ORIGINAL ARTICLE

UNRAVELLING ATRIAL FIBRILLATION AETIOLOGY AND ANTICOAGULATION TRENDS IN STROKE. WHERE DO WE STAND? A STUDY FROM NORTHERN PAKISTAN

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Background: Atrial Fibrillation is a heart arrhythmia causing stroke and associated with many modifiable risk factors. A number of strokes can be prevented by identifying these risk factors and adopting primary prevention and anticoagulation. **Methods:** This Cross-Sectional observational study on 160 stroke patients; identified frequency and risk factors of Atrial Fibrillation and their prior anticoagulation status. Correlation of risk factors associated with Atrial Fibrillation in stroke was done through Chi Square test. **Results:** Among 160 patients, 72 (45%) were males and 88 (55%) females. Mean age was 64.29±13.44SD with range of 31–92 years. Among patients, 113 (70.6%) had ischemic stroke, and 32(20%) had Atrial Fibrillation. Among risk factors, 136(85%) had hypertension, 37(23.1%) had diabetes, 52(32.5%) had ischemic heart disease, 27(16.9%) had valvular heart disease, 9 (5.6%) had hyperthyroidism, 37 (23.1%) had hyperlipidemia, 17(10.6%) had chronic respiratory disease, 19 (11.9%) were smokers, 61(38.1%) had family history of stroke, 12(7.5%) were obese. Only 8 of 32 with AF (25%) had prior anticoagulation. Correlation analysis of risk factors show ischemic heart disease (p=.000285), rheumatic heart disease (p=.000061), hyperlipidemia (p=.0004), chronic respiratory disease (p=.003175) and smoking (p=.00148) as significantly associated with Atrial Fibrillation. **Conclusion:** Ischemic heart disease, hyperlipidemia, smoking and respiratory disease are significant risk factors for stroke in non-valvular atrial fibrillation. All these factors are modifiable so primary prevention and prophylactic anticoagulation should be emphasized.

Keywords: Atrial Fibrillation; Stroke; Risk factors; Modifiable; Anticoagulation

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INTRODUCTION

Atrial fibrillation (AF) is the commonest heart arrhythmia, and in clinical practice, it frequently presents as a risk factor for ischemic stroke. The frequency of AF in ischemic stroke is different considerably in different studies. The prevalence of AF is 1–2% in general population which increases with age up to 10%[1] and prevalence of AF is far higher in stroke patients than general population; as determined from previous studies. A recent systematic review and meta-analysis from studies in Asian countries found wide variation and prevalence of 0 .3–28.3% of AF in stroke.[2] The same variation was observed in a systematic review in 2012 where global burden of AF in stroke varied between 0.1–0.4% in community and 2.8–14% in hospital.[3] The studies show worldwide increasing prevalence of AF over the years.[4]

Multiple risk factors are associated with AF, and once it is developed; can lead to formation of left atrial clots causing embolic stroke. These risk factors are non- modifiable and modifiable. Most common non-modifiable risk factors include age, family history, ethnicity and male gender. Modifiable risk factors comprise cardiac and non-cardiac factors. Cardiac factors include ischemic heart disease, cardiac failure, congenital heart disease, valvular heart disease, pericarditis, endocarditis and hypertension, while non-cardiac factors include hyperthyroidism, pulmonary diseases, diabetes, chronic kidney disease, obesity, obstructive sleep apnoea and alcohol intake.[5] In a study by Ahmed I *et al*. from Pakistan sepsis was identified as important risk factor with worse prognosis.[6]

If diagnosed and managed in time, a significant number of strokes could be avoided through anticoagulation. Oral anticoagulation can reduce the risk of embolic stroke by 64%.[7]

The epidemiology of AF may differ among countries due to differences in prevalence of underlying risk factors and ethnicity. Studies have shown lower prevalence of AF in Asians as compared to whites.[8] A few modifiable risk factors are less prevalent in our country including alcohol intake, obesity, hyperlipidemia and obstructive sleep apnoea.

On the other hand, patients in our country are more at the risk of developing AF due to rheumatic heart diseases, infections and chronic respiratory diseases etc. AF related complications like stroke are mostly encountered due to late diagnosis, lack of proper follow up, and infrequent anti-coagulation.[9]

Keeping in view all these factors we conducted this study to determine: a) The frequency of AF among cerebro-vascular stroke patients admitted in our study period, b) The risk factors of AF leading to stroke and significance of each risk factor in patients with or without atrial fibrillation, and c) Prior status of anticoagulation in stroke patients with AF.

We hypothesized that the frequency of AF among stroke in our setup is lower as compared to western countries due to lack of alcohol intake, lower prevalence of obesity, hyperlipidemia and obstructive sleep apnoea. On the other hand, the frequency of prior anticoagulation was expectedly lower in our setup due to late diagnosis and lack of proper follow-up of patients.

Our study will be helpful to determine the frequency of AF in all stroke patients, associated risk factors and their prior state of anticoagulation. It will also help to identify the most significant risk factors and draw a conclusion to manage the heart arrhythmia according to its aetiology.

MATERIAL AND METHODS

This cross-sectional analytical study was conducted in the medical units of Ayub Teaching Hospital, Abbottabad; a tertiary care hospital serving most of the Northern region of Pakistan. Patients admitted with stroke in the medical units were selected through non-probability convenience sampling.

Calculated sample size for this study was 160 using following formula, with 95% confidence Interval, 20% population proportion[10] and 6.2% margin of error.

$N=z^2\times p\ (100-p)/\ e^2$ where n=sample size, z is 1.96 for 85% confidence level, p is the population proportion and e is the margin of error.

All patients admitted during the study period with stroke of cerebro-vascular origin were included in the study. Patients with stroke due to other causes were excluded, as were patients with stroke and arrhythmia other than atrial fibrillation (AF).

Basic information about the patients, including name, age, and gender, was recorded. A detailed history was taken, encompassing previous stroke, atrial fibrillation (AF), and prior anticoagulation therapy. Additionally, histories of hypertension, diabetes, ischemic heart disease, valvular heart disease, hyperlipidemia, thyroid disorders, respiratory diseases, family history, smoking, and alcohol consumption were documented. A comprehensive examination was conducted to diagnose AF and other related cardiovascular conditions. Blood pressure (BP) and body mass index (BMI) were measured, and patients were categorized as normal, overweight or obese based on their BMI. Thorough examinations of the thyroid, cardiovascular, respiratory, and neurological systems were also performed.

Atrial fibrillation (AF) was confirmed through electrocardiography (ECG), and stroke was confirmed through computed tomography (CT) scan of the brain in all patients. All baseline investigations, including blood glucose and fasting lipid profile were done. Echocardiography and thyroid profile tests were performed in selected patients where clinically indicated. All information was recorded on a proforma after taking informed consent from patients or their caretakers. All the data was entered and analyzed using IBM SPSS Statistics 23. The Chi-square test was applied to determine the significance of associations among variables. Ethical approval for the study was obtained from Institutional Review Board (IRB).

RESULTS

Total 160 patients were included in our study. Among 160, 72 (45%) were males and 88 (55%) were females. Mean age was 64.29 years ±13.44SD ranging from 31–92 years. Forty-two patients (26.25%) were below 55 years, 49 patients (30.62%) were from 56–65 years and 69 patients (43.12%) were above 65 years of age. Quantitative variables like age, blood pressure and BMI analyzed and Systolic Blood Pressure (SBP) >140 mmHg and Diastolic Blood Pressure (DBP) >90 mmHg was taken as hypertension while BMI > 30 was labelled as obese. (Table-1)

Among 160 stroke patients 113 (70.6%) had ischemic stroke while 47 (29.4%) had haemorrhagic stroke. Among 160 patients 32(20%) had AF while 128 (80%) had no atrial fibrillation. Among 160 patients 55(34.4%) had recurrent stroke while 105(65.6%) had first stroke.

While analyzing the risk factors for stroke, among 160; 136(85%) patients had hypertension, 37(23.1%) had diabetes, 52(32.5%) had heart failure or ischemic heart disease, 27(16.9%) had structural/ valvular heart disease, 9(5.6%) had hyperthyroidism, 37(23.1%) had hyperlipidemia, 17(10.6%) had chronic respiratory illness, 19(11.9%) had smoking history, 61(38.1%) had family history of stroke, 12(7.5%) were obese. None of patients had history of alcohol intake.

Stroke risk factors were Cross analyzed in patients with and without Atrial Fibrillation and Chi Square test was applied to determine the significance of various risk factors. *P-value* < .05 was taken as significant. (Table-2)

Table-1: General Demography and descriptive analysis of variables

Variable	n	Range	Mean	SD
Age	160	31–92	64.29	13.45
SBP	158	60–250	146.71	34.57
DBP	157	40–140	88.36	17.25
BMI	160	20–42	29	6.25

Abbreviations: SBP (Systolic blood pressure), DBP (Diastolic Blood Pressure), BMI (Body Mass Index)

Table-2: Stroke risk factors cross analyzed in patients with and without atrial fibrillation

Variable	Atrial fibrillation		Total	*p*-value
	yes	No		
Male	15	57	72	.81
Female	17	71	88	
Prior stroke (yes)	13	42	55	0.4
Prior stroke (No)	19	86	105	
Hypertension (Yes)	30	106	136	.12
Hypertension (No)	2	22	24	
Diabetes (yes)	8	29	37	.77
Diabetes (No)	24	99	123	
IHD/ CCF (yes)	19	33	52	.000285
IHD/ CCF (No)	13	95	108	
RHD (yes)	13	14	27	.000061
RHD (No)	19	114	133	
Hyperthyroidism (Yes)	4	5	9	.0591
Hyperthyroidism (No)	28	123	151	
Hyperlipidemia (yes)	15	22	37	.0004
Hyperlipidemia (No)	17	105	122	
Respiratory dis (Yes)	8	9	17	.003175
Respiratory disease (No)	24	119	143	
Obesity (yes)	5	7	12	3.8063
Obesity (No)	27	121	148	
Smoking (Yes)	9	10	19	.00148
Smoking (No)	23	118	141	
Family history (yes)	14	47	61	.421
Family history (No)	17	79	96	
Current stroke (Ischemic)	31	82	113	.000267
Stroke (Hemorrhage)	1	46	47	
Anticoagulation (yes)	8	0	8	–
Anticoagulation (No)	24	128	152	

DISCUSSION

Our study investigated the frequency and implications of atrial fibrillation (AF) among stroke patients admitted to Ayub Teaching Hospital, Abbottabad; a tertiary care facility in Northern Pakistan. In our study on 160 patients with stroke, 32 (20%) patients had Atrial Fibrillation. Out of 32 stroke patients with AF, 31 had ischemic stroke while only one patient had haemorrhagic stroke. While analyzing the risk factors among stroke patients, ischemic heart disease/CCF (*p*=.000285), rheumatic heart disease (*p*=.000061), hyperlipidemia (*p*=.0004), chronic respiratory disease (*p*=.003175), smoking (*p*=.00148) were significantly associated with AF. The association with hyperthyroidism was borderline non significant (*p*=.0591) which can be re-evaluated with larger sample size to clarify the association. Out of 32 patients with AF; only 8(25%) were on anticoagulants. While comparing ischemic versus haemorrhagic stroke, the ischemic stroke was found very significantly associated with AF (.000267). Due to this high association of ischemic stroke to AF, most of the studies do not take haemorrhagic stroke into account. We included haemorrhagic stroke in our study to document frequency of haemorrhagic stroke in AF. Secondly, our study also takes into account the prior status of anticoagulation; which can be associated with haemorrhagic stroke. We found one out of 32 patients with haemorrhagic stroke and 1 out of 8 patients on prophylactic anticoagulants developed the haemorrhagic stroke. Due to small sample size these findings cannot be generalized and need further study about anticoagulants related haemorrhagic complications.

In our study, the frequency of atrial fibrillation (AF) among 160 patients was 32 (20%), which is comparable to the frequency reported by Shah SA *et al.* (2018), who found a 20.2% frequency.[10] Shah SA *et al.*'s study shares many similarities with ours, such as the geographic region, study design, and sample size. However, their study included only patients with ischemic stroke. In our study, the frequency of AF among ischemic stroke patients alone was 31 out of 113 (27.4%), which is notably high and alarming.

In another study by Imtiaz H *et al.* (2023), a 35% prevalence of AF in ischemic stroke was reported, [11] which aligns with data from other studies in region. Similarly, a study by Goel D *et al.* (2020) from India reported a frequency of AF in ischemic stroke patients at 25.2%.[12] These findings underscore the significant prevalence of AF among ischemic stroke patients in this region.

Among cardiac risk factors valvular heart disease was most significantly associated with AF, and 13 out of 14 patients had AF (*p*= .000061), In a meta-analysis by Noubiap JJ *et al*. Global data suggest 32.8% prevalence of AF in rheumatic heart disease.[13]

Among associated non-valvular cardiac risk factors, we found highly significant association of AF to ischemic heart disease and congestive cardiac failure, hyperlipidemia and smoking. We did not consider ischemic heart disease and congestive cardiac failure separately, as the underlying aetiology is same and frequently; they co-exist, but found very significant association which is comparable to study by Lee CJ *et al*. (2021).[14]

Contrary to the results of our study, the study by Warikowicz P *et al*. (2018) identified older age, female gender, diabetes, hyperlipidemia, hypertension, coronary heart disease, and smoking as significant risk factors for ischemic stroke in patients

with non-valvular AF. In our study, however, we did not find a significant association of female gender, diabetes, and hypertension with stroke in patients with and without AF.[15]

Among non-cardiac causes, chronic respiratory disease was another significant risk factor for AF related stroke; indentified in our study (.003175). The same was the observation by Liu CC *et al*. (2022) in their study where they found a statistically significant association between new onset AF in Chronic Obstructive Pulmonary Disease (COPD) and ischemic stroke.[16]

Anticoagulation therapy is mainstay of treatment in most of the patients with chronic AF to prevent embolic stroke. In our study 8 out of 32 (25%) patients received prophylactic anticoagulation. These findings correlate with findings of study by Ikramullah *et al*. where only 27.5% eligible patients with AF received anticoagulation.[17]

Studies from all over the world have reported inadequate practices of anti-coagulation. Study by Gong X et al. (2022) from China revealed inadequate anticoagulation practices in hospitalized patients. Only 20% ischemic stroke with known AF received prophylactic anticoagulation and only 42.7% eligible patients were anti-coagulated at discharge.[18] while in another large epidemiological study from China by Chen M *et al*. (2022) revealed increasing trend of prophylactic anticoagulation from 19.46% in 2015 to 56.57% in 2020.[19]

In other large epidemiological study from Japan by Akao M *et al*. (2022) anticoagulant prophylaxis trend has increased from 53–70% from 2011–2021.[20]A lot of research is underway and a study by Bayer *et al*. from data of a large clinical trial has shown that the patients are not started anti-thrombotic therapy after the diagnosis of AF, and lowest trends were observed in Latin America and Asia, which is a matter of concern worldwide.[21] In the light of above mentioned studies on anticoagulation trend and observation of our study; we think that anticoagulation trend in our region should be a matter of concern for future studies.

Strengths and Limitations:

There were certain limitations in our study, our study design was cross sectional; so temporal relation among risk factors and AF could not be determined. Our data sample was relatively small and limited to patients admitted in medical units, so findings could not be generalized.

The large epidemiological studies on prevalence of AF are lacking in our county and even in hospital setting; few studies have evaluated the prevalence of AF in stroke patients. Therefore, we think that our study could be a little contribution to foundation of future planning regarding AF and its management; and will be helpful to adopt strategies to prevent and better manage its complications, both at institutional and national level.

Future research:

As evident from available demographic data, the AF patients are not being anti-coagulated according to management guidelines in many counties of the world including Pakistan; which should be the focus of future studies and all the factors related to inadequate anticoagulation practices should be determined and resolved.

Conflict of interest declaration: No conflict of interest to declare.

Conclusion: Ischemic heart disease, cardiac failure, hyperlipidemia and smoking are significant risk factors for stroke in patients with non-valvular atrial fibrillation, while chronic respiratory disease is a significant risk factor for stroke in non cardiac atrial fibrillation. All these factors are modifiable so more emphasis should be paid to primary prevention. Anticoagulation practice is not adequate in our area compared to rest of the world; which needs larger studies to discover the associated factors and lack of adherence to management guidelines.

AUTHORS' CONTRIBUTION

FN: Conceptualization of study, write up.
SM: Supervision, Data analysis, Proof read.
KA: Literature review, editing.
MM: Data Collection
SR: Data Interpretation
NR: Literature Review

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