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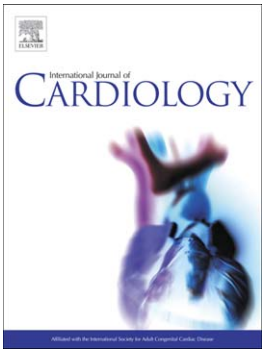

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Sex differences in clinical characteristics and inpatient outcomes amongst 2442 hospitalized Chinese patients with nonvalvular atrial fibrillation: The Nanchang Atrial Fibrillation Project

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ABSTRACT

Background Limited data exists on the impact of sex on clinical characteristics and outcomes amongst nonvalvular AF patients from China. We investigated the impact of gender on risk factors and inpatient mortality in a hospitalised nonvalvular AF cohort in Nanchang, China.

Methods We studied consecutive patients hospitalised with nonvalvular AF between May 2011 and December 2013. Predictors of inpatient mortality were evaluated using multivariate regression analyses.

Results We studied 2,442 patients (43.7% female; mean age 71.8), with a median hospital stay of 10 days (IQR: 7-14). Inpatient mortality was 2.2%. Mean age, $CHADS_2$ and CHA_2DS_2-VASc scores were higher in females vs. males (all $p<0.0001$). Oral anticoagulation use during hospitalization was 33.3% without sex differences, and length of stay and inpatient outcomes were comparable between sexes.

On multivariate analyses, the significant risk factors of inpatient death in females were previous ischemic stroke/transient ischemic attack (TIA)/thromboembolism (TE) (Odds Ratio (OR): 2.27; 95% Confidence Intervals (CI): 1.43-3.61), peripheral artery disease (OR: 5.75, 95% CI: 1.49-22.16) and chronic renal disease (OR: 5.68, 95% CI: 1.46-22.13). Among males, only age (OR: 1.06, 95% CI: 1.02-1.11) and previous ischemic stroke/TIA/TE (OR: 1.81, 95% CI: 1.25-2.63) were independent predictors of inpatient mortality.

Conclusion Sex related differences in clinical characteristics and stroke risk profile were evident in Chinese nonvalvular AF patients, but no sex disparity was evident in the low

antithrombotic therapy use or inpatient mortality. Previous ischemic stroke/TIA/TE was an important predictor of inpatient mortality in both female and male patients.

KEY WORDS: Atrial fibrillation; Inpatient mortality; Oral anticoagulation; Sex

INTRODUCTION

Atrial fibrillation (AF) is the most common heart rhythm disorder and the global burden of AF and its high risk of stroke are well documented in both Western and Asia countries [1-4]. Findings from the prospective community-based Rotterdam study demonstrate that the number of AF patients aged >55 years old will be more than double to 17.9 million in European Union from 2010 to 2060[5]. An investigation in the southwest of China has shown that the prevalence of AF had increased 20-fold over an 11-year period, while AF-related stroke increased 13-fold[4]. Due to the increasing epidemic of AF with an aging population, AF burden has become a growing public health concern worldwide.

In recent years, sex related differences in incidence, presentations, outcomes and clinical management among patients with nonvalvular AF have been demonstrated in previous epidemiologic studies from Western countries[6, 7], with a greater prevalence of AF usually among males, while female patients are at higher risk of stroke and thromboembolism[8].

Indeed, females with AF tended to be older and sicker, with a worse cardiovascular risk profile and a lower quality of life [9]. In the original Framingham cohort, for example, AF was associated with a 1.9 fold higher risk of death among female patients compared to males [10]. The Anticoagulation and Risk factors In Atrial fibrillation (ATRIA) cohort prospectively studied 13 559 AF patients and have shown that females were at 1.6 fold higher risk for AF-related thromboembolism than males [11]. The increased risk of stroke among females with AF can be further demonstrated by a systemic review and meta-analysis [8]. Due to the higher risk of stroke among females AF patients, female

sex has been incorporated in CHA_2DS_2-VASc score as a risk factor of stroke or systemic embolism among AF patients[12].

However, most sex-related investigations of AF are based on data from Western populations [8], whilst few studies have investigated the impact of sex on clinical characteristics and inpatient outcomes amongst nonvalvular AF patients from China.

Hence, the aim of this study was to investigate sex-related differences in clinical characteristics and inpatient outcomes amongst a hospitalised cohort of Chinese nonvalvular AF patients, in the Nanchang Atrial Fibrillation Project.

METHODS

Study population

All consecutive patients with nonvalvular AF admitted to our tertiary care hospital, the second affiliated hospital of Nanchang university, from May 2011 till December 2013, were included. This is a teaching hospital which covers the health management of a population of over 5 million. Patients admitted with a concomitant diagnosis of AF were eligible for inclusion in this registry. Those with AF combined with the presence of valvular heart disease requiring management were excluded. The diagnosis of AF was made by the attending physician confirmed with an electrocardiogram or Holter monitor.

Data collection

The demographic and clinical characteristics of included patients were extracted from our hospital electronic data system, including date of birth, sex, length of stay, diagnoses

and death prior to discharge. Medical records were reviewed by hospital personnel to determine the following data: current smoking; weight and height; systolic and diastolic blood pressure (BP) levels on admission; laboratory data during hospitalization; concomitant diseases; oral anticoagulant therapy before admission and during hospitalization. Both $CHADS_2$ (one point each for congestive heart failure, hypertension, age >=75 years, diabetes; two points for previous stroke/transient ischemic attack (TIA)/Thromboembolism(TE)) and CHA_2DS_2-VASc (one point each for systolic heart failure, hypertension, age 65-74 years, diabetes, vascular disease and female sex; two points each for age ≥75 years and previous stroke/TIA/TE) scores were calculated to assess the risk of stroke and thromboembolism[12, 13].

Definitions

Inpatient ischemic stroke was defined as a focal neurologic deficit of sudden onset newly diagnosed by a neurologist and confirmed by CT or MRI. Inpatient major bleeding was defined as intracranial or gastrointestinal haemorrhage which was newly diagnosed during the current admission. Inpatient death was defined as death from any cause occurring during hospitalization. Length of hospital stay was calculated as the number of nights spent in hospital.

Heart failure was defined as the presence of signs and symptoms of either right or left ventricular dysfunction, or both, confirmed by left ventricular ejection fraction (LVEF) <40%, documented by echocardiogram, or NYHA classification class ≥II. All other concomitant diseases were collected on the basis of the medical notes, including hypertension, diabetes, coronary artery disease, peripheral artery disease, cardiomyopathy, chronic renal disease, hyperthyroidism and cancer. Any discrepancies were resolved by rechecking the medical records.

Statistical analysis

All analyses were performed using the IBM SPSS Version 21.0 (SPSS, Inc., Chicago, IL). The distribution of continuous variables was examined by the Kolmogorov-Smirnov test. Normally distributed variables are presented as mean (standard deviation, SD) and analysed by *t*-test, while the non-normally distributed are presented as median with interquartile range (IQR) and analysed by Mann-Whitney *U*-test. Categorical variables are presented as n (%) and analysed using Chi-square test or a Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to evaluate the risk factors associated with inpatient death amongst both males and females. Variables for the multivariable logistic regression model included age, heart failure, hypertension, diabetes, previous ischemic stroke/TIA/TE, coronary artery disease, peripheral artery disease, and chronic kidney disease. The variables were selected after performing a univariate regression analysis first and then choosing those variables with a P value ≤ 0.2 as candidates for multivariate analysis. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

In total, 3327 AF patients were admitted between May 2011 and December 2013. Of these, 875 (26.3%) were excluded due to the presence of valvular heart disease requiring management, and 10 were excluded for insufficient basic clinical data, leaving a final cohort population of 2442 non-valvular AF patients (Figure 1). Of the whole cohort, there were 1453 patients hospitalised in the cardiovascular department, and 1030 patients admitted with a primary or secondary diagnosis of AF.

Males were more prevalent than females (56.3% vs 43.7%, P<0.0001). Other demographic and clinical characteristics are summarized in Table 1. Overall mean±SD age was 70.6±11.3 years, with females being significantly older (p<0.0001) and with more females aged ≥75 years (45.7% vs 39.8%; p=0.001). Body mass index (BMI) was similar, but current smoking was more common in males Females had higher systolic BP on admission (p<0.0001). Among the 1830 (74.9%) patients with LVEF assessed, almost three-quarters of the females had LVEF ≥ 55% and a significantly higher mean LVEF value (p<0.0001).

Concomitant diseases

There were no significant sex differences in the subtypes of AF (p=0.13). Hypertension and heart failure were the most common concomitant diseases among the whole cohort. As shown in Table 1, females had a significantly higher prevalence of hypertension, diabetes, and hyperthyroidism, but a lower prevalence of coronary artery disease, cardiomyopathy, chronic renal disease, and cancer than males.

CHA_2DS_2-VASc and $CHADS_2$ scores

Both the median CHA_2DS_2-VASc and $CHADS_2$ scores were higher in female AF patients ($p<0.0001$) (see Table 2). When those patients with $CHADS_2$ of 0 or 1 were further refined using CHA_2DS_2-VASc score, more female patients were classified into the group of CHA_2DS_2-VASc ≥2 ($p=0.009$).

Medication therapy at discharge

Among the 2389 (97.8%) patients discharged alive, there were low proportions of patients with intervention therapy such as catheter ablation or pacemakers, 3.0% and 2.2%, respectively (Table 3). No sex differences were evident. More female patients received angiotensin receptor blockers (ARB) and calcium channel blockers (CCB), but there were no statistical differences in other drugs.

Antithrombotic therapy

Only 173 (7.3%) patients received warfarin prior to admission; this increased to 791 (33.3%) during hospitalization (see Table 3). No information on quality of anticoagulation control, as reflected by time in therapeutic range (TTR) was recorded. Rates of aspirin or clopidogrel use at discharge were 38.9% and 10.7%, respectively. No sex differences were evident in the choice of antithrombotic therapy.

Inpatient outcomes

Fifty-three (2.2%) patients died during hospitalization, with no sex differences (see Table 4). The incidence rates of inpatient ischaemic stroke or major bleeding were 11.6% and 3.3%, respectively. Median (IQR) length of stay was 10 (7-14) days. There were no sex differences in these inpatient outcomes.

On multivariate analyses (see Table 5), the risk factors significantly associated with inpatient death in females were previous ischemic stroke/TIA/TE (OR: 2.27; 95% CI: 1.43-3.61), peripheral artery disease (OR: 5.75, 95% CI: 1.49-22.16) and chronic renal disease (OR: 5.68, 95% CI: 1.46-22.13). Hypertension was found to be associated with a lower risk of inpatient death in females (OR: 0.35, 95% CI: 0.14-0.88).

Among males, only age (OR: 1.06, 95% CI: 1.02-1.11) and previous ischemic stroke/TIA/TE (OR: 1.81, 95%CI: 1.25-2.63) were independent predictors of inpatient mortality.

DISCUSSION

Since there is some evidence that AF patients from Asian cohorts are at particularly high risk of adverse outcomes, further information is needed on their clinical epidemiology. In the present study, sex-related differences in clinical characteristics and stroke risk profile were evident in Chinese nonvalvular AF patients. Compared with males, females patients were significantly older with higher $CHADS_2$ and CHA_2DS_2-VASc scores. Hypertension, diabetes, and hyperthyroidism were more commonly found with AF in females, but males had a higher prevalence of concomitant diseases including coronary artery disease, cardiomyopathy, chronic renal disease, and cancer. Previous ischemic stroke/TIA/TE was an important predictor of inpatient mortality in both males and

females. However, no sex disparity was evident in the low antithrombotic therapy use in this Chinese hospital-based cohort or inpatient mortality.

Consistent with previous studies on other populations [9, 14], our analyses shows that more of the patients admitted with AF were male, but that female AF patients were significantly older with a higher proportion in the elderly group (≥75 years), which can perhaps be explained by the longer life expectancy for females. The higher incidence of AF in males and the older age in females is also consistent with a study from Southwest of China[4] but contrasts with a recent cross-sectional study in rural China which reported no significant sex differences at any age [15]. The discrepancy in these findings may be due the study setting and patient demography from different districts.

Female AF patients tended to be more symptomatic and may be more likely to seek medical attention as a result [9]. However, there was no impact of sex on antithrombotic therapy. The use of warfarin prior to admission was sub-optimal, with only 7.3% receiving warfarin. This figure increased to 33.3% during hospitalization, with no sex differences evident.

These data can be further reinforced by the data from a prospective multicentre international observational registry, which demonstrates the comparable anticoagulant use in males and females overall (60.9% versus 60.8%) [16]. However, among those patients with CHA_2DS_2-VASc score of ≥2, 64.6% of males versus 61.6% of females received anticoagulant therapy in this global registry, with combination therapy with anticoagulant plus antiplatelet more frequently used in males. Another study based on data from 11 general practices in Darlington in the UK found more females who were

not receiving anticoagulants, with a higher risk of stroke, compared with males [17]. The low overall use of warfarin is compounded by lack of recorded information on TTR, which has been closely related to the efficacy and safety related to warfarin; current guidelines recommend a TTR of >70%[18, 19]. None of our patients were using the non-Vitamin K oral anticoagulants (NOACs), and whether their subsequent widespread introduction would improve anticoagulation uptake remains uncertain.

Sex differences in the risk of thromboembolism and death have been shown among AF patients in several large Scandinavian nationwide cohort studies [20-23]. Female sex has been established as a risk factor for thromboembolism and death among AF patients, and incorporated in the CHA_2DS_2-VASc score. Nonetheless, whether female sex per se is intrinsically associated with higher thromboembolic events has been debated. In a Danish study, a lower stroke risk was identified for females in relatively young patients with AF[22]. According to the current results, both CHA_2DS_2-VASc and $CHADS_2$ scores were higher in female patients, indicating greater risk of stroke for females than males. Regardless of female sex as a risk factor, the higher CHA_2DS_2-VASc scores were observed among female patients, as reflected by more females with score of ≥3 than males with score of ≥2. Additionally, more female patients with $CHADS_2$ of 0 or 1 were identified to have higher risk of stroke, presented with CHA_2DS_2-VASc of ≥ 2. Hence, our data may further support the greater risk of thromboembolic events among female AF patients.

For inpatient outcomes, no significant sex differences were found. The incidence of inpatient death and inpatient ischemic stroke was comparable between males and females. Previous ischemic stroke/TIA/TE was independently associated with

increased inpatient mortality for both males and females. In addition, older age was associated with higher risk of inpatient death among men, while PAD and chronic renal disease were independent predictors of inpatient mortality for females.

Our data also show that female AF patients with hypertension had a lower risk of inpatient death, a finding that was not consistent with the traditional conception. One possible explanation is the underdiagnosis of hypertension among female patients and those with hypertension were well-treated with antihypertensive drugs which can protect patients from death. However, a slightly higher mean systolic BP was seen amongst females and the mortality observation could also be a chance finding or residual confounding.

Limitations

There are several limitations to be addressed in the present study. Firstly, the data was extracted based on medical records from a single centre, which may not be generalizable to the whole population of China. Secondly, AF was not the primary or secondary cause for admission in 1412 (57.8%) patients. Third, only risk factors associated with inpatient mortality were analyzed for both males and females. Finally, all included patients were admitted to various departments, not limited to cardiovascular department.

In **conclusion**, sex related differences were evident in clinical characteristics and stroke risk profile among Chinese patients with nonvalvular AF. Previous ischemic stroke/TIA/TE was an important predictor of inpatient mortality in both males and females. However, no sex disparity was evident in the low antithrombotic therapy use or inpatient mortality.

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CONFLICTS OF INTEREST

DAL has received investigator-initiated educational grants from Bayer Healthcare, Boehringer Ingelheim and Bristol Myers Squibb. She has also been on the speaker bureau for Boehringer Ingelheim, Bayer, and Bristol Myers Squibb/Pfizer. GYHL has served as a consultant for Astellas, Bayer, Merck, Sanofi Aventis, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim. He has also been on the speaker bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Roche and Sanofi Aventis. The other authors (QX, AS, QZ, YL, YS, XC and KH) have no conflicts of interest to declare.

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Table 1. Baseline characteristics of the 2442 AF patients

N (%)	Total	Males	Females	P value
No. of subjects	2442	1376(56.3)	1066(43.7)	<0.0001
Age				
Mean±SD (years)	70.6±11.3	69.6±11.8	71.8±10.4	<0.0001
<65	636 (26.0)	397 (28.9)	239(22.4)	0.001
65-74	772 (31.6)	432 (31.4)	340 (31.9)	
≥75	1034 (42.3)	547 (39.8)	487 (45.7)	
Body mass index, n=1150*				
mean±SD (kg/m2)	23.5±3.9	23.6±3.4	23.4±4.4	0.53
Smoking status				
Never/Former	2078(85.1)	1035(75.2)	1043(97.8)	<0.0001
Current	364(14.9)	341(24.8)	23(2.2)	
Blood pressure on admission, n=2424*				
SBP, mean±SD (mmHg)	131.3±21.4	129.9±21.2	133.1±21.5	<0.0001
DBP, mean±SD (mmHg)	78.4±13.0	78.2±12.9	78.7±13.2	0.36
LVEF, n=1830*				
mean±SD	58.7±11.7	57.6±12.0	60.0±11.2	<0.0001
<55%	537 (29.3)	332(32.7)	205(25.2)	<0.0001
≥55%	1293(70.7)	683(67.3)	610(74.8)	
Type of AF				
Paroxysmal	357 (14.6)	188(13.7)	169(15.9)	0.13
Persistent/Permanent	2085 (85.4)	1188(86.3)	897(84.1)	
Concomitant Conditions				
Previous Ischemic stroke/TIA/TE	624(25.6)	347(25.2)	277(26.0)	0.67
Heart failure	872(35.7)	474(34.4)	398(37.3)	0.15
Hypertension	1375(56.3)	730(53.1)	645(60.5)	<0.0001
Diabetes	223(9.1)	108(7.8)	115(10.8)	0.01
CAD	467(19.1)	307(22.3)	160(15.0)	<0.0001
PAD	86(3.5)	49(3.6)	37(3.5)	1.00
Cardiomyopathy	169 (6.9)	118 (8.6)	51 (4.8)	<0.0001
Chronic Kidney disease	140 (5.7)	94 (6.8)	46 (4.3)	0.01

Hyperthyroidism	125 (5.1)	59 (4.3)	66 (6.2)	0.04
Cancer	142 (5.8)	97 (7.0)	45 (4.2)	0.003

AF, atrial fibrillation; CAD, Coronary artery disease; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; PAD, Peripheral artery disease; SBP, systolic blood pressure; TE, thromboembolism; TIA, transient ischemic attack; * the number of patients with available data

Table 2. CHA_2DS_2-VASc and $CHADS_2$ scores for the whole cohort and by sex

	Total	Males	Females	p- value
CHA_2DS_2-VASc Score				
Median (IQR)*	3.0 (2.0-4.0)	3.0 (1.0-4.0)	4.0 (3.0-5.0)	<0.0001
Male=0 or female=1	191(7.8)	122(8.9)	69(6.5)	0.009
Male=1 or female=2	384(15.7)	233(16.9)	151(14.2)	
Male≥2 or female≥3	1867(76.5)	1021(74.2)	846(79.4)	
$CHADS_2$ Score				
Median (IQR)*	2.0 (1.0-3.0)	2.0 (1.0-3.0)	2.0 (1.0-3.0)	<0.0001
$CHADS_2$=0/1 subdivided by CHA_2DS_2-VASc				
$CHADS_2$=0 and CHA_2DS_2-VASc=1	161(6.6)	92(6.7)	69(6.5)	<0.0001
$CHADS_2$=0 and CHA_2DS_2-VASc≥2	76(3.1)	7(0.5)	69(6.5)	
$CHADS_2$=1 and CHA_2DS_2-VASc=1	141(5.8)	141(10.2)	0(0.0)	
$CHADS_2$=1 and CHA_2DS_2-VASc≥2	533(21.8)	256(18.6)	277(26.0)	

*Mann-Whitney U test

Table 3. Antithrombotic therapy for patients discharged alive overall and by sex

N (%)	Total (n=2389)	Males (n=1344)	Females (n=1045)	P value
Warfarin use-Before Admission	174 (7.3)	98 (7.3)	76 (7.3)	1.00
Warfarin use-During hospitalization	791 (33.3)	428 (32.1)	363 (35.0)	0.09
Aspirin	930 (38.9)	517 (38.5)	413 (39.5)	0.61
Clopidogrel	256 (10.7)	155 (11.5)	101 (9.7)	0.16

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Table 4. In-hospital outcomes for the whole cohort and by sex

	Total	Males	Females	P value
In-hospital outcomes				
Inpatient ischemic stroke	283 (11.6)	153 (11.1)	130 (12.2)	0.41
Inpatient major bleeding	80 (3.3)	54 (3.9)	26 (2.4)	0.05
Inpatient death	53 (2.2)	32 (2.3)	21 (2.0)	0.58
Length of stay, Median (IQR)*	10 (7-14)	10 (7-14)	10 (7-14)	0.80
Length of stay >10 days, n (%)	1077 (44.4)	606 (44.3)	471 (44.5)	0.93

*Mann-Whitney U test

Table 5 Multivariate analyses for risk factors associated with inpatient mortality by sex

	Males		Females	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	**1.06 (1.02-1.11)**	**0.004**	1.02 (0.97-1.07)	0.40
Hypertension	1.00 (0.48-2.12)	1.00	0.35 (0.14-0.88)	0.03
Heart failure	0.40 (0.15-1.05)	0.06	1.44 (0.56-3.71)	0.46
Diabetes	-	1.00	0.93 (0.21-4.19)	0.93
Previous ischemic Stroke/TIA/TE	**1.81 (1.25-2.63)**	**0.002**	**2.27 (1.43-3.61)**	**<0.0001**
Coronary artery disease	2.02 (0.90-4.54)	0.09	2.09 (0.72-6.08)	0.18
Peripheral arterial disease	0.63 (0.08-4.85)	0.65	**5.75 (1.49-22.16)**	**0.01**
Chronic Renal disease	1.80 (0.52-6.21)	0.35	**5.68 (1.46-22.13)**	**0.01**

TE, thromboembolism; TIA, transient ischemic attack;

Figure 1. Flow chart of the study cohort recruitment