Impact of atrial fibrillation among stroke patients in a Malaysian teaching hospital

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SUMMARY

Objectives: Atrial fibrillation (AF) is a well-recognised, major risk factor for ischaemic stroke. The presence of atrial fibrillation in a stroke patient translates into higher mortality rates and significant disability. There is lack of data on the impact of atrial fibrillation on stroke patients in Malaysia. The aim of this study was to determine the prevalence of AF in a hospital setting and determine the risk factors, clinical profile and discharge outcomes in ischaemic stroke patients with and without atrial fibrillation from a tertiary centre in Malaysia.

Methods: This was a retrospective review of patients admitted consecutively to the University Malaya Medical Centre, Kuala Lumpur with the diagnosis of stroke during the first six months of 2009. The presence of AF was confirmed with a 12-lead ECG. All patients had neuroimaging with either cranial computed tomography (CT) or magnetic resonance imaging (MRI). Other variables such as clinical features, risk factors, stroke subtypes, length of acute ward stay, complications and evaluation at discharge (mortality) with modified Rankin scale (mRS) were also recorded.

Results: A total of 207 patients were admitted with stroke during the study duration. Twenty two patients (10.6%) were found to have non valvular AF. Patients with AF were found to be older with a mean age of 71.0 ± 2.2 than those without AF with a mean age of 63.6 ± 0.89 ($p<0.05$). Risk factors for stroke such as diabetes mellitus and hypertension were equally common between the two groups while the proportion of patients with ischaemic heart disease was higher among patients with AF ($p<0.005$). Most of the stroke subtypes among patients with AF were of ischaemic type (n=192; 92.8%) while haemorrhagic stroke was uncommon (n=15; 6.2%). Patients with AF had a longer median hospital stay, higher mortality rate and greater functional disability on hospital discharge compared to non AF patients.

Conclusion: The prevalence of AF among stroke patients in a tertiary centre in Malaysia was 10.6%. Stroke patients with AF were observed to have a higher mortality rate and disability on hospital discharge.

KEYWORDS: *atrial fibrillation, cerebrovascular accident, stroke, epidemiology, functional disability, mortality*

INTRODUCTION

Stroke is the leading cause of adult disability worldwide and the third most common cause of death worldwide[1]. 20% of all ischaemic strokes are of cardiac origin. Non-valvular atrial fibrillation (AF) is the most common cause of cardioembolism and an independent risk factor for stroke. The presence of AF confers a fivefold increase in stroke risk[2, 3].

Western population based studies with data obtained from multiple hospital registries have revealed that the prevalence of non-valvular atrial fibrillation range from 9.3% to 31.2%[4-10]. These studies were published from the 1990's to date. Studies from the Asia Pacific region have observed a low prevalence of atrial fibrillation in the general population. A community study to estimate the prevalence of AF in Singaporeans aged 55 years or older revealed that AF is present in only 1.5% of this population[11]. Malaysian publications have reported the prevalence of AF among hypertensive patients and among acute undifferentiated general medical admissions. The prevalence was estimated to be 0.75% and 2.8% respectively[12,13]. In contrast, stroke registry data from a previous study at the University Malaya Medical Centre, Kuala Lumpur described the prevalence of AF at 7%[14]. Other centres in the Asia Pacific region reported a prevalence rate ranging from 9.2% to 15%[15, 16].

There is a substantial body of literature to suggest that the presence of AF is associated with higher morbidity and mortality among patients with ischaemic stroke[17-21]. The bedridden state was more common with stroke associated with AF compared to stroke patients without AF[20]. In addition, the presence of AF also predicted severe stroke and early death. The mortality rate after a stroke in AF patients was 8% higher than non-AF patients in one large study[22]. Furthermore, non-valvular atrial fibrillation increases with age and is associated with numerous risk factors. These disabilities and mortality have major implications to both caregivers and health authorities.

Due to a lack of systematic data in many countries in the Asia-Pacific region, our study was undertaken to determine the prevalence of atrial fibrillation among stroke patients in Malaysia and to establish the impact of atrial fibrillation on mortality and the neurological status. This study was based on an admission cohort of stroke patients in a tertiary care centre. The information acquired will cover the gap in local data.

METHODS

This was a retrospective review of patients admitted consecutively to the hospital with a diagnosis of stroke during the first six months of 2009. The stroke was defined as a focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin. Both ischaemic and hemorrhagic

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Table I: Patients' characteristic.

Patient Characteristics	Patients with AF (n=22)	Patients without AF (n=185)	P value
Male : Female	12:10	120:65	p>0.05
Age (Mean)	71.0	63.6	p<0.05*
Diabetes Mellitus (%)	9 (40.9%)	95 (51.4%)	p>0.05
Hypertension (%)	15 (68.2%)	145 (78.4%)	p>0.05
Hyperlipidaemia (%)	5 (22.7%)	49 (26.5%)	p>0.05
Ischemic heart disease (%)	6 (27.7%)	22 (11.9%)	p<0.05*
Previous CABG (%)	2 (9.1%)	6 (3.2%)	p>0.05
Smoking (current or ex-smoker) (%)	5 (22.7%)	53 (28.7%)	P>0.05
Concomitant Medicines			
- Aspirin	4 (18.2%)	15 (8.1%)	p>0.05
- Anticoagulants	4 (18.2%)	0 (0%)	P<0.05*
- ACE inhibitors or Angiotensin receptor blockers	11 (50%)	70 (37.8%)	p>0.05
- Beta Blockers	6 (27.3%)	51 (27.6%)	p>0.05
- Calcium Channel Blockers	6 (27.3%)	37 (20.0%)	p>0.05
- Statin	5 (22.7%)	48 (26.0%)	p>0.05

CABG = Coronary artery bypass graft surgery. * denotes significant p value.

Table II: Stroke characteristics including clinical presentation, affected vascular territory and brain imaging studies' findings.

Stroke characteristics	Patients with AF (n=22)	Patients without AF (n=185)	P value
Clinical presentation:			
- Cortical signs	13 (59.1%)	120 (64.9%)	p>0.05
- Subcortical signs	19 (86.4%)	140 (75.7%)	p>0.05
- Brainstem signs	0 (0%)	16 (8.7%)	p>0.05
Vascular territory			
- Anterior	14 (63.6%)	79 (42.7%)	p>0.05
- Posterior	0 (0%)	19 (10.3%)	p>0.05
- Lacunar	4 (18.2%)	48 (26.0%)	p>0.05
- Undetermined	4 (18.2%)	39 (21.0%)	p>0.05
Brain Imaging findings			
- Multifocal infarct	13 (59.1%)	124 (67.0%)	p>0.05
- Ischemic stroke	17 (77.3%)	149 (81.0%)	p>0.05
- Haemorrhagic stroke	1 (4.6%)	15 (8.1%)	p>0.05

Table III: Impact of various clinical risk factors on the outcome of the stroke.

Clinical parameters	Odds ratio for outcome (95% Confidence interval)	
	Death	Bedridden state at discharge
Univariate model		
Atrial fibrillation	3.48 (1.19 – 10.20)*	0.28 (0.11 – 0.72)
Age at least 65 years old	0.91 (0.38 – 2.13)	1.53 (0.81 – 2.89)
Age at least 75 years old	0.70 (0.27 – 1.81)	2.83 (1.39 – 5.77)*
Diabetes mellitus	3.38 (1.26 – 9.08)*	0.74 (0.39 – 1.40)
Hypertension	1.54 (0.50 – 4.76)	1.18 (0.57 – 2.48)
Ischemic heart disease	1.32 (0.42 – 4.22)	1.01 (0.40 – 2.53)
History of smoking	2.09 (0.68 – 6.50)	0.53 (0.24 – 1.15)
Female gender	0.94 (0.38-2.27)	1.94 (1.02 – 3.71)*
Multivariate model		
Atrial fibrillation	1.47 (0.35 – 2.59)*	N/A
Diabetes mellitus	1.36 (0.35 – 2.36)	N/A
At least 75 years old	N/A	0.97 (0.27 – 1.67)*
Female gender	N/A	0.56 (-0.09 – 1.22)

* denotes p value < 0.05

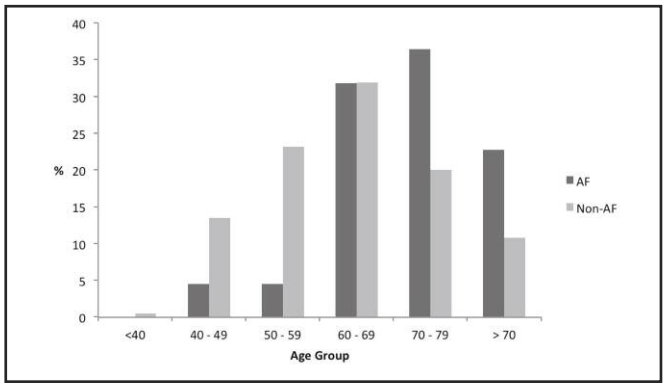

Fig. 1: Percentage of patients with AF & without AF by age group. AF = Atrial Fibrillation.

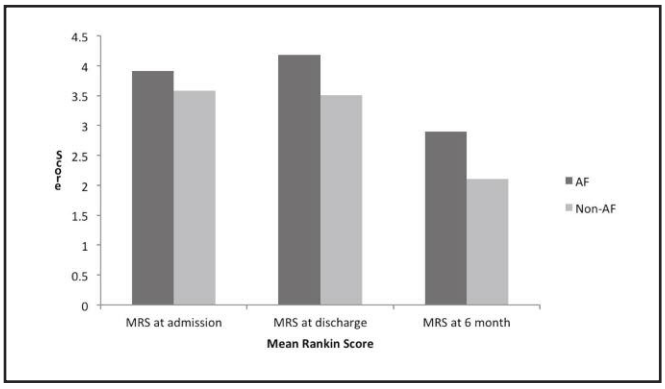

Fig. 2: Modified Rankin Score (MRS) on admission, discharge and six months later.

stroke subtypes were included. All the patients were investigated with at least cranial computed tomography (CT) or magnetic resonance imaging (MRI). AF was diagnosed if there was a previous history of AF or if it was discovered on electrocardiography (ECG) during admission. Data included demographic information (age at onset, sex, race and smoking habit) and risk factor profile (hypertension, diabetes mellitus, hypertriglyceridemia, hypercholesterolemia and smoking). Hypertension was present when the patient was diagnosed to have the condition previously with BP noted to be above 140/90 and on oral antihypertensives prior to admission. Diabetes mellitus (DM) was defined as patient who had previously been diagnosed to have DM and was on oral hypoglycemic and/or insulin before admission. Patients who had smoked at least 100 cigarettes in their life time were considered to be smokers. Hypercholesterolemia and hypertriglyceridemia were defined as previous diagnosis of these conditions with total cholesterol level of ≥ 5.2 mmol/L and triglyceride levels ≥ 1.8 mmol/L. Ischaemic heart disease was defined as a previous diagnosis of acute coronary syndrome, angioplasty or prior coronary artery bypass graft operation before admission. Other characteristics such as clinical features, stroke subtypes, length of acute ward stay, complications and evaluation at discharge and modified Rankin scale were also reviewed. The modified Rankin Scale (mRs) was a widely accepted scale for measuring the degree of disability in stroke patients. The higher score translated into a higher degree of disability[4].

Power calculations showed that a total of 196 patients allowed an estimation of the prevalence of atrial fibrillation to approximately 3.5 percentage points on either side of the estimated prevalence with a 95% confidence interval, assuming that the prevalence is approximately 10%. All data were analysed using Stata version 12 (StataCorp LP, Texas, USA). Descriptive and inferential statistics were used for the analysis of the variables collected.

RESULTS

In our study, 207 patients were admitted with stroke during the six month study duration. Twenty two patients (10.6%) were found to have non valvular AF. Thirteen of these patients with AF (59.1%) were diagnosed to have AF before the admission while the remaining nine patients (40.9%) were diagnosed during the index admission. However, only four of the patients who were known to have AF before admission (30.7%) were prescribed warfarin and another two patients were given aspirin. Novel oral anticoagulants such as dabigatran were not used in this study population.

On average, patients with AF were found to be older (M = 71.0 ± 2.2, range 43 to 86 years old) than those without AF (M= 63.6 ± 0.89, range 38 to 95 years old). This difference was significant with $t(206) = 2.75$, $p<.05$. Fig. 1 showed that the age distribution was skewed to the right in patients with AF while the patients without AF showed a normal distribution. As shown in Table I, additional risk factors for stroke such as diabetes mellitus, hypertension and smoking were similar between patients with and without AF.

Ischemic heart disease was significantly more common among patients with AF. 27.7% of AF patients had concomitant ischemic heart disease. Other characteristics of the patients were shown in Table I. No difference was noted in the concomitant medications of the patients on admission with the exception of anticoagulant usage in patients with atrial fibrillation.

There was no difference in clinical presentation of stroke between patients with AF or without AF (Table II). The frequency of the clinical presentations of weakness, seizure and reduced sensorium was similar between both groups. The most common stroke subtype of patients with AF was ischaemic stroke (86.4%) followed by mixed ischaemic-haemorrhagic. Haemorrhagic stroke was not seen among patients with AF despite warfarin use. Cerebral infarction of anterior circulation territory was more common in patients with AF (73.7%) compared with patients without AF (52.7%). The length of stay in the hospital showed was longer among AF patients with stroke. The median length of stay of patients with AF was 6 days and the median length of stay of patients without AF was 3 days. The difference in the median length of stay was a result of poor of neurological status of AF patients with stroke. Furthermore, the outcome of the stroke patients with AF was found to be less favourable. Indeed, the mortality rate among patients with AF was 25% (6 patients) in contrast with 8.7% (18 patients) among patients without AF. The difference in mortality was statistically significant.

The AF patients were more debilitated compared with non-AF patients. The disability was measured with modified Rankin scores. The mean mRS was not significantly different on admission for patients with or without AF. However, the score on discharge was 4.18 ± 1.6 for AF patients and 3.51 ± 1.4 for non-AF patients. This difference in the modified Rankin Score on discharge was significant with $t(207)=2.12$, $p<0.05$. Additionally, there were significantly more patients who had modified Rankin Score more than 5 among patients with AF then those without AF. In other words, patients with AF were more likely to be discharged in a state where they required

constant nursing care and attention or were bedridden or were incontinent[23].

Modified Rankin score at six month after discharge was only available in about half of the study population. The disability maintained among patients with AF six months after discharge. However, the difference between patients with or without AF was not statistically significant with t(113)=1.39, p>0.05. The mRs were summarised in Fig. 2. The difference in the mRs did not correlate with age of the patients despite a significant difference of age among patients with or without AF.

Table III showed the impact of atrial fibrillation on the outcome of patient with stroke. Presence of atrial fibrillation was a strong independent predictor of death in this group of patients (Odds ratio = 1.47). Diabetes mellitus was also a strong predictor for the outcome (odds ratio = 1.36). Female gender and age more than 75 years old predicted bedridden state among patients with stroke (Odds ratio = 0.56 for female and 0.97 for age more than 75 years old).

DISCUSSION

To our knowledge, this is the first study from a hospital based registry in Malaysia to document the prevalence, clinical profile and outcome of stroke patients stratified by the presence or absence of AF. This study showed the prevalence of atrial fibrillation at 10.6% in a cohort of stroke admissions into our centre. As expected from this highly selected population of stroke patients, the prevalence of atrial fibrillation was higher within a hospital setting when compared to the lower prevalence of AF in the Malaysian patients with hypertension[12]. The likely reason for this finding was related to the higher mean age of stroke patients at 64.4 years and the concomitant presence of multiple conventional risk factors.

This prevalence rate was also noted to be higher than reported from our centre in 1994[14]. The increased rate of AF can be explained by the effect of aging as the mean age of our patients from the earlier study was 61.8 years while the mean age from our current study was 64.4 years. In contrast, a recent Malaysian study of young patients with cerebral infarction in Malaysia showed that non-valvular atrial fibrillation was not found as a cause of cardioembolic strokes. In this study, young stroke patients had cardioembolism from valvular heart disease and cardiomyopathies[24].

The prevalence rate of atrial fibrillation in our study was comparable to stroke admissions from other regional centres which reported prevalence rates from 9.2 to 15 per cent[15, 16]. The overall lower rates in Malaysia and Asia compared with Western populations were also compatible with the existing body of literature. In general, AF was less prevalent among Asian stroke patients compared to the West. The prevalence of AF among stroke patients was reported to be 7 to 10 % in Taiwan[17] and Singapore[18] but the prevalence was observed to be between up to 17% to 32% in United Kingdom, Ireland and Denmark[4, 5, 25]. One obvious difference in these prevalence studies of different countries was that the patients were older in the Western series. For example, the mean age of Danish study[25] was about 70.6 years old compared with 64.1 years old in Singapore study[18]. A similar trend was demonstrated in region studies. In a Chinese hospital stroke registry, AF patients with stroke were significantly older compared to patients without AF (66.1 vs 63.6 years)[19]. Thus, the presence of AF among stroke patients is expected to increase, given the higher age in stroke cohorts.

Our data was also consistent with previous studies that showed that older age was associated with higher mortality and morbidity rates[5-9] as well as poorer clinical outcome[19,20]. This was shown in our cohort where old age was significantly associated with poor outcome. The older AF patients also had higher mortality and morbidity rate. The disability from strokes has been shown to rise with increasing age but this association has been shown to be independent of age[19, 20]. Outcome of our stroke patients with AF was found to be less favourable compared with those without AF, demonstrated by a longer median inpatient stay, greater disability and higher in-hospital mortality on discharge. The overall mean mRS on discharge was higher compared to patients without AF. Patients with AF were also noted to have a higher frequency of disability or nursing care dependency on hospital discharge.

As noted in numerous publications, stroke associated with AF was typically more severe than stroke due to other aetiologies[15-17, 26]. The patients with AF tend to have higher mortality rates compared to patients' in sinus rhythm. These findings give weight to the theory that cardio-embolic strokes cause a sudden occlusion of large cerebral arteries without adequate time for collateral blood supply. This occlusion may also worsen the lower existing hemispheric cerebral blood flow in patients with atrial fibrillation[20].

In our cohort of patients, medical co-morbidities were similar between patients with or without AF with the exception of ischaemic heart disease that was found to be more frequent among patients with AF. While this can be attributed to an older age group, the concomitant presence of ischaemic heart disease with atrial fibrillation has been observed to confer a poorer overall prognosis[27].

Acute ischaemic stroke was the most common stroke subtype among patients with AF. Haemorrhagic stroke was infrequent despite the use of anticoagulation. There was no difference in the clinical presentations of stroke in patients with AF in this study. Total anterior circulation infarction was reported commonly among stroke patients with AF[4]. Multifocal infarctions have also been reported to be more frequent among stroke patients with AF[21]. However, these findings were not detected in this study. One of the possibilities for not identifying these changes may be due to the smaller numbers obtained after dividing the patients into the various subtypes of strokes. The limitation of this study was due to its retrospective design and subjected to problems such as selection bias and inadequate case ascertainment. Patients may not have required admission if they had minor strokes or transient ischaemic attacks with or without the presence of atrial fibrillation. Thus, the data collected was less robust compared to a prospective study. In addition, longer follow up of patients and prolonged ECG recording with Holter or implantable loop recorders[23,28] may diagnose undetected paroxysmal or asymptomatic atrial fibrillation. Therefore, our data was likely to be an underestimation of the total clinical impact of atrial fibrillation in Malaysian stroke patients.

While anticoagulation has been shown to reduce the stroke risk significantly[29], less than half of our patients with existing atrial fibrillation were treated with appropriate therapy, clear evidence that there is further room for improvement. Overall, physician awareness and patient education are important to improve the use of anticoagulation in these high-risk patients. The recent approval of novel oral anticoagulants should encourage more widespread adoption of anticoagulation for stroke prevention among patients with non-valvular AF[30,31].

In summary, our single centre study suggested that AF was not uncommon among our stroke patients and associated with a poorer outcome. This data was obtained through an adequately powered study and is generalisable to other similar urban Malaysian hospitals. The direct implication of AF was an increased burden to the healthcare system and underscores the importance of stroke prevention in atrial fibrillation.

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