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Original Research Article

Sex-specific variations in patients with atrial fibrillation: a retrospective study

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ABSTRACT

Background: The most common and persistent arrhythmia today is atrial fibrillation (AF). There is conflicting data as to whether or not gender plays a role in the association of various risk factors and the development of AF. There are many gaps in our knowledge of the gender differences in AF and many opportunities for future research. The purpose of this study is to determine the clinical, laboratory and echocardiographic gender variations in patients with AF.
Methods: This retrospective study included 90 patients with persistent and paroxysmal form of AF who were hospitalized to the Grodno Regional Cardiology Center for treatment from January to December 2024. Patients were divided into 2 groups. Group 1 consists of 44 male patients, while Group 2 consisted of 46 female patients. The following diagnostic and instrumental techniques of clinical, laboratory and transthoracic echocardiography. The exclusion criteria from the study included patients with chronic rheumatic heart disease, valvular pathology of the heart requiring surgical correction, with prosthetic heart valves, with oncological diseases and with severe concomitant extracardiac pathology.
Results: Female patients with AF were older and more prone to hypertension, while both groups demonstrated high percent of comorbidities such as coronary artery disease, obesity and diabetes. Male patients had significantly lower levels of renal function parameters; and female patients had a tendency to electrolyte imbalance.
Conclusions: This retrospective study illustrates the importance of sex-specific variations in patients with AF for earlier diagnosis and how to implement better interventional strategies to improve latter prognosis.

Keywords: Atrial Fibrillation, Adult patients, Echocardiography, Gender Variations, Laboratory biomarkers

INTRODUCTION

Atrial fibrillation (AF) is a prominent cardiac disorder presenting with atrial pathology, irregular heartbeat with either a regular rhythm or irregular rhythm, elevating risk of development of thrombosis or heart failure consequently leading to predisposition of stroke and dementia.[1] In terms of epidemiology, AF is considered to be long-term progressive condition with following disease progression either with incidental exacerbations and relapsing stage. In addition, the current literature indicates the general prevalence of AF in the range of 1-2% population worldwide, with an incidence rate of 0.8 to 28.3 cases per 1000 individuals annually.[2] A cohort study depicted how age and sex became to be strong predictor alongside other co-morbidities in the incidence of AF after an history of ischemic stroke.[3] Therefore, with increasing age of the population, the prevalence of AF events is higher. Furthermore, the influence of co-morbidities on each gender affected the prevalence of AF in the selected study groups. The incidence of AF events is rather low in group of individuals with female gender without a cardiovascular disease (CVD) than group with male individuals.[4]

In addition, women had a lower rate of AF than men due to protective nature of estrogen against CVD in premenopausal period. But females are more prone to

suffer adverse progression of the disease after menopause, including stroke, heart failure and death.[5-7] Therefore, recognizing the specific risk factors may alter the course of AF burden contrastingly between women and men, which is considered importance. The results from an observational study revealed that Body Mass Index (BMI) association with AF in men than in females.[8] Another study evaluated the contribution of anthropometric measures and other AF risk factors to sex differences in incident AF risk and investigated whether AF risk factors differ for women vs men.

Other reported risk factors for AF such as obesity, arterial hypertension, higher blood lipid profile, diabetes mellitus (DM), smoking, alcohol consumption and history of cardiovascular diseases revealed a distinctive distribution by gender and thus requires consideration as a possible reason for observed differences in AF epidemiology.[9] However, biomarkers such as B-type natriuretic peptide (BNP) and C-reactive protein (CRP) can be prominent predictors of the risk of AF events. Application of CHARGE-AF score was helpful for assessment of clinical risk factors for AF. The following factors such as race, age, weight, height, smoking status, DM, blood pressure (systolic and diastolic), past application of antihypertensive medications, history of heart failure and myocardial infarction.[10]

The clinical picture of AF differs between the both genders. Women with AF are more prone to be diagnosed with an underlying hypertension and valvular disease; in contrary, men with AF are more prone to have a history of coronary artery disease, myocardial infarction and abnormal left ventricular function.[1] Furthermore, laboratory biomarkers such as BNP and CRP were routinely revealed in clinical practice, depicting the significant association with AF.[11-13] The investigation of addition of measurements of laboratory parameters such as BNP and CRP to the CHARGE-AF risk score revealed the improvement of the prediction of AF in racially and geographically cohort analysis. This novel approach may redefine the AF risk classification.[10]

In addition, some literature depicted that female patients illustrated more advanced atrial remodelling on high-density mapping and a significant increment of post-AF ablation arrhythmia recurrence in comparison to males. These changes may present to sex-based differences in the clinical course of AF in females and elaborate the higher risk of recurrence.[14] In the present study, we examined sex differences in two study groups (male and female), which included clinical characteristics of patients, clinical and laboratory parameters of AF risk in a retrospective analysis of men and women with cardiovascular disease (CVD).

METHODS

This retrospective study consisted of 90 patients with persistent and paroxysmal form of AF, admitted to the Grodno Regional Cardiological Centre for treatment from January to December 2024. This retrospective analysis included two study groups, differentiated according to gender. Group 1 included 44 male patients, while Group 2 included 46 female patients. Exclusion criteria from the study were: chronic rheumatic heart disease, valvular pathology of the heart requiring surgical correction, prosthetic heart valves, oncological diseases and severe concomitant extracardiac pathology. All patients underwent clinical, laboratory and instrumental studies, including transthoracic echocardiography.

The echocardiography was performed on Phillips iE33 device with a multi-frequency sensor (frequency 2.5-5.0 MHz). This procedure was performed with the patient lying on his left side with his back to the researcher or on his back. The study protocol included the following indicators: LA and right atrium (RA) diameter in 2-chamber and 4-chamber mode, end-systolic diameter and end-diastolic diameter (mm) of the left ventricle (LV), LVEF; assessment of the state of the valvular apparatus of the heart, degree of regurgitation on the valves.

The statistical analysis was implemented with STATISTICA 12.0 software with an observation of the normal distribution using a histogram in the distributive nature. The quantitative data were elaborated as a median, 25% (Q1) and 75% quartiles (Q3). However, most of the quantitative characteristics did not suit the law of normal distribution and non-parametric methods were used for comparison.

The Mann-Whitney test was implemented to assess peculiarities in quantitative traits between two different independent groups. The p value significance was determined at a value less than 0.05, it was noted that this indicator revealed the compared groups with statistically significant differences.

The study was performed in under the guidance of good clinical practice standards and the principles of the declaration of Helsinki. The informed consent was collected from all participants prior to inclusion in the study.

RESULTS

The following results depicted male patients with AF were younger than females (61 (55; 70) vs 68 (63; 75) years, p=0.001) and had slightly lower, however insignificantly, body mass index (29 (25; 33) vs 31 (26; 36), p>0.05). More than a half of patients in each group had obesity (52% vs 58%, p>0.05). Also, patients of both groups were comparable in prevalence of coronary artery disease, stable angina and diabetes mellitus (p>0.05). Female patients were more prone to predispose hypertension (100% vs 79%, p=0.002) than the male patients. However, there were no significant differences in stages of hypertension and heart failure NYHA functional class (p>0.05). The characteristics of clinical manifestations for these patients are presented in Table 1.

In biochemical blood analysis, the following data revealed that male patients had a higher level of creatinine (93 (79; 102) vs 79 (68; 90) µmol/l, p=0.01) and lower eGFR (79 (69; 93) vs 68 (58; 75) ml/min/1.73m^2, p=0.001) than females. However, the urea levels were comparable in both genders (7.9 (4.8; 7.1) vs 5.9 (4.5; 7.3) mmol/l, p=0.29). In addition, there were no intergroup differences in values of total cholesterol (p=0.92), glucose (p=0.17) and sodium (p=0.14). But potassium levels were lower in females than in males (4.4 (4.1; 4.8) vs 4.7 (4.4; 5.0) mEq/l, p=0.004). Laboratory parameters of patients are presented in Table 2. According to the results of transthoracic echocardiography, male and female patients had significant differences in the linear and volumetric parameters of both atria and ventricles (p<0.05), which demonstrated undeniable correlation between gender and heart diameters and volumes. Consistently, the female patients with AF were diagnosed with lower systolic septal thickness and posterior wall thickness (p<0.05). Furthermore, the diastolic thickness of both interventricular septum and posterior wall of the left ventricle didn't reveal significant intergroup differences (p>0.05). The female patients also had higher prevalence of grade 3 mitral regurgitation (15% vs 2%, p=0.031). On the contrary, there were no differences observed in regurgitation stages. Echocardiographic parameters of patients are provided in Table 3.

Table 1: Clinical characteristics of patients.

Parameters	Males (n=44) N (%)	Females (n=46) N (%)	P value
Age, years, Me (25%; 75%)	61 (55; 70)	68(63; 75)	0.001
Body mass index, kg/m^2, Me (25%; 75%)	29 (25;33)	31 (26; 36)	>0.05
Obesity	23 (52)	27 (58)	>0.05
Stage 1	13 (29)	11 (23)	>0.05
Stage 2	9 (20)	13 (28)	>0.05
Stage 3	1 (2)	3 (6)	>0.05
Hypertension	35 (79)	46 (100)	0.002
Stage 1	6 (13)	7 (15)	>0.05
Stage 2	24 (54)	32 (69)	>0.05
Stage 3	1 (2)	4 (8)	>0.05
Diabetes mellitus	12 (27)	17 (37)	>0.05
History of myocardial infarction	11 (25)	20 (43)	>0.05
Heart failure NYHA Class	-	-	
Class 1	10 (22)	16 (34)	>0.05
Class 2	14 (31)	17 (36)	>0.05
Class 3	7 (15)	12 (26)	>0.05
Class 4	2 (4)	-	>0.05

Table 2: Laboratory parameters of patients (Me (25%;75%)).

Parameters	Males (n=44)	Females (n=46)	P value
RBC, 10^{12}/l	4.7 (4.41; 5.4)	4.50 (4.10; 4.87)	>0.05
Haemoglobin, g/l	142.0 (133; 157)	131.81(125.25; 142.5)	>0.05
WBC, 10^9/l	7.82 (5.9; 8.48)	6.40 (5.39; 7.03)	>0.05
ESR, mm/h	12.4 (5; 13)	12.7 (5.25; 15)	>0.05
Platelets, 10^9/l	237.8 (169; 291)	244.37 (206.5; 267)	>0.05
Urea, mmol/l	7.87 (4.87;7.12)	5.93 (4.52; 7.28)	>0.05
Creatinine, µmol/l	92.7 (79.1;102)	79.32 (68; 90.52)	0.011
eGFR, ml/min/1.73 m^2	79.18 (69;92.75)	68.13 (58.75; 75.25)	0.001
Cholesterol, mmol/l	3.97 (3.47;4.31)	4.09 (3.28; 5)	>0.05
Glucose, mmol/l	6.17 (4.81;5.97)	6.36 (5.06; 6.62)	>0.05
AST, mmol/l	24.05 (14.07;26.5)	22.73 (16.3; 27.25)	>0.05
ALT, mmol/l	34.46 (21.25;45.67)	25.22 (15.45; 32.8)	0.052
Sodium, mEq/l	139.24 (140.45;144)	141.19(139; 143)	>0.05
Potassium, mEq/l	4.7 (4.4; 5.0)	4.4 (4.1; 4.8)	0.004
NT-proBNP, pg/ml	4720.5 (1178.75; 3852)	3804 (797.25; 6698.25)	>0.05

Abbreviations: RBC–red blood cells; WBC–white blood cells; ESR–erythrocyte sedimentation rate; eGFR–estimated glomerular filtration rate; AST-aspartate aminotransferase; ALT-alanine aminotransferase; NT-proBNP-N-terminal pro-brain natriuretic peptide.

Table 3: Echocardiographic parameters of patients (Me (25%;75%)).

Parameter	Males (n=44)	Females (n=46)	P value
LA diameter (2 chamber), mm	44.26 (42;48)	41.34 (37;44)	0.011
LA diameter (medial to lateral), mm	43.57 (41; 45.25)	41.65 (39; 43.75)	0.035
LA diameter (front to back), mm	60.48 (58; 64.25)	58.02 (53.5; 62.75)	0.001
RA diameter (medial to lateral), mm	41.63 (38.75;44)	38.5 (35; 42)	<0.001
RA diameter (front to back), mm	58.29 (54.75; 62)	53.76 (49; 58)	<0.001
LV ESD, mm	38.87 (34; 42.25)	33.10 (29; 34.75)	<0.001
LV EDD, mm	54.46 (51.12; 59)	48.32 (45; 51.75)	<0.001
LV ESV, ml	68.5 (49; 87.75)	44.56 (33; 47.75)	<0.001
LV EDV, ml	146.02 (126; 170.25)	111.69 (93.25; 122.75)	<0.001
LVEF, %	54.20 (47.75; 60.25)	61.56 (59.25; 67)	<0.001
Septal thickness (systolic), mm	17.1 (15; 17)	16.52 (14; 17)	>0.05
Septal thickness (diastolic), mm	12.5 (11; 14)	11.63 (10; 13)	0.047
Posterior wall thickness (systolic), mm	15.38 (15; 16)	15.08 (14; 16)	>0.05
Posterior wall thickness (diastolic), mm	11.31 (10; 12)	10.77 (10; 11)	0.020
Right ventricle diameter, mm	26.86 (25; 30)	25.21 (23.25; 28)	0.030
MR grade 1, N (%)	17 (38%)	20 (43%)	>0.05
MR grade 2, N (%)	26 (59%)	19 (41%)	>0.05
MR grade 3, N (%)	1 (2%)	7 (15%)	0.031
TR grade 1, N (%)	9 (20%)	16 (4%)	>0.05
TR grade 2, N (%)	32 (72%)	24 (52%)	>0.05
TR grade 3, N (%)	3 (6%)	6 (13%)	>0.05

DISCUSSION

AF is the most prevalent cardiac arrhythmia worldwide. The incidence rate is increasing with the increasing age of the patient, mainly due to decline in bodily functions such as hyposecretion of estrogen in post-menopausal females and inadequate lifestyle with bad social habits in both genders such as atherosclerosis, diabetes mellitus (DM), hypertension, previous history of heart failure and myocardial infarction. Current literature depicts the prevalence of AF in general population is approximately 1 in 3 to 5 individuals after the age of 45 years is categorized as "high risk".[15]

Sex specific variations in AF epidemiology is poorly elaborated. In European community cohorts, there was an increment of 24% in lifetime risk for AF events after the age of 90 years in both genders.[8] In addition, the following risk factors such as age, gender, ethnicity, smoking status, hypertension, DM, prominent cardiovascular disease and previous MI revealed association for lifetime risk for future AF events. Gender specific differences were more prominent in females after menopausal period than males in the same age group, this is mostly due to protective effects of estrogen in females during the premenopausal period such as reduction of oxidative stress in the cardiovascular system by upregulation of reactive oxygen species (ROS) enzymes leading to enhanced ROS clearance.[16] Furthermore, the disbalance between ROS and the antioxidant defence mechanism leads to accumulation of ROS, thus destroying cell macromolecules, causing cell dysfunction and ultimately kill cells; which is pathogenetic mechanism for development of atherosclerosis, dysfunction of myocardium, hypertrophy of myocardium, heart failure and myocardial ischemia.[17] In general, male gender has a higher prevalence than females, but the risk of thromboembolic events is considerably high in females after menopause. But with long-term therapy, the risk of bleeding and mortality reduced despite the higher risk of stroke events.[18] Certain studies have revealed conflicting results about the association of AF with DM, hypertension and dyslipidemia in both genders. But males had significant higher prevalence of AF with coronary artery disease and females with heart failure and valvular disease had an incline in AF events.[19] The application of CHA2DS2-VASc score was important in determining the relapsing of AF during first 30 days after cardioversion (electrical or pharmacological).[20]

This retrospective study investigated the following parameters between two study groups (males and females) such as clinical characteristics of all patients, laboratory parameters and echocardiographic parameters to determine the sex specific differences in patients with AF. However, the results were rather conflicting for both genders in analysis of clinical characteristics depicting females had a greater prevalence of hypertension than males, with data being statistically significant, but no changes in the NYHA staging for heart failure. Furthermore, the laboratory parameters revealed elevated levels of CRP and NT-proBNP, which was further supported by recent publications distinct relationship between biomarkers and incidence if AF events.[12,13] In addition, low serum potassium levels were associated with

greater risk of AF events, which was indicated in this study by the female study group exhibiting lower serum potassium levels in contrast to male study group.[21] The echocardiographic parameters of this study revealed females were had a higher prevalence of valvular disease (Mitral Regurgitation), in comparison to males, which was suggestive feature alongside with hypertension for implementation of greater risk for AF events.[1]

This retrospective study illustrated importance of sex specific variations in patients with AF, which highlight significant parameters such as clinical manifestations, laboratory parameters and echocardiographic specifications, enhancing the approach epidemiologically for early diagnosis and timely treatment of AF; thus, improving the prognosis of AF patients.

This study has some limitations. It lacked a control study group, with a biased possibility in clinical evaluation and the absence of objectively measurable parameters were noted.

CONCLUSION

The collected data surmised a sex-specific variation of patients with AF in terms of clinical characteristics, laboratory parameters and echocardiographic parameters in two gender specific study groups. The following results supported the current literature about females more prone to have hypertension and valvular diseases than male patients and males were presented with abnormal left ventricular function. This study may improve the AF risk stratification in both genders. Furthermore, the clinical gaps in the literature about sex specific variations may be filled with this study, but further research is necessary for better elaboration of this section of AF.

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