Journal of
Cardiology and Vascular Medicine

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Research Article Open Access

Predictors of Short-Term and Long-Term Clinical Outcomes after an Admission for Atrial Fibrillation or Flutter

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Received Date: March 30, 2022 **Accepted Date:** May 24, 2022 **Published Date:** May 26, 2022

Citation: Jia Yi Anna Ne, Clara K Chow, Stuart Thomas, Saurabh Kumar, Liza Thomas, et al. (2022) Predictors of Short-Term and Long-Term Clinical Outcomes after an Admission for Atrial Fibrillation or Flutter. J Cardio Vasc Med 8: 1-17

Abstract

Background: Atrial fibrillation (AF) is a major cause of mortality and morbidity and a significant healthcare burden. We undertook an observational study to identify predictors of AF-related rehospitalization and all-cause mortality following an acute AF/flutter admission.

Methods: Consecutive patients admitted to Westmead Hospital with a primary diagnosis of AF/flutter from 1 May 2014 to 31 May 2018 were included and followed up until 31 May 2019. We examined predictors of short-term outcomes (primary outcome: AF-related rehospitalization) with multivariable logistic regression and predictors of long-term outcomes (primary outcome: composite of AF-related hospitalization and mortality) with multivariable Cox regression. AF-related rehospitalization was defined as an admission due to recurrent AF/flutter, congestive heart failure, stroke and/or myocardial infarction.

Results: Of 1664 consecutive patients admitted with AF/flutter, 55.8% were male and the median age was 68.0 years. At 30 days, 123 (7.4%) had an AF-related rehospitalization. During a mean follow-up period of 2.1 ± 1.5 years, 683 (41.0%) of patients had at least one AF-related rehospitalization (38.1%, n= 634) or died (2.9%, n=49). Chronic kidney disease (OR 1.94, 95% CI 1.07 – 3.50) was an independent predictor of 30-day AF-related rehospitalization. Age (HR 1.01, 95% CI 1.01 – 1.02 for each additional year), initial admission via emergency (HR 1.29, 95% CI 1.08 – 1.54), CKD (HR 1.63, 95% CI 1.23 – 2.16), chronic obstructive pulmonary disease (HR 1.41, 95% CI 1.09 – 1.83) and having ≥1 comorbidity (HR 1.37, 95% CI 1.04 – 1.83) were independent predictors of first AF-related rehospitalization or all-cause mortality (all $p < 0.05$).

Conclusions: Rehospitalization for recurrent AF/flutter and associated cardiovascular outcomes is common following an acute AF/flutter admission. AF/flutter patients with comorbidities, especially renal and pulmonary disease, are at high risk of readmission. Such patients could be targeted for increased surveillance and additional post-discharge support.

Keywords: Atrial Fibrillation, Rehospitalization, Mortality, Heart failure, Stroke, Myocardial Infarction

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is a major cause of mortality and morbidity globally, with an estimated global prevalence of 3% in adults aged 20 years or older [1,2], increasing to nearly 6% in adults > 65 years old [3]. Despite major advances in management and prophylaxis, AF continues to be associated with a high relative risk of death [4] and increased morbidity [5], with rising incidence and prevalence over the years and projected further increases [6]. A significant component of the burden to healthcare systems due to AF is attributed to recurrent hospitalizations [6,7] not only for AF but also for related complications [7,8]. AF is associated with stroke, heart failure (HF) and myocardial infarction (MI) and increases the risk of these conditions by 5-, 3- and 2-fold respectively [9]. Patients with these conditions and concurrent AF also consistently have worse outcomes [6,10,11]. For instance, the recent TACOS study showed that AF/atrial flutter at admission and/or discharge independently predicted poorer long-term outcome in ACS patients, with 66% higher mortality within the ≥10-year follow-up time when compared to patients with sinus rhythm [12]. In the prospective international observational TIGRIS study comprising of patients who were 1-3 years post-MI, patients with AF had poorer quality of life and increased risk of all-cause hospitalization compared to those without AF [13].

The multinational ROCKET-AF study involving 14 171 AF patients from 1178 participating sites in 45 countries demonstrated that AF patients were not only hospitalized for AF but also for other cardiovascular and non-cardiovascular conditions [7]. In Australia, an observational study by Gallagher et al., which extracted data from the National Hospital Morbidity Database, showed that hospitalizations for a primary diagnosis of AF increased 295% over the 21-year period (1993 – 2013) from 15 555 in 1993 to a total of 61 424 in 2013, surpassing presentations with MI (73% increase) and HF (39% increase) [14]. This is likely driven by an ageing population, [14] coexistent cardiovascular risk factors and non-cardiac conditions such as chronic obstructive pulmonary disease, obesity and obstructive sleep apnoea [15,16]. However, clinical outcomes associated with AF such as stroke, heart failure and myocardial infarction, which are likely to account for a significant component of AF-related hospitalizations, were not accounted for in the study data [14]. A prospective study in Greece by Simantirakis et al. on the recurrence of AF using continuous cardiac rhythm monitoring also did not report AF-related rehospitalization rates [17]. Few studies have explored predictors of AF-related rehospitalization in unselected populations of AF patients.

Accordingly, we undertook a retrospective observational study with the following aims: 1) To investigate AF-related clinical outcomes (including mortality and AF related morbidity as a composite) after an acute AF/flutter admission, and 2) identify independent predictors of AF-related clinical outcomes at short and long-term follow-up, including AF-related hospitalization, all-cause mortality and a composite outcome of AF-related hospitalization and all-cause mortality.

Materials and Methods

Setting and study population

Consecutive patients admitted to Westmead Hospital, a major Australian tertiary hospital, with a primary diagnosis of AF/flutter from 1 May 2014 to 31 May 2018 were included in the study and followed up until 31 May 2019. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Ethics approval was granted by the Western Sydney Local Health District (Reference number: 2002 – 11). WSLHD Ethics was approved from January 2020-January 2021; analysis was conducted in this period. A censored date of 31 May 2019 was pre-determined to allow a minimum follow-up time of 1 year for each patient.

Inclusion and exclusion criteria

We included patients admitted to Westmead Hospital (planned elective admissions to the hospital wards and unplanned admissions to the hospital wards via Emergency Department) with the primary diagnosis of AF / flutter. For patients who presented with recurrent AF / flutter hospital admissions during the study period, only the index admission was included. Patients from overseas or interstate (n = 35) were excluded to minimise incomplete tracking of clinical outcomes during the follow-up period.

Definitions and data collection

The primary diagnosis of AF/flutter was coded as I48 based on the International Classification of Diseases 10th revision Australian Modification (ICD-10AM) which is a derived version of World Health Organisation (WHO) ICD-10.

The primary outcome at 30 days was AF-related rehospitalization defined as an admission due to recurrent AF/flutter, congestive heart failure (CHF), stroke and/or myocardial infarction (MI). The primary outcome at longer-term follow-up was the composite of AF-related hospitalisation and mortality. We included mortality in longer-term follow-up to factor in the competing risk of death.

Data on sociodemographic characteristics, presenting symptoms, emergency status, medical conditions and clinical outcomes of patients was extracted from the Westmead Hospital electronic medical record database by the clinical analytics team, deidentified and analyzed. All comorbidities and clinical outcomes were also coded based on ICD-10AM. Procedures were coded based on the Australian Classification of Health Interventions (ACHI).

In this study, patients with additional comorbidities refer to patients with at least one medical condition in addition to their primary diagnosis of AF/flutter. These medical conditions include cardiac risk factors, cardiac conditions and non-cardiac conditions (Table 1). The CHA2DS2VASc score was calculated to assess the stroke risk of each patient admitted with atrial fibrillation/flutter. It was calculated by adding points for each of the following: Congestive heart failure: 1 point, Hypertension: 1 point, Age ≥ 75 years: 2 points; Age 65 – 74: 1 point, Diabetes: 1 point, Stroke / TIA/ Thromboembolism: 2 points, Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque): 1 point, Sex category (Female sex): 1 point.

Table 1: Baseline patient characteristics during index acute AF/flutter admission at Westmead Hospital from 1 May 2014 to 31 May 2018

Parameters	Patients admitted with a primary diagnosis of AF /flutter (from New South Wales) N = 1664
Age, years	68.0 (58.0 – 77.0)
Age ≥ 75 years old	540 (32.5%)
Males	928 (55.8%)
Aboriginal / Torres Strait Islander	16 (1.0%)
Born in Australia	854 (51.3%)
Admitted via Emergency Department	1129 (67.8%)
Additional diagnosis during current admission	1444 (86.8%)
Length of hospital stay, days (IQR)	2.0 (1.0 – 4.0)
ICU* admissions	20 (1.2%)
Length of ICU stay (for patients admitted to ICU), hours (IQR)	44.5 (13.5 – 132.5)
Composite score	
‡CHA_2DS_2VASc score	2.0 (1.0 – 3.0)
AF related procedures	
Electrical cardioversion	213 (12.8%)
Pulmonary vein isolation	91 (5.5%)
Current comorbidities	
Cardiac risk factors:	
Hypertension	630 (37.9%)

Smoking	415 (24.9%)
Diabetes mellitus	341 (20.5%)
Obesity	90 (5.4%)
Alcohol consumption	18 (1.1%)
Hypercholesterolaemia	6 (0.4%)
Cardiac conditions:	
Heart failure	178 (10.7%)
Ischaemic heart disease	149 (9.0%)
Acute coronary syndromes: Unstable angina or Myocardial infarction	30 (1.8%)
Atrioventricular block	28 (1.7%)
Supraventricular tachycardia	25 (1.5%)
Ventricular tachycardia or ventricular fibrillation	23 (1.4%)
Sick sinus syndrome	23 (1.4%)
Pulmonary embolism	9 (0.5%)
Cerebral infarction	7 (0.4%)
Peripheral vascular disease	3 (0.2%)
Cardiac arrest	3 (0.2%)
Transient ischaemic attack	2 (0.1%)
Non-cardiac conditions:	
COPD†	124 (7.5%)
Chronic kidney disease	107 (6.4%)
Acute kidney failure	84 (5.0%)
Asthma	61 (3.7%)
Anaemia	59 (3.5%)
Thyrotoxicosis	24 (1.4%)
Hyperkalaemia	24 (1.4%)
Obstructive sleep apnoea	15 (0.9%)
Sepsis (flagged for sepsis)	13 (0.8%)
Pulmonary hypertension	3 (0.2%)
Presenting symptoms in patients presenting via ED (N = 1129)	1006 (89.1%)
Syncope	38 (3.4%)
Chest pain	363 (32.2%)
Shortness of breath	120 (10.6%)
Palpitations	438 (38.8%)
Dizziness	46 (4.1%)

Continuous variables are expressed as medians with interquartile range in brackets; all others represent numbers of patients with values in brackets representing percentages.

Abbrevations: *ICU: Intensive Care Unit

†COPD: Chronic obstructive pulmonary disease

‡CHA2DS2VASc score is calculated by adding points for each of the following:

Congestive heart failure: 1 point, Hypertension: 1 point, Age ≥ 75 years: 2 points; Age 65 – 74: 1 point, Diabetes: 1 point, Stroke / TIA/ Thromboembolism: 2 points, Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque): 1 point, Sex category (Female sex): 1 point

Statistical analysis

Continuous variables were expressed as either mean ± SD (standard deviation) or median (IR) (interquartile range) based on Shapiro-Wilk test of normality. Categorical variables were expressed as frequencies and percentages. Univariable and multivariable analyses were performed to explore factors associated with the study outcomes.

Multivariable logistic regression was used to identify independent predictors of 30-day AF-related rehospitalization.

Multivariable Cox proportional hazards regression method was used to identify independent predictors of long-term outcomes - all-cause mortality and first clinical outcome (AF-related rehospitalization or all-cause mortality) after an acute AF/flutter admission.

Only variables with $p<0.05$ on univariable analyses were included in the multivariable analyses, except for age and gender which were included irrespective of p value.

All variables were examined for interaction and multicollinearity. Results are presented as odds ratios, hazard ratios and 95% confidence intervals.

For some variables of interest that had $p<0.05$ on univariable analyses, we conducted Kaplan–Meier survival curve analyses to examine time to AF-related rehospitalization or all-cause mortality during the follow-up period and differences between groups were assessed using log rank tests.

All statistical analyses were performed using SPSS v26.0 (IBM, USA).

A 2-tailed probability value < 0.05 was considered statistically significant.

Results

The study cohort consisted of 1664 patients who were admitted with a primary diagnosis of AF/flutter from 1 May 2014 to 31 May 2018 and followed up until 31 May 2019. The mean follow-up time for the entire cohort to either all-cause mortality, first AF-related rehospitalization or last censored date 31 May 2019 was 2.1 ± 1.5 years.

Baseline characteristics

The baseline characteristics of the patients are shown in Table 1. Of the 1664 patients, 55.8% were male and the median age for the overall cohort was 68.0 years (58.0 – 77.0 years). In this study cohort, 67.8% of the admissions were unplanned via the Emergency Department (ED) and 86.8% of the patients had at least one additional comorbidity during the admission. The median length of hospital stay was 2.0 (1.0 – 4.0) days. 20 patients (1.2%) were admitted to Intensive Care Unit (ICU), of which the median length of hospital stay was 44.5 (13.5 – 132.5) hours. The most common presenting symptom in patients who presented via the Emergency Department was palpitations (n = 438, 38.8% of patients admitted via ED). Hypertension was the most common comorbidity (n = 630, 37.9%). The median CHA_2DS_2VASc score was 2.0 (1.0 – 3.0). In terms of procedures, 213 (12.8%) of the patients received electrical cardioversion during their admission while 91 (5.5%) received pulmonary vein isolation. Of the 1129 patients who presented via the Emergency Department, 1006 (89.1%) of them were symptomatic. The most common presenting symptom in these patients was palpitations (n = 438, 38.8% of patients admitted via ED).

Clinical outcomes

Table 2 shows the clinical outcomes of patients till the end of the study follow-up on 31 May 2019. At 30 days, 123 patients (7.4%) had an AF-related rehospitalization (110 rehospitalized with a primary diagnosis of AF/flutter and 13 with a primary diagnosis of CHF, stroke or MI). During a mean follow-up period of 2.1 ± 1.5 years, 683 (41.0%) of patients had at least one AF-related rehospitalization (38.1%, n= 634) or died (2.9%, n=49). The cumulative AF-related rehospitalization rates within 1, 2, 3, 4 and 5 years of initial admission were 26.2%, 33.4%, 36.4%, 37.4% and 38.1% respectively (Table 2).

A total of 119 patients died by the end of the study follow-up period. Of these, 9 patients (0.5%) died during their initial admission. Of the 119 patients, 49 had 'all-cause mortality' as their first adverse outcome after initial admission and 70 had at least one AF-related rehospitalization, and subsequently died.

During the index AF-related rehospitalization at both short-term (30 days) and long-term follow-up, recurrent AF/flutter (78%) was the most common adverse clinical outcome of interest, followed by congestive heart failure (15%), myocardial infarction (5%) and stroke (2%).

Table 2: AF-related outcomes of AF/flutter patients admitted to Westmead Hospital from 1 May 2014 to 31 May 2018 and followed up till 31 May 2019

Parameters	**Patients admitted with a primary diagnosis of AF / flutter (from New South Wales) N = 1664**
AF-related rehospitalization for: recurrent AF/flutter, CHF, MI and / or stroke	
Clinical outcomes at short-term follow-up (30 days)	
30-day AF-related rehospitalization	123 (7.4%)
30-day rehospitalization with a primary diagnosis of AF/flutter AF/flutter only AF flutter and at least 1 cardiovascular outcome of interest: CHF/MI and /or stroke (as secondary diagnosis)	110 (6.6%) 93 (5.6%) 17 (1.0%)
30-day rehospitalization with a primary diagnosis of CHF, MI or stroke CHF, MI or stroke only CHF, MI or stroke + AF/flutter (as secondary diagnosis)	13 (0.8%) 9 (0.5%) 4 (0.2%)
First composite outcome during long-term follow-up: AF-related rehospitalization or all-cause mortality (over a mean follow-up of 2.1 ± 1.5 years)	
1st AF-related rehospitalization OR all-cause mortality 1st AF-related rehospitalization All-cause mortality	683 (41.0%) 634 (38.1%) 49 (2.9%)
1st rehospitalization with a primary diagnosis of AF/flutter AF/flutter only AF flutter and at least 1 cardiovascular outcome of interest CHF/ MI and / or stroke (as secondary diagnosis)	549 (33.0%) 483 (29.0%) 66 (4.0%)
1st rehospitalization with a primary diagnosis of CHF, MI or stroke-CHF, MI or stroke only CHF, MI or stroke + AF/flutter (as secondary diagnosis)	85 (5.1%) 66 (4.0%) 19 (1.1%)
All-cause mortality	
Deaths during initial admission	9 (0.5%)
Deaths (till end of study 31 May 2019)	119 (7.2%)
Cumulative event rate	
AF-related rehospitalization within 1 year of initial admission AF-related rehospitalization within 2 years of initial admission AF-related rehospitalization within 3 years of initial admission AF-related rehospitalization within 4 years of initial admission AF-related rehospitalization within 5 years (+ 1 month) of initial admission	436 (26.2%) 556 (33.4%) 606 (36.4%) 622 (37.4%) 634 (38.1%)

All-cause mortality within 1 year of initial admission	56 (3.4%)
All-cause mortality within 2 years of initial admission	87 (5.2%)
All-cause mortality within 3 years of initial admission	104 (6.3%)
All-cause mortality within 4 years of initial admission	116 (7.0%)
All-cause mortality within 5 years (+ 1 month) of initial admission	119 (7.2%)

We also found that there was a significant difference in the 30-day AF-related rehospitalization outcome (p = 0.004) but not the long-term (composite outcome of 1st AF-related rehospitalization and all-cause mortality) (p = 0.295) between the symptomatic (89.1%) and asymptomatic (10.9%) AF/flutter patients admitted via Emergency Department.

Univariable predictors

Univariable logistic regression and Cox regression analyses are presented in the Supplementary data Tables 3-5. Significant univariable predictors for 30 day AF-related rehospitalization included age, age ≥ 75 years, admission via Emergency, having ≥ 1 comorbidity, hypertension and chronic kidney disease. Significant univariables for first AF-related rehospitalization or all-cause mortality after an acute AF / flutter admission included age, age ≥ 75 years, admission via Emergency, having ≥ 1 comorbidity, admitted length of stay, hypertension, diabetes, ischaemic heart disease, heart failure, stroke, pulmonary embolism, chronic obstructive pulmonary disease, acute kidney failure, chronic kidney disease and cardiac arrest. These were subsequently entered into the multivariable models after a collinearity check.

Table 3: Univariable logistic regression of potential predictor factors for AF-related rehospitalization 30 days after an acute AF / flutter admission

Univariable analysis			
Parameters	Unadjusted Odds Ratio	95% Confidence Interval	p value
Age at episode, per 1 year	1.02	1.00 – 1.03	0.016
Age at episode ≥ 75 years	1.52	1.05 – 2.22	0.027
Males	0.82	0.57 – 1.19	0.29
Aboriginal and Torres Strait Islander	0.83	0.11 – 6.35	0.86
Length of hospital stay	0.99	0.96 – 1.03	0.62
Admission via Emergency	1.75	1.13 – 2.72	0.013
Having ≥1 comorbidity	2.01	1.00 – 4.02	0.049
Hypertension	1.46	1.01 – 2.11	0.045
Diabetes	1.28	0.83 – 1.96	0.27
Obesity	1.24	0.58 – 2.62	0.58
Smoking	0.88	0.57 – 1.36	0.56
Alcohol consumption	0.74	0.10 – 5.57	0.77
Ischaemic heart disease	1.22	0.67 – 2.23	0.52
Heart failure	1.08	0.60 – 1.93	0.80
Sick sinus syndrome	0.57	0.08 – 4.23	0.58
Chronic kidney disease	2.38	1.35 – 4.20	0.003
Acute kidney failure	1.34	0.63 – 2.85	0.45
Asthma	1.66	0.74 – 3.73	0.22
Chronic obstructive pulmonary disease	1.52	0.83 – 2.79	0.17
Anaemia	1.17	0.46 – 2.97	0.75

Table 4: Univariable Cox regression analysis of potential predictor factors for first AF-related rehospitalization or all-cause mortality after an acute AF / flutter admission

Univariable analysis			
Parameters	Unadjusted Hazard Ratio	95% Confidence Interval	p value
Age at episode, per 1 year	1.02	1.01 – 1.02	< 0.001
Age at episode ≥ 75 years	1.43	1.23 – 1.67	< 0.001
Males	0.89	0.76 – 1.03	0.11
Aboriginal and Torres Strait Islander	0.89	0.40 – 2.00	0.78
Admission via Emergency	1.50	1.26 – 1.78	< 0.001
Having ≥1 comorbidity	1.86	1.43 – 2.42	< 0.001
Admitted length of stay	1.01	1.00 – 1.02	0.005
Hypertension	1.45	1.25 – 1.69	< 0.001
Diabetes	1.28	1.08 – 1.53	0.006
Obesity	0.99	0.69 – 1.41	0.94
Smoking	0.93	0.78 – 1.10	0.38
Alcohol consumption	0.51	0.19 – 1.36	0.18
Ischaemic heart disease	1.37	1.07 – 1.74	0.012
Heart failure	1.52	1.22 – 1.89	< 0.001
Stroke	0.61	0.15 – 2.43	0.48
Ventricular fibrillation or tachycardia	0.87	0.44 – 1.75	0.70
Chronic obstructive pulmonary disease	1.69	1.31 – 2.17	< 0.001
Acute kidney failure	1.84	1.39 – 2.45	< 0.001
Chronic kidney disease	2.20	1.73 – 2.81	< 0.001

Mean follow-up of 2.1 ± 1.5 years to first AF-related rehospitalization or all-cause mortality or last censored date (till end of study follow-up 31 May 2019)

Table 5: Univariable Cox regression analysis of potential predictor factors for all-cause mortality after an acute AF / flutter admission

Univariable analysis			
Parameters	Unadjusted Hazard Ratio	95% Confidence Interval	p value
Age at episode, per 1 year	1.07	1.05 – 1.09	< 0.001
Age at episode ≥ 75 years	3.22	2.24 – 4.64	< 0.001
Males	1.07	0.75 – 1.54	0.71
Aboriginal and Torres Strait Islander	0.91	0.13 – 6.50	0.92
Admission via Emergency	1.68	1.09 – 2.59	0.02
Having ≥1comorbidity	2.65	1.24 – 5.70	0.012
Length of hospital stay, days	1.03	1.02 – 1.04	< 0.001
ICU stay	5.23	2.30 – 11.9	< 0.001
Sepsis	5.20	1.92 – 14.1	0.001
Hypertension	2.29	1.59 – 3.30	< 0.001
Diabetes mellitus	1.83	1.24 – 2.69	0.002

Obesity	0.60	0.19 – 1.90	0.39
Smoking	1.51	1.03 – 2.21	0.034
Ischaemic heart disease	1.86	1.09 – 3.15	0.022
Heart failure	4.07	2.75 – 6.02	< 0.001
Ventricular tachycardia or ventricular fibrillation	3.72	1.52 – 9.12	0.004
Chronic obstructive pulmonary disease	3.23	2.01 – 5.19	< 0.001
Acute kidney failure	3.42	2.02 – 5.79	< 0.001
Chronic kidney disease	5.53	3.66 – 8.37	< 0.001

Mean follow-up of 3.0 ± 1.3 years to all-cause mortality or last censored date (till end of study follow-up 31 May 2019)

Independent predictors of short and long-term clinical outcomes

Table 6 shows the independent predictors of first 30-day AF-related rehospitalization after an acute AF/flutter admission. Chronic kidney disease (CKD) emerged as an independent predictor of first 30-day AF-related rehospitalization after an acute AF/flutter admission (adjusted OR 1.94, 95% CI 1.07 – 3.50, p = 0.028).

Table 6: Independent predictors of AF-related rehospitalization 30 days after an acute AF/flutter admission

Multivariable analysis*			
Parameters	Adjusted Odds Ratio	95% Confidence Interval	p value
Age at episode, per 1 year	1.01	1.00 – 1.02	0.17
Males	1.08	0.73 – 1.58	0.71
Having ≥1 comorbidity	1.53	0.74 – 3.16	0.25
Hypertension	1.10	0.74 – 1.65	0.63
Chronic kidney disease	1.94	1.07 – 3.50	0.028
Admission via Emergency	1.52	0.97 – 2.38	0.07

*Multivariable logistic regression method was used to identify independent predictors of first 30 day rehospitalization after an acute AF / flutter admission.

Only variables with p<0.05 on univariable analysis were included in the multivariable analysis, except for age and gender which were included irrespective of p value.

Table 7 shows the independent predictors of first AF-related rehospitalization or all-cause mortality after an acute AF/flutter admission over a mean follow-up period of 2.1 ± 1.5 years. The independent predictors of first AF-related rehospitalization or all-cause mortality were age (adjusted HR 1.01, 95% CI 1.01 – 1.02 for each additional year), initial admission via emergency (adjusted HR 1.29, 95% CI 1.08 – 1.54), CKD (adjusted HR 1.63, 95% CI 1.23 – 2.16), chronic obstructive pulmonary disease (COPD) (adjusted HR 1.41, 95% CI 1.09 – 1.83) and having ≥1 comorbidity (adjusted HR 1.37, 95% CI 1.04 – 1.83) (all p < 0.05).

Table 8 shows the independent predictors of all-cause mortality after an acute AF/flutter admission over a mean follow-up period of 2.9 ± 1.3 years. The independent predictors of all-cause mortality after an acute AF/flutter admission were age, male gender, heart failure, COPD, CKD, ventricular fibrillation or ventricular tachycardia, smoking and sepsis (all p < 0.05).

Table 7: Independent predictors of first AF-related rehospitalization or all-cause mortality after an acute AF/flutter admission

Multivariable analysis *			
Parameters	Adjusted Hazard Ratio	95% Confidence Interval	p value
Age at episode, per 1 year	1.01	1.01 – 1.02	< 0.001
Males	0.99	0.85 – 1.16	0.91
Aboriginal and Torres Strait Islander	1.00	0.45 – 2.25	0.99
Admission via Emergency	1.29	1.08 – 1.54	0.005
Having ≥1 comorbidity	1.37	1.04 – 1.83	0.03
Length of hospital stay, days	1.00	0.99 – 1.01	0.99
Hypertension	1.09	0.92 – 1.29	0.32
Diabetes mellitus	1.06	0.89 – 1.28	0.51
Ischaemic heart disease	1.03	0.80 – 1.34	0.81
Heart failure	1.11	0.88 – 1.40	0.38
Chronic obstructive pulmonary disease	1.41	1.09 – 1.83	0.008
Acute kidney failure	1.10	0.79 – 1.53	0.56
Chronic kidney disease	1.63	1.23 – 2.16	0.001

*Multivariable Cox proportional hazards regression method was used to identify independent predictors of first AF-related rehospitalization or all-cause mortality after an acute AF / flutter admission.

Only variables with p<0.05 on univariable analysis were included in the multivariable analysis, except for age and gender which were included irrespective of p value.

Mean follow-up of 2.1 ± 1.5 years (till end of study follow-up 31 May 2019)

Table 8: Independent predictors of all-cause mortality after an acute AF / flutter admission

Multivariable analysis *			
Parameters	Adjusted Hazard Ratio	95% Confidence Interval	p value
Age at episode, per 1 year	1.07	1.05 – 1.09	< 0.001
Males	1.54	1.04 – 2.28	0.03
Hypertension	1.23	0.83 – 1.83	0.30
Diabetes	1.15	0.76 – 1.73	0.51
Heart failure	2.03	1.33 – 3.10	0.001
Ischaemic heart disease	0.78	0.44 – 1.39	0.41
Chronic obstructive pulmonary disease	1.91	1.16 – 3.15	0.011
Acute kidney failure	0.92	0.49 – 1.70	0.78
Chronic kidney disease	2.97	1.79 – 4.90	< 0.001
Ventricular fibrillation or ventricular tachycardia	2.75	1.10 – 6.90	0.031
Sepsis	2.82	1.01 – 7.88	0.049
Smoking	1.51	1.01 – 2.26	0.043

*Multivariable Cox proportional hazards regression method was used to identify independent predictors of first AF-related rehospitalization or all-cause mortality after an acute AF / flutter admission.

Only univariables with p<0.05 were included in the multivariable analysis, except for age and gender which were included irrespective of p value. Cardiac arrest, anaemia and hyperkalaemia were not included in the models

Mean follow-up of 3.0 ± 1.3 years to all-cause mortality or last censored date (till end of study follow-up 31 May 2019)

Kaplan–Meier survival curves of variables of interest are presented in the Supplementary data (Figures 1-5). Patients with at least 1 additional comorbidity (Figure 1), hypertension (Figure 3), chronic kidney disease (Figure 4), chronic obstructive pulmonary disease (Figure 5) and electrical cardioversion (Figure 2) had a significantly higher rate of AF-related rehospitalization or all-cause mortality after an acute AF/flutter admission, compared to patients without these clinical characteristics respectively (all $p < 0.001$). In our study cohort, a greater percentage of patients who received electrical cardioversion had heart failure (15.5% vs 10.0%, $p = 0.015$), COPD (10.8% vs 7.0%, $p = 0.046$) and were smokers (36.2% vs 23.3%, $p < 0.001$) compared to patients who did not receive electrical cardioversion, which could explain why they were at higher risk of AF-related rehospitalization. In the patients admitted via the Emergency Department, a greater percentage of patients who received electrical cardioversion were symptomatic (94.6% vs 88.0%, $p < 0.001$) compared to patients who did not receive electrical cardioversion.

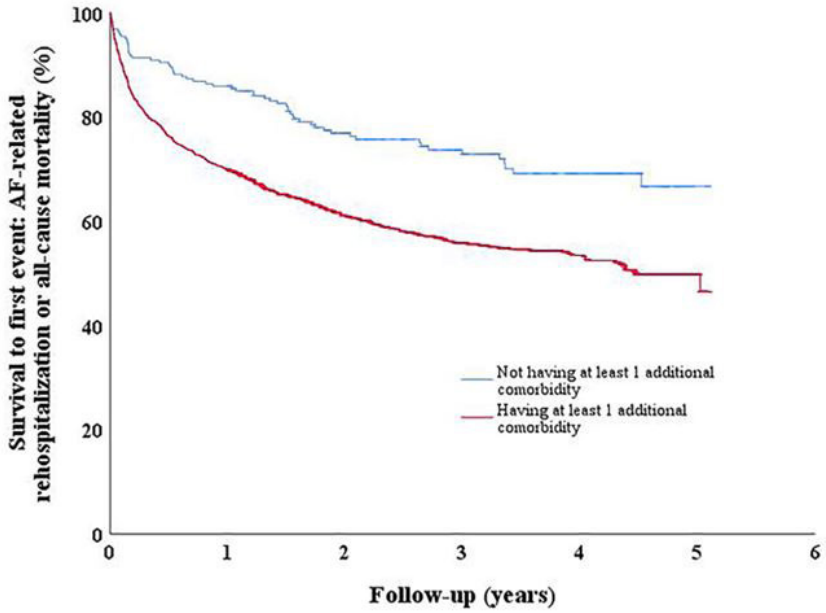

Figure 1: Kaplan-Meier survival curves for all-cause mortality or AF-related rehospitalization in patients having atleast 1 comorbidity vs patients with AF alone.

Log Rank Chi-Square 21.71, 1df, p<0.001

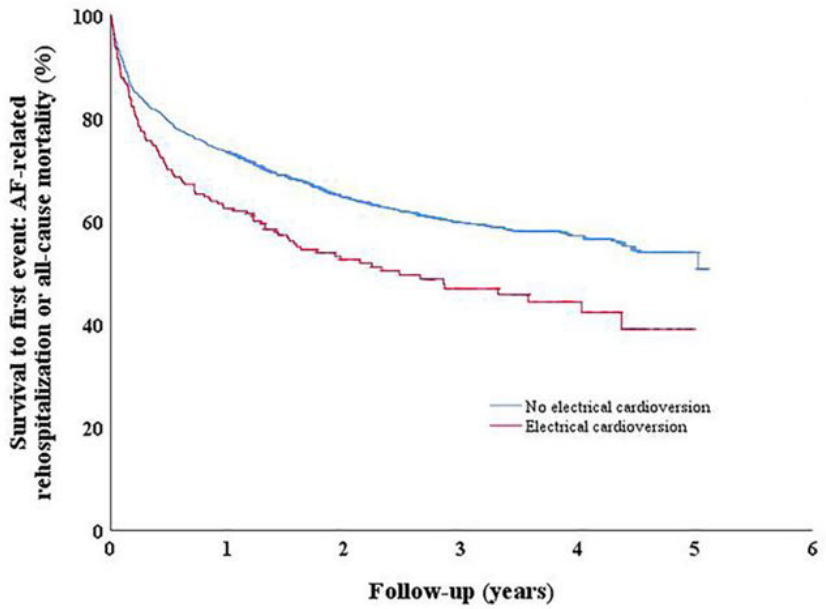

Figure 2: Kaplan-Meier survival curves for all-cause mortality or AF-related rehospitalization in patients with and without electrical cardioversion during index hospitalization

Log Rank Chi-Square 13.96, 1df, p<0.001

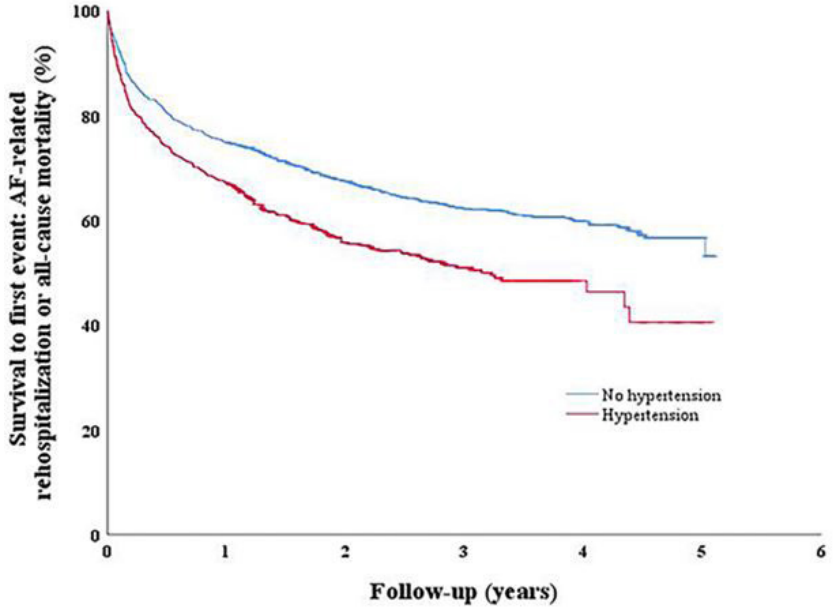

Figure 3: Kaplan-Meier survival curves for all-cause mortality or AF-related rehospitalization in patients with and without hypertension

Log Rank Chi-Square 23.18, 1df, p<0.001

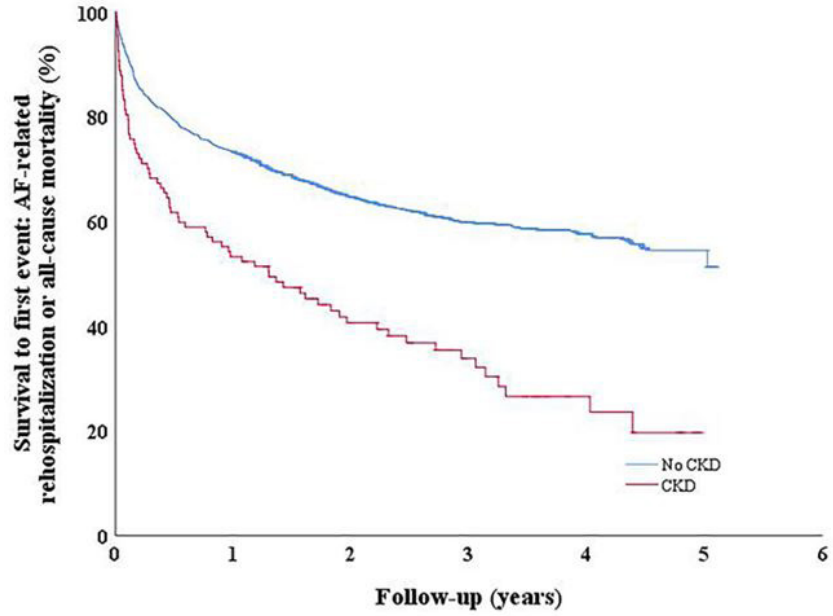

Figure 4: Kaplan-Meier survival curves for all-cause mortality or AF-related rehospitalization in patients with and without chronic Kidney disease (CKD)

Log Rank Chi-Square 42.68, 1df, p<0.001

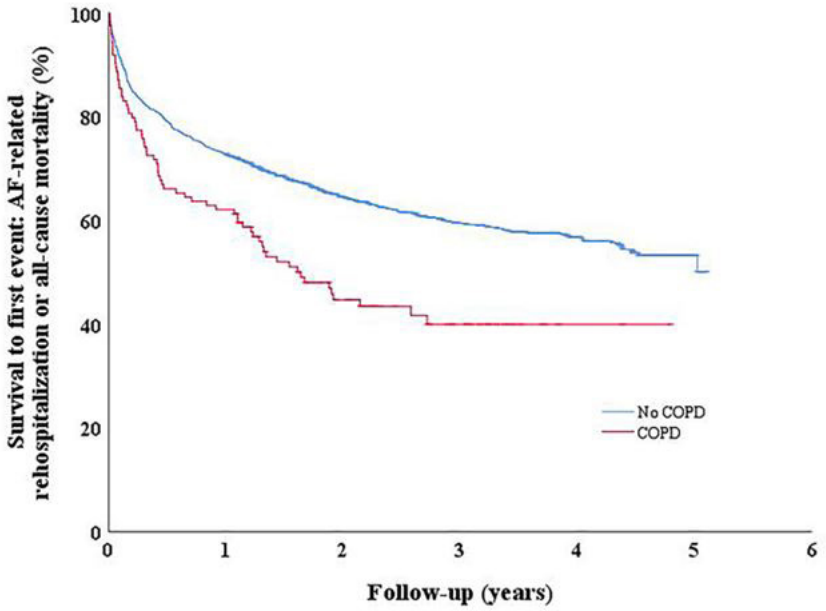

Figure 5: Kaplan-Meier survival curves for all-cause mortality or AF-related rehospitalization in patients with and without chronic obstructive pulmonary disease (COPD)

Log Rank Chi-Square 17.17, 1df, p<0.001

Discussion

In this study, we report a high rate of AF-related rehospitalization and all-cause mortality after an acute AF / flutter admission. Over a mean follow-up period of 2.1 ± 1.5 years, a significant percentage (41.0%) of patients had at least one AF-related rehospitalization or died. Patients with comorbidities other than AF are at higher risk of both short-term and long-term adverse outcomes, particularly those with chronic kidney disease and chronic obstructive pulmonary disease.

In a 10-year longitudinal prospective observational study of 156 AF patients in Denmark by Qvist et al., there were 472 admissions per 1000 patient years in the first observational period 1999-2001 to 2002-2003 and 341 admissions per 1000 patient years in the second observational period 2002-2003 to 2010. The distribution of AF-related hospitalization reasons in the first observational period was similar to our study, with recurrent AF/flutter being the most common, followed by congestive heart failure and ischaemic stroke [18]. Our study confirms and extends the findings of this earlier study by identifying predictors of rehospitalization specifically for recurrent AF/flutter and associated cardiovascular outcomes - CHF, MI and stroke. In both the multinational ROCKET-AF study [7] and the Atherosclerosis Risk in Communities Study (ARIC) in United States [19], healthcare utilisation among AF patients were attributable mainly to non-AF conditions. Furthermore, the prospective study by Simantirakis et al found that a significant percentage of patients either suffer no AF recurrence after their first symptomatic episode or show a low recurrence rate [17]. In contrast to these findings, our study showed that rehospitalization for recurrent AF/flutter was the most common cardiovascular outcome of interest, surpassing CHF, MI and stroke. This may be attributed to a high prevalence of concurrent cardiac and non-cardiac comorbidities in AF patients as evident in the ARIC study [19], as well as a smaller cohort of 30 patients in the study by Simantirakis et al [17]. In the study by Qvist et al, the causes of hospitalization shifted over time from AF relapse to the most frequent complications of AF - ischaemic stroke and congestive heart failure [18]. This change in hospitalization pattern was not captured in our study possibly because our follow-up time period was shorter.

In the GARFIELD-AF study, involving 52 032 AF patients, major outcomes (all-cause mortality, non-haemorrhagic stroke / systemic embolism and major bleeding) do not differ between asymptomatic (25.4%) and symptomatic (74.6%) atrial fibrillation presentations[20]. Unlike this study, we found that there was a significant difference in the 30-day AF-related rehospitalization outcome but not the long-term (composite outcome of 1st AF-related rehospitalization and all-cause mortality) between the symptomatic (89.1%) and asymptomatic (10.9%) AF/flutter patients admitted via Emergency Department. However, our study outcomes were slightly different from the GARFIELD-AF study as we included all-cause mortality, rehospi-

talization due to recurrent AF/flutter, congestive heart failure, stroke and / or myocardial infarction, but not systemic embolism and major bleeding.

We found that patients with ≥1 comorbidity had a significantly higher rate of AF-related rehospitalization or all-cause mortality. This is similar to a UK Biobank longitudinal observational study by Jani et al.[21] which found that both cardiometabolic and non-cardiometabolic comorbidities were very common among AF patients. They also showed that survival in middle-aged to older individuals with self-reported AF was strongly correlated with the level of multimorbidity, with an increase in the number of comorbid long-term conditions alongside AF being associated with a higher risk of all-cause mortality [21]. Our study extended these findings by including AF-related rehospitalization as an outcome in addition to all-cause mortality. Similar to the UK Biobank study [21], our study also found that COPD was associated with a higher risk of all-cause mortality in AF patients. The Fushimi AF registry study found that HR of MACNE (major adverse cardiovascular or neurological events) were significantly higher in the elderly and patients with comorbidities [22], indicating that age and the presence of comorbidities are associated with AF and AF-related clinical outcomes. However, the extent to which each individual comorbidity affected the clinical outcomes was not reported in this study, unlike our study which explored this. A study by Donnellan et al. reported that lower cardiorespiratory fitness assessed using exercise stress test was associated with a higher rate of AF rehospitalization after AF ablation. However, it did not specify which comorbidities were associated with AF rehospitalization [23].

We also found that CKD was an independent predictor of both short-term and long-term AF-related outcomes after an acute AF/flutter admission. Age and COPD were independent predictors of all-cause mortality and the composite end-point of AF-related rehospitalization and/or all-cause mortality after an acute AF/flutter admission. Our findings are consistent with the multinational ROCKET-AF study which also showed that lung disease and renal dysfunction were associated with increased hospitalization risk in AF patients [7]. However, the ROCKET-AF study investigated all-cause rehospitalization as an endpoint [7], unlike our study which focused on AF-related rehospitalization for AF/flutter, congestive heart failure, myocardial infarction and / or stroke.

Study strengths

This study carefully identifies predictors of AF-related clinical outcomes in AF/flutter patients at short and long-term follow-up and underscores the importance of risk factors and comorbidities in predicting the risk of rehospitalization and all-cause mortality. The study included a large sample size of patients from a tertiary centre with a primary diagnosis of AF/flutter, a significant follow-up time period of at least 1 year for all patients. Additionally, we identified independent predictors not only for readmission for AF/flutter, but also common and clinically important AF-related adverse outcomes (congestive heart failure, MI, stroke) and a comprehensive analysis of short-term and long-term outcomes. The inclusion of only patients admitted with a primary diagnosis of atrial fibrillation / flutter increases the robustness of our study design and results and reduces the heterogeneity of the study cohort.

Study limitations

Our study has several limitations. As it is a single-centre study with a retrospective design, the number of outcomes may potentially be an underestimate, and the study findings may not be representative of all patients with AF in Australia. The exact timing and chronicity of most comorbidities in the hospital database were not clearly defined. We could not perform subgroup analyses according to the type of AF (paroxysmal, persistent and permanent AF) as this was not specified for some patients. Some common modifiable risk factors of AF such as alcohol consumption, obesity and obstructive sleep apnea (OSA) were likely to be underreported. The prevalence of OSA (0.9%) was lower than the reported rate in the literature (6 to 17%) [24] probably because not all patients were screened for OSA. Furthermore, there was no cause-specific mortality analysis as such information was not available from the hospital database. Information on medications, pathology results, investigations, haemodynamic status and whether patients reverted to sinus rhythm could not be extracted for analysis. Hence, we were unable to assess how the utilization of different AF medications for rate or rhythm control as well as the anticoagulation status of patients impact on AF-related rehospitalization.

Clinical implications

Our results identify high-risk patients requiring increased surveillance and additional post-discharge support from amongst those presenting with acute AF/flutter and reinforces the importance of management and optimisation of risk factors and comorbidities in AF/flutter patients. In order to reduce the burden of AF, it is important to identify patients at high risk of rehospitalization after an acute AF/flutter admission and develop strategies to improve patient management and prevent subsequent readmission. Our findings highlight the need for future prospective cohort studies and interventional studies to examine ways of optimising management of risk factors and comorbidities in patients at high risk of recurrent AF and AF-related clinical outcomes.

Conclusions

Rehospitalization for recurrent AF/flutter and associated cardiovascular outcomes is common following an acute AF/flutter admission. AF/flutter patients with comorbidities, especially renal and pulmonary diseases, are at high risk of readmission. Such patients could be targeted for increased surveillance and additional post-discharge support to prevent rehospitalization.

Acknowledgements

We thank Joanne Han for extracting raw data from the electronic medical records system at Westmead Hospital.

Sources of Funding

Dr. Jia Yi Anna Ne was supported by a Commonwealth Government Research Training Program (RTP) Stipend Scholarship. Professor Clara K Chow is supported by a NSW Health CVD Clinician Scientist Grant.

Disclosures

None.

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