Sex Differences in Presentation, Quality of Life, and Treatment in Chinese Atrial Fibrillation Patients: Insights from the China Atrial Fibrillation Registry Study

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Background: There is a growing recognition of sex-related disparities in atrial fibrillation (AF). However, limited data is available in Chinese AF patients.

Material/Methods: We compared symptoms, quality of life (QoL), and treatment of AF according to sex from the China AF Registry study.

Results: We studied 14,723 patients with non-valvular AF, of whom 5,645 patients (38.3%) were female. Women were older than men (67.5±10.6 vs. 62.2±12.2). Compared to men, women had more comorbidities and a higher proportion of CHA\textsuperscript{2}DS\textsuperscript{2}-VASc score ≥2. Women with AF experienced more severe or disabling symptoms than men (33.7% vs. 22.9% in age <75 group; 40.3% vs. 28.7% in age ≥75 group; both \(P<0.0001\)). After multivariate analysis, women with AF still had lower QoL (OR 0.69; 95%CI, 0.63–0.76; \(P<0.0001\)). Women tended to have lower rates of ablation and rhythm-control drug use in those aged <75 years. Oral anticoagulant use was low and had no sex difference in AF patients with a CHA\textsuperscript{2}DS\textsuperscript{2}-VASc score ≥2.

Conclusions: In Chinese AF patients, women were older and more symptomatic, and had worse QoL. Despite all these differences, women tended to receive less rhythm-control treatment in those aged <75 years. Oral anticoagulant use was substantially underused in high stroke risk patients, regardless of sex.

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MeSH Keywords: Atrial Fibrillation • Quality of Life • Sex Characteristics • Therapeutics

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Background

Atrial fibrillation (AF), the most common arrhythmia, affected more than 33 million individuals in 2010 worldwide. It increases the burden of stroke, heart failure, cognitive decline, and mortality [1,2]. Sex-related disparities in AF are increasingly acknowledged [3–5]. Western countries have reported that clinical presentations and quality of life (QoL) differed between women and men with AF [6–8], and women with AF seemed to be under-treated compared to men [8–10]. However, sex differences are not well-examined in Chinese AF patients.

The China AF Registry study is an ongoing prospective registry – one of the largest for Asian AF patients. It will provide an excellent opportunity to evaluate this knowledge gap. A better understanding of the sex differences in AF may have important implications for quality improvement to reduce or even eliminate the sex disparities in AF care.

In this study, we used data from the China AF Registry to evaluate sex-related differences with the presentation, QoL, and treatment in Chinese AF patients.

Material and Methods

The China AF Registry study is a prospective, multicenter, ongoing registry study of AF patients from 31 hospitals in Beijing, China. The design of the study had been published [11]. Local ethics committee approval was obtained and all participants provided signed informed consent.

Study population

The China AF Registry study had enrolled 19,515 AF patients from August 2011 to December 2016. In this analysis, we excluded 546 patients with mitral stenosis or valvular surgery, 3380 patients without valid Atrial Fibrillation Effects on Quality of Life (AFEQT) questionnaires, and 866 patients without European Heart Rhythm Association (EHRA) classification data. Finally, we included 14,723 participants. Figure 1 shows a flowchart of the study.

Data collection

Clinicians in participating hospitals collected data from medical charts. Collecting information included necessary socio-demographic data, AF type and duration, medical history, symptom and AFEQT questionnaires, and previous and current treatment. We defined variables according to the ACC/AHA recommendations on AF clinical data standards [12].

AF symptoms and QoL evaluation

AF-related symptoms were evaluated using the EHRA AF symptom classification: no symptoms (EHRA I), mild symptoms (EHRA II), severe symptoms (EHRA III), and disabling symptoms (EHRA IV) [13].

A Chinese version of the AFEQT questionnaire was collected to assess health-related quality of life (HRQoL) at baseline. The AFEQT questionnaire is an AF-specific QoL evaluation which was recently developed and validated, supporting its use as a self-administered outcome measure in studies and as a tool for disease management [14]. The AFEQT questionnaire contains 20 questions to evaluate the influence of AF on patients’ HRQoL during the past 4 weeks. The 18 items generate 3 individual subscales – Symptoms, Daily Activities, and Treatment Concern. The last 2 indicate the Treatment Satisfaction domain. Overall AFEQT score is calculated based on the first 3 functional subscales. To be valid, the AFEQT questionnaires must have should at least half of the questions answered for each domain. AFEQT is scored with a 7-point Likert scale. The range of overall AFEQT or subscale scores is 0–100. Score 0 represents extremely disability and 100 indicates not at all limited. Thus, higher ratings indicate a better health status. For a percentage grading system of AFEQT scores, we set ≥60 as passing scores indicating a ‘normal level’ of QoL, and the lower score sections as mild impairment of QoL (AFEQT scores 40–59), moderate impairment of QoL (AFEQT scores 20–39) and severe impairment of QoL (AFEQT <20).

Statistical analysis

Continuous variables showed a mean±standard deviation or median (interquartile range); differences were assessed using the t test or Wilcoxon rank-sum test. Categorical variables are
Table 1. Baseline characteristics according to sex and age.

| Characteristics                        | Age <75 (N=11151) |          | Age ≥75 (N=3208) |          |
|----------------------------------------|-------------------|----------|------------------|----------|
|                         | Female | Male   | P value | Female | Male   | P value |
| Age (years)               |        |        |         |        |        |         |
| Age <75 (N=11515)         |        |        |         |        |        |         |
| Age ≥75 (N=3208)          |        |        |         |        |        |         |
| Health insurance coverage |        |        |         |        |        |         |
| None                     | 300/4053 | 512/7462 | &lt;0.0001 | 95/1592 | 65/1616 | &lt;0.0001 |
| Low                      | 1729/4053 | 2510/7462 |         | 781/1592 | 673/1616 |         |
| High                     | 2024/4053 | 4440/7462 |         | 716/1592 | 878/1616 |         |
| Completed high school     | 839/3624 | 2975/7109 | &lt;0.0001 | 320/1592 | 548/1616 | &lt;0.0001 |
| BMI                      | 25.6±4.0 | 25.9±3.4 | &lt;0.0001 | 24.6±4.0 | 24.2±3.3 | 0.001   |
| Smoking                  | 76/4042 | 2244/7441 | &lt;0.0001 | 41/1579 | 179/1605 | &lt;0.0001 |
| Drinking                 | 60/4045 | 2832/7428 | &lt;0.0001 | 177/1578 | 277/1605 | &lt;0.0001 |
| Medical History           |        |        |         |        |        |         |
| Heart failure             | 502/4053 | 746/7462 | &lt;0.0001 | 561/1592 | 472/1615 | 0.0003  |
| Hypertension              | 2651/4052 | 4135/7458 | &lt;0.0001 | 1319/1589 | 1215/1615 | &lt;0.0001 |
| Diabetes mellitus         | 987/4052 | 1611/7460 |         | 526/1592 | 454/1615 |         |
| Previous stroke/TIA/SE    | 550/4051 | 993/7455 | 0.001   | 397/1589 | 424/1614 | 0.405   |
| Vascular disease          | 520/4050 | 1029/7455 | 0.042   | 398/1588 | 458/1612 | 0.032   |
| Previous bleeding         | 170/4051 | 321/7455 | 0.001   | 101/1585 | 114/1612 | 0.421   |
| Hyperlipidemia            | 1290/4043 | 2075/7448 | &lt;0.0001 | 602/1587 | 477/1608 | &lt;0.0001 |
| eGFR <60 mL/min/1.73 m²    | 110/3180 | 79/5919 | &lt;0.0001 | 185/1538 | 111/1317 | &lt;0.0001 |
| AF type                   |        |        |         |        |        |         |
| Newly diagnosed           | 232/4050 | 286/7455 | &lt;0.0001 | 151/1591 | 151/1616 | 0.528   |
| Paroxysmal                | 2643/4050 | 4163/7455 |         | 774/1591 | 757/1616 |         |
| Persistent                | 1175/4050 | 3006/7455 |         | 666/1591 | 708/1616 |         |
| AF duration (years)       | 2.4 | 2.5 | 0.052 | 3.0 | 3.6 | 0.001 |
| CHA<sub>2</sub>DS<sub>2</sub>-VASC |        |        |         |        |        |         |
| 0 or 1                    | 722/4050 | 4073/7452 | &lt;0.0001 | 0 | 0 | – |
| ≥2                       | 3328/4050 | 3379/7452 | &lt;0.0001 | 1588/1588 | 1612/1612 |         |

Values are n/N (%), mean±SD or median (IQR). Denominators may be subject to missing data. BMI – body mass index; TIA – transient ischemic attack; SE – systemic embolism; eGFR – estimated glomerular filtration rate; AF – atrial fibrillation; IQR – interquartile range; CHA<sub>2</sub>DS<sub>2</sub>-VASC – cardiac failure or dysfunction, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke (doubled)–vascular disease, age 65–74 years, and sex category (Female).
AF-related symptoms

Female AF patients experienced more severe or disabling symptoms, with a higher proportion of EHRA III and IV classification, than men (35.6% vs. 24.0%, P<0.0001). Only 5.4% of women had no symptom, compared with 8.4% of men (Figure 2). Both age groups had similar results.

Quality of life

Figure 3 summarizes the proportion of the overall and each subscale of AFEQT scores by sex and age. Women had a lower percentage of an average QoL level (AFEQT ≥60 scores) than men (54.1% vs. 66.7% in overall patients, 57.0% vs. 68.5% in age <75 years group and 46.8% vs. 58.4% in those aged ≥75 years group, both P<0.0001). The subscales of Symptoms, Daily Activities, and Treatment Concern all showed consistent results (Figure 3). We also compared the mean value of overall AFEQT and each subscale score by sex, type of AF, and CHA\_DS\_2-VASc scores, as shown in Figure 4. Women had lower overall AFEQT scores than men in those aged <75 years (59.6±15.0 vs. 64.4±14.2, P<0.0001) and in older groups (57.5±15.1 vs. 61.2±15.3, P<0.0001). In newly diagnosed, paroxysmal AF, or persistent AF, women had lower overall AFEQT scores than men (All P<0.05 except for newly diagnosed AF in age ≥75 years group). Also, the AFEQT scores decreased in women across all CHA\_DS\_2-VASc score groups. After the correction of demographics, comorbidities, and pharmacological treatments, female sex remained independently associated with lower overall AFEQT score (OR 0.69; 95%CI, 0.63–0.76; P<0.0001).

AF-related treatment

We found no sex disparity in the prior use of electrical cardioversion (Table 2). Women tended to receive less AF ablation (5.7% vs. 6.7%, P=0.025) in those aged <75 years, but not in patients age ≥75 years (2.0% vs. 2.0%, P=0.949). In the group age <75 years, women were more likely to receive the rate control (51.4% vs. 46.9%, P<0.0001), but fewer received rhythm-control drugs (35.5% vs. 39.8%, P<0.0001). However, in the elderly group, current rhythm-control drug use had no significant difference between women and men (20.2% vs. 20.9%, P=0.664), while women still were more likely to receive rate control therapy (65.2% vs. 59.3%, P=0.001). Both women and men with CHA\_DS\_2-VASc score ≥2 had low rates of oral anticoagulant (OAC) use (32.1% vs. 30.1% in those aged <75, P=0.081; and 34.6% vs. 35.3% in those aged ≥75, P=0.700).

Discussion

This massive Chinese AF cohort study indicated that women with AF tended to be older, with more comorbidities and

Figure 2. Proportions of each EHRA classification by Sex. European Heart Rhythm Association (EHRA) AF symptoms classification was defined as no symptoms (EHRA I), mild symptoms (EHRA II), severe symptoms (EHRA III), and disabling symptoms (EHRA IV). F – Female; M – Male. * P<0.0001, Female vs. Male.

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A two-tailed P value <0.05 was considered statistically significant. We used SAS software 9.2 for data analyses.

Results

Among 14 723 patients with AF included in this study, 5645 (38.3%) were women. Table 1 shows the characteristics of the patients. Since women were older on average by 5 years than men in the study (67.5±10.6 vs. 62.2±12.2, P<0.0001), we stratified the patients by age<75 and age ≥75 groups. In both age groups, women had higher rates of heart failure, hypertension, diabetes, and renal dysfunction, but a lower rate of vascular disease. Previous thromboembolism was similar according to sex in both 2 age groups. Paroxysmal AF (65.3% vs. 55.8%, P<0.0001) and a CHA\_DS\_2-VASc score ≥2 (82.2% vs. 45.3%, P<0.0001) was more prevalent in women for those aged <75 years.
After adjustment, women had lower QoL than men. Moreover, despite being much more likely to be symptomatic, women tended to receive less rhythm-control treatment in those aged <75. OAC use was low and had no sex difference in high stroke risk AF patients.

Prior extensive cohort studies have shown sex disparities in clinical features, treatment, and outcomes of AF in Western countries [6,7]. Female AF patients tended to be older, and were more likely to have a high burden of hypertension and heart failure with a preserved ejection fraction [15]. However, few studies have reported the association between sex and symptom burden and QoL [16,17]. In a European survey, the EORP-AF study, women were found to have more symptoms, including palpitations, fear, and anxiety [7]. A systematic review suggested that asymptomatic AF was less common among women than among men [18]. A Europe survey reported that women had a lower general QoL using EuroQol scores [8]. The ORBIT-AF registry [6], a US-based observational study, has demonstrated that female AF patients had more significant impairment of HRQoL as measured by specific AFEQT scores. Such sex differences were consistent with our large cohort study of Chinese AF patients, and a recently published systemic review has confirmed this [19]. The physical and psychosomatic characteristics of female patients may be related to the observed differences in clinical characteristics and presentation [20–24]. Older age may also contribute to the differences in comorbidities, since women were older by an average of 5 years compared with men [20]. However, the differences in QoL were still significant after multivariable adjustment.

Guidelines indicate rhythm-control therapy to improve the symptom of AF patients (Class I, level B) [25]. In our study, younger (age <75) female AF patients were treated more conservatively with less catheter ablation or antiarrhythmic drugs than men, despite having a higher proportion of paroxysmal AF.

**Figure 3.** Proportions of each section in overall AFEQT and subscales scores by sex. AFEQT scores were classified as 4 sections: normal level of QoL (AFEQT scores ≥60), mild impairment of QoL (AFEQT scores 40–59), moderate impairment of QoL (AFEQT scores 20–39), and severe impairment of QoL (AFEQT <20). (A) Overall patients; (B) Patients aged <75 years old; (C) Patients aged ≥75 years old. AFEQT – Atrial Fibrillation Effects on QualiTy of Life; SY – symptoms; DA – daily activities; TC – treatment concern; TS – treatment satisfaction; F – Female; M – Male. * P<0.0001, ** P=0.025, *** P=0.01, Female vs. Male.
Table 2. AF-related treatment stratified by sex and age.

| Treatment                          | Age <75 (N=11515) |  | Age ≥75 (N=33208) |  |
|-----------------------------------|-------------------|---|------------------|---|
|                                   | Female (N=4053)   | Male (N=7462) | Female (N=1592) | Male (N=1616) |
| Prior electrical cardioversion    | 76 (1.9)          | 178 (2.4)      | 0.075            | 10 (0.6)      | 15 (0.9)      | 0.334 |
| Prior AF catheter ablation        | 230 (5.7)         | 503 (6.7)      | 0.025            | 32 (2.0)      | 33 (2.0)      | 0.949 |
| Current rhythm-control drugs      | 1437 (35.5)       | 2970 (39.8)    | <0.0001          | 332 (20.9)    | 327 (20.2)    | 0.664 |
| Propafenone                       | 757 (18.7)        | 1213 (16.3)    | 0.001            | 108 (6.8)     | 116 (7.2)     | 0.661 |
| Amiodarone                        | 564 (13.9)        | 1621 (21.7)    | <0.0001          | 157 (9.9)     | 171 (10.6)    | 0.501 |
| Sotalol                           | 90 (2.2)          | 128 (1.7)      | 0.058            | 26 (1.6)      | 20 (1.2)      | 0.346 |
| Current rate control drugs        | 2083 (51.4)       | 3502 (46.9)    | <0.0001          | 1038 (65.2)   | 959 (59.3)    | 0.001 |
| β-blocker                         | 1921 (47.4)       | 3232 (43.3)    | <0.0001          | 895 (56.2)    | 807 (49.9)    | <0.0001 |
| Calcium-channel blockers          | 199 (4.9)         | 270 (3.6)      | 0.001            | 138 (8.7)     | 107 (6.6)     | 0.029 |
| Digoxin                           | 252 (6.2)         | 384 (5.1)      | <0.016           | 234 (14.7)    | 201 (12.4)    | 0.062 |
| * Current OAC(CHA\(_2\)-VASC ≥2) | 1002/3328 (30.1)  | 1084/3379 (32.1)| 0.081            | 560/1588 (35.3)| 558/1612 (36.6)| 0.700 |

Values are n (%), except where indicated. * Rates of current OAC are expressed as the number of patients received oral anticoagulant treatment divided by the number of patients who have indication for anticoagulation treatment (i.e., CHA\(_2\)-VASC ≥2). AF – atrial fibrillation; OAC – oral anticoagulant; CHA\(_2\)-VASC – cardiac failure or dysfunction, hypertension, age ≥75 years (doubled), diabetes mellitus, stroke (doubled)–vascular disease, age 65–74 years, and sex category (Female).

more severe AF-related symptoms, and worse QoL. The ORBIT-AF study did not find sex-specific differences in the use of antiarrhythmic drugs [6], but women tended to receive less effective cardioversion or ablation therapy. The EORP-AF study reported similar differences in treatment [7]. Women with symptomatic AF received less rhythm-control treatment, and we observed the same treatment pattern in asymptomatic patients.

Nevertheless, these studies did not adjust for some critical factors, including age, comorbidities, duration, and symptom burden of AF. The reasons for the disparities remain mostly unknown, and potential explanations include sex differences in patient preferences and other clinical and socioeconomic factors [26]. Age may play an essential role in treatment strategy referral [15]. In our study, there was no sex-specific difference in rhythm-control treatment for patients ≥75 years. The efficacy and safety of antiarrhythmic drugs for women may influence the treatment preferences [27–29]. In addition, women tended to be less educated and less covered by health insurance than men in our study. Thus, they may be more likely to delay seeking medical care and to accept more conservative treatment than men.

Our study observed that OAC for preventing stroke in high-risk patients was substantially underused regardless of sex, and women received OAC use similarly to men. Previous substantial worldwide cohort research reported no sex differences in the use of OAC [30,31]. The EORP-AF and ORBIT-AF study found similar results [6, 7]. However, in another outpatient AF cohort, with a CHA\(_2\)-VASC score ≥2, women were associated with less frequent prescription of OAC [32]. Although the previous research suggested that female sex is not an independent risk factor of thromboembolism [33], women had poorer long-term outcomes among stroke survivors [34,35]. The extensive treatment gap in OAC use for stroke prevention remains in Chinese AF patients of both sexes. Therefore, great efforts are warranted to promote OAC therapy among high-risk patients with AF in China.

Limitations

First, the China AF Registry is a hospital-based registry; thus, patient selection bias is possible. Women may tend to not seek medical help until they experienced severe symptoms and significantly impaired QoL. However, these patients are representative of the patients we meet in clinical practice and thus are clinically relevant. Second, participating hospitals in this study are in Beijing, China’s capital; however, about half of the participants came from all over the country, thus increasing the population samples’ representativeness. Finally, statistical methods cannot adequately correct for residual or unmeasured confounders in a registry study.
Conclusions

In this prospective Chinese Registry, women with AF tended to be older, with more comorbidities, and had more severe symptoms and poorer QoL, compared to men. Despite all these factors, women tended to receive less rhythm-control treatment than men in those aged <75 years. OAC was substantially underused in high stroke risk patients regardless of sex.

Figure 4. Mean overall AFEQT and subscales scores by sex and type of AF and CHA2DS2-VASc scores between females and males. (A) Mean overall AFEQT and subscales scores by sex; (B) Mean overall AFEQT and subscales scores by sex and type of AF. (C) Mean overall AFEQT and subscales scores by sex and CHA2DS2-VASc scores. AFEQT – Atrial Fibrillation Effects on Quality of Life; SY – symptoms; DA – daily activities; TC – treatment concern; TS – treatment satisfaction. * P<0.0001, ** P<0.05, Female vs. Male.
Disclosures

Dr. Jian-Zeng Dong received honoraria for giving lectures from Johnson & Johnson.

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Other authors declare no conflict of interest.

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