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ORIGINAL ARTICLE

Prevalence of Atrial Fibrillation in Patients With end Stage Renal Disease

Maria da Graça Lepre Hawerroth,[1] Lucas Yuji Sonoda,[1] Jean José Silva,[2] Walter Alvarenga de Oliveira[2]

Universidade do Estado de Minas Gerais,[1] Passos, MG – Brazil
Santa Casa de Misericórdia de Passos,[2] Passos, MG – Brazil

Abstract

Background: Atrial fibrillation (AF) is the most common arrhythmia in patients with end-stage renal disease (ESRD). The coexistence of high thromboembolic and hemorrhagic risks, added to the lack of strong scientific evidence on the safety of anticoagulants in the setting of renal failure, makes this a clinically challenging situation.

Objectives: To describe the clinical-demographic profile and prevalence of AF in the population with ESRD undergoing dialysis. Secondary objectives include the assessment of thromboembolic (CHA_2DS_2VASC) and bleeding (HASBLED) risk scores.

Methods: Cross-sectional analytical-descriptive study, carried out between January and March 2020. Patients with ESRD were evaluated by means of a medical history questionnaire, physical examination, and 12-lead electrocardiogram. A chi-square ($\chi 2$) association test was applied to calculate association between clinical variables and AF, with a significance level of $\alpha = 0.05$.

Results: This study evaluated 295 patients, most of whom were men (170), elderly (63, IQR 53-71), current smokers (130), with associated cardio-endocrine comorbidities. The prevalence of AF was 6.7% (20). Heart failure (HF) ($\chi 2$=15.417; p<0.001), age of 65 years or older ($\chi 2$=14.584; p<0.001), and anticoagulation ($\chi 2$=5.715; p<0.01) were associated with AF. The median CHA_2DS_2VASC and HASBLED was 4 and 3, respectively. Eight patients were taking warfarin and five were receiving apixaban.

Conclusion: The prevalence of AF in this study is similar to that reported in other published articles on the subject, and patients were at high risk for cardiovascular outcomes. Non-anticoagulation strategy was commonly adopted due to controversies in the literature as well as the absence of published randomized clinical trials.

Keywords: Atrial fibrillation; chronic renal insufficiency; renal dialysis.

Mailing Address: Maria da Graça Lepre Hawerroth
Universidade do Estado de Minas Gerais. Rua dos Brandões, CEP: 37900-104. Passos, MG – Brazil
E-mail: mariadagracalh@gmail.com

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Central Illustration: Prevalence of Atrial Fibrillation in Patients With end Stage Renal Disease

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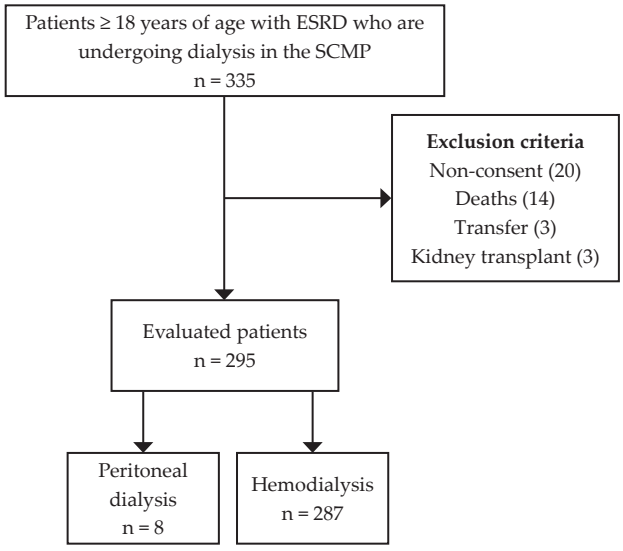

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ESRD: end-stage renal disease; SCMP: Santa Casa de Misericórdia de Passos.

Introduction and objectives

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice worldwide. The prevalence of AF increases with age and is associated with higher rates of morbidity and mortality, social and economic impacts for these patients.[1] Studies show that there is a bidirectional pathway between chronic kidney disease (CKD) and AF, due to complex pathophysiological mechanisms, patients with renal dysfunction are at higher risk of this arrhythmia, as AF can accelerate the decline in renal function.[2,3]

Both conditions share common risk factors, which increase the risk of cardiovascular events, such as stroke, thromboembolism, bleeding, and death.[4,5] Patients with CKD requiring dialysis have a higher prevalence and risk of developing AF, as well as worse outcomes.[5]

Data from clinical trials evaluating anticoagulation in chronic kidney failure did not provide solid evidence, and a gap can been observed in the management of these patients.[4] The new oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) and the vitamin K antagonist (warfarin) are strongly recommended for the prevention of thromboembolic phenomena;[6-11] however, its use in patients with end-stage renal disease (ESRD) remains unclear.

The lack of robust evidence to treat this population remains a challenge. In addition, few studies in the literature have evaluated the prevalence of AF in patients with ESRD. Thus, the objective of this paper was to evaluate the prevalence of AF in patients with ESRD who are undergoing dialysis and, secondarily, calculate the thromboembolic (CHA_2DS_2VASC) and bleeding (HASBLED) risk scores, as well as describe the sociodemographic profile of patients and their use of oral anticoagulants.

Methods

This is an observational, cross-sectional, analytical-descriptive study carried out in the nephrology service at Santa Casa de Misericórdia de Passos (SCMP) in patients with ESRD who are undergoing dialysis. This study was approved by the local Research Ethics Committee, and informed consent was obtained from all patients.

Through hospital databases, all patients with ESRD who were undergoing dialysis were identified between January and March 2020. Patients were considered eligible for this study if they were aged 18 years or over. Exclusion criteria included: patients undergoing kidney transplantation, patients who did not participate in a follow-up analysis in the dialysis service, and those who did not agree to participate. Moreover, patients who died

from any cause before data collection was completed were excluded. After having selected the study participants, 295 patients were evaluated (Central Illustration).

Data collection was performed during the weekly dialysis session, and patients answered a medical history questionnaire, and underwent physical examination and a 12-lead electrocardiogram, between January and March 2020.

Statistical Analysis

Descriptive data of clinical and demographic variables were presented by the median and interquartile range (IQR) for continuous variables. Absolute and relative frequencies were applied for categorical variables. The Kolmogorov-Smirnov was used with Lilliefors significance correction for continuous variables: age, time on renal replacement therapy, creatinine, CHA_2DS_2VASC and HASBLED. The normality test identified non-normal distribution for continuous variables, except for creatinine.

The chi-square ($\chi 2$) test was used to analyze the association between the variables and AF. For all analyses, $\alpha = 0.05$ was adopted as being statistically significant. Analysis were performed using the Statistical Package for the Social Sciences (IBM® SPSS® Statistics), version 20.0.[12]

Table 1 – Clinical and demographic profile of the population

Baseline characteristics	n (%)	Median (IQR*)
Serum creatinine (mg/dl)	295(100)	8.1(5.7-10.5)
Age (years)	295(100)	63(53-71)
BMI† (kg/m²)	273(92.5)	24.65(21.59-28.30)
Time from onset of RRT‡ (months)	181(61.3)	30(12-60)
Gender female	125(42.4)	
Gender male	170(57.6)	
Procedence Passos	109(36.9)	
Procedence non-Passos	184(62.3)	
Smoking	130(44)	
Most prevalent comorbities		
Hypertension	267(90.5)	
Diabetes	144(48.8)	
HF	91(30.8)	
Acute myocardial infarction	49(16.6)	

IQR: interquartile range; BMI†: body mass index; RRT‡: renal replacement therapy; HF: heart failure. Source: Drafted by the author.*

Results

A total of 295 patients with ESRD who were undergoing dialysis were included in this analysis. Of these, most were males, the median body mass index (BMI) was normal weight, and the majority of patients were from neighboring municipalities of the city of Passos, MG (two patients were unable to report their precedence). The median time on renal replacement therapy was 30 months. Current smokers corresponded to 44% (130) and former smokers to 15.9% (47). The median serum creatinine was 8.1.

Hypertension was the most prevalent comorbidity, followed by diabetes mellitus and heart failure (HF). Data related to the baseline characteristics of the study participants can be found in Table 1. The prevalence of AF after reviewing the electrocardiograms was 6.7%.

Only 1 patient had a previous diagnosis of intermittent AF in 24-hour Holter monitoring, and 1 patient presented an atrial flutter. A high thromboembolic risk was observed in the sample. All women had a CHA_2DS_2VASC score ≥ 4. As for male patients, only one patient had a $CHA_2DS_2VASC = 1$, whereas others had a score ≥ 2. The HASBLED score showed a high risk of hemorrhage in 70% of the patients with AF. These data are summarized in Table 2.

Anticoagulation was present in 13 patients, of whom 5 were taking apixaban and 8 were taking warfarin. Of these, 3 patients had a diagnosis of AF, two of whom on apixaban therapy and one with warfarin, due to a mechanical heart valve and an aortic prosthesis. Among the other anticoagulated patients, two had mechanical heart valves and six had previous episodes of thrombosis.

The Chi-square test showed that AF was associated with HF and age over 65 years, and anticoagulation was associated with AF (Table 3).

Discussion

Patient characteristics and the prevalence of AF in the setting of patients with ESRD who were undergoing dialysis was evaluated in this study. Three aspects can be revealed in this study. First, the clinical profile of the patients was described, as shown in Table 1.

Table 2 – Clinical profile of patients with AF

Baseline characteristics	n (%)	Median (IQR*)
CHA^2DS^2-VASC	20(100)	4(3-5)
HASBLED	20(100)	3(2-4)
Serum cratinine (mg/dl)	20(100)	7.5(5.6-10.2)
Age (years)	20(100)	72(68-79)
BMI† (kg/m^2)	18(90)	24.8(22-28.8)
Time from onset of RRT‡ (months)	20(100)	36(11.2-72.7)
Anticoagulation	3(15)	
Female Gender	5(25)	
Male Gender	15(75)	
Procedence Passos	7(35)	
Procedence non-Passos	13(65)	
Smoking	11(55)	
CHA^2DS^2-VASC SCORE		
0	0(0)	
1	1(5)	
≥2	19(95)	
HASBLED SCORE		
0-1	1(5)	
2	5(25)	
≥3	14(70)	
Most prevalent comorbities		
Hypertension	17(85)	
HF	14(70)	
Diabetes	6(30)	
Acute myocardial infarction	6(30)	

IQR: interquartile range; BMI†: body mass index; RRT‡: renal replacement therapy; HF: heart failure. Source: Drafted by the author.*

Table 3 - Variables associated with AF

	AF		Chi-square test	p
	Yes	No		
HF				
Yes	14	77	15.417	<0.001
No	6	198		
Age				
<65	3	162	14.584	<0.001
≥65	17	113		
Anticoagulation				
Yes	3	10	5.715	<0.01
No	17	265		

AF: atrial fibrillation; HF: heart failure. Source: Drafted by the author.

The high prevalence of cardiovascular diseases and diabetes mellitus, as well as a sample consisting predominantly of men, who were elderly and smokers, are risk factors for the development of AF.[13] In addition, despite the differences in the literature, according to a meta-analysis by Ng et al.[14] hemodialysis is more associated with the development of AF when compared to peritoneal dialysis, present in 8 of the 295 patients undergoing treatment.

The prevalence of AF in this study was 6.7%. This is similar to previous studies, with a prevalence range of 3.5-27%.[5,15,16] Several authors have emphasized the underdiagnosis of this arrhythmia in the population of ESRD who were undergoing dialysis, which contributes to the remarkable fluctuation in the prevalence rate, a fact that is also attributable to the methodological design of the surveys.[15-17]

HF and age over 65 years were statistically associated with AF. Cardiovascular involvement requires attention due to the impact on the morbidity and mortality of the ESRD population undergoing dialysis. That is, cardiovascular disease is the most prevalent group of diseases and the leading cause of death in these patients. In addition, the relationship between AF and HF is highlighted, as AF contributes to a worsening of the cardiac function.[18] Advanced age has a triple role in the scenario of renal failure by contributing as a risk factor to the development of cardiovascular diseases, an increased risk of bleeding, and thromboembolic events.[13,18]

The median CHA_2DS_2VASC = 4 and HASBLED = 3 points to a paradoxical high risk of stroke and bleeding in patients with ESRD and AF.[13] The CHA_2DS_2VASC score was similar to that obtained in the control and intervention groups of the first randomized clinical trial with the ESRD population, which evaluated the safety profile of apixaban versus warfarin - RENAL-AF

(NCT:02942407).[19] However, differences in population size must be emphasized.

Considering only the median of $CHA_2DS_2VASC = 4$ in most patients with AF from this study, thromboembolic prophylaxis would be recommended. Although such scores are used in the assessment of the population with AF, the high coexistence, especially of cardiovascular comorbidities in ESRD, makes the results of the score doubtful.[16,20]

Anticoagulation was statistically associated with AF. The concomitance of ESRD and AF restrict the use of these drugs, since they depend on renal clearance to purify the patient's metabolic activity. When the renal function is reduced, the risk of bleeding increases significantly.[21] Based on this, clinical trials that, to a great extent, investigated the profile of the new anticoagulants commonly excluded patients with a glomerular filtration rate < 30, that is, stage IV and V CVD.[6-9]

Among the other anticoagulants, warfarin stands out due to extrarenal metabolism and elimination;[21] however, its use increases the risk of anticoagulant-related nephropathy,[22] vascular calcification,[23] platelet dysfunction, increased risk of bleeding,[24,25] and hemorrhagic stroke.[25] Thus, the warfarin regimen remains uncertain, considering the risks and the imprecision concerning the real efficacy to prevent thromboembolic events and predisposition to hemorrhagic events, as suggested by meta-analyses and other studies.[24-26]

Recent guidelines are divergent regarding the level of scientific evidence on the use of both warfarin and NOACS (Non-vitamin K antagonist oral anticoagulants) in the ESRD setting. A 2019 publication by the American Heart Association, in conjunction with the American College of Cardiology and the Heart Rhythm Society, presents an intermediate level of evidence (B-NR) and a weak recommendation class (IIb) for both apixaban and warfarin, with an international normalized ratio (INR) between 2 and 3, considering the $CHA_2DS_2VASC \geq 2$ for men and ≥ 3 for women.[27] In the United States of America, apixaban has already been used in patients with AF who are undergoing dialysis.[28]

However, the 2020 Canadian Cardiovascular Society guidelines, together with the Canadian Heart Rhythm Society Comprehensive Guidelines as well as the 2020 European Society of Cardiology Guidelines, refute the use of both the NOACS and warfarin in patients with ESRD who are undergoing dialysis, given the scarcity of studies published on the subject.[29]

Thus, due to the lack of robust scientific evidence to guide medical management, there were no anticoagulated patients due to AF. Given the worldwide prevalence of AF associated with ESRD and its clinical outcomes, randomized clinical trials have been carried out.[30-32]

Recent systematic reviews and meta-analyses[33,34] state that the efficacy of new oral anticoagulants is not inferior to warfarin. However, other publications[35-37] state that anticoagulation in patients with AF and ESRD still remains controversial in daily practice. The present study aims to understand the clinical and sociodemographic profile of patients with AF and ESRD, providing tools for a better treatment of these patients according to current scientific literature.

The limitations inherent to this study are: it is exploratory, observational, and descriptive, which restricts it to only make associations and not establish a causal effect. In addition, the electrocardiogram was performed during the hemodialysis session, while the 24-hour Holter monitoring was unavailable for all patients to screen paroxysmal AF, possibly leading to an underdiagnosis of this arrhythmia.

Conclusion

AF was present in 6.7% of the population, despite the clinical risk profile. The thromboembolic and bleeding scores have demonstrated a high risk in these patients. Considering the absence of strong scientific evidence, the non-anticoagulation approach of patients with AF has been commonly adopted in this service. Further studies on the efficacy and safety of anticoagulants are necessary to improve the management of patients with AF and ESRD.

Author Contributions

Conception and design of the research, statistical analysis and critical revision of the manuscript for intellectual content: Hawerroth MGL, Sonoda LY, Silva JJ, de Oliveira WA; acquisition of data, analysis and interpretation of the data and writing of the manuscript: Hawerroth MGL, Sonoda LY.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Santa Casa de Misericórdia de Passos under the protocol number 3.740.556.CAAE: 26364819.5.0000.8043. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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