Original Article

Multivariate Analysis and Scoring Prediction Model of Risk Factors for Atrial Fibrillation after Stroke: A Retrospective Study in Indonesia

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Abstract

Background: Several studies have shown that atrial fibrillation (AF) detected after stroke (AFDAS) occurs in approximately 23.7% of patients with ischemic stroke. **Aim:** This study aimed to determine the relationship between the type, location, volume, and therapy of stroke as risk factors for AF. **Methods:** This retrospective study was composed of adult patients diagnosed with stroke in the High Care Unit (HCU) of Dr. Moewardi General Hospital. The type and location of stroke, hemorrhage volume, history of medication administration, and serum low density lipoprotein-cholesterol (LDL-c) level were studied. Multivariate regression was used to determine the risk factor scoring for AF likelihood after diagnosis. **Results:** From 549 included patients, 262 (47.7%) had AF. The elderly (55.9%) and women (52.1%) constituted the majority of the study population. Seven variables that significantly contributed to AF incidence were ischemic stroke (AOR 4.12, CI 2.40–7.07, $P < 0.001$), cerebral cortex location (AOR 2.34, CI 1.35–4.06, $P = 0.003$), administration of the neuroprotective agent (AOR 0.24, CI 0.15–0.41, $P < 0.001$), history of hypertension (AOR 2.46, CI 1.09–5.56, $P = 0.031$), coronary heart disease (AOR 7.61, CI 3.82–15.15, $P < 0.001$), heart failure (AOR 2.80, CI 1.37–5.73, $P = 0.005$), and serum LDL-c with a cutoff level of 112 mg/dL (AOR 5.10, CI 3.04–8.57, $P < 0.001$). A scoring system from logistic regression analysis showed that a score of >1.7 may be interpreted as a risk factor AF. **Conclusion:** A scoring system from the risk factors can be used to predict the probability of AFDAS.

Keywords: *Atrial fibrillation, hemorrhagic stroke, ischemic stroke, scoring system for risk of AF*

Introduction

Several studies had explored the association between dysrhythmias after stroke, but they failed to meet the causal relationship.[1] Some dysrhythmias can also occur after brain tumors, seizures, and head traumas. A previous study stated that electrocardiogram (ECG) changes after brain ischemia and hemorrhage, subarachnoid hemorrhage, brain tumors, seizures, and head trauma manifested in 15–30% of cases, although these alterations could be incidental due to the similarity in the risk factors for stroke and coronary heart disease.[2]

In recent times, numerous studies have concentrated on identifying clinical indicators that could forecast atrial fibrillation (AF) detected after stroke (AFDAS), leading to the creation of several risk-scoring systems aimed at stratifying the risk for patients with stroke. Those risk-scoring systems include $CHADS_2$, CHA_2DS_2-VASc, and STAF. A Taiwanese study reported adding stroke severity and neuroimaging findings to the CHADS2 and CHA2DS2-VASc scores also significantly improved their ROC-AUC.[3]

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The CHADS2 score is determined by assigning 1 point each for age 75 or older, hypertension, diabetes mellitus (DM), and congestive heart failure (CHF) and 2 points for a previous stroke or TIA. The CHA2DS2-VASc score is calculated by giving 1 point each for age 65–74, hypertension, DM, CHF, vascular disease including coronary artery disease (CAD) and peripheral artery disease (PAD), and female sex and 2 points for a prior stroke or TIA and age 75 or older. Each score exhibited different ROC-AUC values in predicting AFDAS, ranging from 0.558 to 0.597 for CHADS2 and from 0.603 to 0.644 for CHA2DS2-VASc. The poor performance of CHADS2 and CHA2DS2-VASc may be due to the inclusion of DM, which is inversely associated with AFDAS risk. Additionally, both DM and AF elevate the risk of ischemic stroke. Consequently, in diabetic patients with ischemic stroke, the stroke might be more likely attributable to mechanisms such as large artery atherosclerosis or small vessel occlusion, rather than paroxysmal AF.[3]

The STAF score is calculated based on the patient's age, the National Institutes of Health Stroke Score (NIHSS) at admission, the presence of left atrial (LA) dilatation, and the absence of symptomatic intra- or extracranial stenosis and clinical-radiological lacunar syndrome. The STAF score demonstrates a sensitivity of 89% and a specificity of 88% for detecting AF. However, it requires detailed information on the intra- and extracranial vasculature.[4]

There are limited studies on the incidence and relationship of AF after stroke.[1,5–7] Therefore, this study aimed to determine the relationship between the risk factors for AFDAS. From them, we also try to propose a scoring system based on the analysis of the risk factors so that it might be used in the future to predict the possibility of stroke occurrence after AF.

Methods

Study design and setting

This retrospective cohort study was conducted from April to July 2023 at Dr. Moewardi General Hospital. The sample population comprised adult patients in the High Care Unit (HCU) who were diagnosed with stroke. Furthermore, the participants were selected using the consecutive sampling technique over a period of 1 year (2022).

The participants were adult patients diagnosed with ischemic or hemorrhagic stroke based on ICD-10 (International Classification of Diseases-10) with codes I.60–I.64 and AF according to ICD-10 with code I.48. The inclusion criteria were individuals aged 18–80 years, with brain computed tomography scan (CT-scan) reports, which showed the type, location, and volume of the lesion. An ECG examination result of AF should be provided, and the ECG examination was carried out after the diagnosis of stroke, during admission, or a few days after admission. Patients with known AF based on ICD-10 with code I.48 before admission or before the diagnosis of stroke were excluded.

Data collection

Data were obtained through medical records of patients undergoing critical care in the HCU. Furthermore, the data collected included history of comorbidities, ECG, and CT-scan reports. The risk factors for developing AFDAS investigated in this study included the type of stroke (ischemic or hemorrhagic); types of infarction stroke (lacunar, thrombus, embolism); stroke location; side of the lesion (right, left, or bilateral); hemorrhage volume; administration of neuroprotective, anti-inflammatory, antihypertensive, and lipid-lowering agents; and serum LDL levels.

Ethical considerations

Before the study, an approval was obtained from The Health Research Ethics Committee of Dr. Moewardi General Hospital issued in Surakarta 23 May 2023 with registered number 855/V/HREC/2023.

Data analysis

IBM SPSS Statistics version 26 for Windows (Armonk, NY: IBM Corp.) was used to analyze the collected data. They were sorted into nominal and numerical variables, which were presented in amounts (percentage) and average values ± standard deviation, respectively. Furthermore, factors associated with the AF were identified using binary logistic regression. Variables considered for the regression analyses included age; administration of neuroprotective, anti-inflammatory, antihypertensive, and lipid-lowering agents; serum LDL levels; and stroke location. The variables with $P < 0.25$ were further analyzed using a stepwise, multivariate, logistic regression analysis. When $P < 0.05$, the results were considered statistically significant.

Results

A total of 549 patients were admitted in this study, with 262 (47.7%) of them having AFDAS, while 287 (52.3%) had no AF. The elderly (55.9%) and women (52.1%) constituted the majority of the population. In this study, 161 patients from 305 patients with ischemic stroke (61.5%, $P = 0.008$) had AF, and the majority of them were of embolic type (77.1%, $P = 0.000$). Cerebral cortex locations (45.0%, $P < 0.001$) were also a significant risk factor for AF. In stroke with AF

group, the mean LDL-c serum level was 91.64 ± 0.34.45 (P < 0.001). The demographic characteristics of the patients are presented in Table 1.

The characteristics of the patients with the incidence of AF between individuals with ischemic and nonischemic stroke are presented in Table 2 and Figures 1-3.

In ischemic stroke patients, some risk factors such as age, history of antihypertensives, antilipids, neuroprotector administration, history of coronary heart disease, heart failure, heart valve disease, cardiomyopathy, and LDL-c levels were associated with the development of AFDAS (P < 0.05). Furthermore, patients with hemorrhagic stroke who have a hemorrhage volume between 10 and 30 ml were more likely to have AF, although this association was not significant (P = 0.223).

The relationship of ischemic stroke as a risk factor for AF was assessed using a multivariate logistic regression analysis. The assessment comprised characteristic variables with a P value of <0.250. The results of the multivariate analysis are presented in Table 3.

Table 1: Demographic characteristics of the patients

Variable		Total (n=549)		With AF (n=262)		Without AF (n=287)		P
		n	%	n	%	n	%	
Age	Young Adult¶	7	1.3%	3	1.1%	4	1.4%	0.002*
	Adult	55	10.0%	25	9.5%	30	10.5%	
	Old Adult	180	32.8%	66	25.2%	114	39.7%	
	Elderly	307	55.9%	168	64.1%	139	48.4%	
Gender	Woman	286	52.1%	137	52.3%	149	51.9%	0.930*
	Man	263	47.9%	125	47.7%	138	48.1%	
	Yes	67	12.2%	51	19.5%	16	5.6%	
LDL‡ Level	Mean±SD§	110.54±43.40		91.64±0.34.45		127.95±43.46		<0.001†
Lesion location	cerebral cortex	205	37.3%	118	45.0%	87	30.3%	<0.001*
	basal ganglia	156	28.4%	58	22.1%	98	34.1%	
	insula cortex	53	9.7%	38	14.5%	15	5.2%	
	midbrain	82	14.9%	34	13.0%	48	16.7%	
	CMA‖	53	9.7%	14	5.3%	39	13.6%	
Lesion Side	Right	225	41.0%	112	42.7%	113	39.4%	0.254*
	Left	176	32.1%	75	28.6%	101	35.2%	
	bilateral	148	27.0%	75	28.6%	73	25.4%	
Stroke	ischemic	305	55.6%	161	61.5%	144	50.2%	0.008*
	hemorrhagic	244	44.4%	101	38.5%	143	49.8%	

*Chi-Square Test (categorical data). †Mann–Whitney test (numerical data not normally distributed). ‡Low Density Lipoprotein, §Standard Deviation, ‖Cerebral Middle Artery. ¶Young adult (18-25 age), Adult (26-44 age), Old Adult (45-59 age), Elderly (≥60 age)[8]

Table 2: Characteristics of the patients with the incidence of AF between individuals with ischemic and nonischemic stroke

Variable		Ischemic					Hemorrhagic				
		With AF (n=161)		Without AF (144)		P	With AF (n=101)		Without AF (n=143)		P
		n	%	n	%		n	%	n	%	
Age	Young Adult‖	1	0.6%	3	2.1%	<0.001*	2	2.0%	1	0.7%	0.223*
	Adult	6	3.7%	15	10.4%		19	18.8%	15	10.5%	
	Old Adult	31	19.3%	59	41.0%		35	34.7%	55	38.5%	
	Elderly	123	76.4%	67	46.5%		45	44.6%	72	50.3%	
Gender	Woman	84	52.2%	66	45.8%	0.269*	53	52.5%	83	58.0%	0.389*
	Man	77	47.8%	78	54.2%		48	47.5%	60	42.0%	
LDL‡ Level	Mean±SD§	87.13±36.64		125.82±46.05		<0.001†	98.37±29.53		130.10±40.74		<0.001†
Hemorrhage volume	<10 mL						31	30.69%	43	29.9%	0.223
	10-30 mL						50	49.50%	74	51.4%	
	30 mL						20	19.80%	27	18.7%	
Ischemic stroke	Thrombotic	37	22.9%	103	71.5%	0.000					
	Embolism	124	77.1%	41	28.5%						

*Chi-Square Test (categorical data). †Mann–Whitney test (numerical data not normally distributed). ‡Low Density Lipoprotein, §Standard Deviation. ‖Young adult (18-25 age), Adult (26-44 age), Old Adult (45-59 age), Elderly (≥60 age)[8]

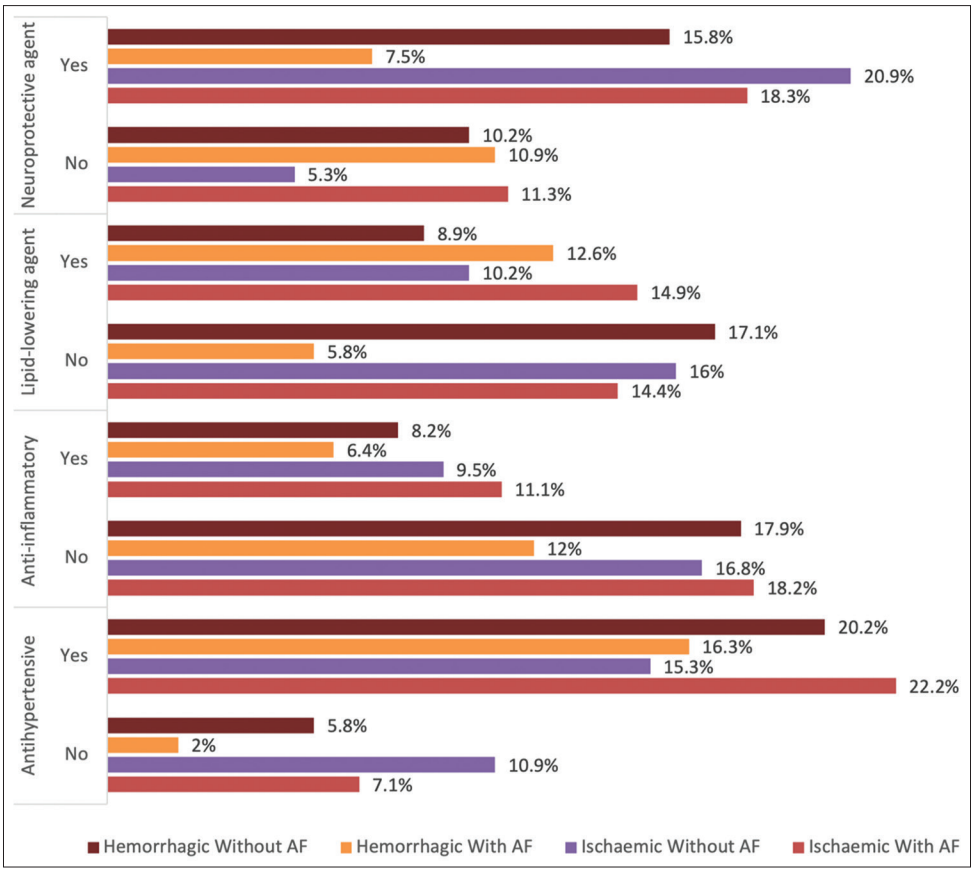

Figure 1: Frequency of use of medications in patients with stroke who developed AF

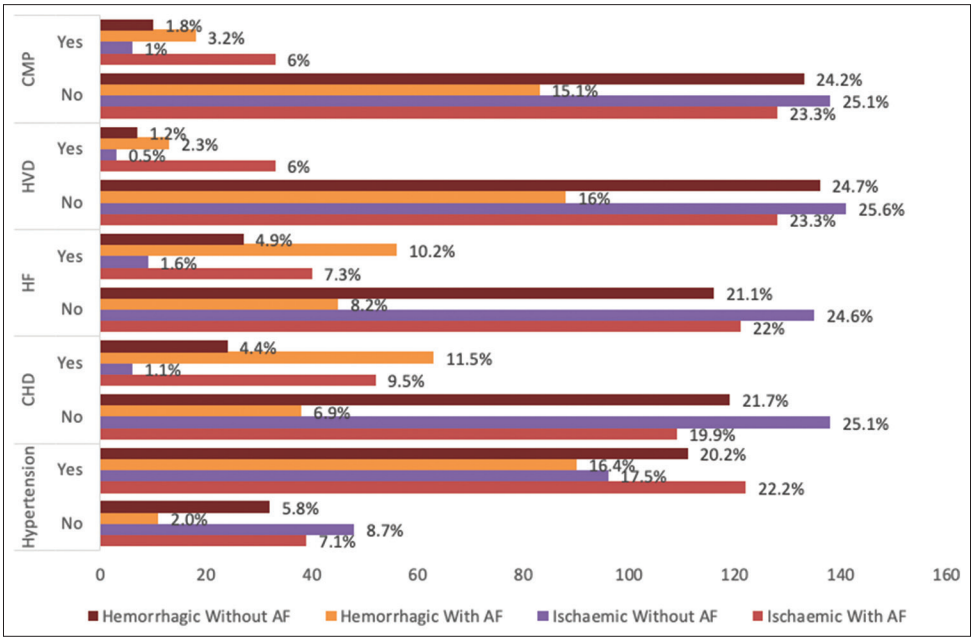

Figure 2: Frequency of comorbidities in patients with stroke who developed AF; CHD: coronary heart disease; HF: heart failure; HVD: heart valve disease; CMP: cardiomyopathy

The results showed ischemic stroke (OR = 4.12; P = <0.001) was a risk factor for AF. Patients with this condition were over 4 times more likely to suffer from AF compared with nonischemic (hemorrhagic) stroke. Other significant risk factors (OR>1) included elderly age, history of hypertension, coronary heart disease, heart failure, LDL level <112, and location of lesion in cerebral cortex and midbrain. Furthermore, our study

Table 3: Multivariate analysis of variables related to the incidence of atrial fibrillation

Variable		*P*	Adjusted OR*	95%CI†	
				Lower	Upper
Age§§	Young Adult	Ref			
	Adult	0.870	1.17	0.19	7.26
	Old Adult	0.206	3.12	0.53	18.19
	Elderly	0.771	1.30	0.23	7.44
Drugs	Antihypertensive	0.067	0.20	0.09	1.46
	Lipid-lowering agent	0.915	0.97	0.57	1.65
	Neuroprotective agent	<0.001‡‡	0.24	0.15	0.41
Comorbid	Hypertension	0.031‡‡	2.46	1.09	5.56
	CHD‡	<0.001‡‡	7.61	3.82	15.15
	HF§	0.005‡‡	2.80	1.37	5.73
	HVD‖	0.363	0.65	0.25	1.65
	CMP¶	0.931	0.96	0.36	2.54
LDL** Level <112		<0.001‡‡	5.10	3.04	8.57
Location	Cerebral cortex	0.003‡‡	2.34	1.35	4.06
	Basal ganglia	0.141	0.53	0.23	1.24
	Insula cortex	0.090	1.86	0.91	3.81
	Midbrain	0.056	1.89	0.92	3.79
	CMA††	Ref.			
Stroke	Ischemic	<0.001‡‡	4.12	2.40	7.07
	Hemorrhagic	Ref.			

*Odd Ratio, †Confidence interval, ‡Coronary Heart Disease, §Heart Failure, ‖Heart Valve Disease, ¶Cardiomyopathy, **Low Density Lipoprotein, ††Cerebral Middle Artery, ‡‡significance (P<0.05), §§Young adult (18-25 age), Adult (26-44 age), Old Adult (45-59 age), Elderly (≥60 age)[8]

Table 4: AF predictor scoring system

Variable	Score		Scoring
	Score 1	Score 0	
Stroke	Ischemic=1	Non-Ischemic=0	1.5
Neuroprotective agent	Yes=1	No=0	-1.4
HT*	Yes=1	No=0	0.9
CHD†	Yes=1	No=0	2.1
HF‡	Yes=1	No=0	1.1
LDL§ level (mg/dL)	<112=1	>112=0	1.7
Cerebral Cortex	Yes=1	No=0	0.9

*Hypertension, †Coronary Heart Disease, ‡Heart Failure, §Low Density Lipoprotein

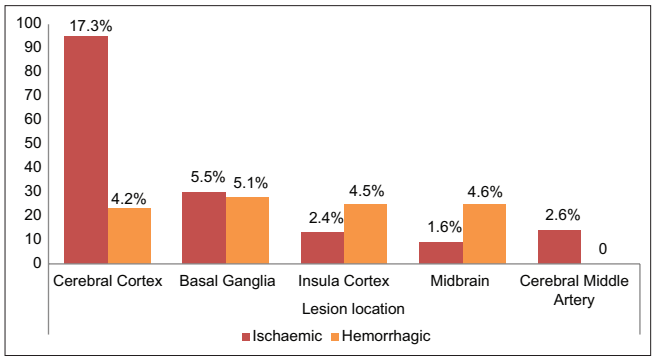

Figure 3: Frequency of anatomical site of stroke in patients with AF

showed that the use of antihypertensives, lipid-lowering agents, and neuroprotectants could be a protective factor for occurrence of AF.

The results of logistic regression analysis using the backward LR method showed a scoring system for variables that were significantly related to the incidence of AF using the formula below:

$$Y = \frac{EXP\ (\sum)}{1 + EXP\ (\sum)}$$ with Σ= 1.5 × ischemic stroke -1.4 × Neuroprotective agent + 0.9 × hypertension + 2.1 × coronary heart disease + 1.1 × heart failure + 1.7 × LDL level + 0.9 × cortex cerebri -1.7

Based on the results of the scoring system, when the result was >1.7, it could be a risk factor for AF. When the value obtained was <1.7, there was no risk of the condition. The AF predictor scoring system is presented in Table 4.

Discussion

This study showed that there was relationship between the type, location, volume, and therapy of ischemic and hemorrhagic stroke as risk factors for AF. Seven variables that contributed to AF occurrence were ischemic stroke, cerebral cortex location, administration of the neuroprotective agent, history of hypertension, coronary heart disease, heart failure, and serum LDL-c. It showed that ischemic stroke was more likely to cause AF compared to the hemorrhagic variant. This is similar to the report of a previous study that showed

that AFDAS was found in 23.7% of ischemic stroke and TIA patients.[1] Acute ischemia of the cerebral cortex, especially within the insula, often led to a major autonomic imbalance. Systemic inflammation played an important role in the occurrence of AFDAS through focal impulses (autonomic cascade) and re-entry circuits (atrial myocarditis) mechanism.[1]

The proposed mechanisms of AF in embolic ischemic stroke are significantly higher plasma levels of TNF-α, IL-1β, and IL-6, leading to AF and autonomic imbalance.[1] An infarct stroke volume >10 mL had a greater risk of transformation into hemorrhagic stroke,[9,10] with hemorrhagic stroke volume >30 mL having the worse prognosis.[11] The authors suggested that a larger intracranial hemorrhage corresponded to more tissue damage and clinical severity, resulting in more disturbance in cardiac autonomic function.[12] Another study of 650 patients with intracranial hemorrhage found that larger hematoma volume was associated with new-onset paroxysmal atrial fibrillation, although the authors stated that the underlying mechanism remains unclear.[13]

In other studies, the correlation between cortical involvement in stroke and AF is still conflicting; however, a study involving 755 stroke patients reported that cortical involvement was more frequent in patients who had AF.[14] Ischemic lesions of the insular cortex affected blood pressure control and triggered severe cardiac complications, such as arrhythmias and autonomic dysfunction.[6,15] Compared to noncortical areas, cortical stroke is more likely to be more symptomatic, in which autonomic regulation of cardiac rhythm is influenced by cerebral cortex and cortical infarction may lead to dysregulation of autonomic regulation and triggers AF.[16,17]

The right and left hemispheres helped in controlling the sympathetic and parasympathetic activity, respectively. In a clinical study of 103 patients with acute ischemic stroke, the occurrence of complex arrhythmias was more pronounced in individuals with right insular cortex infarction.[6] It is suggested that stroke in the right hemisphere was more arrhythmogenic and increased sympathetic activity.[18,19]

Based on the findings, there was a relationship between hypertension and coronary heart disease and development of AFDAS. The ageing heart offered an ideal environment for AF development by predisposing to "anatomic substrate" abnormalities. This was caused by various conditions, such as hypertension, ischemic heart disease, heart failure, valvular disease, and dilated/hypertrophic cardiomyopathy. Hypertension can contribute to increased risk of AF by inducing structural remodeling of the left atrium with excessive fibroblast proliferation, predisposing to left ventricular hypertrophy, stimulating apoptosis and inflammation of cardiac myocytes, activation of the renin-angiotensin-aldosterone system, and autonomic dysregulation. Hypertension is also associated with histopathological and atrial chamber abnormalities, leading to myocardial fibrosis and atrial dilatation as well as increased risk of AF.Click or tap here to enter text.[20,21] The increased pulse pressure may be an independent predictor of atrial stiffness, which presents as another modifiable AF risk element.Click or tap here to enter text.[22] The presence of CHD may generate re-entry formation, focal ectopic activity, and neural remodeling, which can promote the progression of AF through reparative fibrosis on dead cardiac mycocytes, local aseptic inflammation, and remodeling by the innate immune system.[23]

The use of neuroprotective agents could be a protective factor against the incidence of AF. Neuroprotective drugs, such as citicoline, edaravone, cerebrolysin, and minocycline had been reported to have beneficial effects on stroke.[24] Kuryata *et al*.[25] reported that citicoline, a neuroprotective agent, proved beneficial in AF, which may be mediated by increasing neuronal viability, axonal injury protection, decreasing reactive astrogliosis, preventing blood-brain integrity deficiencies, and reducing intensity of demyelination. Another study on rats found that intravenously injected CDP-choline can prevent cardiac arrhythmias and death by activation of the central muscarinic receptor and vagal pathway.[26]

The use of anti-inflammatory medications increased the risk of AF in ischemic stroke patients. The most likely cause was the intake of ketolorac and indomethacin. NSAIDs, including cyclooxygenase inhibitors, were widely used to treat inflammatory and painful conditions. History of using NSAIDs had also been associated with a higher risk of myocardial infarction, stroke, and heart failure.[27] Antihypertensive treatment with ARBs and ACEIs prevented the onset of nonvalvular AF, a common condition in people with hypertension and associated with a 5 times increased risk of embolic stroke.[28] A previous study reported that statins reduced the risk of recurrent stroke and death and also improved outcomes in patients with ischemic stroke.[29]

Another significant risk factor for stroke was dyslipidemia, which was implicated in the development of atherosclerosis and coronary heart disease and closely related to the development of AF. High LDL-c levels and low high density lipoprotein-cholesterol (HDL-c) levels were closely associated with the development of coronary

artery disease.[30] LDL-c levels, however, showed an inverse correlation with AF, as shown in a systematic review by Yao *et al*.,[31] which showed that higher levels of LDL-c were associated with lower risk of new-onset AF. The underlying mechanism of the paradoxical effects of LDL-c may be caused by the stabilizing effect of cholesterol on myocardial cell membranes, in which cholesterol may affect the regulation of ion channels and sensitivity of volume-regulated anion current to osmotic gradients. Reduced levels of cholesterol may also be reflective of an underlying inflammatory process.[32]

This study had several limitations, including the use of a small sample population. Therefore, further studies with larger and more representative sample sizes should be carried out. It was also necessary to examine other lipid profiles, such as HDL-c and triglycerides, to compare their effects as risk factors for AF in stroke patients. More specific types of medications and their relationship as risk factors for AF in affected individuals should also be studied.

Conclusion

In conclusion, embolic ischemic stroke was identified as a greater risk factor than hemorrhagic stroke for AF. Also, the cerebral cortex was the most affected location in causing AF. A scoring system (score >1.7) from the risk factor multivariate analysis can be used to predict the probability of AF occurrence after stroke, and it is easy to use in our clinical setting.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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