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Morbidity and Mortality Outcomes in Atrial Fibrillation Patients with Different Phenotypes of Heart Failure

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common arrhythmia in heart failure (HF), with both preserved and reduced ejection fraction (EF), worsening the prognosis. the prognostic implications of AF in HF remain controversial.
Aim of the Work: evaluation of the outcomes in with AF patients and various HF phenotypes.
Patients and methods: The study conducted on 90 symptomatic HF patients presented by AF (either paroxysmal or non-paroxysmal). They were classified into three groups: HF with preserved ejection fraction (HFpEF), HF with mildly reduced EF (HFmrEF), HF with reduced EF (HFrEF). All participants were subjected to thorough history taking, ECG and comprehensive echo-Doppler evaluation including left ventricular (LV) dimensions and functions, left atrial (LA) volume and 2D-speckle tacking echocardiography for assessment of LV longitudinal strain (LV-GLS) and LA phasic function.
Results: Patients with HFrEF had more significant LA structural and functional changes than those with HFpEF and HFmrEF, including LA enlargement and reduced LA phasic function. In comparison to patients with paroxysmal AF, non-paroxysmal AF patients in all HF groups had larger LA diameters and higher LA volumes. In HFrEF patients, non-paroxysmal AF had a substantially higher all-cause morbidity than paroxysmal AF.
Conclusions: Only in patients with HFrEF experienced all-cause morbidity substantially higher in non-paroxysmal AF than in paroxysmal AF, according to all-cause mortality and morbidity within HF categories. Nevertheless, non-paroxysmal and paroxysmal AF did not differ in all-cause mortality within recruited HF group.
Keywords: AF, HF, LA-reservoir, LA-contractile, LA-conduit, LV-GLS.

INTRODUCTION

Heart failure (HF) affects 1% to 2% of adults in developed countries, is a rising global epidemic [(1)]. The most prevalent arrhythmia in HF is AF, which exacerbates symptoms and raises the risk of cardioembolic events in both HF with preserved and reduced ejection fraction [(2)].

Prognostic implications arise when AF develops in HF since it is probably a marker of more serious structural heart disease [(3)]. There is ongoing debate on the prognostic significance of AF in patients with different types of HF [(4)]. We aimed to investigate the mortality and morbidity outcomes of AF patients with various heart failure phenotypes.

PATIENTS AND METHODS

This was an observational prospective study conducted on 90 symptomatic HF patients presented by AF (either paroxysmal or non-paroxysmal). All patients were reciuted from Al-Zahraa University Hospital Cardiology Outpatients Clinic, in the period from October 2023 to December 2024. Enolled patients were presented by paroxysmal or non-paroxysmal AF documented by 12 leads surface ECG or 24 hours Holter monitoring). We have excluded patients with significant valvular heart disease, congenital heart diseases, primary severe pulmonary hypertension, previously implanted cardiac devices (pacemaker, defibrillator or cardiac resynchronization therapy) and debilitating diseases (e.g. liver cell failure, kidney failure or malignancy).

METHODOLOGY

All studied patients were subjected to careful history taking including etiology of HF, and patients' symptoms were assessed using New York Heart Association (NYHA) classification, clinical examination including weight, height, body mass index (BMI), and body surface area (BSA). Laboratory investigations included complete blood count, ESR, CRP, renal functions, liver functions, coagulation profile and lipid profile. Standard 12-lead surface electrocardiogram perfomed to detect heart rate, rhythm, evidence of ischemia, chamber enlargment. Different scores were used to assess stroke risk (CHA_2Ds_2-VASc score), bleeding risk score (HAS-BLED score) and HFA-PEFF algorithm (for diagnosis of HFpEF patients).

All recorded echocardiographic pictures and loops were shown alongside a trans-thoracic echo-Doppler investigation using the Vivid-E9 GE system equipped with a multi-frequency (2.5 MHz) matrix probe M3S and simultaneous ECG physio-recording data. The following parameters were assessed, left ventricular end diastolic and systolic dimensions (LVEDD) and (LVESD), LV ejection fraction (LVEF) by M-mode and 2D methods, mitral annular plane systolic excursion (MAPSE), LV diastolic function using tissue Doppler at the mitral annuli to measure E/E' ratio, LA dimension LA volume and LA volume index (LAVI).

2D speckle tracking echocardiography was used to assess LV global longitudinal strain (LV-GLS),

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LA reservoir (LA-R), LA conduit (LA-CD) and LA contractile (LA-CT) function.

Follow up for at least 6 months was applied for assessment of the following:

1- HF hospitalization or death.
2- Secondary end points; included systemic embolization, major bleeding, non HF hospitalization (renal failure or chest infection) or ischemic events.

Heart failure patients were classified into 3 groups: 30 patients with HFpEF ≥50%, 30 HF patients with mildly reduced EF 41-49% (HFmrEF), and 30 HF patients with reduced ejection fraction ≤ 40% (HFrEF). Each group was further sub-classified into non-paroxysmal and paroxysmal AF.

Ethical Approval:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Al-Azhar University. Written informed consents were obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis

The Shapiro-Wilk test was employed to determine whether the variables were normally distributed. The mean and SD were used to represent quantitative variables. Absolute frequencies and percentages were used to express qualitative characteristics. Unpaired t-test was used to compare the means of 2 groups and one-way ANOVA test with post hoc Tukey s HSD test was used to compare the means of more than 2 groups. Mann-Whitney test is used to compare non normally distributed data. The categorical variables were compared using the relevant Chi-squared or Fisher's exact test. To compare the event-free survival rate using the log rank test, we created a Kaplan-Meier curve. Using all the variables, we created a univariate Cox regression analysis. Statistical significance was defined as a P-value of less than 0.05. SPSS 23.0 for Windows (SPSS Inc.; Chicago, Illinois, United States) was used for the statistical analysis.

RESULTS

Regarding demographic data, HFpEF patients had female preponderance compared to both HFmrEF and HFrEF patients. Additionally, HFpEF patients showed increased weight and BMI in comparison to HFmrEF and HFrEF patients (Table 1).

Table (1): Comparison of demographics among the studied groups

Variables	HFpEF N=30	HFmrEF N=30	HFrEF N=30	P^a	P^b	P^c
Age (years) (mean±SD)	67.3±7.5	62.7±7.9	61.6±13.5	0.183	0.083	0.922
Sex (no., %)						
• **Male**	5 (17%)	20 (66.7%)	23 (76.6%)	**0.0001**	**0.001**	0.643
• **Female**	25(83%)	10 (33.3%)	7 (23.3%)			
Weight (Kg) (mean±SD)	89.9±10.5	82.5±8.6	81.5±9.3	**0.01**	**0.003**	0.907
Height (cm) (mean±SD)	169.3±5.6	172.7±6.2	169.9±6.9	**0.096**	**0.927**	0.201
BMI (Kg/m^2) (mean±SD)	31.8±4.0	29.5±5.5	27.9±4.0	0.143	**0.003**	0.323
BSA (m^2) (mean±SD)	1.95±0.2	2.02±0.2	1.93±0.2	0.334	0.166	0.328

Abbreviations: P^a: between HFpEF and HFmrEF, **P^b**: between group HFpEF and HFrEF, **P^c**: between HFmrEF and HFrEF. BMI: body mass index, BSA: body surface area.

In the current study, HFrEF patients demonstrated significant increased LA diameter, volume, and LAVI compared to HFpEF and HFmrEF patients. Meanwhile, HFrEF patients showed significantly reduced phasic function evaluated by 2D STE (including LA-R, LA-CD and LA-CT) regarding HFpEF and HFmrEF patients (Table 2).

Table (2): Comparison of LA echocardiographic parameters among the studied groups

Variables	HFpEF N=30	HFmrEF N=30	HFrEF N=30	P^a	P^b	P^c
LA diameter (mm) (mean ±SD)	44.7±4.0	47.9±5.5	49.0±5.0	0.04	**0.003**	0.625
LAV (ml) (mean ±SD)	65.0±15.7	79.2±20.5	100.6±31.9	0.05	**0.0001**	**0.002**
LAVI (ml/m^2) (mean ±SD)	40.1±6.8	48.8±9.4	60.0±15.7	0.011	**0.0001**	**0.001**
LA-R (%) (mean ±SD)	16.6±4.2	12.6±3.2	9.0±2.9	**0.001**	**0.0001**	**0.0001**
LA-CD (%) (mean ±SD)	11.9±2.5	8.6±2.2	5.9±2.1	**0.0001**	**0.0001**	**0.0001**
LA-CT (%) (mean ±SD)	6.4±2.3	5.6±1.8	3.4±1.6	0.175	**0.0001**	**0.0001**

Abbreviations: P^a: between HFpEF and HFmrEF, **P^b**: between group HFpEF and HFrEF, **P^c**: between HFmrEF and HFrEF. LA: left atrium, LAV: left atrium volume, LAVI: left atrium volume index, LA-R: left atrium reservoir function, LA-CD: left atrium conduit function, LA-CT:LA contractile function.

Comparison between non-paroxysmal and paroxysmal AF within the studied group

Our study demonstrated that non-paroxysmal AF showed significantly increased LA diameter, volume and LAVI compared to paroxysmal AF patients. Meanwhile, LA phasic function (both LA-R and LA-CT) and LV-GLS in non-paroxysmal AF patients were significantly impaired regrading paroxysmal AF patients in all groups; HFpEF group (Table 3), HFmrEF group (Table 4), and HFrEF group (Table 5).

Table (3): Comparison between non-paroxysmal and paroxysmal AF in HFpEF regarding different score and echocardiographic parameters

Variables	Non-paroxysmal AF N=17	Paroxysmal AF N=13	P
HFpEF score (mean ±SD)	7.8±1.0	8.0±0.9	0.505
CHA_2Ds_2-VASc score (mean ±SD)	2.8±0.9	3.1±1.3	0.546
HAS-BLED score (mean ±SD)	2.5±0.9	2.1±1.0	0.250
LV-GLS (%) (mean ±SD)	13.5±2.8	15.9±3.1	**0.03**
LA diameter (mm) (mean ±SD)	47.0±3.4	41.8±2.5	**0.0001**
LV Av. E' (mean ±SD)	6.7±0.7	8.0±1.1	**0.001**
LV E/E' (mean ±SD)	15.1±4.7	15.4±3.7	0.857
MAPSE (mm) (mean ±SD)	13.3±0.7	13.4±1.0	0.848
LAV (ml) (mean ±SD)	73.9±11.6	53.4±12.5	**0.0001**
LAVI (ml/m^2) (mean ±SD)	42.5±8.0	37.1±2.8	**0.03**
LA-R (%) (mean ±SD)	15.2±3.3	18.5±4.7	**0.04**
LA-CD (%) (mean ±SD)	11.5±2.3	12.4±2.7	0.353`
LA-CT (%) (mean ±SD	6.3±1.5	7.9±1.5	**0.01**

LV AV. E': left ventricle early diastolic velocity**,** MAPSE: mitral annular plane systolic excursion, LA: left atrium, LAV: left atrium volume, LAVI: left atrium volume index, LA-R: left atrium reservoir function, LA-CD: left atrium conduit function, LA-CT:LA contractile function, LVE/e'=ratio of early diastolic mitral valve annulus velocity/average early diastolic mitral annular velocities by TDI.

Table (4): Comparison between non-paroxysmal and paroxysmal AF in HFmrEF regarding different score and echocardiographic parameters

Variables	Non-paroxysmal AF N=19	Paroxysmal AF N=11	P
CHA_2Ds_2-VASc score (mean ±SD)	2.4±1.2	3.1±1.5	0.186
HAS-BLED score (mean ±SD)	1.8±1.3	2.9±1.3	**0.04**
LV-GLS (%) (mean ±SD)	11.2±2.1	13.0±1.6	**0.03**
LA diameter (mm) (mean ±SD)	49.5±5.9	45.1±3.3	**0.03**
LV Av. E' (mean ±SD)	5.2±1.5	7.5±1.2	**0.0001**
LV E/E' (mean ±SD)	16.0±3.8	15.6±3.2	**0.769**
MAPSE (mm) (mean ±SD)	10.4±2.8	10.0±0.8	0.610
LAV (ml) (mean ±SD)	87.2±20.1	65.5±12.8	**0.003**
LAVI (ml/m^2) (mean ±SD)	53.0±9.0	44.7±3.8	**0.01**
LA-R (%) (mean ±SD)	12.3±2.2	14.8±2.4	**0.01**
LA-CD (%) (mean ±SD)	8.7±2.1	8.5±2.6	0.872`
LA-CT (%) (mean ±SD	5.1±1.1	6.5±1.3	**0.001**

Table (5): Comparison between non-paroxysmal and paroxysmal AF in HFrEF regarding different score and echocardiographic parameters

Variables	Persistent AF N=19	Paroxysmal AF N=11	P
CHA_2Ds_2-VASc score (mean ±SD)	3.7±1.7	2.8±1.5	0.181
HAS-BLED score (mean ±SD)	2.4±0.8	2.5±1.3	**0.819**
LV-GLS (%) (mean ±SD)	7.7±2.3	9.6±1.3	**0.03**
LA diameter (mm) (mean ±SD)	51.5±3.3	46.0±3.7	**0.0001**
LV Av. E' (mean ±SD)	4.4±1.2	6.5±1.2	**0.0001**
LV E/E' (mean ±SD)	19.4±5.4	19.4±6.0	**0.997**
MAPSE (mm) (mean ±SD)	8.9±1.3	8.6±0.9	0.484
LAV (ml) (mean ±SD)	108.1±36.9	82.2±8.3	**0.03**
LAVI (ml/m^2) (mean ±SD)	67.0±13.2	53.2±8.6	**0.005**
LA-R (%) (mean ±SD)	7.1±1.9	9.9±2.7	**0.03**
LA-CD (%) (mean ±SD)	5.5±2.1	6.5±2.0	0.242
LA-CT (%) (mean ±SD	3.1±1.2	4.9±1.4	**0.001**

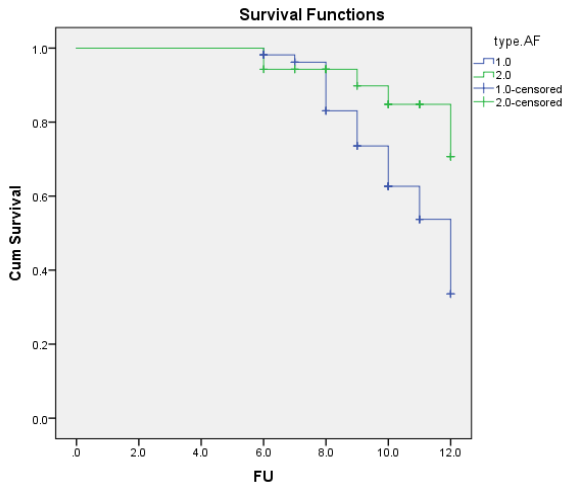
Mortality and morbidity outcomes of non-paroxysmal and paroxysmal AF across and within the studied groups

All-cause mortality did not differ between

- Non-paroxysmal and paroxysmal AF across all studied groups (Table 6 and figure 1).
- Non-paroxysmal and paroxysmal AF in HFpEF (Figure 2), in HFmrEF (Figure 3), and in HFrEF (Figure 4).

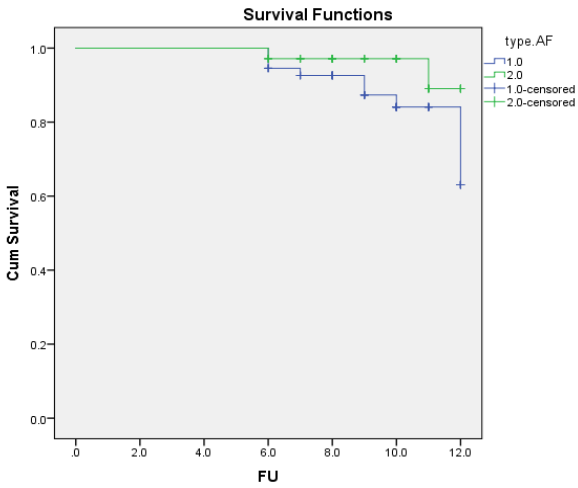
Table (6): The all-cause mortality and morbidity outcome of non-paroxysmal and paroxysmal AF across all studied groups.

Variables	N=90	Non-paroxysmal AF N= 55	Paroxysmal AF N= 35
All-cause mortality:	11 (12.2%)	7 (12.7%)	4 (11.4%)
• **Worsening of heart failure**	4 (4.4%)	3 (5.5%)	1 (2.9%)
• **Sudden cardiac death**	3 (3.3%)	2 (3.6%)	1 (2.9%)
• **Cerebrovascular stroke**	2 (2.2%)	1 (1.8%)	1 (2.9%)
• **Unknown etiology**	2 (2.2%)	1 (1.8%)	1 (2.9%)
All-cause morbidity:	26 (28.9%)	17 (30.9%)	9 (25.7%)
• **Heart failure hospitalization**	10 (11.1%)	8 (14.5%)	2 (5.7%)
• **Major bleeding**	8 (8.9%)	3 (5.5%)	5 (14.3%)
• **Cerebrovascular stroke**	6 (6.7%)	4 (7.2%)	2 (5.7%)
• **Non-heart failure hospitalization (renal failure or chest infection)**	2 (2.2%)	2 (3.6%)	



A

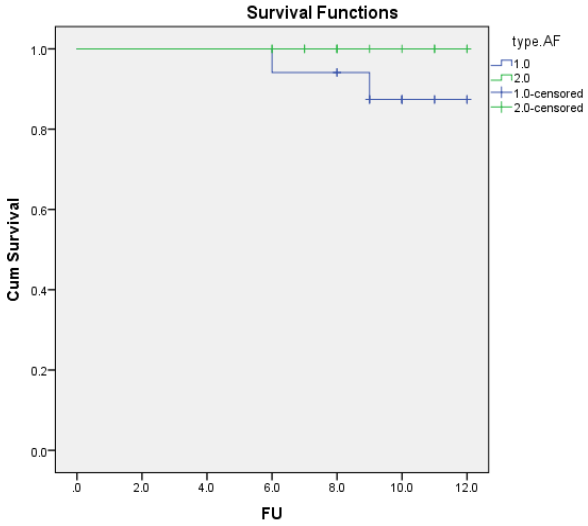
Chi square	P value
2.28	0.131



B

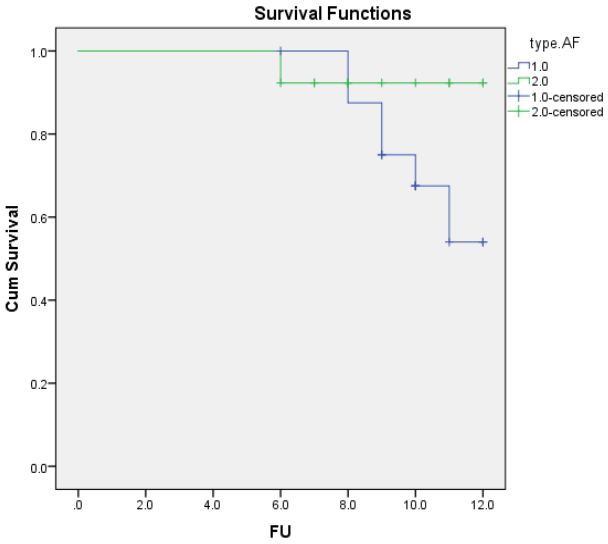
Chi square	P value
5.1	0.03

Figure (1): Kaplan-Meier curves of non-paroxysmal and paroxysmal AF (A) all-cause mortality and (B) all-cause morbidity across the studied groups. 1=non-paroxysmal AF, 2=paroxysmal AF.



A

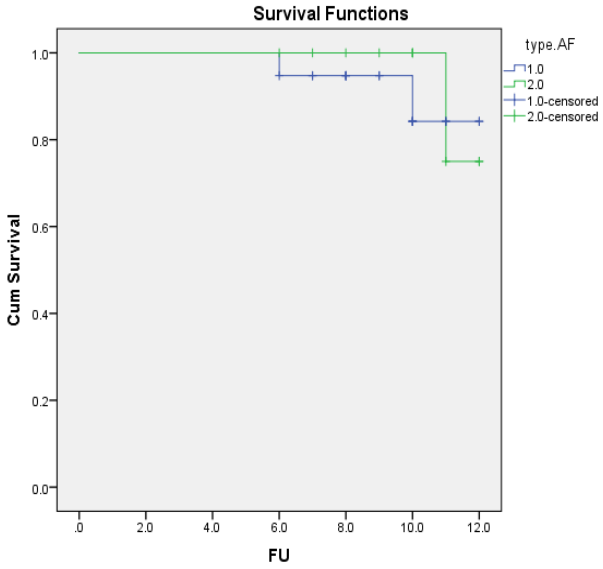
Chi square	P value
1.50	0.219

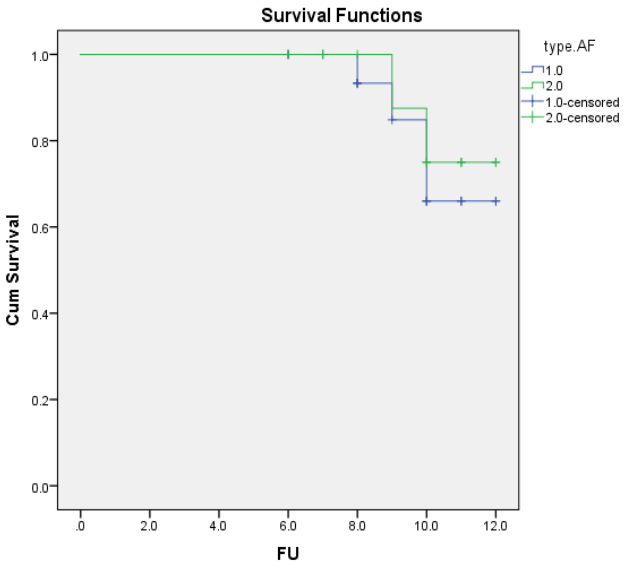


B

Chi square	P value
1.18	0.277

Figure (2): Kaplan-Meier curves of non-paroxysmal and paroxysmal AF (A) all-cause mortality and (B) all-cause morbidity in HFpEF patients. 1=non-paroxysmal AF, 2=paroxysmal AF.





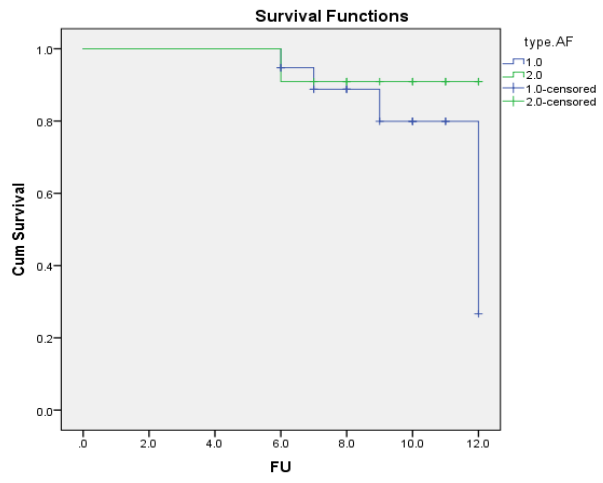
A

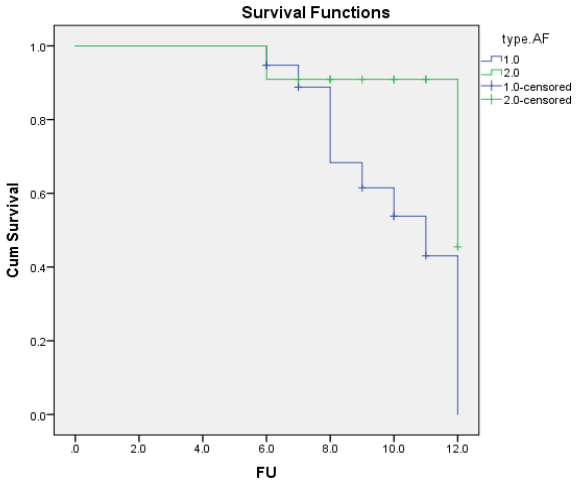
Chi square	P value
0.13	0.722

B

Chi square	P value
0.21	0.647

Figure (3): Kaplan-Meier curves of non-paroxysmal and paroxysmal AF (A) all-cause mortality and (B) all-cause morbidity in HFmrEF patients. 1= non-paroxysmal AF, 2=paroxysmal AF.





A

Chi square	P value
1.37	0.241

B

Chi square	P value
4.5	0.03

Figure (4): Kaplan-Meier curves of non-paroxysmal and paroxysmal AF (A) all-cause mortality and (B) all-cause morbidity in HFrEF patients. 1= non-paroxysmal AF, 2=paroxysmal AF.

DISCUSSION

HF and AF are two extremely common cardiovascular conditions that impact millions of people globally [(5)]. Furthermore, those two conditions are frequently linked, most likely because they have a risk profile and causal mechanisms, such as elevated atrial filling pressures that result in mechanical atrial wall fibrosis and strain, which are critical elements in the development and maintenance of atrial fibrillation [(6)]. Nonetheless, there is ongoing debate over the prognostic significance of AF in patients with various forms of HF [(4)].

Our results demonstrated that LA structural and functional remodeling (evidenced by LA enlargement and impaired LA phasic function using 2D-STE) was more pronounced in patients with HFrEF compared with those with HFpEF and HFmrEF.

Our findings are supported by **Melenovsky *et al.*** [(7)], which included 40 controls without HF and 198 HF patients, of whom 51% had HFpEF and 49% had HFrEF. Compared to controls, the LA was more dilated and dysfunctional in all HF patients. At identical LA mean pressure, patients with HFrEF had more severe

LA hypertrophy and dysfunction than those with HFpEF.

Our results were in partial agreement to those reported by **Horodinschi *et al.*** [8] who stated that LAVI was higher in patients with HFrEF.

Our data also came in agreement with **Jin *et al.*** [9] who reported that LA function including LA-reservoir, LA-conduit were worse in patients with HFrEF. Furthermore, prior research comparing the HFrEF and HFpEF phenotypes discovered that HFrEF had a higher impairment in LA phasic function [7].

According to **Al Saikhan *et al.*** [10] patients with HFmrEF exhibited lower LA reservoir, conduit, and pump function than those with HFpEF, even though both HF groups (HFpEF and HFmrEF) displayed aberrant LA size and function overall.

While HFrEF is typically thought of primarily an LV disease, LA dysfunction and an increase in LA pressure have long been recognized as characteristics of HFpEF [11]. However, HFrEF patients had worse LA function than HFpEF patients. The higher prevalence of moderate to severe functional mitral regurgitation in HFrEF patients may help to explain this. Because the LA-reservoir depends on its baseline length, patients with HFrEF are more likely to have eccentric ventricular remodeling, which can cause the mitral leaflets to become tethered. Additionally, the LA elongates maximally during LV systole, indicating a high dependence on LV longitudinal strain [9].

Our study demonstrated that non-paroxysmal AF patients across all HF groups showed enlarged LA diameter as well as increased LA volume and LAVI compared to paroxysmal AF patients. Crucially, compared to patients with paroxysmal AF, non-paroxysmal AF patients had significantly compromised LV-GLS and LA phasic function (both LA-reservoir and LA-contractile function) .

Concordantly, **Park *et al.*** [12] who demonstrated that patients with persistent AF showed more impairment of LV systolic function, and higher LAVI than those with paroxysmal AF. In a comparable manner, **Reddy *et al.*** [13] examined individuals with HFpEF and AF and found that AF, especially persistent AF, was linked to greater LA stiffness, decreased LA reservoir function, higher filling pressures, and more biventricular systolic dysfunction. Greater atrial dilatation was seen in patients with permanent AF, meaning that pericardial constraint and ventricular interdependence were responsible for a larger percentage of LA hypertension. The significance of a particular atrial fibrillation or LA myopathy phenotype and the pivotal role of LA reservoir function in the progression of AF in HFpEF are highlighted by these data, which also identify significant and distinct pathophysiologic mechanisms by which AF contributes to morbidity and mortality in HFpEF.

The current study's results showed that across all groups examined, there was no difference in all-cause mortality between non-paroxysmal and paroxysmal AF. In contrast, non-paroxysmal AF had a considerably higher all-cause morbidity rate than paroxysmal AF across all groups under study. Only in HFrEF patients was all-cause morbidity significantly greater in non-paroxysmal AF than in paroxysmal AF, according to an examination of all-cause mortality and morbidity within HF categories. However, within recruited HF groups, there was no difference in all-cause mortality between non-paroxysmal and paroxysmal AF.

Our data were partially concordant to **Hamatani *et al.*** [14] who concluded that persistent AF had significantly higher incidence of cardiovascular death and HF hospitalization but not all cause death than paroxysmal AF in patients with HFrEF and HFpEF. The explanation is that AF burden is a predictor of poorer clinical outcomes in patients with AF and HF. Also, AF burden has a strong relationship with AF type. Similarly, **Steinberg *et al.*** [15] found that after uniform anticoagulation between the groups (after randomization), patients with persistent AF had worse outcomes, such as thrombo-embolic events and mortality.

In contrast, **Taillandier *et al.*** [16] showed that HFpEF and a greater risk of readmission attributable to HF were linked to persistent AF in HF. In patients with LVEF <50%, persistent AF was less obviously linked to a poorer prognosis; in patients with HF, it was not linked to an increased risk of stroke or thrombo-embolization. The discrepancy between our results and the results of previous studies could be attributed to a longer follow up in the previous studies compared to our study in addition to different heart failure patients' categorization and inclusion criteria .

Our findings contradicted those of **Mogensen *et al.*** [17], who looked into the relationship between AF and HFrEF outcomes. They came to the conclusion that a higher risk of the composite outcome of HF hospitalization or death from cardiovascular causes was linked to paroxysmal AF, but not to persistent or permanent AF. While persistent or permanent AF was not linked to an increased risk of stroke, paroxysmal AF was. Perhaps HF instability in general (e.g., increases in atrial pressure causing both AF episodes and decompensation resulting in hospitalization) is reflected in AF paroxysms. In addition, patients with paroxysmal AF may receive less treatment to control the ventricular rate. Furthermore, the greater risk of stroke associated with paroxysmal AF reflects the lower use of oral anticoagulants in these patients.

Our findings concluded that impaired LA-reservoir and LV-GLS were powerful predictors for mortality and morbidity in patients with paroxysmal AF (regardless of HF phenotype). Moreover, in patients with non-paroxysmal AF and irrespective of HF phenotype, LV-GLS, LA-reservoir, and increased LAVI were all good predictors of morbidity, while LV-GLS, LA-conduit, and decreased LA-reservoir were all reliable predictors of mortality.

Consistently, **Li *et al.* [18]** enrolled 80-non chronic AF patients on dialysis with preserved LVEF and identified that only LA peak longitudinal strain of reservoir function was the independent predictor of all-cause mortality and morbidity in the multivariate Cox regression analysis matching previous studies [19,20].

CONCLUSION

Unlike HFpEF and HFrEF, AF in HFrEF patients evidenced more significant structural deterioration in the form of severe LV diastolic dysfunction, more substantial LA dilatation and more severe impairment of LA function. Patients with non-paroxysmal AF in all HF groups displayed significantly worse LV-GLS and LA phasic function as assessed by 2D-STE (both LA-reservoir and LA-contractile function). Only in HFrEF patients, all-cause morbidity substantially was higher in non-paroxysmal AF than in paroxysmal AF, according to all-cause mortality and morbidity within HF categories. However, non-paroxysmal and paroxysmal AF did not vary in all-cause mortality within enrolled HF groups.

LIMITATIONS

- Small sample size
- single center collection of patients
- Short duration of follow up.

So, we categorized the patients into paroxysmal and non-paroxysmal AF to overcome this limitation.

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Conflict of interest: None.

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