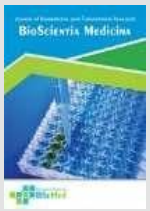
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Differences in Clinical Characteristics of Patients with Valvular and Non-Valvular Atrial Fibrillation

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ARTICLE INFO

Keywords:
Atrial fibrillation
Mitral stenosis
Non-valvular
Rheumatic heart disease
Valvular

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v6i17.718

A B S T R A C T

Background: There is an increasing global prevalence of atrial fibrillation (AF), including in Indonesia. Based on the presence of mitral stenosis and/or prosthetic valve, AF is divided into two groups, namely valvular AF and non-valvular AF. The differences in clinical characteristics between valvular and non-valvular AF in Indonesia, especially in Semarang, have not been described. This study aimed to determine the differences in clinical characteristics between valvular and non-valvular AF in Semarang. **Methods:** This study was an observational analytic study with a cross-sectional design and was performed in July-August 2020. The subjects were 54 AF patients, which were divided into two categories, namely valvular (n=28) and non-valvular (n=26) AF. The data were collected from medical records. The differences between the two groups were analyzed with bivariate analysis. **Results:** The patients with valvular AF were predominantly female (82.1% vs 69.2%; p <0.001), of a younger age (46.54 ± 12.20 vs 61.04 ± 8.68; p <0.001), more likely to have rheumatic heart disease (46.4% vs 3.8%; p <0.001), and have had heart surgery (57.1% vs 0%; p <0.001). The patients with non-valvular AF were more likely to have hypertension (17.9% vs 80.8%; p <0.001), myocardial infarction (0% vs 19.2%; p = 0.021), dyslipidemia (7.1% vs. 42.3%; p = 0.003), and higher BMI (21.03 ± 4.16 vs 25.48 ± 4.20; p <0.001). The INR values in most of the AF patients have not reached the target. The valvular AF patients were more likely to be taking warfarin (100% vs 80,8%, p=0,021) and diuretic therapy (96,4% vs 57,7%, p=0,001). **Conclusion:** There are significant demographic and clinical characteristics differences between valvular and non-valvular AF.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is a major health burden worldwide. The prevalence of AF in Indonesia was 7.1% in 2010 and kept steadily increasing year by year to 9.0% (2011), 9.3% (2012), and 9.8% (2013). Atrial fibrillation is associated with an increased risk of myocardial infarction, strokes, sudden cardiac death, heart failure, chronic kidney disease, peripheral artery disease, and death. The risk of stroke in AF patients is six times higher than in the population without AF.[1-5]

Based on the presence of mitral stenosis or prosthetic valve, AF is divided into two groups, namely valvular AF and non-valvular AF. Mitral valve stenosis is a common complication in patients with rheumatic heart disease (RHD). Rheumatic heart disease results from valve damage caused by an abnormal immune response to group A beta haemolyticus *Streptococcus* (GABHS) infection. It remains a cause of mortality and morbidity in developing countries.[6,7]

The global prevalence of AF continues to increase, including in Indonesia. This is followed by high mortality and morbidity of AF, both valvular and non-valvular AF. Based on the research that has been performed before, there are differences in the clinical characteristics of valvular and non-valvular AF patients.[8] This study was conducted in Kenya, East Africa. In contrast, a similar study in Indonesia had never been performed, and the differences in characteristics between valvular and non-valvular AF in Indonesia, especially in Semarang, have not been described. This study aimed to determine the differences in demographic and clinical characteristics between valvular and non-valvular AF patients as well as the appropriate therapy for corresponding patients in Semarang, Central Java.

2. Methods

This study was an observational analytic study with a cross-sectional design and was performed in July-August 2020. The subjects of this study were AF patients who underwent treatment at the cardiac polyclinic of Diponegoro National Hospital and Dr. Kariadi General Hospital Semarang. The inclusion criteria of this study were AF patients with complete medical records data. The diagnosis of non-valvular AF was made by excluding mitral stenosis and/or prosthetic valve through medical history and echocardiogram. The subjects were divided into two groups, the valvular AF group, and the non-valvular AF group. In this study, the sampling technique was carried out by consecutive sampling, and a total of 54 AF patients were assigned as the study subjects. Of the 54 AF patients, there were 28 valvular AF patients and 26 non-valvular AF patients. This research has been approved by the Ethical Commission for Medical and Health Research, Faculty of Medicine, Universitas Diponegoro (Ref. Number: 59/EC/KEPK/FK-UNDIP/V/2020).

The demographic and clinical characteristics and the therapy were compared between valvular and non-valvular AF patients. Descriptive statistics for numeric variables are expressed as mean ± standard deviation [SD] (min-max), while categorical variables are expressed as frequency and percentage. The data obtained were tested for data normality with Shapiro-Wilk to see the distribution of the data. To analyze the differences between groups, data with interval and ratio scales normally distributed, including age and heart rate data, were tested using a parametric unpair T-test. Data that were not normally distributed, including SBP, DBP, body mass index (BMI), creatinine, and international normalized ratio (INR) data, were tested with a non-parametric Mann-Whitney U test. Chi-square tests were performed on gender, hypertension, RHD, dyslipidemia, heart surgery, beta blocker, digoxin, ACE inhibitor, ARB, diuretic, and CCB data. Data that did not meet the requirements for the Chi-square test, including thyroid disease, IM, warfarin, aspirin, and antiplatelet data, were tested using Fisher's exact test. $P<0.05$ was considered statistically specific. Statistical analysis was performed using IBM SPSS version 25.

3. Results

Demographic and clinical characteristics

The characteristics of valvular and non-valvular AF patients are shown in Table 1. The valvular AF patients, compared with the non-valvular AF patients, were significantly younger, more often females, and had a history of rheumatic heart disease and heart surgery. The valvular AF patients were less likely to have hypertension, myocardial infarction, and dyslipidemia. The creatinine levels, BMI, systolic blood pressure, and diastolic blood pressure were higher in non-valvular AF patients. Meanwhile, the INR was higher in non-valvular AF patients. The mean CHA2DS2-VAS score of non-valvular AF patients was 3 ± 2.

Therapeutic characteristics

Prescription of beta-blocker, digoxin, ACE inhibitor, ARB, and antiplatelet therapy was similar between the two groups. Warfarin therapy and diuretics were more prevalent in valvular AF patients. Meanwhile, aspirin and CCB therapy were more

prevalent in non-valvular AF patients. Sixteen valvular AF patients had a history of heart surgery for valve replacement or valve repair. The mean INR in this study was 1.52 ± 0.61. The mean INR of valvular AF patients was higher, but both were in the sub-therapeutic range. Of the 28 valvular AF patients and 26 non-valvular AF patients, 71.4% vs 88.5% were in the sub-therapeutic range (<2.0), 25% vs 11.5% in the therapeutic range (2.0-3.0) and 3.6% vs 0% above the therapeutic range (>3.0).

Table 1. Characteristics of valvular and non-valvular atrial fibrillation patients.

Variables	Atrial fibrillation		p
	Valvular	Non-valvular	
Demographics			
Gender			
Male	5 (17,9%)	18 (69,2%)	<0,001†*
Female	23 (82,1%)	8 (30,8%)	
Age	46,54 ± 12,20	61,04 ± 8,68	<0,001§*
Medical history			
Heart failure	27 (96,4%)	21 (80,8%)	0,080£
Hypertension	5 (17,9%)	21 (80,8%)	<0,001†*
RHD	13 (46,4%)	1 (3,8%)	<0,001†*
Thyroid disease	1 (3,6%)	0 (0%)	0,519¶
IM	0 (0%)	5 (19,2%)	0,021¶*
Dyslipidemia	2 (7,1%)	11 (42,3%)	0,003†*
Heart surgery	16 (57,1%)	0 (0%)	<0,001†*
Clinical characteristics			
SBP	115,54 ± 17,78	129,42 ± 24,59	0,013‡*
DBP	71,75 ± 9,97	79,23 ± 12,69	0,022‡*
Heart rate	79,29 ± 11,35	86,69 ± 17,33	0,072§
CHA2DS2-VAS score		3,27 ± 1,80	–
BMI	21,03 ± 4,16	25,48 ± 4,20	<0,001‡*
< 18,5	8 (28,6%)	1 (2,8%)	0,003†*
18,5 – 25,0	16 (57,1%)	11 (42,3%)	
> 25,0	4 (14,3%)	14 (53,8%)	
Laboratories values			
Creatinine	0,99 ± 0,27	1,33 ± 0,77	0,006‡*
INR	1,69 ± 0,63	1,34 ± 0,54	0,008‡*
< 2,0	20 (71,4%)	23 (88,5%)	0,254†
2,0 – 3,0	7 (25%)	3 (11,5%)	
> 3,0	1 (3,6%)	0 (0%)	
Therapy			
Beta-blocker	21 (75%)	20 (76,9%)	0,869†
Warfarin	28 (100%)	21 (80,8%)	0,021¶*
Aspirin	0 (0%)	5 (19,2%)	0,021¶*
Digoxin	16 (57,1%)	11 (42,3%)	0,276†
ACE-inhibitor	7 (25%)	11 (42,3%)	0,178†
ARB	9 (32,1%)	10 (38,5%)	0,627†
Diuretic	27 (96,4%)	15 (57,7%)	0,001†*
CCB	1 (3,6%)	11 (42,3%)	0,001†*
Antiplatelet	3 (10,7%)	4 (15,4%)	0,457¶

* Significant (p < 0,05); § Independent t; ‡ Mann Whitney; † Pearson chi-square; ¶ Fisher's exact RHD = Rheumatic heart disease; MI = Myocardial Infarction; CHA_2DS_2-VAS score = Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, Stroke, Vascular disease, Age 65-74, Sex category female; BMI = Body Mass Index; INR = International Normalized Ratio; ACE-inhibitor = Angiotensin Converting Enzyme Inhibitor; ARB = Angiotensin Receptor Blocker; CCB = Calcium Channel Blocker.

4. Discussion

Based on gender, valvular AF patients were more often females than males. The mean age of this group was 46.54 ± 12.20, which was significantly younger than non-valvular AF patients, consistent with a study by Temu et al., which showed that valvular AF is more common in females than males, and of younger age. This is because the incidence of rheumatic fever is highest at the age of 5-14 years. Rheumatic fever can progress to chronic RHD with a peak prevalence at the age of 25-45 years and cause mitral stenosis complications. The prevalence of mitral stenosis is higher and continues to increase in female patients.[8-12]

The incidence of heart failure in AF patients, both valvular and non-valvular AF, was relatively high. This is in contrast to the results of a study conducted by Temu et al., which stated that the prevalence of heart failure was higher in non-valvular AF. Heart failure in valvular AF patients was mostly caused by mitral stenosis. In mitral stenosis patients, the narrowing of the valve causes the left ventricle to be unable to fill maximally. This results in a decrease in cardiac output and progresses to congestive heart failure.[8,12]

The prevalence of hypertension, myocardial infarction, and dyslipidemia was higher in non-valvular AF patients. Following previous studies, hypertension is a risk factor for non-valvular AF and less common in valvular AF. Myocardial infarction and dyslipidemia can be risk factors for AF through the mechanism of structural changes and left atrial fibrosis. A systematic review conducted by Violi et al. regarding non-valvular AF stated that AF patients have a significant risk of myocardial infarction despite receiving anticoagulant therapy.[8,13-14]

Rheumatic heart disease (RHD) and a history of heart surgery were more common in valvular AF patients. RHD is a sequence of rheumatic fever caused by group A beta haemolyticus *Streptococcus* (GABHS) infection and often causes mitral valve stenosis complications. This is what underlined RHD being more common in valvular AF patients compared to non-valvular AF patients. In this study, all heart surgery carried out by the subjects was heart valve surgery, either replacement or repair. This has been linked to heart valve abnormalities, including mitral stenosis and prosthetic heart valves.[6,7]

This study did not show any significant differences in the characteristic of thyroid disease between both valvular AF and non-valvular AF patients. There was only one subject with thyroid disease in this study. This subject was a non-valvular AF patient.

The characteristics of systolic and diastolic blood pressure between valvular and non-valvular AF patients showed significant differences. Although the average blood pressure of non-valvular AF patients cannot be categorized as hypertension, this group's average blood pressure tends to be higher than valvular AF patients. This is slightly different from the study conducted by Temu et al., which stated a significant difference in the systolic pressure, but there was no significant difference in the diastolic pressure. This difference in blood pressure is thought to be related to the higher incidence of hypertension in non-valvular AF patients, so the blood pressure tends to be higher despite being on medication.[8]

This study showed no significant difference in heart rate between valvular and non-valvular AF patients. Both groups showed an average heart rate within normal limits, 80 ± 11 vs. 87 ± 17. This suggests that most of the subjects, both valvular and non-valvular AF patients, have a normal ventricular response.

The mean CHA2DS2-VAS score of non-valvular AF patients in this study was 3 ± 2, with a range of 0-8. The CHA2DS2-VAS score is a scoring system used as consideration for prescribing anticoagulant therapy in non-valvular AF patients based on the risk of stroke.[15] A mean score of 3 ± 2 indicated that most non-valvular AF patients observed in this study were at risk of stroke and were more recommended to receive anticoagulant therapy.

The BMI of non-valvular AF patients was mostly above normal, and the mean BMI of this group was higher than valvular AF patients. Being overweight is associated with AF through the mechanism of hemodynamic changes and the role of adipose tissue,

inflammation, fibrosis, and electrophysiological changes. Also, being overweight is associated with various cardiovascular diseases, which are the risk factors for non-valvular AF.[16]

The creatinine levels of non-valvular AF patients were above the reference creatinine level. The creatinine levels in this group were higher than in valvular AF patients. Creatinine level is one of the parameters for assessing kidney function. In decreasing kidney function, the increase in creatinine level is caused by a decrease in creatinine clearance by the kidneys. However, creatinine levels are not only determined by kidney function but are also affected by age and body muscle mass.[17]

The mean INR of valvular AF patients tended to be higher than non-valvular AF patients. Nonetheless, most of the subjects in both groups were in the sub-therapeutic range (<2.0). This indicates that anticoagulant therapy in both groups has not reached the recommended target INR to achieve a balance between reduced risk of stroke and bleeding control. INR in the sub-therapeutic range indicates that the patients are at risk for stroke. The study conducted by Urbonas et al. showed that most of the AF patients on anticoagulant therapy had INR in the sub-therapeutic range. The sub-therapeutic INR is mostly caused by inadequate anticoagulant therapy. Wittkowsky's study suggested that INR in the sub-therapeutic range may be due to response to dose changes, non-adherence or inappropriate doses, and initiation therapy. Other things that can affect INR include medication changes, the patient's medical condition, vitamin K intake, alcohol use, and the patient's activity level. However, the cause in some patients cannot be determined.[18-19]

Warfarin and diuretics therapy were more prevalent in valvular AF patients. Meanwhile, aspirin and CCB therapy were more prevalent in non-valvular AF patients. The most widely used stroke prevention therapy in this study was warfarin. Warfarin was used by all valvular AF patients in this study. This corresponds to the AF therapy guideline indicating the use of warfarin in all valvular AF patients because of the higher risk of stroke. Aspirin was only used by 9.3% of the total study subjects. Subjects on aspirin therapy were non-valvular AF patients with CHA2DS2-VAS scores ≤ 2 in females and ≤ 1 in males. Another therapy used in this study was antiplatelets, such as clopidogrel. Only a small proportion of the research subjects received antiplatelet therapy. Subjects who use antiplatelet therapy have a history of IHD or PCI and thus require a combination of anticoagulant and antiplatelet therapy.[15]

5. Conclusion

There are differences in characteristics between valvular AF and non-valvular AF patients in Semarang, Central Java. There are also differences in warfarin, aspirin, diuretics, and CCB therapy. Most AF patients, both valvular and non-valvular, have INR in the sub-therapeutic range therefore, it is necessary to evaluate anticoagulant therapy for the prevention of stroke complications in patients with AF.

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