# Prognostic Impact of Atrial Fibrillation Pattern and other Clinical Biomarkers in Patients with Stroke Admitted in a Tertiary Hospital in Cebu City from 2015-2022

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## ABSTRACT

**Background.** The effect of atrial fibrillation (AF) patterns and clinical biomarkers among patients with AF-related stroke is still controversial.

**Objectives.** The objective of this study is to determine the association of the pattern of AF and markers on routine blood tests with the outcome of patients after an AF-related stroke.

**Methods.** This is a retrospective cohort study of patients with stroke and AF admitted in a tertiary hospital in Cebu City from 2015-2022. Patients' baseline characteristics, laboratory tests, ECG, and radiologic data were collected. Descriptive statistics such as mean and frequency were computed. The Kaplan–Meier method and the log-rank test were used to calculate the incidence time. The Cox regression analysis was used to determine factors associated with survival. A stepwise regression technique was used in model building.

**Results.** The mortality rate of patients with AF-related stroke was 0.02. A Kaplan Meier survival estimate shows that patients with paroxysmal AF have better survival. Upon model building of variables, age, red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), platelet count, low density lipid cholesterol (LDL-C), and pattern of AF were predictive of mortality in patients with AF-related stroke.

**Conclusions.** Among AF-related stroke patients admitted at a tertiary hospital in Cebu City, pattern of AF, age, RDW, NLR, platelet count, and LDL-C were associated with mortality. The parameters associated with increased mortality could be easily assessed using an ECG, CBC, and lipid profile. These are all readily available and cost-efficient.

*Keywords: atrial fibrillation, pattern, clinical biomarkers, prognosis, stroke*



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## INTRODUCTION

Cerebrovascular disease is associated with significant morbidity and death. In the Philippines, an estimated half a million people are affected annually by stroke. Currently, stroke is the third most common cause of mortality among Filipinos.[1] Locally, there are limited studies on stroke, atrial fibrillation (AF), and AF-related stroke.

Atrial fibrillation was noted to be one of the most frequent causes of ischemic stroke and this was associated with increased mortality. In patients with no obvious cause of stroke, paroxysmal atrial fibrillation was noted later on. Atrial fibrillation can be classified according to its pattern of occurrence: paroxysmal and permanent. The pattern of atrial fibrillation is a simple and quick way to assess patients' AF

burden without much examination. Though the effects of AF pattern and stroke risk had been investigated for several years, little is known of the association between the pattern of atrial fibrillation and AF-related stroke outcomes.[2] In addition, certain biological markers of inflammation have been evaluated to be predictors for atrial fibrillation; however, few studies have assessed the association of these markers with mortality in patients with AF-related stroke.[3] Although clinical characteristics are often used to prognosticate patients, this study would also like to look at clinical biomarkers as these blood tests are often routinely taken when a patient is admitted for stroke and atrial fibrillation. Up to this writing, no local data is available on atrial fibrillation patterns, markers of routine blood tests, and stroke outcomes. With limited studies on the epidemiology of stroke and atrial fibrillation in the Philippines, this study can add to our local health data and this analysis can improve patient care in our country.

## OBJECTIVES

This quantitative, retrospective cohort study aims:

(1) to compare the baseline characteristics (age, gender, body mass index, comorbidities) of patients by pattern of atrial fibrillation (paroxysmal versus permanent);
(2) to determine if there is an association between pattern of atrial fibrillation and mortality after a stroke;
(3) to determine if there is an association between pattern of atrial fibrillation and length of hospital stay after a stroke;
(4) to determine if there is an association between levels of red blood cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet count, uric acid, low density level cholesterol (LDL-C), high density level cholesterol (HDL-C), with survival.

### Definition of Terms

1. Ischemic stroke: This refers to an episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction.
2. Intracerebral Hemorrhage: This refers to the rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.
3. Hemorrhagic Infarction: This refers to a spectrum of ischemia-related brain hemorrhage and is a frequent complication of ischemic stroke especially after thrombolytic therapy.
4. Atrial Fibrillation: This is defined as an irregularly irregular heart rhythm.
    a. Paroxysmal Atrial Fibrillation: AF that is self-limiting and last shorter than one week.
    b. Permanent Atrial Fibrillation: AF lasting longer than one week without any intercurrent sinus rhythm.
7. Biomarker: Any characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

### Ethical Considerations

The protocol was submitted to the Ethics Review Board for review and approval. All the information gathered remained confidential and were used exclusively for this research. The study only involved review of the patient's medical abstract, discharge summary, medical chart, laboratory results, and CT scan/MRI results. No conflict of interest was involved in the study.

### Review of Related Literature

Stroke affects millions of people worldwide and is a cause of significant disability and death. Cardioembolic stroke accounts for 14-30% of all cerebral infarctions, with atrial fibrillation as the most common cause of cardioembolic stroke.[1] In approximately 25% of cases of ischemic stroke, no obvious cause of stroke can be found.[1] Recent observations have shown that paroxysmal atrial fibrillation could be responsible for a significant number of cryptogenic stroke events. A consensus definition for the classification of the temporal occurrence of atrial fibrillation (AF) is as follows: paroxysmal AF are self-limiting and last shorter than one week; persistent AF are episodes lasting longer than one week; and permanent AF refers to AF without any intercurrent sinus rhythm.[2]

### Patterns of Atrial Fibrillation

Previous studies on the relation between AF pattern and the risk of stroke have yielded conflicting results. Some trials did not report a significant difference between permanent and paroxysmal AF while other studies reported higher stroke rates in patients with permanent AF.[2] In addition, although cardioembolic stroke was shown to be associated with poor functional prognosis compared with other types of cerebral infarction, little is known of the outcome between patients with paroxysmal AF and permanent AF who had a stroke.[3] This study aims to assess the mortality rate and length of hospital stay in patients with stroke according to the type of AF.

### Markers of Routine Blood Tests

In recent years, biological markers (biomarkers) have been constituted as a very powerful tool in the early diagnosis, risk stratification, and prognosis prediction in many cardiovascular diseases. A number of studies have explored the role of biomarkers in non-valvular AF for the prediction or early diagnosis of ischemic stroke. Certain biological markers of inflammation have also been evaluated to be predictors for the pattern of atrial fibrillation; however, few studies have assessed the association of these markers with mortality in patients with AF-related stroke.[4]

It is believed that cerebral ischemia triggers an inflammatory response in both the brain and peripheral circulation, which leads to the up-regulation of inflammatory cytokines.[3] Increased circulating levels of inflammatory cytokines have been regularly associated with poor outcomes after stroke.[4] The complete blood count is one of the most frequently ordered laboratory tests in clinical practice. The red cell distribution width (RDW) is a quantitative measurement of differences in the size and volume of circulating red blood cells. An increased RDW reflects the existence of erythrocytopenia which is caused by impaired erythropoiesis or erythrocyte degradation, and this reflects an underlying chronic inflammation and high levels of oxidative stress. The clinical significance of RDW in stroke has not been comprehensively investigated owing to variations in sample populations and methodologies among current studies. Although, in one study, poor outcome in stroke is associated with a high baseline RDW.[5]

In a study by Shang et al., it was noted that the neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation and significantly correlated with $CHA_2DS_2$-VASC score in non-valvular AF. A high NLR has a predictive effect on the prognosis in stroke patients.[4] Also mentioned in the same study was the mean platelet volume (MPV) which correlates with the intensity of an inflammatory process and risk of thrombotic complications. High MPV was found to be a predictive marker for long term recurrent stroke and mortality after.[4]

Serum uric acid is another molecular indicator of inflammation and oxidative stress. It was suggested that serum uric acid impaired vascular tone and endothelial dysfunction contributing to ischemic changes.[6] Serum uric acid levels were also associated with all-cause mortality in patients with cardiovascular disease.

Dyslipidemia is an important predictor and therapeutic target of cardiovascular risk. An elevated low density lipid cholesterol (LDL-C)/high density lipid cholesterol (HDL-C) has been associated with an imbalance between atherosclerotic and anti-atherosclerotic components, and an increase in pro-inflammatory components, which may affect the development of ischemic stroke in AF and associated with post-stroke mortality.[4]

The clinical significance of these biologic markers in cerebrovascular disease will be assessed in this study.

## METHODS

### Study Design

This study was conducted using a retrospective, cohort design on adult patients admitted at Chong Hua Hospital from 2015-2022 for AF-related stroke.

### Study Population

The study included all patients >18 years old admitted at a tertiary hospital in Cebu City who were diagnosed with AF-related stroke.

### Inclusion Criteria

This study included all adult patients diagnosed with stroke due to AF. The diagnosis of stroke was done with imaging modalities. Atrial Fibrillation was diagnosed through ECG or 24-hour Holter monitoring.

### Exclusion Criteria

Patients with stroke who did not have AF.

### Sample Size

In a prospective, observational study by Hagii et al., a total of 358 patients with non-valvular atrial fibrillation were enrolled. Mortality and MRS scores at discharge were higher in the permanent atrial fibrillation than in the paroxysmal atrial fibrillation group (13% vs. 4%, respectively). It was estimated that a total of 511 patients with stroke due to atrial fibrillation will be enough to test the hypothesis at 80% power with a two-sided confidence interval of 95%.[7]

### Data Collection

The study was implemented upon approval of the protocol by the Hospital Institutional Review Board and the Office of the Medical Director.

The monthly census of the hospital's Internal Medicine Department from 2015-2022 was reviewed. Patients with a final diagnosis of atrial fibrillation and stroke were included in the study. Through review of the patient's medical chart, medical abstract, discharge summary, triage form, laboratory results, and brain imaging results, the following data were gathered: age, sex, body mass index (BMI), pre-admission medications, comorbidities, complete blood count (CBC), uric acid, cholesterol, electrocardiogram (ECG), and brain imaging findings.

### Data Analysis

The data were processed using STATA 20. Thirty patients who were discharged against medical advice and were transferred were not included from the list. Only the latest admission was considered for patients who had multiple admissions. Descriptive statistics such as mean, standard deviation, frequency, and proportions were computed to describe the demographic and clinical profile of the patients. We used the Kaplan–Meier method and the log-rank test to calculate the incidence time and compared among different groups of patients. The Cox regression analysis was used to determine factors associated with survival. A stepwise regression technique was used in model building. We considered covariates with a p-value of less than 0.20 in the bivariate analysis as a potential candidate for multivariate Cox regression analysis. During Model building, variables with a P-value of less than 0.10 were considered statistically significant.

## RESULTS

Baseline characteristics of patients with paroxysmal and permanent atrial fibrillation are shown in Table 1. Among the 488 patients included in the study, the mean age for both paroxysmal and permanent atrial fibrillation was 70 years old. For both groups, there were more male patients, majority were Filipinos, with a normal BMI, who were hypertensive and non-diabetic. Majority of the patients were non-smokers and non-alcohol drinkers. Regardless of the type of AF, the most prevalent neurologic symptom was aphasia, followed by changes in sensorium, and changes in memory.

### Incidence Rate

A total of 5,506 person-years of analysis time has been recorded. The maximum length of stay varied from 1 day to 168 days with a mean of 11.3 days. The mortality rate due to stroke was 0.02.

There were lower incidence rates for survival in patients with permanent AF, females, and Filipinos as shown in Table 2. The median survival time for paroxysmal group is 49 days while permanent atrial fibrillation has median survival time of 37 days. The median survival time for males is 49 days while females have median survival time of 27 days. The median survival time for Filipinos is 37 days while for other ethnicity, the median survival time is 13 days.

**Table 1.** Comparison of the Baseline Characteristics across Patterns of Atrial Fibrillation

| | Paroxysmal AF (n = 322) | Permanent AF (n = 166) | Total AF (N = 488) |
|---|---|---|---|
| ***Outcome*** | | | |
| Alive | 250 (77.7%) | 133 (80.1%) | 383 |
| Death | 72 (22.3%) | 33 (19.87%) | 105 |
| ***Length of Time*** | 11.5 ±13.7 (9.9, 13.0) | 10.9 ± 12.1 (9.1,12.8) | 11.3 ±13.4 (10.1, 12.5) |
| ***Baseline Characteristics*** | | | |
| Age | 70.3 ±11.8 (CI 69.0, 71.6) | 71.1 ±13.3 (CI 69.1, 73.1) | 70.6 ± 12.4 (CI 69.5, 71. 7) |
| Sex | | | |
| Male | 176 (55%) | 92 (55%) | 268 |
| Female | 146 (45%) | 74 (45%) | 220 |
| Ethnicity | | | |
| Filipino | 317 | 163 | 480 |
| Others | 5 | 3 | 8 |
| Body Mass Index | 24.8 ± 4.3 (24.3, 25.3), n=305 | 24.7 ± 4.0 (24.1, 25.3), n=159 | 24.8 ± 4.2 (24.4, 25.3) |
| ***Clinical Data*** | | | |
| Hypertension (HTN) | | | |
| With HTN | 262 (81%) | 138 (83%) | 400 |
| Without HTN | 60 (19%) | 28 (17%) | 88 |
| Diabetes Mellitus (DM) | | | |
| With DM | 109 (34%) | 55 (33%) | 164 |
| Without DM | 213 (66%) | 111 (67%) | 324 |
| ***Complete Blood Count*** | | | |
| RDW (NV: 11-16) | 14.1 ± 1.6 (13.9, 14.3), n=308 | 14.0 ± 1.8 (13.7,14.3), n=153 | 14.1 ± 1.6 (13.9,14.2) |
| NLR (NV: 1.5-2.1) | ± 6.21 (6.1, 7.5), n=318 | 7.6 ± 10.8 (5.9, 9.2), n=161 | 7.1 ±7.9 (6.3,7.8) |
| Platelet (NV:130-400) | 217.7 ±75.2 (209.4, 225.9), n=318 | 221.7 ± 88.2 (208.0, 235.5), n=161 | 219.0 ± 79.7 (211.9, 226.2) |
| Uric Acid (NV:3-8) | 6.5 ±2.5 (6.0, 7.0), n=95 | 7.5 ± 3.2 (6.6, 8.5), n=45 | 6.8 ± 2.8 (6.4, 7.3) |
| LDL-C (NV: 0-150) | 99.7 ±40.7 (94.5, 104.8), n=243 | 93.5± 38.3 (86.4,100.6), n=115 | 97.7 ±40.0 (93.5, 101.8) |
| HDL-C (NV: 35-65) | 45.9 ±25.2 (42.7,49.1), n=243 | 46.6 ±17.7 (43.3,49.9), n=115 | 46.1 ±23.0 (43.7,48.5) |

**Table 2.** Incidence Rates of Death Stratified by Variables

| | Time at risk | Incidence rate | Number of subjects | Survival Time | | |
|---|---|---|---|---|---|---|
| | | | | 25% | 50% | 75% |
| ***Pattern*** | | | | | | |
| Paroxysmal AF | 3,703 | .0194437 | 322 | 14 | 49 | 79 |
| Permanent AF | 1,813 | .0182019 | 166 | 14 | 37 | 75 |
| ***Sex*** | | | | | | |
| Male | 2,939 | .0193944 | 268 | 14 | 49 | 64 |
| Female | 2,577 | .0186263 | 220 | 14 | 27 | 79 |
| ***Ethnicity*** | | | | | | |
| Filipino | 5,457 | .0186916 | 480 | 14 | 37 | 75 |
| Others | 59 | .0508475 | 8 | 13 | 13 | 23 |

As seen on Figure 1, a Kaplan Meier survival estimate showed that patients with paroxysmal atrial fibrillation have better survival.

As shown in Table 3, age, RDW, NLR, platelet count, LDL-C had a p value of 0.2 and were considered for multivariate COX regression analysis.

Upon model building of variables (Table 4), age, RDW, NLR, platelet count, LDL-cholesterol, and pattern of atrial fibrillation were predictive of mortality in patients with AF-related stroke.

## DISCUSSION

In a study by Talamera et al., the mortality rate of stroke in the Philippines was 3.9%. This study included both AF- and non-AF-related stroke patients.[8] Local studies on stroke have yet to specify the mortality rate of AF-related stroke. Our study found that mortality rate of patients with AF-related stroke admitted in a tertiary hospital in Cebu City from 2015-2022 was 0.02.

The effect of the AF pattern on outcomes has been controversial for nearly two decades. Furthermore, there were few data in the Asian, specifically the Filipino population. Our study noted that patients with paroxysmal atrial fibrillation had better survival compared to those with permanent atrial fibrillation. Our study was in line with the results reported in one study done in China.[9] They noted that the risk of all cause death increased from paroxysmal to permanent atrial fibrillation. They further noted that AF progression significantly increased the risk of adverse events. However, with oral anticoagulation, post stroke mortality rate was decreased and in one study, this rate was halved.[10]

In our study, the variables predictive of mortality in patients with AF-related stroke were age, RDW, NLR, platelet count, LDL-C, and atrial fibrillation pattern.

The average age of our patient population was 70 years old and age was noted to be associated with mortality in stroke according to our study. This age was older compared to the mean age of 64 years old observed in a global survey evaluating patients with atrial fibrillation and stroke. It is known that the risk of stroke and death is strongly associated with age and concomitant comorbidities.[1]

In our study, the mean RDW was 14.1, a level on the higher range of normal. As cytokines are released during stroke induced-inflammation, erythropoiesis and erythropoietin production are affected. An increased RDW reflects the existence of erythrocytopenia and a higher RDW has a positive association with plasma inflammatory biomarkers. Higher RDW, even within the normal range, may worsen the inflammatory state in stroke, leading to worse outcomes following ischemic stroke.[5,11,12]

Our study showed that an elevated NLR was associated with mortality in patients with stroke. It was noted in the study by Shang et al. that the NLR is a marker of systemic inflammation and significantly correlated with $CHA_2DS_2$-

**Table 3.** Summary of Univariate Analysis of the Clinical Factors Associated with Mortality in Patients with AF-related Stroke

| Variables | -2LogL | P value |
|---|---|---|
| ***Null*** | -302.12 | |
| ***AFIB Pattern*** | -302.08 | 0.7807 |
| ***Age*** | -301.52 | 0.2700 |
| ***Sex*** | -302.07 | 0.7615 |
| ***Ethnicity*** | -300.90 | 0.1178 |
| ***BMI*** | -277.74 | 0.4820 |
| ***Hypertension*** | -301.90 | 0.5104 |
| ***Diabetes Mellitus*** | -302.11 | 0.8840 |
| ***Complete Blood Count*** | | |
| RDW | -284.15935 | 0.0739 |
| Neutrophil | | |
| Lymphocyte | | |
| NLR | -294.26727 | 0.0002 |
| ***Platelet*** | -300.39284 | 0.1696 |
| ***Uric Acid*** | -91.484384 | 0.8306 |
| ***LDL-C*** | -181.82277 | 0.0267 |
| ***HDL-C*** | -184.19018 | 0.6780 |

*Level of significance: 20%*

**Table 4.** Model Building of Variables

| | | -2LogL | p value |
|---|---|---|---|
| ***Model 1*** | Age + RDW + NLR + PLT + LDL-C | -173.63 | 0.0322 |
| ***Model 2*** | **Age + RDW + NLR +PLT + LDL-C + AFIB Pattern** | **-171.95** | **0.0600** |
| ***Model 3*** | Age + RDW + NLR + PLT + LDL + Pattern + HTN | -171.88 | 0.1738 |
| ***Model 4*** | Age + RDW+ NLR + PLT + LDL + HTN | -173.47 | 0.6054 |

*Level of significance: 90%*

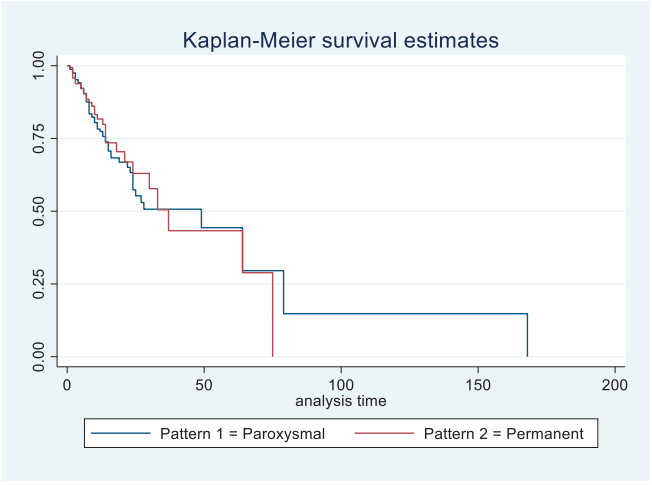


**Figure 1.** Kaplan Meier survival estimates between patients with paroxysmal and permanent atrial fibrillation.

VASC score in non-valvular AF. As there is an association with $CHA_2DS_2$-VASC score and NLR, and a higher $CHA_2DS_2$-VASC score is associated with stroke severity, thus a high NLR may be predictive of poor outcome in AF related stroke.[4]

In our study, majority of the patients were on statin medications with levels of low-density lipoprotein cholesterol below 100 mg/dl. Low LDL cholesterol levels were associated with a more than 20-year risk of cardiovascular and all-cause mortality.[9] An inverse relation between stroke severity and cholesterol levels exists.[12] Cholesterol plays a more prominent role in the development of small vessel disease of the brain and less severe stroke.

Our study showed that a mean platelet count of 219 x $10^9$/L was associated with mortality. In a study by Yang et al., patients with a platelet count above 186–212 × $10^9$/L was significantly associated with worse clinical outcomes. They noted that highly reactive and numerous platelets presented a greater risk for pro-thrombotic and pro-inflammatory states.[13]

In our study, the median number of days spent in the hospital after AF-related stroke was 11 days. In a study by Goette et al., the median number of nights spent in the hospital per year for patients with atrial fibrillation with a $CHA_2DS_2$-VASc ≥2 was 4 days. In patients with AF-related stroke, the length of hospital stay is noted to be longer.[14]

### Limitations of the Study

Some clinical data such as the $CHA_2DS_2$-VASC score, NIHSS score, MRS score were not included as these were not available for all patients. This study also did not consider the COVID-19 status of the patient. Also, not all patients had 24-hour Holter monitoring thus the diagnosis of atrial fibrillation may have been missed.

## CONCLUSION

There are limited studies on the epidemiology of AF-related stroke in the Philippines. Our study noted a mortality rate of 0.02 for patients with AF-related stroke. Patients with stroke and paroxysmal atrial fibrillation had better survival compared to stroke patients with permanent AF. Other variables predictive of mortality in patients with AF-related stroke based on our study were age, red cell distribution width, neutrophil-lymphocyte ratio, platelet count, and low-density level cholesterol. Up to this writing, no local data has been published on AF-related stroke outcomes. The parameters associated with increased mortality could be easily assessed using an ECG, CBC, and lipid profile.

### Recommendations

We recommend that further studies be done on patients with non-AF related stroke and their outcomes, and to compare this data with our findings on AF-related stroke. We also recommend that clinical data including $CHA_2DS_2$-VASC score, MRS score, and NIHSS score be included in future studies.

### Statement of Authorship

SMSI contributed in the acquisition and analysis of data, and drafting and revising of manuscript. MTAC contributed in the conceptualization of work and final approval of version to be published.

### Author Disclosure

Both authors declared no conflicts of interest.

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None.

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