Research Square

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

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Abstract

Background: There are inconsistent and conflicting data among males and females with AF.

Objective: This study intends to analyze whether the sex-based differences among AF patients were influenced by age, co-morbidities, and treatment strategy rather than solely gender difference.

Methods: We analyzed 327 consecutive patients admitted to the ED due to AF for three years and follow-up for a year.

Results: Females with AF were older (p<.001), had higher BMI (p<.001), and a higher rate of co-morbidities as hypertension (p<.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<.001). AF males had a higher rate of coronary disease (p<.001) and heart disease with reduced ejection fraction (p<.001). As a result, the mean $CHADS_2$ and CHA_2DS_2-VASc scores were significantly higher in females (p<.001 for both). Female tends to be treated with rate control medications and less with antiarrhythmic agents (p<.001). Univariate analysis reveals that females had a higher rate of recurrent AF, heart failure hospitalization, CVA, and myocardial infarction. Yet, adjusting gender to age and co-morbidities shows that the females remain to have a higher rate of heart failure hospitalization (OR 2.73 95%CI 1.04-5.89, P-value <.001) and recurrent AF (OR 3.86, P-value =0.02). Thyroid dysfunction and the lack of antiarrhythmic treatment significantly increase the risk of AF (OR 5.95 95%CI 3.15-9.73, OR 3.42, respectively, P-value<.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<.001).

Conclusion AF males and females differ significantly in baseline characteristics. Females are older, have more co-morbidities, and tend to be treated unnecessarily differently for AF. Following age and co-morbidities adjustments, a female gender remains significant for heart failure hospitalization and recurrent AF. Thyroid dysfunction and AF treatment may explain the sex-based difference of recurrent AF.

Introduction

Atrial fibrillation (AF) is a worldwide epidemic (1). It is one of the most frequent cardiovascular diseases, with estimates predicting it will affect up to 12 million people in the USA by 2050 and up to 17.9 million in Europe by 2060 (2–4). AF is also a very common comorbidity in older adults and the most common cardiac dysrhythmia, occurring in 3.3%-10% of all emergency admissions (2, 5).

AF, in and of itself, 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).

sex differences have been long recognized and are well documented in AF, encompassing a different distribution of risk factors, comorbidities, clinical presentation to the Emergency department (ED), and

Major Adverse Cardiovascular Events (MACE) (13–15). Some studies investigating these differences have had conflicting results, regarding epidemiology, long-term risks etc. (2, 14, 16).

This aspect of sex-based differences, although well-studied, is still scantily understood. It is not clear whether the aforementioned disparities are due to sex-based pathophysiologic differences, dissimilarities in presentation and baseline 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 the same diagnostic and therapeutic management, indiscriminate of sex (27). The seeming contradiction between major sex-differences observed in AF and recommended equivalent treatment may require further inquiry and revision of guidelines if evidence-based explanations are discovered.

In this study, we investigate sex-differences in epidemiology, risk factors prior to the onset of AF, clinical manifestations in the ED, immediate management, long-term therapeutic strategies, and 1-year outcome composite of MACE and recurrent AF. The purpose of this study is to characterize the sex-based differences in AF, identify the underlying causes for these differences, obtain a better understanding of the phenomenon, and 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. Included were subjects ≥ 18 years. Data was collected retrospectively regarding patients who admitted to the ED during the study period (June 2014 to June 2017) from internal computer systems ("Orion", "Offek" and "Chameleon") in accordance with International Diagnostic Code ICD-10. Patients were contacted for any missing details. Inclusion and Exclusion criteria are displayed in Table 1.

Table 1
Inclusion and Exclusion Criteria for the Study

Inclusion Criteria	Exclusion Criteria
Atrial fibrillation with clear evidence that began earlier than 48 hours prior ER admission (mainly based on patient complains (	Permanent or Chronic atrial fibrillation
Persistent AF or patient can't 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 a clear evidence that there is no left atrial appendage clot.	AF that was a result of the following: 1. Ischemic heart disease 2. Heart failure 3. Sepsis 4. 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

Statistical analyses

Categorical variables were presented using frequencies and percentages and continuous variables were presented as mean, standard deviation, median and range. To test for sex differences (univariate analysis), t-test was applied for continuous variables and Chi-square or Fisher's exact tests as appropriate for categorical variables. Multivariable analysis was performed using two-steps analysis (for age and gender) and nominal logistic Fit for all the following variables: age, age-specific group (< 64, $\leq 64 < 75$ and ≤ 75), Co-morbidities (BMI, hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, peripheral artery disease, heart failure, previous CVA or TIA and thyroid dysfunction), chronic medication use (beta-blocker, calcium channels blocker, anti-arhythmic drugs, NOAC, warfarin, anti-platelets, and combined antiplatelets and anticoagulation 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 $p < 0.05$.

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 respective data analysis from computerized medical records. Emek Medical Center IRB waived the need of 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.

Results

Baseline Characteristics and Treatment

We enrolled 343 patients in the study; 175 (51%) were female and 168 (48%) male. Descriptive analysis reveals that females were significantly older than males ($p < .001$) 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, $p < .001$, OR 0.9) and a higher rate of co-morbidities as hypertension ($p < .001$) hyperlipidemia ($p = 0.01$), diabetes mellitus ($p = 0.05$), and valvular heart disease ($p = 0.05$). On the other hand, Males had a higher rate of coronary artery disease ($p < .001$) and heart failure with a reduced ejection fraction ($p < .001$). As a result, females had a higher mean score of $CHADS_2$ (1.85 ± 1.3 vs. 1.23 ± 1.2) and CHA_2DS_2-VASc (3.61 ± 1.7 vs. 1.79 ± 1.7) than males ($p < .001$ for both).

Females also had a significantly higher prevalence of thyroid dysfunction than males (18.3% vs. 1.8%, OR 0.08, $p < .001$) and used antiarrhythmic medication less frequent (24.0% vs. 42.8%, $p < .001$*)* [Table 2].

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	63.67 ± 14.6 [21–91]	69.30 ± 11.9 [27–91]	57.79 ± 14.8 [21–87]	< .001	0.93	0.92–0.95
CHA_2DS_2-VASc Score	2.72 ± 1.9 [0–8]	3.61 ± 1.7 [0–8]	1.79 ± 1.7 [0–7]	< .001	0.69	0.58–0.82
$CHADS_2$ Score	1.55 ± 1.3 [0–6]	1.85 ± 1.3 [0–6]	1.23 ± 1.2 [0–6]	< .001	0.55	0.47–0.64
BMI	31.05 ± 6.1 [19–56]	32.65 ± 6.9 [19–56]	29.37 ± 4.6 [20–41]	< .001	0.90	0.87–0.94
Hypertension	217 (63.1)	123 (73.3)	88 (52.4)	< .001	0.4	0.25–0.62
Hyperlipidemia	202 (58.7)	114 (64.8)	88 (52.4)	0.01	0.59	0.38–0.92
Diabetes Mellitus	116 (33.7)	67 (38.1)	49 (29.2)	0.05	0.67	0.42–1.05
Coronary artery disease	67 (19.5)	14 (8.0)	53 (31.5)	< .001	5.33	2.82–10.06
Peripheral Vascular Disease	11 (3.2)	3 (1.7)	8 (4.8)	0.09	2.86	0.74–10.99
CVA	37 (10.8)	22 (12.5)	15 (8.9)	0.18	0.68	0.34–1.36
Heart Failure				< .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)	< .001	0.08	0.02–0.27

BMI, Body mass index; HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; NOAC, New oral anticoagulation.

Highlighted cells denoate a statisticallty siginifican values.

Patient Characteristic	All study population N = 343	Female N (%) = 175 (51)	Male N (%) = 168 (48)	P-value	OR	95 CI%
Valvular Heart Disease	24 (7.0)	17 (9.7)	7 (4.2)	0.05	0.4	0.16-1.00
Chronic renal failure	32 (9.3)	18 (10.2)	14 (8.3)	0.33	0.79	0.38–1.66
Chronic use of medication						
Warfarin	42 (12.2)	26 (14.9)	16 (9.5)	0.09	0.82	0.44–1.53
NOAC	99 (28.8)	60(34.1)	39 (23.2)	0.03	0.58	0.36–0.94
Calcium Chanel blockers	17 (4.9)	9 (5.1)	8 (4.8)	1.00	0.92	0.34–2.46
Beta-blockers	184 (53.5)	107 (60.8)	77 (45.8)	0.04	0.54	0.35–0.83
Anti-platelet	81 (23.5)	28 (15.9)	53(31.5)	< .001	2.43	1.45–4.09
Anticoagulation and Antiplatelet	34 (9.9)	16 (9.1)	18 (10.7)	0.38	1.19	0.58–2.42
Antiarrhythmic agents	114 (33.2)	42 (24.0)	72 (42.8)	< .001	2.41	1.13–4.16
BMI, Body mass index; HFREF, Heart failure with reduced ejection fraction; HFPEF, Heart failure with preserved ejection fraction; NOAC, New oral anticoagulation.						
Highlighted cells denoate a statisticallty siginifican values.						

A sex-based difference was also observed regarding presenting symptoms, admission, and treatment strategy. Females tend to seek medical care much longer (p = 0.01) than males, and more than 10% of the females present with atypical symptoms such as weakness, dizziness, and dyspnea (p = 0.01).

More AF Females tends to be treated with a rate control agent as a sole treatment for rhythm conversion as compared to males (44.9% vs. 20.8%, p < .001, OR 2.55, 95% CI 1.79–3.63) and the use of electrical cardioversion was much lower (7.4% vs. 22%). Consequently, the success rate and the recovery of the sinus rhythm was lower in females (73.9% Vs. 89.9%, p < .001) [Table 3].

Table 3
Sex difference in patient's treatment and outcome (univariate analysis)

Characteristics	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				< .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)	< .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)	< .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

Characteristics	All study population N = 343	Female N (%) = 175 (51)	Male N (%) = 168 (48)	P-value	OR	95 CI%
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

Outcomes

There were 52 (15.16%) cases of MACE, with 12 (3.5%) having CVA, 26 (7.6%) HF admissions, 1 (0.3%) Pulmonary embolism (PE) or Deep vein thrombosis (DVT) and 13 (3.79%) IHD admissions. Unadjusted univariate analysis shows that females had higher heart failure hospitalization, recurrent AF, and CVA than males and had less risk for myocardial infarction [Table 3]. However, following multivariate analysis of adjusting sex to age and co-morbidities (the full list of adjusted variables appears in the statistical analysis paragraph), CVA and myocardial infarction are no longer remain significantly [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-Mayer survival curve**, Fig. 3]. Thyroid dysfunction was found to be an 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-Mayer survival curve**, Fig. 4].

Table 4
Gender and non-gender based outcome (multinomial regression analysis)

Outcome	*Independent risk factor* [X]	*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	< .001	1.2–3.4
Non-Gender-based risk factors					
Recurrent AF	Rate control treatment	3.42	17.18	< .001	1.81–6.46
Recurrent AF	Thyroid dysfunction	5.95	27.94	< .001	3.15–9.73
CVA	Rate control treatment	7.49	36.18	< .001	2.44–16.12
Death	HF on admission	5.8	7.39	0.02	0.39–98.60

Multivariate analysis was done to all of the following factors: hypertension, hyperlipidemia, diabetes mellitus, heart failure at baseline, thryoid dysfunction, chronic use of beta-blocker, anti-arrythmic drugs, anticoagulation and antiplatet treatment and treatment strategy. $CHADS_2$ and CHA_2DS_2-VASc scores were excluded from analysis due to collinearity collison problem.

The presence of atypical symptoms as nausea, dizziness, weakness, and dyspnea correlated with higher risk for recurrent AF (OR 4.09, χ2 5.17, P-value = 0.02, 95% CI [1.08–15.41]) and HF hospitalization (OR 3.93, χ2 3.75, P-value = 0.05, 95% CI [1.34–6.87].

During follow-up, 9 (2.62%) patients died, six female 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, χ2 20.16, P < .001, 95%CI 1.2–3.4) [Table 4], and the survival time was much shorter (HR 63.35, χ2 4.19, P-value = 0.04, 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, χ2 7.39, P value = 0.02, 95% CI [0.3–95.60]).

Correlation between Treatment Strategy and Outcomes

The use of a rate control strategy as a sole treatment for AF conversion, followed by rate control medication for maintenance was associated with a higher rate of recurrent AF (OR 3.42, χ2 17.18, P-value < 0.0001, 95% CI [1.81–6.46] and CVA (OR 7.49, χ2 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, presenting signs and symptoms, immediate therapeutic approach, and 1-year outcomes.

Our study shows that females and males with AF have different clinical profiles. Females are much older and had significantly higher cardiovascular comorbidities. As a result, the mean CHADS2 and CHA2DS2–VASc scores among females are much higher and correlate with higher CVA rates seen in prior reports (28–30, 37–39) and our population. However, using multivariate analysis and adjusting gender for age and comorbidities discard females as an independent factor for CVA and indicate that the main contribution for the high CVA rate is the risk profile of AF females.

Concerning other outcomes, like heart failure, MACE, and recurrent AF, the literature seems more supported that the differences could not be explained by factors other than gender.

We reported a significantly high incidence of recurrent AF and a shorter time-to-AF among females even after adjusting to age and comorbidities, suggesting that gender plays a major role in recurrent events. Moreover, we believe that disparity in clinical presentation and the treatment strategy may further contribute to the outcome. Females had more atypical symptoms, sought medical care much longer than males, and had a significantly higher rate of thyroid dysfunction. Females were treated differently with less anti-arrhythmic drugs (AAD) for rapid AF conversion and sinus rhythm maintenance. We assume that physicians' tendency for a more cautious and conservative approach due to frailty and fragility and patient preference could explain the difference in treatment approaches and should be recognized as sex-based risk factors that potentially contribute to a recurrent event.

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 supporting the outcome 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, alongside a much shorter survival time. This finding may explain some of the variability of 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 that admitted to the ED due to the rhythm disorder and may thus not be indicative to all patients with AF, specifically those 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. Lastly, the follow-up period outcomes are related to patients' compliance with medical treatment, which could not be accurately and genuinely evaluated.

Conclusion

AF Males and Females have distinctive clinical profiles, risk factors, and outcomes. Females are older, have more co-morbidities, and tend to be treated more conservatively for AF, for no clear reason. Univariate analysis shows higher incidence of MACE in men, while higher incidence of CVA, heart failure and recurrent AF in women. Yet, following age and co-morbidities adjustments, female sex remains significant only for HF hospitalizations and recurrent AF. The variances in Thyroid dysfunction rates and AF treatment strategies may be the culprit to the sex-based difference of recurrent AF. We believe that the international guidelines should acknowledge all aspects of sex-based differences in AF patients and recommend a different gender-based approach concerning prevention, screening, and treatment aims for males and females.

Declarations

1. **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 of 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.
2. **Consent for publication – N/A**
3. **Availability of data and materials** – The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.
4. **Competing interests** – The authors declare that they have no competing interests.
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6. **Authors' contributions** – AI, DG, AY, SE and OK contributed to the writing, editing, formatting of the main manuscript, and production of the figures. AY was responsible for main data collection, ER, OK, and YT provided care to the patients and revised the manuscript. OK and AI contributed to statistical analysis and the writing process of the reviewed manuscript. OK certified that all authors have contributed and met the criteria for authorship.
7. **Acknowledgment** – N/A
8. **Authors' information (optional)** – N/A

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Figures

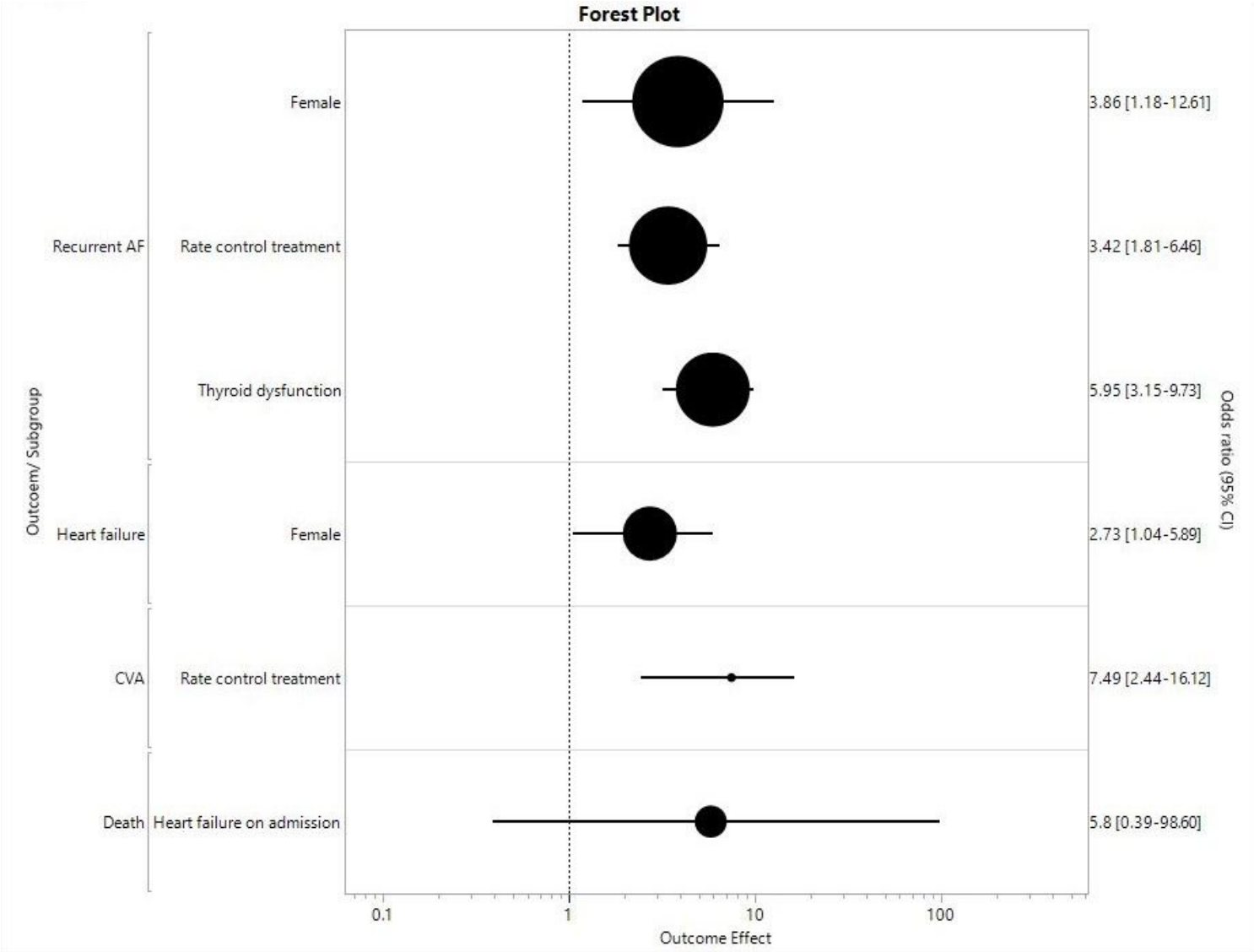
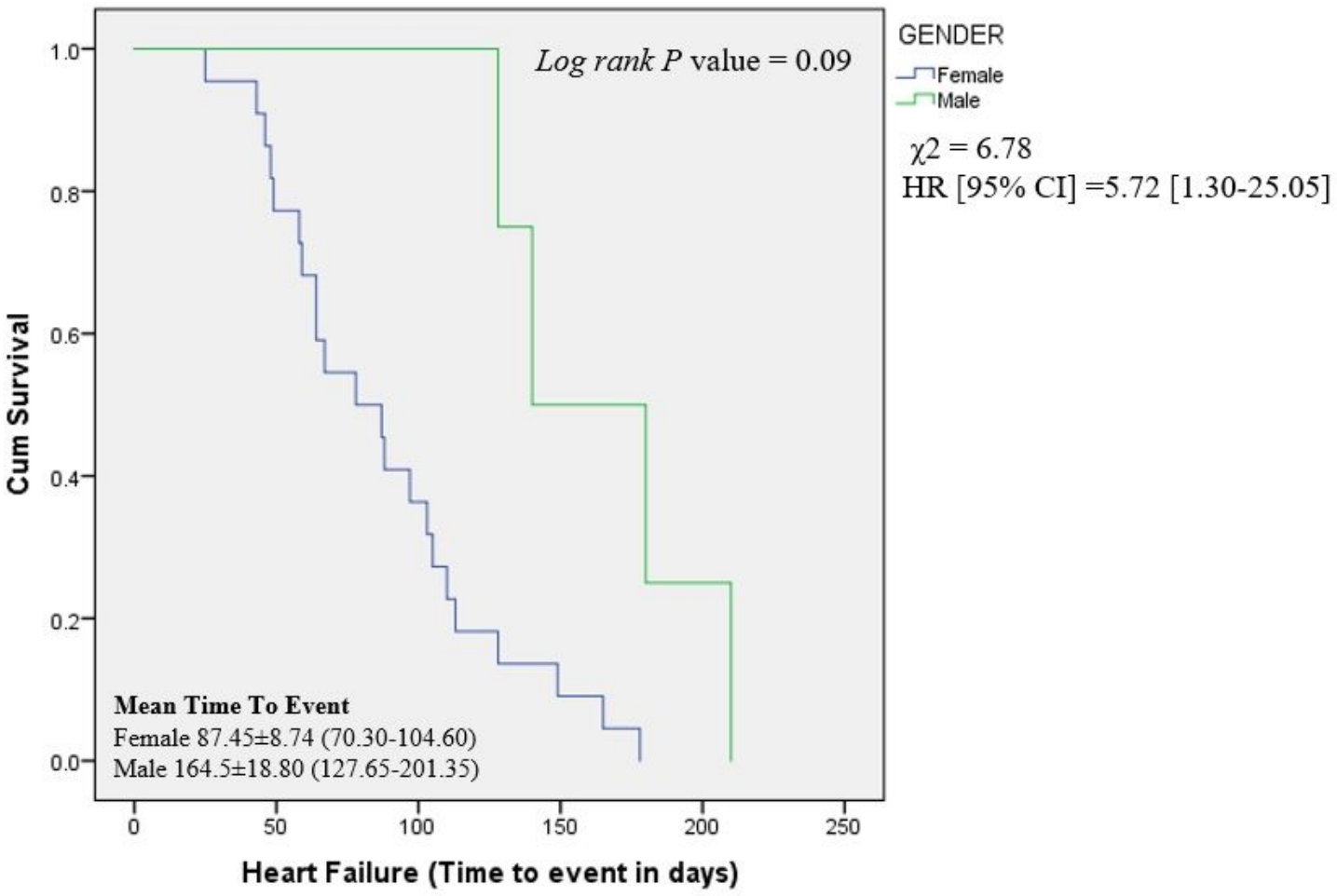


Figure 1

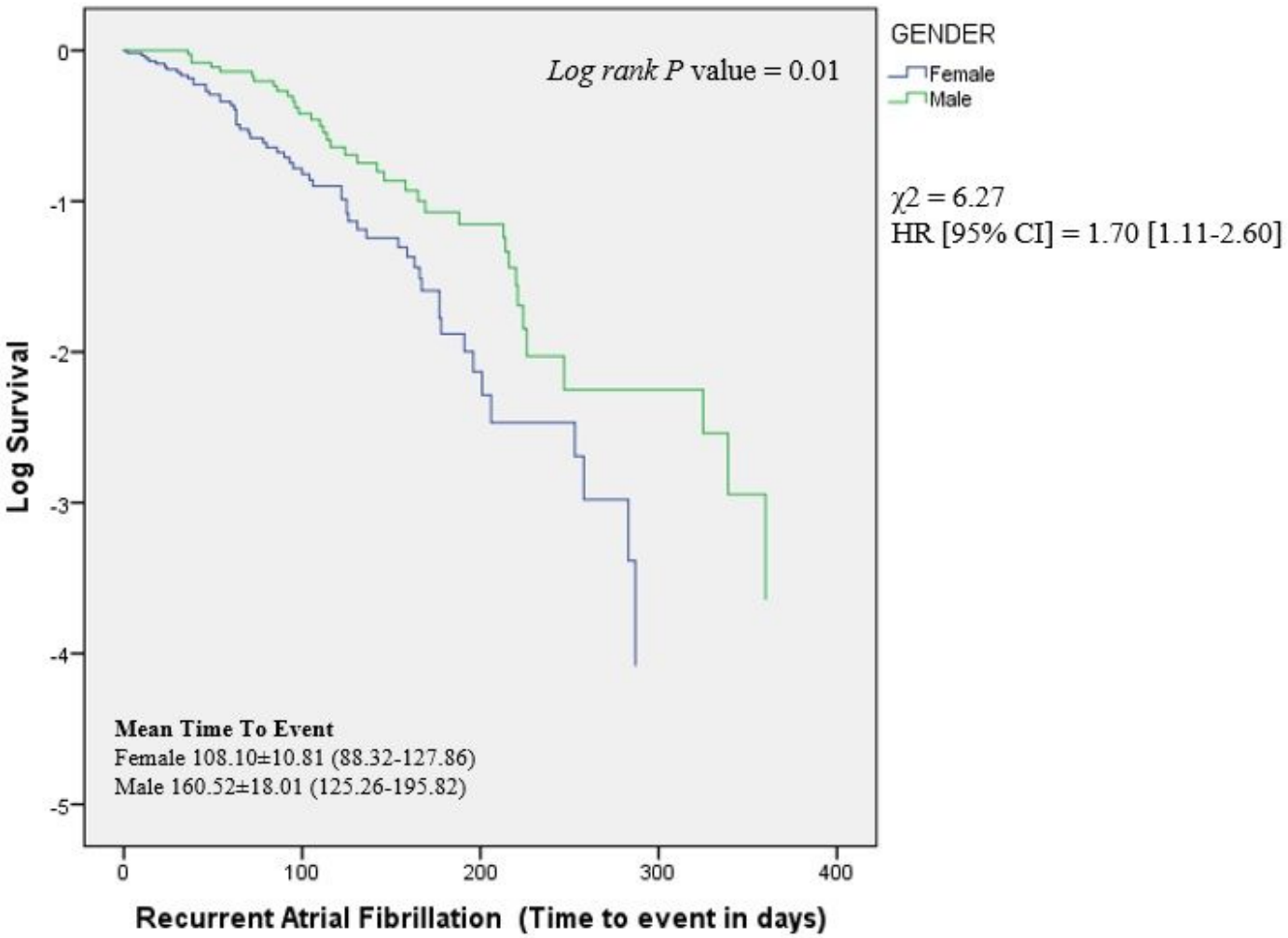
Forest plot subgroup multivaraible analysis for outcome



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

Figure 2

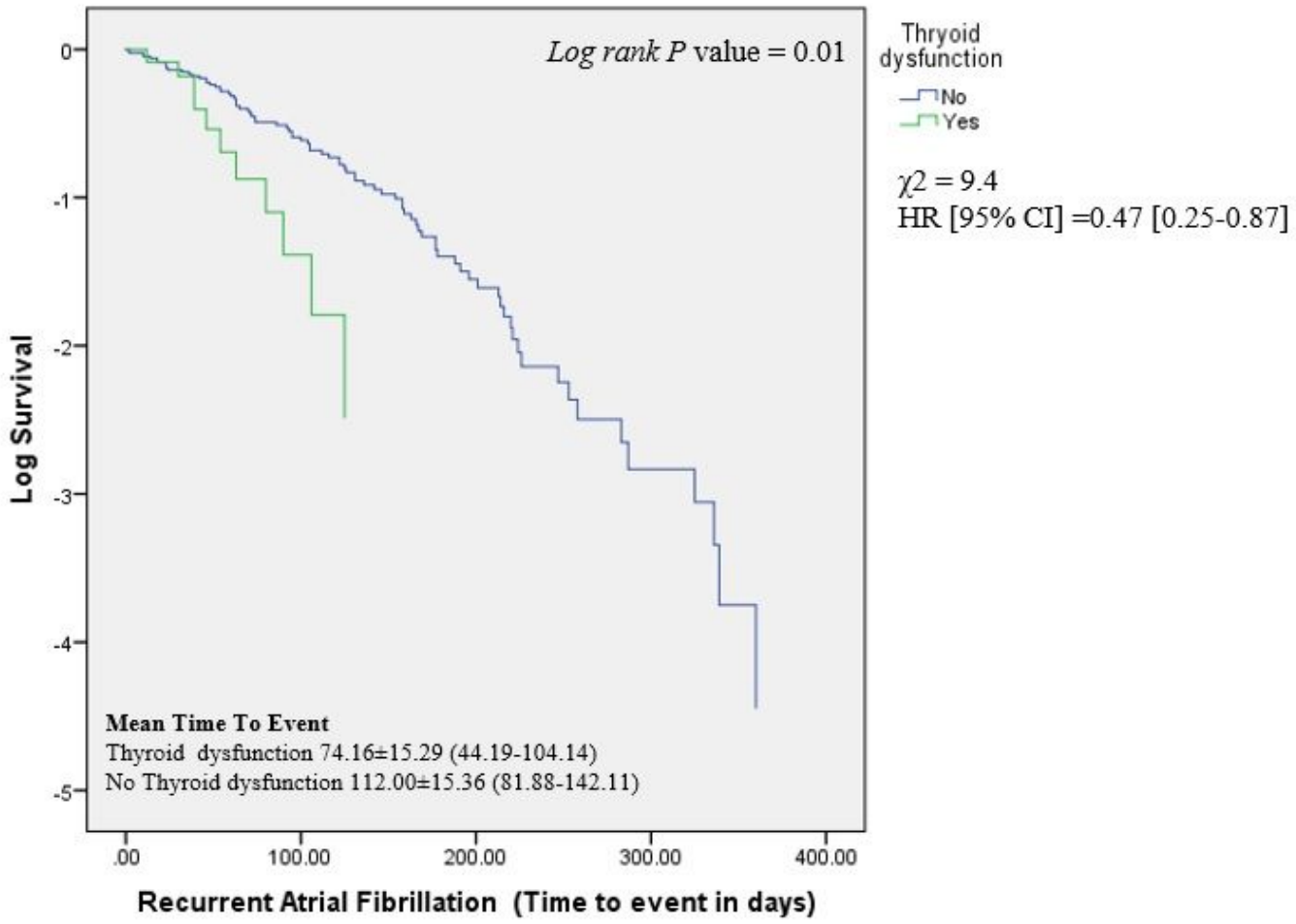
Sex difference in time to Heart Failure hospitalization



	Number at risk during Follow-up (Days)				
	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



	Number at risk during Follow-up (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

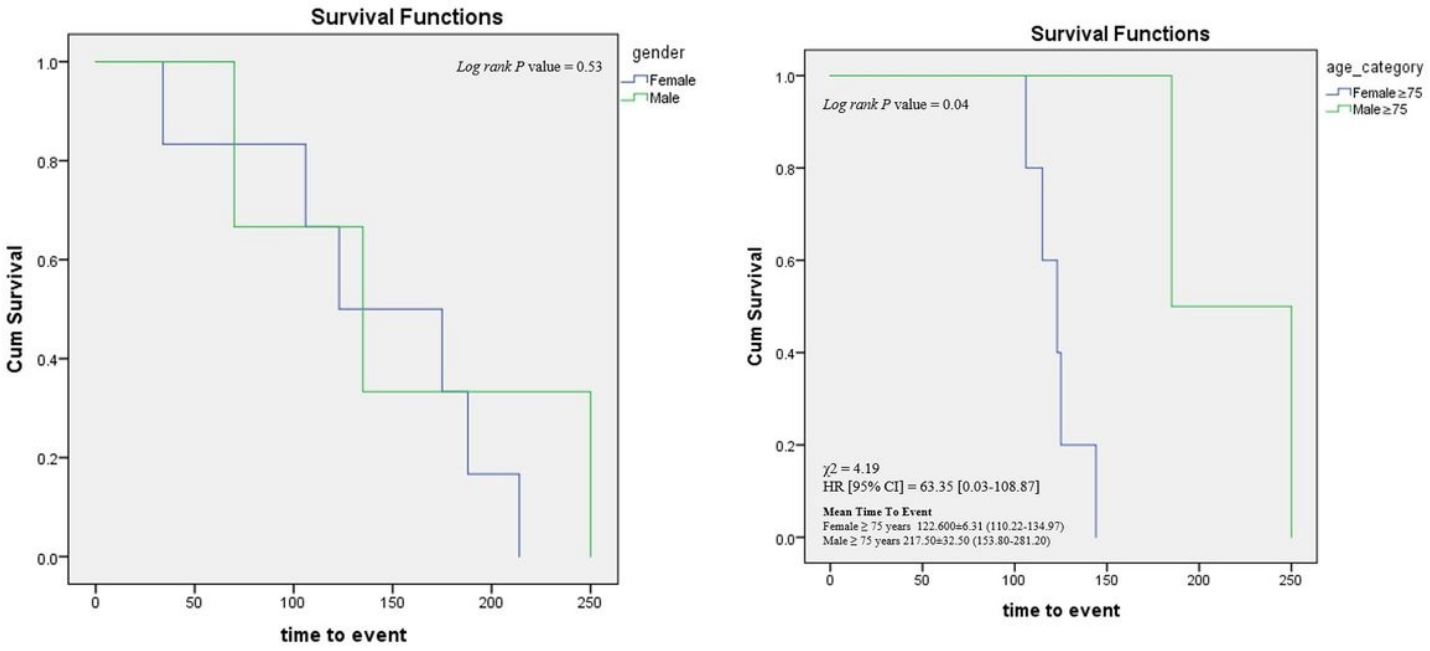


Figure 5

1-Year survival curve (Kaplan-Meier) for gender (A) and for age-group gender (B).