SERUM C-REACTIVE PROTEIN IN HYPERTENSIVE HEART FAILURE WITH AND WITHOUT ATRIAL FIBRILLATION: A CASE-COMPARATIVE STUDY

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ABSTRACT

Background: **Atrial fibrillation (AF) and hypertensive heart failure (HHF) frequently co-exist, causing increased morbidity and mortality. While inflammation is a recognized driver of AF in Western populations, there is a paucity of data regarding the role of c-reactive protein (CRP) in African participants with HHF and AF.**

Aim: **To compare the level of serum C-reactive protein in hypertensive heart failure patients with atrial fibrillation, those in sinus rhythm and apparently normal individuals.**

Methods: **This hospital-based cross-sectional comparative study involved 180 participants divided into three groups (n=60 each): HHF with AF, HHF without AF, and apparently healthy controls. Participants underwent clinical evaluation, 12-lead electrocardiography, transthoracic echocardiography, and high-sensitivity CRP (hs-CRP) analysis.**

Results: **The mean ages of HHF with AF, HHF without AF, and apparently healthy participants were 65.3 ± 9.9years, 66.7 ± 9.7 years, and 64.3 ± 10.5 years, respectively. The concentration of CRP was significantly higher in the HHF without AF compared to HF with AF and the apparently normal controls ($p<0.001$). CRP correlated positively with left ventricular internal diameters and volumes ($p < 0.001$), and inversely with ejection fraction ($r = -0.279$, $p < 0.001$). Multivariate regression identified left atrial diameter (OR 2.26, $p = 0.02$) and ejection fraction (OR 4.02, $p = 0.04$) as independent predictors of AF, while CRP was not.**

Conclusion: **Serum CRP was not significantly elevated in HHF participants with AF compared to those without AF. These findings may suggest that elevated CRP, a surrogate marker for inflammation, is not the primary pathophysiological pathway for AF in this population. However, results may have been influenced by confounding factors such as the use of guideline-directed medical treatment for hypertension and HF.**

Keyword: Hypertension, Heart failure, Inflammation, Atrial fibrillation, C-Reactive protein.

INTRODUCTION

Inflammatory markers are substances produced in response to infections and mitotic lesions.[1] They are increasingly recognized as key players in the pathogenesis of various cardiometabolic conditions including hypertension, diabetes mellitus, atrial fibrillation (AF), and heart failure (HF).[1-4]

These markers such as interleukin-1β, nucleotide-binding domain-like receptor protein 3 (NLRP3), Tumor Necrosis Factor-α (TNF-α), interleukin-6 (IL-6) and acute-phase proteins (APP) have been studied to access its effect on heart failure. The NLRP3 inflammasome- and subsequent IL-1β activation with IL-6, which is synthesized during the early stages of inflammation, leads to low-grade inflammation. Interleukin-6 and high-sensitivity C-reactive protein have become key markers of ongoing inflammatory risk in heart failure (HF). Elevated levels of these biomarkers are linked to a higher likelihood of developing HF and experiencing negative outcomes even in patients with established disease.[1-4]

Atrial fibrillation (AF) stands out as the most common sustained cardiac arrhythmia and a burgeoning global epidemic.[5] It is characterized by disorganized atrial contraction and affects over 1% of the adult population

in western societies and was estimated to affect 33.5 million individuals globally in 2010.[5,6]. While the prevalence is highest in developed nations, the burden in sub-Saharan Africa (SSA) is rising rapidly, often remaining undiagnosed in up to 90% of cases until complications like stroke occur.[7,8,9]

Hypertensive heart failure (HHF) and AF are frequently interrelated, creating a cycle of substantial morbidity and mortality. When they co-exist, the risk of ischemic stroke, dementia, and worsening HF increases significantly. In the Framingham study, AF accounted for 14% of early deaths within the first four months of diagnosis in HF participants.[10] Emerging evidence suggests that inflammation is not merely a bystander but a primary driver that initiates and perpetuates AF through myocyte necrosis and fibrosis.[11,12]

Despite this link, AF has been studied almost exclusively in high-income HF populations. There is a significant paucity of data regarding the role of inflammatory markers, specifically C-reactive protein (CRP), in initiating and maintaining AF among African participants.[13] In Nigeria, previous research has focused largely on traditional risk factors and treatment modalities, but no data on the relationship between systemic inflammation and AF in the setting of HHF. C-reactive protein (CRP) is a well-established biomarker of systemic inflammation. Its connection to atrial AF lies in the fact that inflammation promotes the structural changes in myocardial tissue that initiate and maintain AF.[14,15] Elevated CRP is associated with an increased risk of developing AF, but genetic studies suggest that CRP itself does not directly cause AF; rather, it serves as a useful warning sign of underlying systemic and myocardial inflammation.[14,15] Patients with active AF tend to have higher CRP levels than those in normal sinus rhythm. Elevated baseline CRP levels are also used clinically to help predict the likelihood of AF recurrence after cardiac procedures, e.g., catheter ablation.[14]

Establishing the role of inflammation using CRP may pave the way for novel anti-inflammatory therapies tailored to the Nigerian environment, potentially mitigating the 18.9% increase in disability-adjusted life years associated with the condition.[16] Furthermore, understanding these associations is critical for improving local surveillance and directing preventive strategies.

Therefore, this study aims to compare the level of serum C-reactive protein in hypertensive heart failure patients with atrial fibrillation, those in sinus rhythm, and apparently normal individuals seen at the University College Hospital, Ibadan, Nigeria.

METHODOLOGY

Study design and population

The study was a hospital-based cross-sectional comparative study carried out at the Cardiology Unit of the University College Hospital, (UCH), Ibadan, Nigeria. The study population included consenting adults >18 years old who met the inclusion criteria for the study. Participants were recruited over a period of nine months.

A semi-structured interviewer-administered questionnaire was used for data collection. The questionnaire had sociodemographic and biophysical data (age, gender, weight, height, body mass index, waist circumference, hip circumference, marital status, and socioeconomic status), personal and past medical history (hypertension, diabetes mellitus, chronic kidney disease, medication history, etc.), and social history (cigarette smoking, alcohol use). It also contained data on clinical examination as well as electrocardiographic and echocardiographic measurements.

Definition of study participants

There were 3 groups of participants: 1st Group (or Participants) were participants with HHF and AF; 2nd Group (Control 1) were participants with HHF without AF, and 3rd Group (Control 2) who were apparently normal adults.

Selection criteria

Inclusion criteria for participants

Participants were included if they had electrocardiographic features of AF in the setting of HHF. Heart failure was defined according to the 2016 ESC guideline for the diagnosis of heart failure, presence of typical symptoms of HF and objective evidence cardiac dysfunction by echocardiography. Also, only participants willing to participate in the study were included.

Exclusion criteria for participants

Participants with other etiologies of heart failure other than hypertension and participants with CKD or eGFR <35ml/min/1.73m^{2}were excluded from the study. Also, participants diagnosed with diabetes mellitus, with an ongoing infection, and pregnant women were excluded.

Inclusion criteria for control 1

Participants with a clinical diagnosis of heart failure secondary to hypertension but did not have AF were included. Also, only participants willing to participate in the study were included.

Exclusion criteria for control 1
Participants who had hypertensive heart failure and were in AF, participants who declined to participate, participants younger than 18 years, and pregnant women were excluded.

Inclusion criteria for control 2
Apparently healthy participants who consented to participate in the study.

Exclusion criteria for control 2
Participants younger than 18 years and pregnant women were excluded.

Sample size
Sample size was calculated using the sample size formula for a case-comparative study.[17] The standard deviations of the study group and comparative group were derived from a previous study.[18] The study was 90% powered, and the minimum sample size calculated was approximated to 46 participants per group. To account for non-participation, a total of 60 participants were used. Participants were recruited using simple randomized sampling from the records of participants with AF in the setting of hypertensive heart failure in the Cardiology Unit of the University College Hospital, Ibadan.

Biophysical measurements
Blood pressure was measured using a digital Omron blood pressure machine following standard protocols. Anthropometric measurements, including body mass index (BMI), waist circumference, and hip circumference, were obtained using standardized techniques. Obesity was defined as a BMI $\geq$ 30 kg/m^2.

Electrocardiogram (ECG)
A resting 12-lead electrocardiogram was done for each participant using a Workstation CONTEC 8000G electrocardiograph (Contec Medical Systems Co., Ltd., Qinhuangdao, Hebei Province, 066004, P.R. China). Standard calibration was used according to the American Heart Association (AHA) recommendation at a speed of 25mm/second and sensitivity of 10mm/mV.

Lead II was designated as the rhythm strip. The ECGs were reviewed, the findings recorded, and coded in the data collection form.

Transthoracic Echocardiography
Transthoracic echocardiography was carried out using a General Electric Vivid S60 echocardiography machine. (GE Health Care Technologies Inc., Chicago, Illinois 60661 United States) Parameters measured included left ventricular (LV) internal dimension, interventricular septum, and LV posterior wall thickness measured at end diastole and end systole in the parasternal long axis view at the level of the mitral leaflet tip, according to the American Society of Echocardiography leading edge to leading edge convention[19]. Assessment of right ventricular systolic function was carried out according to the guidelines of the American Society of Echocardiography. The indices of right ventricular systolic function were measured as tricuspid annular plane systolic excursion (TAPSE), which was acquired by placing an M-mode cursor through the tricuspid annulus in the modified apical four-chamber view and measuring the length of the longitudinal motion of the annulus at peak systole. Values less than 16mm indicate right ventricular systolic dysfunction.[19,20]

Laboratory analysis
Venous blood was collected after an overnight fast for lipid profile, glucose, and renal function tests. For the primary variable, high-sensitivity C-reactive protein (hs-CRP), plasma was separated by centrifugation at 3000g and stored at -70°C. Analysis was performed using a Melsin ELISA kit (Sandwich-ELISA principle) on a COBAS C311 analyzer. The minimum detectable limit for CRP was <0.1mg/L.

Ethical considerations
Informed Consent
Adequate information about the purpose of the study and what their participation entailed, including benefits and risks, was given to potential participants. Only participants who gave consent after being adequately informed were recruited. Ethical approval was sought and granted by the joint UI/UCH Research Ethics Committee, Ibadan (Reference number: UI/EC/19/0291). Written informed consent was obtained from all the participants. The study conformed to the international ethical code as enshrined in the Declaration of Helsinki.[21]

Statistical analysis
Statistical analysis was performed using the Statistical Package for the Social Sciences Version 22. (IBM Corporation, 1 New Orchard Road, Armonk, New York 10504, U.S.A.) Categorical variables were presented as proportions or percentages using frequency tables and bar charts as appropriate, while continuous variables were summarized as means and standard deviation, and skewed data were presented as median and interquartile range.

Categorical variables in this study were: sex, educational status, occupation, history of comorbidities, alcohol use, smoking, presence of symptoms and signs of

HF, ECG findings, and left ventricular (LV) geometry. Continuous variables in this study were: age, biophysical measurements, laboratory investigations, LV and atrial parameters. Age of respondents was categorized into < 40, 40- 49yrs, 50-59yrs, 60-69yrs, 70-79yrs and e" 80 years during analysis.

The association among categorical variables was tested using the Chi-square test. Analysis of variance (ANOVA) was employed for comparison of means of continuous variables among HHF with AF, HHF without AF and apparently healthy participants. Kruskal-Wallis test was used for variables that were not normally distributed. The relationship between serum CRP in groups 1 and 2 and some clinical and echocardiographic variables was performed using the Pearson correlation test for continuous variables and Spearman's rank correlation for non-parametric data. All statistical analyses were carried out at a level of significance of $p < 0.05$.

RESULTS

A total of one hundred and eighty participants, consisting of sixty HHF with AF participants, two sets of age and sex matched controls (sixty HHF without AF and sixty apparently healthy participants), were recruited for this study.

Sociodemographic characteristics of participants

Table 1 shows the socio-demographic characteristics of the study participants. The majority of participants were 50 years and above (96.6%). The mean ages of HHF with AF, HHF without AF, and apparently healthy participants were 65.3 ± 9.9years, 66.7 ± 9.7 years, and 64.3 ± 10.5 years, respectively. Generally, the proportion of males was slightly higher than that of females across the three groups (53% vs. 47%). In terms of marital status, the majority of the participants in the different groups were married. Furthermore, the monthly income of most of the participants studied was below 50,000 naira (p=0.010).

Clinical presentation of the participants

Supplementary Table S1 shows the symptoms and signs reported by the participants. A significantly higher number of participants with HHF with AF reported palpitations (p= 0.035) compared to HHF without AF. Participants with HHF without AF were more likely to report paroxysmal nocturnal dyspnea (p=0.004), syncope (p=0.042), and basal crackle (p=0.001) compared to those participants with HHF

Table 1: Sociodemographic characteristics of the study participants

Variable	Category	Group I Normal participants (N=60, %)	Group II HHF(-AF) (N=60, %)	Group III HHF(+AF) (N=60, %)	P value
Age	<40	1(1.7)	0(0.0)	1(1.7)	0.991
(years)	40-49	1(1.7)	1(1.7)	1(1.7)	
	50-59	19(31.7)	19(31.7)	19(31.7)	
	60-69	18(30.0)	17(28.3)	17(28.3)	
	70-79	17(28.3)	18(30.0)	17(28.3)	
	80 and above	4(6.7)	5(8.3)	6(10.0)	
Mean age	**Mean ± SD**	**64.3 ± 10.5**	**66.7± 9.6**	**65.3±9.9**	0.850
Gender	Male	32(53.3)	32 (53.3)	32(53.3)	0.980
	Female	28(46.7)	28(46.7)	28(46.7)	
Marital	Single	1(1.7)	2(3.4)	4(6.7)	0.520
Status	Married	44 (73.3)	42(71.2)	37(61.7)	
	Divorced	1(1.7)	0 (0.0)	0(0.0)	
	Separated	1(1.7)	0(0.0)	0(0.0)	
	Widow	14(23.3)	16(25.4)	18(30.0)	
Monthly	<50,000	38(63.3)	42(70.0)	46(76.7)	0.010*
income	≥50,000	22(36.7)	18(30.0)	14(23.3)	
Smoking	Current	3(5.0))	2(3.3)	0(0.0)	0.350
	Former	6(10.0)	9(15.0)	20(33.3)	
	None	51(85.0)	49(81.9)	40(66.7)	
Alcohol	Yes	10(16.7)	15(25)	13(21.7)	0.026
consumption	No	50(83.3)	45(75)	47(78.3)	
Education	No education	8(13.6)	10(16.9)	10(16.7)	0.410
	Primary	8(13.6)	16(27.1)	12(20.0)	
	Secondary	18(27.1)	18(28.8)	19(31.7)	
	Tertiary	26(45.7)	16(27.2)	19(31.7)	

HHF (+ AF) - Hypertensive Heart Failure with AF; HHF (-AF) - Hypertensive Heart Failure without AF; SD- standard deviation; (=) - significant; p < 0.05 is statistically significant

Table 2: Concentrations of CRP across participant categories

Inflammatory Marker	Total Cohort (N=180) Median (IQR)	Group I Normal participant N=60) Median (IQR)	Group II HHF-AF (N=60) Median (IQR)	Group III HHF + AF (N=60) Median (IQR)	p-value
CRP	1.43(1.03)	1.14(1.01)	1.85 (1.24)	1.34(0.99)	<0.001

HHF (+ AF)- Hypertensive Heart Failure with AF; HHF(-AF)- Hypertensive heart failure without AF; AF- atrial fibrillation; IQR – Interquartile range; CRP- C- reactive protein

with AF. Supplementary Table S2 presented the co-morbidities described among the study participants. History of stroke (p= 0.04) and connective tissue disease (p= 0.011) were more commonly reported in HHF with AF compared to HHF without AF.

Biochemical analysis

Supplementary Table S4 shows the biochemical analysis of the study participants. Platelet count (p<0.001) and serum triglyceride (p=0.010) were significantly higher in healthy participants compared to participants with

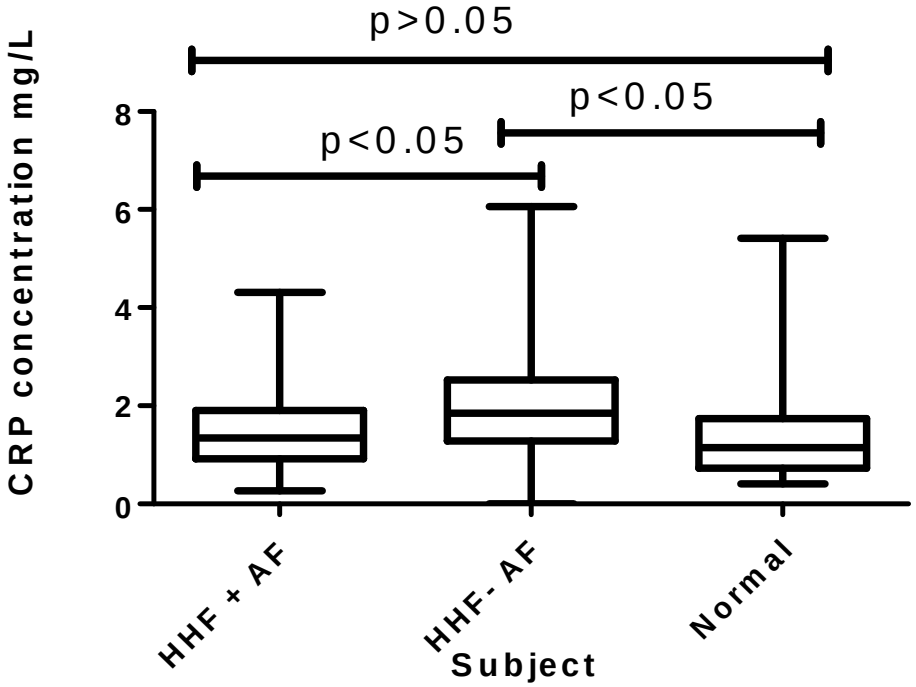


Fig 1: Concentration of CRP across the participant categories

HHF+ AF- Hypertensive heart failure with atrial fibrillation; HHF- AF- Hypertensive heart failure without atrial fibrillation; CRP- C-reactive protein

Biophysical profile

Supplementary Table S3 shows the biophysical profile of the study participants. There was no significant difference between the mean height, weight, body mass index (BMI), waist circumference, hip circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP) in the three groups. There was, however, a significant difference in the mean pulse rate of apparently healthy participants and the HHF without AF group (p= 0.002). Furthermore, a significant difference was reported in the mean respiratory rate of apparently healthy participants and HHF without AF (p=<0.001) and HHF with AF (p=0.003).

HHF without AF. White cell count (p=0.031), fasting blood glucose (p= 0.002), creatinine (p=0.002), and low-density lipoprotein (p=0.012) were significantly higher in HHF without AF compared to apparently healthy participants. Apparently healthy participants had significantly higher packed cell volume (p=0.031), serum sodium (p=0.008), serum bicarbonate (p=0.005), and high-density lipoprotein (p<0.001) compared to those with HHF with AF.

Concentration of CRP across participant categories

Table 2, Figures 1 and 2 show the concentration of CRP across the different study participants. The

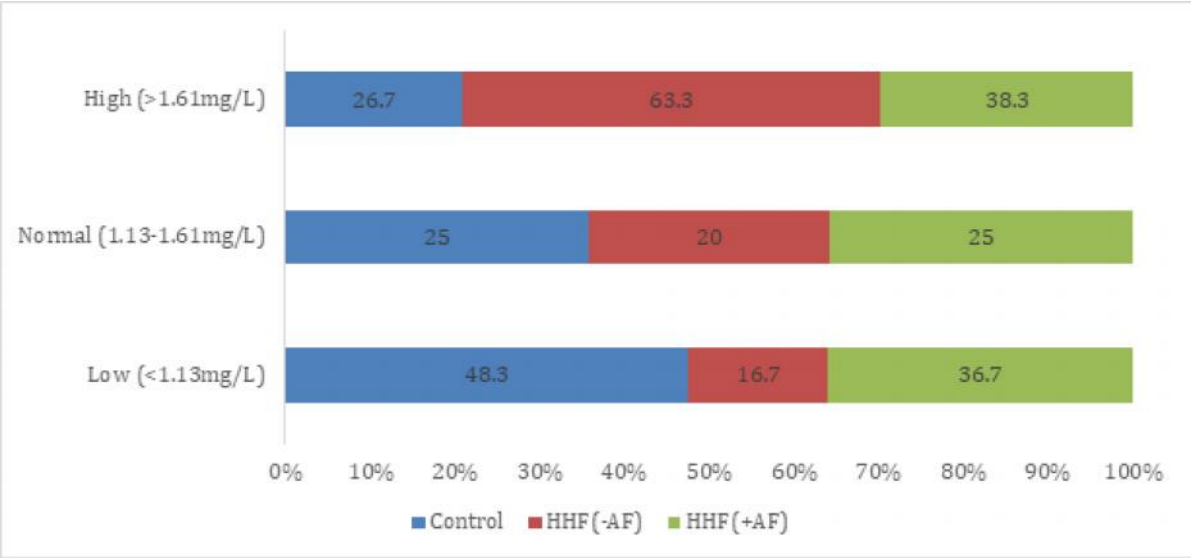


Figure 2: Titre of CRP concentration in the three groups

Table 3: Correlation of CRP and echocardiographic parameters

Variables	CRP	
	rho	p-value
Heart rate	0.149	0.047
LAD	0.131	0.079
LADI	0.152	0.042
LVIDD	0.318	<0.001
LVIDDI	0.289	<0.001
LVIDS	0.284	<0.001
LVIDSI	0.289	<0.001
FS	-0.268	<0.001
LVEF	-0.279	<0.001
EDV	0.312	<0.001
ESV	0.335	<0.001
LVM Index	0.089	0.237
Deceleration time	-0.288	<0.001
LAA	0.264	0.015
LAAI	0.278	0.01

LAD- left atrial dimension; LADI- left atrial dimension index; LVIDD- left ventricular internal diameter at diastole; LVIDDI- left ventricular internal diameter at diastole index; LVIDS- left ventricular internal diameter at systole; LVIDSI- left ventricular internal diameter at systole index; FS- fractional shortening; LVEF- left ventricular ejection fraction; EDV- end diastole volume; ESV-end systolic volume; LVM-left ventricular mass; LAA- left atrial area; LAAI- left atrial area index

concentration of CRP was significantly highest in the HHF without AF compared to HF with AF and the apparently normal controls (p<0.001)

Electrocardiographic findings

Supplementary Table S5 shows the ECG findings among the participants. Individuals with HHF without AF had increased frequency of left axis deviation (LAD), LVH, LVH with strain, and ST segment elevation compared to HHF with AF. More participants with HHF with AF had a higher frequency of premature ventricular complexes (PVC) and ST segment depression.

Measured echocardiographic parameters

Supplementary Table S6 shows the measured echocardiographic parameters of the study participants. Compared to the apparently healthy participants, the two hypertensive groups had significantly different values in the left ventricular dimensions, left atrial dimension, right ventricular dimension, tricuspid annular plane systolic excursion, and aortic valve opening. There was also a significant difference in the left ventricular posterior wall thickness in systole (p=0.016), left atrial dimension (p=0.007), and right ventricular dimension(p=0.001) in HHF with AF individuals compared to those with HHF without AF.

Derived echocardiographic parameters

Supplementary Table S7 shows the derived echocardiographic parameters of the study participants. Compared to the apparently healthy participants, the two hypertensive groups had significantly higher end diastolic volume, end systolic volume, left ventricular ejection fraction, left ventricular mass, and left atrial volume index. There was also a significant difference in end diastolic volume, end systolic volume (ESV), left ventricular ejection fraction (LVEF), and left atrial volume index between HHF with AF individuals and those without AF.

Correlation of CRP and echocardiographic parameters

Table 3 shows the correlation between serum CRP and echocardiographic parameters. CRP correlated positively with heart rate (r= 0.147; p= 0.047), left

Table 4: Multivariate logistic regression of predictors of AF

Predictor	B	p-value	OR	95% CI
CRP	-2.07	0.81	0.13	0.10-1.29
Age	0.38	0.75	1.46	0.15-14.64
Respiratory Rate	-0.21	0.60	0.81	0.36-1.81
LVIDD	0.67	0.32	1.96	0.52-7.46
Left Atrial diameter (LAD)	0.82	0.02	2.26	0.81-6.33
End diastolic volume (EDV)	-1.06	0.04	0.35	0.13-0.93
Right ventricular diameter (RVD)	-0.25	0.59	0.78	0.32-1.93
Ejection fraction (EF)	1.39	0.04	4.02	1.03-15.65

CRP- C-reactive protein; LVIDD- Left ventricular internal diastole diameter; OR- Odd ratio; CI –confidence interval; p < 0.05 is statistically significant

Table 5: Comparison of C-reactive protein (CRP) levels in this study and previous studies

S/no	first author	Year	Country	Study population	Mean age (yrs)	% women	Mean CRP		
							NC	HF	AF
1	Current study	2021	Nigeria	60	65.4	46.7	3.78	5.07	5.77
2	Pavlovic et al(58)	2017	Serbia	32	68.1	34.4	5.47	--	21.66
3	You et al(40)	2010	China/Canada	103	63.1	47	0.62	--	3.67
4	Piral et al(39)	2007	Turkey	39	53.0	45	3.90	--	10.00
5	Sata et al(59)	2004	Japan	26	58.0	0	0.04	--	0.15
6	Chung et al(20)	2001	USA	112	62.7	16	0.10	--	0.21

AF- atrial fibrillation; NC- normal control; HF- heart failure; USA- United States of America; YRS-years

atrial volume index (r= 0.152; p = 0.042), left ventricular internal diameter at diastole index (r= 0.289; p< 0.001), left ventricular internal diameter in systole (r=0.284, p<0.001), end diastole volume (r=0.312; p<0.001), end systolic volume (r=0.335, p=<0.001) and left atrial area index (r=0.278; p=0.010). On the other hand, it correlated negatively with fractional shortening(r=-0.289; p<0.001), left ventricular ejection fraction(r=-0.279; p<0.001) and deceleration time(r=-0.288; p<0.001)

Predictors of AF

Table 4 shows the multivariate logistic regression analysis for the predictors of AF in HHF participants. The independent predictors of AF were left atrial diameter (OR 2.26; 95% CI 0.81 to 6.33, p =0.02), and ejection fraction (OR 4.02; 95% CI 1.03 to 15.65, p =0.04)

Supplementary Table S8 showed the medications used by the participants. Compared to those participants without AF, HHF with AF were more likely to be on

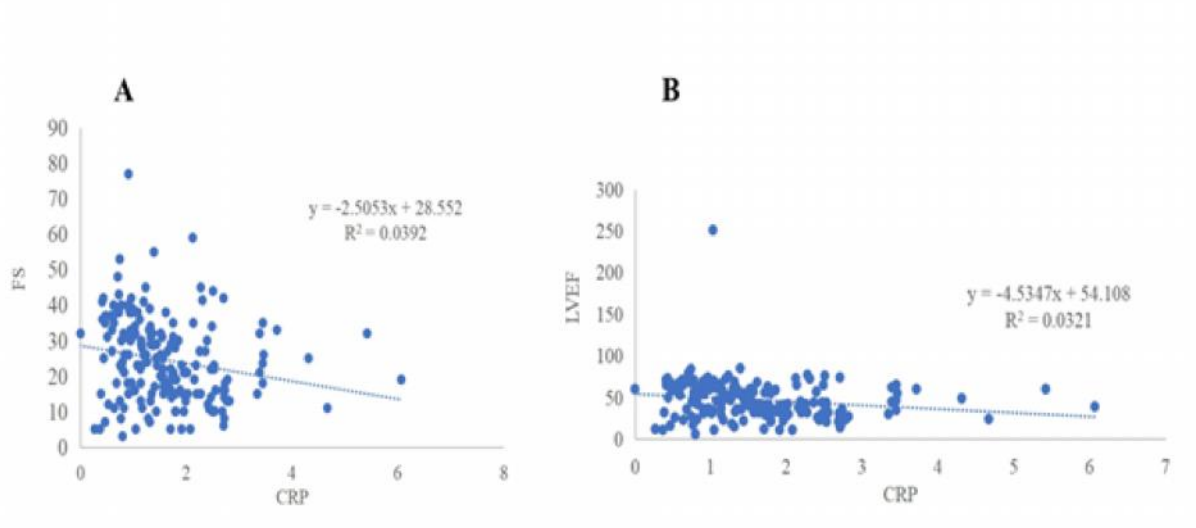


Fig. 3: A) Correlation of CRP to fractional shortening (FS)
B) Correlation of CRP to left ventricular ejection fraction (LVEF)

warfarin (p=0.002). There was no significant difference in the use of other medications.

DISCUSSION

A large number of studies have documented that AF is associated with inflammation.[19,20] The relationship between AF and inflammation is evident in examination of atrial biopsy from participants with paroxysmal AF without other cardiovascular diseases, which documented myocarditis confined to atria in almost two-thirds of cases.[22]

This study employed a cross-sectional comparative design to assess the serum concentration of CRP. It described the risk factors, electrocardiographic characteristics, and echocardiographic characteristics of HHF participants with coexisting AF, those with HHF without AF, and apparently normal age- and sex-matched control.

Socio-demographic characteristics of participants

The mean age of the participants with AF was 65.3 ± 9.9years. This represents the demographic bracket of age group affected by AF in most developing countries. Studies carried out by Ejim *et al.*[22] in Enugu, Nigeria reported a mean age of 61.8 ± 12.6, and Ajayi *et al*[26] in Ado Ekiti found a mean age of 67.4 ± 13.8. The findings by Targonski *et al.*[18] in Poland and Chung *et al*[23] in USA, support these findings. In Europe, among hospitalized participants, the mean age of AF patients was 70.3 ± 9.5years.[18,27] Atrial fibrillation is common in the elderly.

The male preponderance (53.3%) observed in the current study corroborates the findings of Ogah *et al.*[28], and Karaye *et al.*[29] in HF studies. Anisiuba *et al.*[30] and Vaziri *et al.*[31] in the Framingham study observed a higher male preponderance among AF participants. A previous report on global epidemiology of AF indicated the same in both developing and developed countries.[32]

CRP in the study participants

CRP was not significantly elevated in our AF cohort compared with the other groups. This observation was similar to the study done by Marcus *et al.*[33]

Clinical presentation of the participants

The study revealed a higher proportion of AF participants reporting palpitation (61%). This is similar to 57% reported by Kumar *et al.*[34] and 54.1% reported by Levy *et al.*[35] This high frequency of palpitation in our cohort might have been because most of them had high heart rates. About 73.3% of our AF participants reported dyspnea on exertion, similar to 74% noted by Kumar *et al.*[34] in India. None of our AF participants reported syncope, unlike 17% recorded by Ajayi *et al.*[26] This may be due to a high LV ejection fraction seen in the AF cohort.

Comorbidities and biochemical parameters among participants

In this study, cardioembolic stroke and connective tissue disorders were more common in the HHF with AF while COPD was more common in HF without AF. Cerebral embolic event was seen in 6.7% of HHF with AF participants, which was similar to the 7.7% documented by Kalogeropoulos *et al.*[27] A higher frequency, 21.8% was however reported by Ajayi *et al.*[26] The frequency of stroke is expectedly higher in HHF with AF, as observed in other studies.[36,37] The packed cell volume (PCV) was lower in HHF with AF participants compared to HF without AF and healthy participants in this study. This may be because of the presence of more renal dysfunction among the HHF with AF participants. In addition, occult bleeding may be higher in AF participants because they are on anticoagulants/antiplatelets.[38] The lower serum sodium values in HHF with AF compared to HHF without AF may be due to higher dose of diuretics used. In a study by Ketchum *et al*[9], hyponatremia was identified as a marker of poor prognosis in HF participants with AF.

A higher proportion of HHF with AF participants were using anticoagulants, beta blockers, digoxin, and diuretics. Medications with negative chronotropic effect and anticoagulation are important in the management of HHF with AF. Diuretics are a powerful symptom modifier in the acute presentation and also modify short-term disease outcomes. This is similar to the findings by Nielson *et al.*[40] that reported the majority of AF participants being on beta blockers and anticoagulants. According to Olshansky *et al.*[41], beta blockers are highly effective in lowering heart rate by suppressing sympathetic input. A follow-up study of rate control among the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) participants demonstrated that beta blockers used as first-line therapy (with or without the use of digoxin) resulted in the target heart rate in 79% of all participants and 81% of HF participants.[41]

Electrocardiographic abnormality among participants

Cardiac structural adaptations were obvious in the majority of our participants. Hypertensive heart failure without AF participants had a higher frequency of LVH, LVH with strain, and RVH. This is similar to the finding by Ajayi *et al.*[26] where 70.9% presented with LVH. This is most likely due to a background history of hypertension in the study participants. About 15%

of the HHF with AF had more coexisting premature ventricular contractions. This is lower than 50.9% reported by Ajayi *et al.*[26] This may be related to time of presentation and degree of cardiac structural remodeling.

Echocardiographic abnormality among study participants

Hypertensive heart failure without AF had higher LV structural alteration. This was contrary to what was observed by Targonski *et al.*[18], where no significance was observed. Considerable evidence indicates that alterations in LV structure predict the incidence of HF and other forms of cardiovascular disease.[44] Our finding may be related to patient selection.

Left atrial diameter, area, volume index, and right ventricular diameter were found to be significantly higher among HHF with AF than HHF without AF participants in the current study, and this is similar to findings by Liu *et al.*[45] Targonski *et al.*[18] found a statistically significant increase in LA size in participants with AF compared to non-AF participants. Heart failure and AF contribute independently to LA size. Left atrial enlargement is highly predictive of first and recurrent AF, and also predicts the likelihood of postoperative AF.[46]

The relationship between LA size and AF has been well known.[47] The electrophysiological and molecular mechanisms beneath the vicious circle where A1F causes atrial dilatation and vice versa have been demonstrated. Atrial remodeling alters the effective refractory period in different atrial regions, creating the perfect substrate for AF.[48,49]

C-Reactive protein and AF cohorts

We found that serum CRP was not higher in HHF with AF compared to those without AF. A similar observation was observed by Kalogeropoulos *et al.*[27] who found no association with AF. Pirat *et al.*[42] observed no association between CRP and AF at baseline before the electrophysiology study but a statistical significance was seen at 6 hours and 24 hours post-procedure. On the other hand, Targonski *et al.*[18] observed a statistically significant association between AF and CRP (p=0.001). Similarly, Chung *et al.*[23] and You *et al.*[43] demonstrated a significant elevation of CRP in patients with AF.

Limitation

First, the study was hospital-based and may not translate to what obtains in the community. Paroxysmal AF could have been missed because a resting 12-lead ECG was used in screening for AF in the HHF with AF group. A Holter ECG may be a better tool. Also, the participants are not medication naïve. Treatment may have affected the levels of CRP in the participants.

CONCLUSION

This study suggests C-reactive protein (CRP) was not significantly elevated in participants with HHF with AF. Therefore, CRP might not be implicated as an inflammatory marker in AF development in HHF individuals. However, this association might have been affected by potential factors such as drug treatment, which might have modulated the CRP levels. Future study will look at CRP levels in drug-naïve AF patients

Conflict of interest: None declared

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