.6%)	4 (3.4%)	[a]
	Coronary artery bypass grafting	4 (1.7%)	2 (1.7%)	2 (1.7%)	[a]
	Percutaneous coronary intervention	1 (0.4%)	0 (0%)	1 (0.8%)	[a]
	Heart failure event	19 (8.1%)	10 (8.5%)	9 (7.6%)	0.796
	Bleeding	56 (23.8%)	34 (29.1%)	22 (18.6%)	0.061
MACE		67 (28.5%)	25 (21.4%)	42 (35.6%)	0.016
Anticoagulation	At hospital discharge	50 (21.3%)	20 (17.1%)	30 (25.4%)	0.119
	Post-discharge	64 (27.2%)	24 (20.5%)	40 (33.9%)	0.021

Data are expressed as *n* (%) for binary data, and median (Q1–Q3) for non-parametric continuous data. CVA = cerebrovascular accident, MACEs = major adverse cardiac events.
[a]Insufficient data to undertake valid statistical analysis.

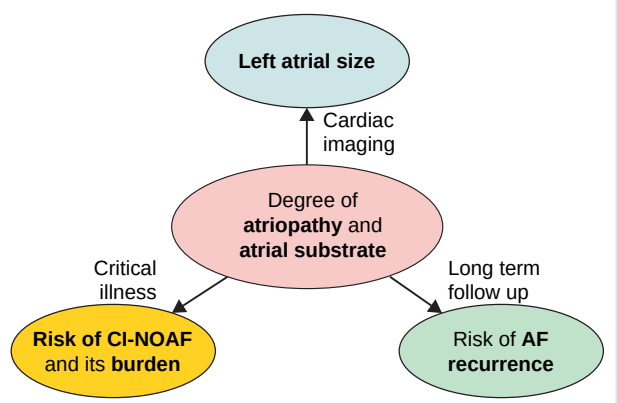


Figure 3 Schematic representation of proposed relationship between degree of atrial substrate and consequent clinical outcomes. CI-NOAF burden and risk of subsequent AF recurrence are driven by underlying atriopathy, of which left atrial size is a marker.

Substantial variation exists in the research definitions of CI-NOAF between studies, including some which excluded patients who were in AF at the time of ICU admission[9,20] due to the possibility of pre-existing undiagnosed AF. However, patients are typically admitted to ICU subsequent to the onset of their acute illness, and therefore patients with CI-NOAF may frequently have AF onset prior to ICU admission. Furthermore, it not feasible to exclude previous unrecognized AF episodes in any given patient. As such, we defined CI-NOAF to reflect the common real-world clinical scenario of incident AF diagnosis in critically unwell individuals without a known history of AF preceding the acute illness.

The optimal metric for AF burden calculation is unknown, both in the ambulatory and ICU setting. Previous CI-NOAF burden studies are limited by non-continuous monitoring, and reliance on arbitrary cutpoints rather than empirically derived thresholds. Our metric of AF burden was in keeping with the 2018 AHA consensus statement, which argued that the preferred definition of AF burden was the proportion of a monitoring period in AF.[16] Furthermore, our study found this metrics outperformed the studied alternatives (longest AF episode, total hours of AF) for the prediction of subsequent AF in multivariable modelling.

Study limitations and considerations

As an observational study, the documented rates of AF recurrence in our study likely underestimate the true incidence, due to the absence of routine active monitoring post-discharge. Future studies incorporating modern portable ECG monitoring devices post-discharge would be of value to elicit the true incidence of AF recurrence.

Our use of hourly monitoring data is an imperfect approximation of true AF burden and may have missed patients with transient AF episodes occurring in between timepoints of rhythm assessment. We were unable to validate the data against raw ECG monitoring, as these were automatically deleted at ICU discharge. In future, dedicated automated ECG analysis software may be able to provide a more accurate quantification of AF burden from continuous ECG recordings.

Conclusions

Patients developing NOAF during critical illness have a high risk of AF diagnoses at subsequent clinical encounters post-hospital discharge. This study demonstrates the novel findings that AF burden extracted from continuous ECG monitoring during ICU stay had a strong independent association with subsequent AF diagnosis post-discharge. LAA was also independently associated with AF. These findings suggest that CI-NOAF should not go unrecognised, and patients who are not commenced on long-term therapeutic anticoagulation prior to discharge may benefit from active monitoring for recurrent AF, particularly those with a high burden of AF during critical illness or LA dilation. Further studies are needed to evaluate the clinical efficacy and safety of anticoagulation for the prevention of AF-related cardioembolic events in this cohort.

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Ethics and consent

Ethical approval was received from the hospital's human research ethics committee, including a waiver of consent as per the National Health and Medical Research Council (NHMRC) guidelines (HREC/15/QRBW/510).

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest: None declared.

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