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ORIGINAL RESEARCH

Sex-Differences in Atrial Fibrillation Patients: Bias or Proper Management?

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Background: Studies analyze the degree to which gender-based differences are affected by age and comorbidities show mixed results.

Methods: Using a retrospective cohort study, we analyzed 327 consecutive patients who presented to the emergency department (ED) due to Atrial Fibrillation (AF) from 2014 to 2017 with follow-up at one year.

Results: Females with AF were older ($p < 0.001$), with higher Body Mass Indexes (BMI) ($p < 0.001$), and a higher rate of hypertension ($p < 0.001$), hyperlipidemia ($p = 0.01$), diabetes mellitus ($p = 0.05$), valvular heart disease ($p = 0.05$), and thyroid dysfunction (18.3% vs 1.8%, $p < 0.001$). AF males had higher rate of coronary artery disease ($p < 0.001$) and heart failure with reduced ejection fraction ($p < 0.001$). Females were managed with rate control medications more frequently than with antiarrhythmic ($p < 0.001$). After adjusting gender to age and comorbidities, females continued to have higher rates of heart failure hospitalization (Odds Ratio (OR) 2.73 95% Confidence Interval (CI) 1.04–5.89, P-value <0.001) and recurrent AF (OR 3.86, P-value=0.02). Thyroid dysfunction and the lack of antiarrhythmic treatments significantly increased the risk of AF (OR 5.95 95% CI 3.15–9.73, OR 3.42, respectively, P-value <0.001 for both) regardless of gender. The mortality rate differs only in a sub-group of females ≥75 years of age (OR 1.60, $P < 0.001$).

Conclusion: AF males and females differ significantly in baseline characteristics and tend to be treated unnecessarily differently for AF. Heart failure hospitalizations and recurrent AF continued to be associated with female AF patients, even after adjusting gender to age and comorbidities. Thyroid dysfunction and AF treatment may explain the higher rates of recurrent AF in female patients.

Keywords: atrial fibrillation, cardioversion, emergency department, MACE, rate control, rhythm control, survival outcomes

Introduction

Atrial fibrillation (AF) is a worldwide epidemic,[1] with estimates predicting it will affect up to 12 million patients in the USA by 2050 and up to 17.9 million in Europe by 2060.[2–4] AF is also very common comorbidity in older adults, and the most common cardiac arrhythmia occurs in 3.3–10% of all emergency department admissions.[2,5]

AF entails additional long-term risks, which altogether utilize substantial health resources impacting health budgets globally.[6–9] The long-term effects of AF have been well studied and reported.[10–12]

Gender differences have been long recognized and are well documented in AF, encompassing a variety of risk factors, comorbidities, clinical presentations, and Major Adverse Cardiovascular Events (MACE).[13–15] To date, studies investigating these gender differences have had conflicting results of epidemiology and long-term risks.[2,14,16]

Despite being extensively studied, gender-based differences continue to be poorly understood. It is unclear whether the disparities mentioned above are due to sex-based pathophysiologic differences, dissimilarities in baseline

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characteristics, or an unjustified bias. In addition, there seem to be notable variations in the management and long-term outcomes of AF among different countries and even within different emergency departments in the same country.[17–26]

Current guidelines recommend similar diagnostic and therapeutic management, indiscriminate of gender. However, there are different recommendations for preventing thromboembolic complications.[27] The seeming contradiction between major sex differences observed in AF and management guidelines require further inquiry.

In our study, we analyzed gender-based differences in AF, focusing on co-morbidities, clinical presentation, management, epidemiological risk factors, and 1-year outcome composites of MACE and recurrent AF.

Our goal was to characterize the sex-based differences in AF to identify the underlying causes for these differences. We also set out to discern evidence-based disparities from unjustified biases.

Materials and Methods

Study Participants and Data Collection

The study was performed at the Department of Cardiology, Heart Institute, "Emek" Medical Center, Afula, Israel. All patients in our study were at least 18 years old. We collected data for all patients admitted to the ED from June 2014 to June 2017 using the internal computer systems ("Orion," "Offek," and "Chameleon") following International Diagnostic Code ICD-10. Patients were contacted for any missing details. Inclusion and Exclusion criteria are displayed in Table 1.

Statistical Analyses

Categorical variables were presented using frequencies and percentages, while continuous variables were presented as means, standard deviations, median, and range. *t*-test was applied for continuous variables, whereas Chi-square or Fisher's tests were used to analyze categorical variables. Multivariable analysis was performed using two-steps analysis (for age and gender) with a nominal logistic fit for all of the following variables: age, age-specific group (<65, 65–74, ≥75), Co-morbidities (BMI, hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, peripheral artery disease, heart failure, previous Cerebrovascular Accident (CVA) or Transient ischemic attack (TIA) and thyroid dysfunction), chronic medication use (beta-blocker, calcium channel blocker, anti-arrhythmic drugs, Direct Oral Anticoagulant (DOAC), warfarin, anti-platelets, and combined anti-platelets and anti-coagulation drugs), admission characteristics as atypical symptoms, heart failure, treatment strategy, sinus recovery following treatment and hospitalization. Kaplan Meier survival analysis was utilized to test differences in 1-year MACE and mortality survival between male and female patients. Cox regression analysis was then performed to adjust for age and comorbidities.

Statistical analysis was performed using SPSS V 23 software (IBM Inc., Armonk, NY, USA) and the JMP pro version 15.1.0 (SAS Institute, Cary, North Carolina, USA). Significance was obtained if $p < 0.05$.

Table 1 Inclusion and Exclusion Criteria for the Study

Inclusion Criteria	Exclusion Criteria
Atrial fibrillation (AF) with clear evidence that began earlier than 48 hours prior Emergency Room (ER) admission (mainly based on patient complains) Persistent AF or patient cannot indicate clearly when arrhythmia appears provided that one of the following conditions is fulfilled: 1. The patient has taken anticoagulant regularly for at least three weeks prior ER admission 2. Had performed a trans esophageal echocardiographic (TEE) test in the past two weeks prior ER admission which there was clear evidence that there is no left atrial appendage clot.	Permanent or Chronic atrial fibrillation AF that was a result of ischemic heart disease, heart failure, sepsis or pulmonary embolism. Atrial fibrillation that spontaneously transformed into a sinus rhythm prior ECG documentation. Lack of significant information in a patient's medical record that could not be completed after contacting the patient or refusal to participate in the study after being contacted to complete details.

Sample Size Calculations

To detect a 10% difference in mean 1-year MACE survival rate between female and male patients with 95% significance (5% alpha) and 80% power, we calculated a total sample size of 316 patients given 84% survival among female patients.

Ethical Issues

The study did not involve human participants and was based on retrospective data analysis from computerized medical records. Emek Medical Center Institutional Review Board (IRB) waived the need for informed consent due to the use of anonymous patient data and the study's retrospective nature (approval No. 18–0105 EMC). Additionally, the study was approved by Emek Medical Center Institutional Review Board and conducted following the ethical standards of the institutional research committee following the 1964 Helsinki Declaration and its later amendments and international guidelines.

Results

Baseline Characteristics and Treatment

We enrolled 343 patients in the study, consisting of 175 (51%) female patients and 168 (48%) male patients. Descriptive analysis reveals that females were significantly older than males ($p < 0.001$) with a mean age of 69.30±11.9 [27–91] vs 57.79±14.8 [21–87].

Males and females were significantly different in terms of cardiovascular risk profile. Females had a higher mean BMI score (32.65±6.9 vs 29.37±4.6, $p < 0.001$, OR 0.9) and a higher rate of comorbidities, including hypertension ($p < 0.001$), hyperlipidemia ($p = 0.01$), diabetes mellitus ($p = 0.05$), and valvular heart disease ($p = 0.05$). Conversely, males had a higher rate of coronary artery disease ($p < 0.001$) and heart failure with reduced ejection fraction ($p < 0.001$). As a result, females had a higher mean score of CHADS2 (1.85±1.3 vs 1.23±1.2) and CHA2DS2-VASc (3.61±1.7 vs 1.79 ±1.7) than males ($p < 0.001$ for both).

Females also had a significantly higher prevalence of thyroid dysfunction than males (18.3% vs 1.8%, OR 0.08, $p < 0.001$) and used antiarrhythmic medication less frequently (24.0% vs 42.8%, $p < 0.001$) [Table 2].

A sex-based difference was also observed regarding presenting symptoms, admission, and treatment strategy. Greater than 10% of the female patients presented with atypical symptoms such as weakness, dizziness, and dyspnea ($p = 0.01$). Female patients were also found to wait for longer durations before seeking medical attention ($p = 0.01$) than males.

A significantly higher proportion of female patients were treated with a rate control agent for rhythm conversion when compared to males (44.9% vs 20.8%, $p < 0.001$, OR 2.55, 95% CI 1.79–3.63). Additionally, electrical cardioversion was much lower in female patients (7.4% vs 22%). Consequently, the success rate of obtaining sinus rhythm was lower in females (73.9% Vs 89.9%, $p < 0.001$) [Table 3].

Outcomes

There were 52 (15.16%) cases of MACE, with 12 (3.5%) having CVA, 26 (7.6%) Heart Failure (HF) admissions, 1 (0.3%) Pulmonary embolism (PE) or Deep vein thrombosis (DVT) and 13 (3.79%) Ischemic Heart Disease (IHD) admissions. Unadjusted univariate analysis shows that females had higher rates of heart failure hospitalization, recurrent AF, and CVA when compared to males. Females also had less risk for developing myocardial infarction [Table 3]. However, following multivariate analysis, which included adjusting gender to age and comorbidities (the full list of adjusted variables appears in the statistical analysis paragraph), CVA and myocardial infarction were no longer statistically significant [Figure 1].

Females exhibited a higher rate of HF events than males (OR 2.73, $\chi 2$ 11.09, P-value <0.001, 95% CI 1.04–5.89) and had shorter mean days-to-HF hospitalization (87.45±8.74 vs 164.5±18.80, HR 5.72, P-value = 0.09, 95% CI 1.30–25.05) [Figure 2]. Females also had a higher incidence of recurrent AF events (OR 3.86, $\chi 2$ 5.06, P-value = 0.02, 95% CI 1.18–12.61) and a shorter time-to-AF (108.10±10.81 vs 160.52±18.0, $p = 0.01$, HR 1.70, 95% CI 1.11–2.60, for mean days) [Kaplan-Meier Survival curve, Figure 3]. Thyroid dysfunction was found to be an

Table 2 Sex Difference in Patient's Baseline Characteristics (Univariate Analysis)

Patient Characteristic	All Study Population N=343	Female N (%) =175 (51)	Male N (%) =168 (48)	P-value	OR	95 CI%
Age	63.7±14.6 [21–91]	69.3±11.9 [27–91]	57.8±14.8 [21–87]	<0.001	0.93	0.92–0.95
Age categories < 65 65–74 ≥ 75	 168 (49.0) 81 (23.6) 94 (27.4)	 83 (47.4) 39 (22.3) 53 (30.3)	 85 (50.6) 42 (25.0) 41 (24.4)	 0.316 0.321 0.316		
CHA_2DS_2-VASc Score	2.7±1.9 [0–8]	3.6±1.7 [0–8]	1.8 ±1.7 [0–7]	<0.001	0.69	0.58–0.82
$CHADS_2$ Score	1.6±1.3 [0–6]	1.9±1.3 [0–6]	1.2±1.2 [0–6]	<0.001	0.55	0.47–0.64
BMI	31.1±6.1 [19–56]	32.7±6.9 [19–56]	29.4±4.6 [20–41]	<0.001	0.90	0.87–0.94
Hypertension	217 (63.1)	123 (73.3)	88 (52.4)	<0.001	0.46	0.25–0.62
Hyperlipidemia	202 (58.7)	114 (64.8)	88 (52.4)	0.014	0.59	0.38–0.92
Diabetes Mellitus	116 (33.7)	67 (38.1)	49 (29.2)	0.053	0.67	0.42–1.05
Coronary artery disease	67 (19.5)	14 (8.0)	53 (31.5)	<0.001	5.33	2.82–10.06
Peripheral Vascular Disease	11 (3.2)	3 (1.7)	8 (4.8)	0.092	2.86	0.74–10.99
CVA	37 (10.8)	22 (12.5)	15 (8.9)	0.184	0.68	0.34–1.36
Heart Failure				<0.001	7.73	2.93–20.43
HFREF	26 (7.6)	0 (0)	26 (15.5)			
HFPEF	15 (4.4)	13 (7.4)	2 (1.2)			
Mixed Type	10 (2.9)	5 (2.8)	5 (3.0)			
Thyroid dysfunction	35 (10.2)	32 (18.3)	3 (1.8)	<0.001	0.08	0.02–0.27
Valvular Heart Disease	24 (7.0)	17 (9.7)	7 (4.2)	0.052	0.42	0.16–1.00
Chronic renal failure	32 (9.3)	18 (10.2)	14 (8.3)	0.334	0.79	0.38–1.66
Chronic use of medication						
Warfarin	42 (12.2)	26 (14.9)	16 (9.5)	0.093	0.82	0.44–1.53
DOAC	99 (28.8)	60 (34.1)	39 (23.2)	0.033	0.58	0.36–0.94
Calcium Chanel blockers	17 (4.9)	9 (5.1)	8 (4.8)	1.002	0.92	0.34–2.46
Beta-blockers	184 (53.5)	107 (60.8)	77 (45.8)	0.044	0.54	0.35–0.83
Anti-platelet	81 (23.5)	28 (15.9)	53 (31.5)	<0.001	2.43	1.45–4.09
Anticoagulation/ Antiplatelet	34 (9.9)	16 (9.1)	18 (10.7)	0.382	1.19	0.58–2.42
Antiarrhythmic agents	114 (33.2)	42 (24.0)	72 (42.8)	<0.001	2.41	1.13–4.16

Abbreviations: BMI, body mass index; HFREF, heart failure with reduced ejection fraction; HFPEF, heart failure with preserved ejection fraction; DOAC, direct oral anticoagulation.

Table 3 Sex Difference in Patient's Treatment and Outcome (Univariate Analysis)

Patient Characteristic	All Study Population N=343	Female N (%) =175 (51)	Male N (%) =168 (48)	P-value	OR	95 CI%
Hemodynamic instability	9 (2.6)	6 (3.4)	3 (1.8)	0.50	0.51	0.12–2.09
Sign of HF at admission	18 (5.2)	13 (7.4)	5 (3.0)	0.08	0.38	0.13–1.10
Duration of symptoms				0.01	0.53	0.31–0.88
< 24h	263 (76.5)	125 (71.0)	138 (82.1)			
> 24h	81 (23.5)	51 (29.0)	30 (17.9)			
Atypical symptoms	27 (7.8)	20 (11.4)	7 (4.2)	0.01	0.33	0.13–0.82
Treatment Strategy				<0.001	2.55	1.79–3.63
Rate control only	114 (33.1)	79 (44.9)	35 (20.8)			
Rhythm control agent	180 (52.3)	84 (47.7)	96 (57.1)			
Cardioversion	50 (14.5)	13 (7.4)	37 (22.0)			
Sinus recovery	281 (81.7)	130 (73.9)	151 (89.9)	<0.001	3.14	1.71–5.74
Hospitalization	124 (36.0)	79 (44.9)	45 (26.8)	<0.01	0.44	0.28–0.70
Outcome						
CVA/TIA	12 (3.5)	10 (5.7)	2 (1.2)	0.03	0.2	0.43–0.92
Heart Failure hospitalization	26 (7.6)	22 (12.5)	4 (2.4)	<0.001	0.17	0.05–0.50
Myocardial Infarction				0.01	0.47	0.42–0.53
STEMI	9 (2.6)	0 (0)	9 (5.4)			
Non-STEMI	4 (1.2)	4 (2.3)	0 (0)			
VTE	1 (0.3)	1 (0.6)	0 (0)	1.00	0.51	0.46–0.56
Recurrent AF	97 (28.2)	59 (33.5)	38 (22.6)	0.03	0.58	0.35–0.93
Death	9 (2.6)	6 (3.4)	3 (1.8)	0.54	0.51	0.12–2.09
Cumulative events	127 (36.9)	77 (43.8)	50 (29.8)	0.08	0.54	0.34–0.85

Abbreviations: HF, heart failure; STEMI, ST-elevation myocardial infarction; CVA, cerebrovascular accident; TIA, transient ischemic attack.

independent risk factor for recurrent AF (OR 5.95, $\chi 2$ 27.94, P value <0.001, 95% CI 3.15–9.73) [Table 4] and was associated with shorter time-to-AF (74.16±15.29 vs 112.00±15.36, meantime in days) [Kaplan-Meier Survival curve, Figure 4].

The presence of atypical symptoms as nausea, dizziness, weakness, and dyspnea correlated with higher risk for recurrent AF (OR 4.09, $\chi 2$ 5.17, P-value = 0.02, 95% CI [1.08–15.41]) and HF hospitalization (OR 3.93, $\chi 2$ 3.75, P-value = 0.05, 95% CI [1.34–6.87]).

During follow-up, 9 (2.62%) patients died, which consisted of six females and three males. The mortality rate among females and males was nonsignificant. Nevertheless, subgroup analysis revealed that females ≥75 years of age had a significantly higher risk for death, in comparison with males of the same age (OR 1.60, $\chi 2$ 20.16, P < 0.001, 95% CI 1.2–3.4) [Table 4], and the survival time was much shorter (HR 63.35, $\chi 2$ 4.19, P-value=0.04,

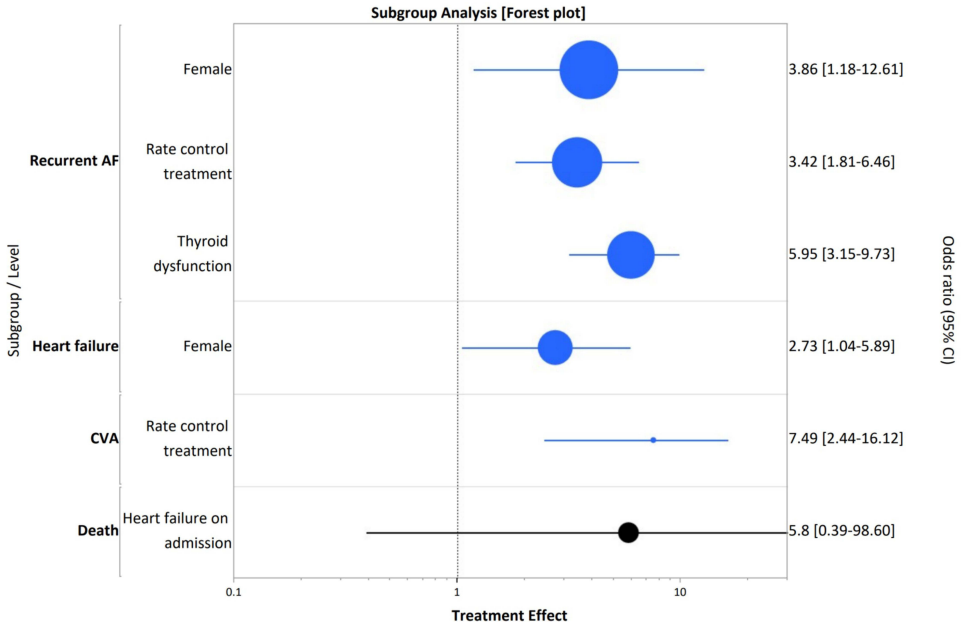
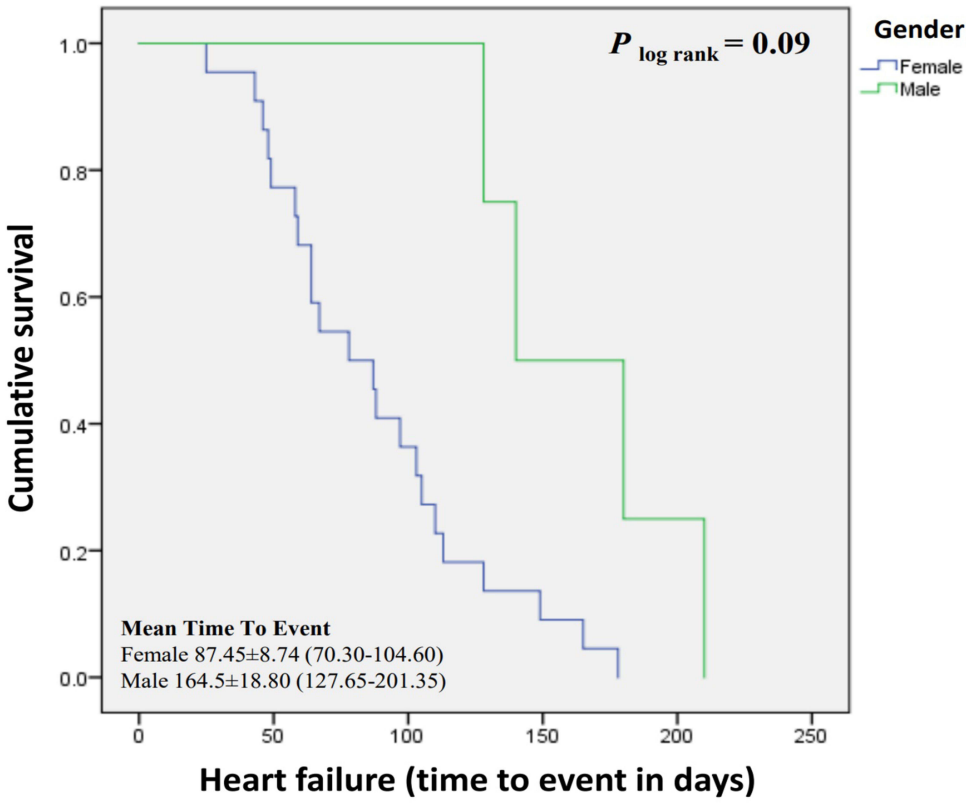
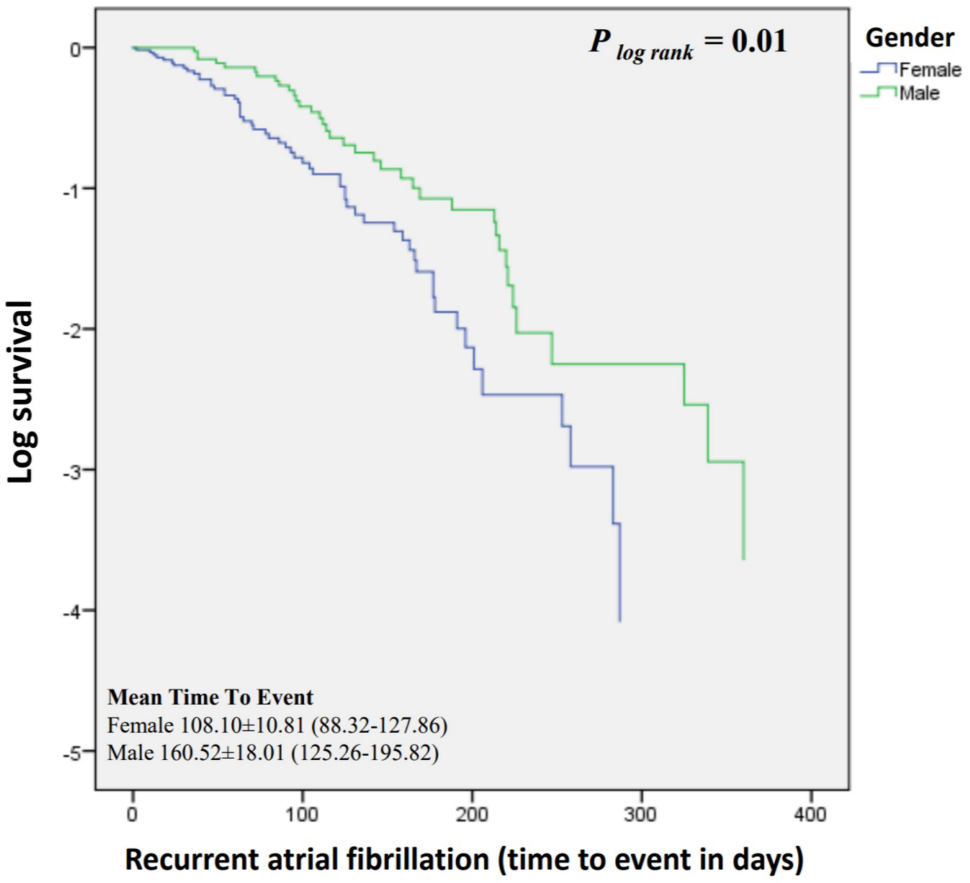


Figure 1 Forest plot subgroup multivariable analysis for outcome.



Number at risk during Follow-up (Days)				
Days	30	60	180	720
Female	1	12	22	22
Male	0	0	3	4

Figure 2 Sex difference in time to Heart Failure hospitalization.



Number at risk during Follow-up (Days)					
Days	30	90	180	270	360
Female	8	31	50	56	59
Male	0	9	25	34	38

Figure 3 Sex difference in time to recurrent AF.

95% CI 0.03–108.78) [Figure 5]. Heart failure on admission was an independent factor for death in both males and females regardless of age (OR 5.8, $\chi 2$ 7.39, P value = 0.02, 95% CI [0.3–95.60]). When assessing the role of catheter ablation, we analyzed twenty-two (6.4%) patients who had undergone at least a single catheter ablation procedure. Fourteen (63.6%) patients were male, and 8 (36.4%) were female. Sinus rhythm was maintained at a higher rate in males after the first ablation (68.7% vs 31.3% at one year, p = 0.04).

Correlation Between Treatment Strategy and Outcomes

Patients who were discharged without anti-arrhythmic agents following sinus conversion exhibited a higher rate of recurrent AF (OR 3.42, $\chi 2$ 17.18, P-value <0.0001, 95% CI [1.81–6.46]) and CVA (OR 7.49, $\chi 2$ 36.18, P-value <0.0001, 95% CI [2.4–16.12]), regardless of treatment success or sex.

Discussion

We described and analyzed sex-based differences in AF patients regarding baseline characteristics, clinical presentations, management, and 1-year outcomes.

Table 4 Gender and Non-Gender-Based Outcome (Multinomial Regression Analysis)

Outcome	Independent Risk Factor	Odds Ratio	Chi-Square	P-value	95 CI%
Gender-based risk factors					
Heart Failure	Female	2.73	11.09	<0.001	1.04–5.89
Recurrent AF	Female	3.86	20.27	0.02	1.18–12.61
Death	Female ≥ 75 years	1.60	20.16	<0.001	1.2–3.4
Non-Gender-based risk factors					
Recurrent AF	Rate control treatment	3.42	17.18	<0.001	1.81–6.46
Recurrent AF	Thyroid dysfunction	5.95	27.94	<0.001	3.15–9.73
CVA	Rate control treatment	7.49	36.18	<0.001	2.44–16.12
Death	HF on admission	5.8	7.39	0.02	0.39–98.60

Notes: Multivariate analysis was done to the following factors: Hypertension, hyperlipidemia, diabetes mellitus, heart failure at baseline, thyroid dysfunction, chronic use of beta-blocker, antiarrhythmic drugs, anticoagulation and antiplatelet treatment and treatment strategy. $CHADS_2$ and CHA_2DS_2-VASc scores were excluded from analysis due to collinearity Collision problem.

Our study shows that females and males with AF have different clinical profiles. Females are much older and have significantly higher cardiovascular comorbidities. Consequently, the mean CHADS2 and CHA2DS2–VASc scores among females are higher and correlate with higher CVA rates seen in prior reports[28–30,37–39] and our population. However, after adjusting gender for age and comorbidities, female sex was no longer an independent risk factor for CVA, suggesting that contributing factor for the high rate of CVA observed is the risk profile of AF females.

The literature suggests that gender-based differences likely play a major role in adverse outcomes such as HF, MACE, and recurrent AF. Interestingly, there is also some data to suggest that catheter ablation, one

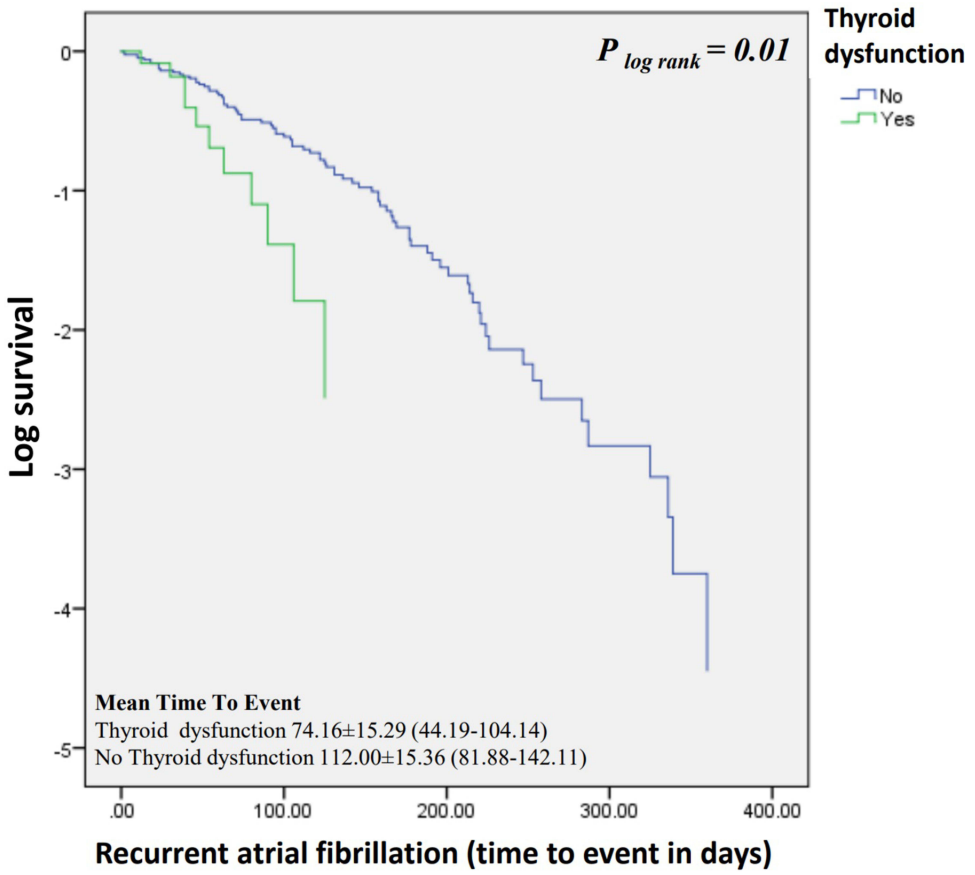
Females had more atypical symptoms, delayed seeking medical care much longer than males, and had a significantly higher rate of thyroid dysfunction. Females were treated less frequently with antiarrhythmic drugs (AAD) for rapid AF conversion and sinus rhythm maintenance. This disparity in treatment may explain the increased incidence of recurrent AF in female patients. Moreover, we believe that existing variations in clinical presentation and the treatment strategy may further contribute to the outcome.

The rate of Heart failure hospitalization was significantly higher among females in our study regardless of age, comorbidities, and heart failure status. Time-to-HF hospitalization was also significantly shorter among females. We could not identify other contributing factors, thus suggesting that the female gender may be a sole risk factor.

While some studies reported higher mortality in women,[29–34] others claimed no difference in mortality.[35,36] Our study did not find a difference in mortality at 1-year. However, subgroup analysis revealed that older (≥75 years) female patients had a significantly higher risk for death than males of the same age, within a much shorter survival time. This finding may explain some of the variability in the data.

Study Limitations

This study has several limitations. Firstly, we employed retrospective methodology using data from computerized systems, obtaining data with no ability to assess its reliability. Secondly, the results were obtained in individuals admitted to the ED due to symptomatic AF. They may not be generalizable to all patients with AF, specifically those



Number at risk during Follow-up (Days)					
Days	30	90	180	270	360
Thyroid dysfunction	11	35	65	79	85
No Thyroid dysfunction	2	6	11	12	12

Figure 4 Thyroid dysfunction and time to recurrent AF.

who may have asymptomatic arrhythmias. In addition, over the 1-year follow-up period, the number of serious medical outcomes was limited compared with the number of predictor variables examined. Our study is also limited due to poor generalizability, given our sample population consisted of only Israeli patients. Lastly, the follow-up period outcomes are related to patients' compliance with medical treatment, which could not be accurately evaluated.

Conclusion

Male and female patients with AF have distinct clinical profiles, risk factors, and outcomes. Females are older, have more comorbidities, and are more frequently treated conservatively. We found a higher incidence of MACE in men, whereas CVA, HF, and recurrent AF were more commonly seen in women. Of note, female sex remained significant only for HF hospitalizations and recurrent AF after gender was adjusted to age and comorbidities. We believe that guidelines should recommend a gender-based approach for prevention, screening, and treatment of AF patients.

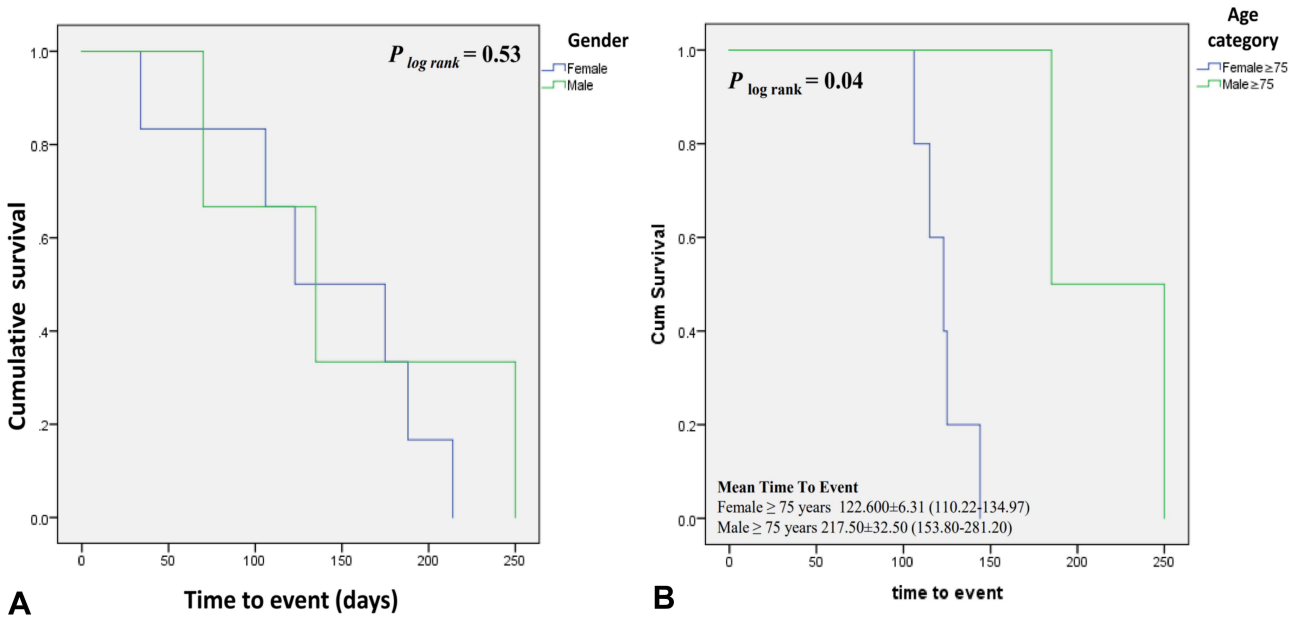


Figure 5 1-Year survival curve (Kaplan-Meier) for Gender (**A**) and for Age-group gender (**B**).

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study did not involve human participants and was based on respective data analysis from computerized medical records. Emek Medical Center IRB waived the need for informed consent due to the use of anonymous patient data and the study's retrospective nature (approval No. 18-0105 EMC). Also, the study was approved by Emek Medical Center Institutional Review Board and conducted following the ethical standards of the institutional research committee following the 1964 Helsinki Declaration and its later amendments and international guidelines.

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Disclosure

All authors report no conflicts of interest in relation to this work and no relationships that could be construed as a conflict of interest.

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