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A retrospective study on the effects of illness severity and atrial fibrillation on outcomes in the intensive care unit

Introduction: Atrial fibrillation (AF) is common in patients in the intensive care unit (ICU) and has been associated with worse outcomes. However, it is unclear whether AF itself adds to the risk of death or is merely a marker of illness severity. We aimed to record the incidence and outcomes of all patients with different categories of AF and determine whether AF was an independent predictor of death.

Methods: This retrospective cohort study was undertaken in the ICU of a tertiary-referral university hospital. Category of AF, sex, C-reactive protein (CRP) level, APACHE II score, predicted hospital mortality and survival outcomes were analysed from 1084 records. Percentages, medians and interquartile ranges were used to describe the sample. Chi-square test and the non-parametric Mann–Whitney U test were used, as appropriate, for statistical analysis. Logistic regression analyses were performed to evaluate the association of AF with death in the ICU adjusting for age, sex, CRP level and APACHE II score.

Results: Overall, 13.6% of patients developed new-onset AF during their critical illness, while 4.3% had a pre-existing history. The hospital mortality rate was higher in those with AF compared with those without (47.9% *vs.* 30.9%, p<0.001) and higher in those with newly diagnosed AF compared with those with a prior history (53.1% *vs.* 31.9%, p=0.012). CRP levels were higher in those with AF (p<0.001) compared with those without and higher in those with newly diagnosed AF compared with those with a prior history (p=0.012). On multivariate logistic regression analysis, only the APACHE II score was found to be an independent predictor of death.

Conclusion: Despite the higher mortality rate in patients with AF, the APACHE II score was the only independent predictor of death within the ICU. Prospective studies are required to explore the apparently reduced risk of dying among those with a prior history of AF.

Atrial fibrillation (AF) is the most common arrhythmia occurring in the critically ill.[1–3] It has been associated with poor outcomes in most,[2–11] but not all,[1] studies to date. Consensus on the definition and classification of AF has recently been achieved between the American College of Cardiology, the American Heart Association and the European Society of Cardiology, and updated European guidelines were published in 2010.[12,13] A new diagnosis of AF associated with a reversible cause such as acute respiratory disease was not included in the consensus classification. While new-onset AF in a critically ill patient with multiorgan failure would not be included in this classification, it may be important to differentiate between a new diagnosis of AF in the critically ill and those with previously diagnosed AF. The latter group would now be classified as having paroxysmal, persistent, longstanding or permanent AF.

There are many ways in which AF can cause adverse events, including haemodynamic compromise, impairment of left ventricular function and thromboembolic complications.[13] While several studies have shown AF in the critically ill to be associated with increased severity of illness, longer length of hospital and critical care unit stay and higher mortality,[4–9] another paper did not confirm these findings.[1] In this study, Annane *et al.* found that the effect on mortality was lost after adjusting for confounders.[1] It is therefore unclear whether arrhythmia is simply a marker of illness severity[5,7–9] or sepsis,[6,10,11,14] or directly contributes to poorer outcomes.

The aim of this study was to look at the incidence of AF in our patient population using prospectively collected data on admission characteristics, severity of illness scores and outcomes. We also wanted to determine whether the characteristics of intensive care unit (ICU) patients who developed AF in association with a critical illness were different to those of ICU patients who were diagnosed with AF in the community. In addition, we aimed to provide further insight into the relationship between illness severity and AF, using C-reactive protein (CRP) as a marker of inflammation. Troponin levels were not routinely monitored in all of our patients during the time period of this study, but would have been taken in the presence of an arrhythmia. To exclude the obvious bias, troponin levels were not analysed in this study.

METHODS

This study used prospectively collected and stored data from an ICU in a large tertiary-referral university hospital in Glasgow, Scotland. These data are used for clinical care, local and national audits, and are incorporated into electronic case records. Only data used and stored as part of routine care were used in this study. The unit predominantly admits patients requiring mechanical ventilation and multiple organ support. Cardiothoracic and cardiology patients are not admitted to our ICU. This is a general ICU and therefore the case mix is derived from the general hospital population, along with tertiary-care cases.

Consecutive patients admitted between April 2006 and September 2009 were included in this study. This period was chosen because of the introduction of the electronic record system (IntelliVue Clinical Information Portfolio, Philips Medical Systems, Amsterdam, The Netherlands). Data collected for all patients included age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, predicted hospital mortality, actual ICU and hospital mortality, length of ICU stay and highest CRP level.

In our system, patients' vital signs are automatically entered into an electronic case record. These parameters, and the cardiac rhythm displayed on the continuous electrocardiogram (ECG) monitor, are then confirmed by the bedside

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Table 1. Characteristics of patients with and without AF during their critical illness

Characteristic	No AF	AF	p-value
Patients	890	194	–
ICU mortality	224 (25.2)	79 (40.7)	<0.001
Hospital mortality	275 (30.9)	93 (47.9)	<0.001
Age, years	53 (39–66)	67 (59–74)	<0.001
APACHE II score	18 (13–24)	23 (18–29)	<0.001
Predicted hospital mortality, %	27.4 (10.7–51.2)	44.4 (26.2–65.4)	<0.001
Length of stay, days	3 (2–7)	7 (3–16)	<0.001
C-reactive protein, mg/L	165 (65–263)	256 (152–317)	<0.001

Values are n, n (%) or median (interquartile range)
AF = atrial fibrillation; APACHE = Acute Physiology and Chronic Health Evaluation II

Table 2. Characteristics patients with new-onset and pre-existing AF

Characteristic	New-onset AF	Prior history of AF	p-value
Patients	147	47	–
ICU mortality	67 (45.6)	12 (25.5)	0.015
Hospital mortality	78 (53.1)	15 (31.9)	0.012
Sex, male	91 (61.9)	32 (68.1)	0.44
Age, years	66 (57–73)	71 (62–77)	0.014
APACHE II score	23 (18–29)	24 (18–29)	0.95
Predicted hospital mortality, %	44.4 (26.2–66.5)	46 (26.2–63.7)	0.65
Length of stay, days	8 (3–17)	7 (3–15)	0.191
C-reactive protein, mg/L	268 (166–326)	198 (115–280)	0.012

Values are n, n (%) or median (interquartile range)
AF = atrial fibrillation; APACHE = Acute Physiology and Chronic Health Evaluation II

nurse and incorporated into the case record. All rhythms other than sinus are confirmed on a printed 12-lead ECG or review of the paper or electronic rhythm strip by medical staff. Using programming techniques to query the database, we used the rhythm documentation to identify the presence and duration of AF. For the nurse to have documented an arrhythmia, it would have been present for at least 30 seconds. After identifying patients with AF from the program-

Figure 1. Flow chart of patients demonstrating how the patients were distributed for analysis.

ming query, the accuracy of the cases retrieved was confirmed by checking for evidence of pertinent treatments or documentation of the correct diagnosis in the medical records.

A previous diagnosis of paroxysmal or permanent AF was established on the basis of a prior hospital admission with documented evidence of AF and confirmation of the arrhythmia by the patient (if able), a relative or the patient's primary-care physician. If these criteria were not met then the patient was assumed to have AF associated with a critical illness. The case records and database of patients with AF were then scrutinised for the following additional data: past medical history, admitting diagnosis, medication, presence of vasopressor or inotrope infusion at the time when AF began and anticoagulants given. Unless contraindicated, our usual practice is for all patients to receive deep vein thrombosis prophylaxis (enoxaparin 40 mg/day). Enoxaparin is not prescribed in the presence of coagulopathy, defined as a prothrombin time international normalised ratio above 1.5, an activated partial thromboplastin time ratio above 1.5 or fewer than 100 platelets/µL.

The APACHE II is a scoring system used to determine illness severity in critically ill patients[15]; it has been validated in the Scottish population. It is used as a measure of illness severity in all Scottish ICUs and forms part of our routine national audit data collection. Patients were excluded from the analysis if they were not appropriate for APACHE II scoring (e.g., burns, short admission stay, age under 16 years).

This project was submitted to the local ethics committee (ref. WoS ASD 83); however, the requirement for a formal review was waived as this was not required under the UK Governance Arrangements for Research Ethics Committees, specifically because we only used data obtained as part of routine clinical care. The corresponding author has full access to all of the data and is responsible for the integrity of that data and the accuracy of the data analysis. Where appropriate, we analysed the data using medians and interquartile ranges, chi-square tests and Mann–Whitney U tests.

Logistic regression analyses were also undertaken to evaluate the association of AF with death in the ICU adjusting for age, sex, CRP level and APACHE II score. Patients were categorised into three groups: no AF, known prior history of AF and new AF at the onset of critical illness. A total of 78 patients had complete information for all factors considered in the modelling except for CRP. Multiple imputation of the 78 missing CRP values was carried out using 10 imputed datasets, thus allowing all 1084 patients in the dataset to be included in the analysis. The 5% level was used to determine statistical significance.

RESULTS

A total of 1234 consecutive admissions were identified from 1176 patients (58 readmissions). After excluding patients with missing APACHE II data (n=92), 1084 complete records were analysed (Figure 1). A total of 194 of these patients had AF (17.9%), of which 147 cases (13.6%) were presumed to be a first diagnosis AF associated with critical illness, while 47 patients (4.3%) had a documented previous history of AF. Patients with AF were older and had higher APACHE II scores, increased length of ICU unit stay and higher peak CRP levels (p<0.001) compared with those without AF (Table 1). Both ICU and hospital mortality rates were higher in patients with AF (p<0.001).

The cohort of patients with AF was divided into those with a first diagnosis of AF and those who had a known his-
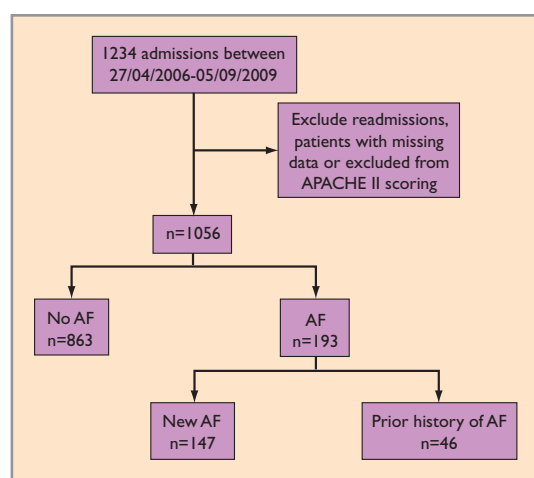
tory of AF (Table 2). While the two groups were similar in terms of APACHE II score, predicted hospital mortality and length of ICU stay, patients with AF associated with a critical illness were younger (p=0.014) and had higher peak CRP levels (p=0.012), ICU mortality (p=0.015) and hospital mortality (p=0.012). The hospital mortality in those with pre-existing AF was similar to those without AF (31.9% and 30.9%, respectively; p=0.889).

The comorbid diseases of patients with AF and the drugs they were taking prior to hospital admission or were administered during their ICU stay are shown in Table 3. Patients with previously diagnosed AF were more likely to be on long-term β-blockers, angiotensin-converting enzyme inhibitors, statins, anticoagulants, digoxin, amiodarone and diuretics. In addition, they were more likely to be given a β-blocker or digoxin during their critical illness. Patients with newly diagnosed AF associated with critical illness were more likely to receive amiodarone and magnesium infusions. There was no significant difference in the use of catecholamine infusions between those with previously diagnosed AF and AF associated with a critical illness. Finally, more of the patients with a previous diagnosis of AF received formal anticoagulation, although more of the patients with newly diagnosed AF were coagulopathic.

In terms of mortality, 220/224 (98%), 11/12 (92%) and 59/67 (88%) of the deaths in the no AF, prior history of AF and new-onset AF groups, respectively, occurred within 30 days. This timepoint cut-off was therefore chosen for the mortality outcome in logistic regression analysis. This process assumed that those who were discharged alive from hospital before 30 days were still alive at 30 days.

At the univariable level, AF category was found to have an association with death (Table 4). Patients with no AF or those with a prior history of AF were found to have a lower risk of death than those with new-onset AF. Age and a higher APACHE II score were associated with an increased risk of death. When the factors were considered together in a multivariable model, however, only APACHE II score retained its association with death (Table 4). AF category and ageing were not found to significantly explain any more of the variation in deaths than that explained by APACHE II score. While overall AF only just failed to reach statistical significance at the 5% level, it was interesting that those with a history of AF were found to have a 62% (15–83%) reduction in the risk of death compared with those with AF at onset (p=0.018). Those with no AF had a 27% reduction (52% reduction to 11% increase) in the risk of death compared with those with new-onset AF (p=0.137).

DISCUSSION

This study reports on one of the largest cohorts of patients with AF in a general ICU setting in the literature. As has been well documented, patients who had AF in the ICU were older and sicker, and had a longer ICU stay and higher mortality. Because postmortem examinations are not routinely carried out in the critically ill, we were unable to establish whether the patients with AF who died had an increased rate of complications that could be directly attributed to AF. This would include conditions such as thromboembolism that had not been clinically recognised.

Previous reports of the consequences of AF in the critically ill have failed to differentiate between AF that was present prior to critical illness and new-onset AF associated with critical illness. From this study, it appears that AF in those with a

Table 3. Demographic and pharmacological data of patients with new-onset AF and pre-existing AF			
Characteristic	New-onset AF, n (%)	Prior history of AF, n (%)	p-value
Comorbid disease			
Ischaemic heart disease	47 (32)	30 (63.8)	<0.001
Hypertension	59 (40.1)	23 (48.9)	0.29
Diabetes	22 (15)	13 (27.7)	0.049
Chronic respiratory condition	35 (23.8)	9 (19.1)	0.51
Congestive cardiac failure	2 (1.4)	1 (2.1)	0.71
Chronic renal failure	18 (12.2)	5 (10.6)	0.77
Valvular heart disease	2 (1.4)	9 (19.1)	<0.001
Other cardiac condition	5 (3.4)	6 (12.8)	0.016
History of malignancy	10 (6.8)	3 (6.4)	0.92
Cerebrovascular disease	12 (8.2)	6 (12.8)	0.34
Peripheral vascular disease	11 (7.5)	6 (12.8)	0.27
Admission drugs			
β-Blockers	27 (18.4)	26 (55.3)	<0.001
ACEI	34 (23.1)	20 (42.6)	0.01
Calcium-channel blocker	31 (21.1)	13 (27.7)	0.36
A2RB	8 (5.4)	6 (12.8)	0.093
Statin	49 (33.3)	27 (57.4)	0.003
Diuretic	36 (24.5)	20 (42.6)	0.018
Aspirin	48 (32.7)	12 (25.5)	0.34
Clopidogrel	4 (2.7)	1 (2.1)	0.82
Nitrates	10 (6.8)	2 (4.3)	0.52
Digoxin	4 (2.7)	18 (38.3)	<0.001
Thyroxine	4 (2.7)	4 (8.5)	0.084
Warfarin	3 (2)	28 (59.6)	<0.001
Amiodarone	4 (2.7)	4 (8.5)	<0.001
Drug therapy for AF			
Magnesium	98 (66.7)	19 (40.4)	0.002
Amiodarone	104 (70.7)	24 (51.1)	0.014
β-Blockers	26 (17.7)	20 (42.6)	<0.001
Digoxin	13 (9)	18 (38.3)	<0.001
Anticoagulation			
DVT prophylaxis (Y/N)	100 (68)	21 (44.7)	0.002
Coagulopathic (Y/N)	72 (49)	12 (25.5)	0.001
Anticoagulated (Y/N)	12 (8)	16 (34)	<0.001
Catecholamine infusion	64 (43.5)	17 (36)	0.153

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; A2RB, angiotensin 2 receptor blocker; DVT = deep vein thrombosis

prior history of the condition exerts a different response in the critically ill. These patients had a similar severity of illness, as determined by APACHE II scores, but lower mortality than patients with new-onset AF.

Table 4. Death within 30 days: univariable and multivariable logistic regression after multiple imputation of missing values

Variable	Univariable regression		Multivariable regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
AF category		0.012		0.051
No AF vs new-onset AF	0.490 (0.341–0.704)	<0.001	0.728 (0.478–1.107)	0.137
History of AF vs new-onset AF	0.456 (0.215–0.966)	0.040	0.376 (0.167–0.848)	0.018
Male vs female	0.808 (0.615–1.061)	0.124	0.842 (0.620–1.143)	0.270
Age	1.029 (1.020–1.038)	<0.001	1.008 (0.998–1.019)	0.107
APACHE II score	1.146 (1.122–1.170)	<0.001	1.140 (1.116–1.166)	<0.001
C- reactive protein	1.001 (0.999–1.002)	0.281	0.999 (0.998–1.001)	0.464

AF = atrial fibrillation; APACHE = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; OR = odds ratio

On multivariable analysis, the APACHE II score was the only independent predictor of death. The finding that, overall, AF is not an independent predictor of death is similar to that of the study by Annane et al.[1] This may support the view that AF does not independently contribute to poor outcomes, but rather that AF associated with critical illness is a marker of illness severity.

The finding that 13.6% of patients admitted to our unit developed AF associated with critical illness is in the mid-range of that reported in other studies.[1,2,4,7–9] Support for the hypothesis that the development of new-onset AF is related to illness severity comes from the finding that CRP (a marker of inflammation) was significantly higher in those with AF compared with those without. Interestingly, while there was no difference in APACHE II scores, the CRP level was significantly higher in those with new-onset as opposed to previously diagnosed AF. This supports the hypothesis that inflammation may play a role in the pathogenesis of AF.[16]

National and international guidelines regarding rate versus rhythm control and the use of anticoagulation aim to reduce the morbidity and mortality associated with AF.[12,13,17] Nearly 50% of our patients were on catecholamine infusions at the onset of AF and therefore using rate-limiting therapies such as β-blockers and calcium-channel blockers would only further compromise the mean arterial pressure. It is also recommended that anticoagulation be considered to reduce the risk of stroke in patients with AF; however, a significant number of our patients were coagulopathic or had absolute or relative contraindications to formal anticoagulation. It is also difficult to determine how best to appraise an abnormal clotting screen in the context of the immobile critically ill patient who may be prothrombotic. Furthermore, there is a lack of information regarding the long-term sequelae of AF associated with a critical illness. Importantly, it is not clear whether these patients are more likely to develop paroxysmal or chronic AF in the future.

The flaws in this study stem from its retrospective nature, although it is reassuring that the incidence of new AF, prevalence of chronic AF and associated increased mortality are consistent with those reported in current literature.

Although AF is a relatively common arrhythmia in the ICU population, there is remarkably little literature available to apply an 'evidence-based' approach.

The difference in outcomes between patients with a first diagnosis of AF associated with critical illness and those with previously diagnosed AF needs to be confirmed in prospective studies, but this study does highlight the need to consider these populations separately. The possibility that AF confers some additional risk cannot be excluded, since the use of rate-limiting drugs and formal anticoagulation was more widespread in patients with persistent AF, possibly off-setting an increased risk from the arrhythmia.

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