# Alcohol consumption in relation to the incidence of atrial fibrillation in an elderly Chinese population

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#### ABSTRACT

**BACKGROUND** Alcohol consumption is a known modifiable risk factor for atrial fibrillation. The association, however, might differ according to gender. We investigated gender-specific associations between alcohol consumption and incident atrial fibrillation in an elderly Chinese population.

**METHODS** Our study participants were elderly residents ( $\geq$  65 years) recruited from five community health centers in the urban area of Shanghai (n = 6,618). Alcohol intake was classified as never drinkers and current light-to-moderate (< 40 g/day) and heavy drinkers ( $\geq$  40 g/day). Atrial fibrillation was detected by a 30-s single-lead electrocardiography (ECG, AliveCor<sup>®</sup> Heart Monitor) and further evaluated with a regular 12-lead ECG.

**RESULTS** During a median of 2.1 years (interquartile range: 2.0–2.2) follow-up, the incidence rate of atrial fibrillation was 1.10% in all study participants. It was slightly but non-significantly higher in men (n = 2849) than women (n = 3769, 1.30% vs. 0.96%, P = 0.19) and in current drinkers (n = 793) than never drinkers (n = 5825, 1.64% vs. 1.03%, P = 0.12). In both unadjusted and adjusted analyses, there was interaction between sex and current alcohol intake in relation to the incidence of atrial fibrillation (P < 0.0001). After adjustment for confounding factors, current drinkers had a significantly higher incidence rate of atrial fibrillation than never drinkers in women (12.96% [7/54] vs. 0.78% [29/3715], adjusted odds ratio [OR] = 10.25, 95% confidence interval [CI]: 3.54–29.67, P < 0.0001), but not in men (0.81% [6/739] vs. 1.47% [31/2110], OR = 0.62, 95% CI: 0.25–1.51, P = 0.29).

**CONCLUSIONS** Our study showed a significant association between alcohol intake and the incidence of atrial fibrillation in elderly Chinese women, but not men.

ith the increasing longevity worldwide, there is an emerging epidemic of atrial fibrillation in many countries,<sup>[1,2]</sup> including the most populous country of China.<sup>[1,3]</sup> Atrial fibrillation confers huge risks of stroke and its related deaths.<sup>[2–4]</sup> Indeed, according to a most recent study in elderly Chinese, it was associated with nearly five-fold increased risks of stroke mortality.<sup>[3]</sup> However, the risks can be substantially reduced, if proper management, such as the use of oral antico-

agulants, is implemented.<sup>[5,6]</sup> Thus, current consensus recommends systemic screening for early detection and treatment of atrial fibrillation in high risk groups.<sup>[7]</sup>

Alcohol consumption is a proven risk factor of atrial fibrillation, especially binge drinking<sup>[8]</sup> and habitual heavy drinking.<sup>[8–12]</sup> Meta-analyses combining a large number of studies showed that regular moderate alcohol intake also increased the risk of incident atrial fibrillation.<sup>[8,13,14]</sup> A randomized con-

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trolled trial in excessive drinkers demonstrated that alcohol restriction reduced the recurrence rate of atrial fibrillation, indicating that alcohol consumption is a modifiable risk factor of atrial fibrillation.<sup>[15]</sup>

Although alcohol drinking is common in almost all populations, not only the alcohol but also the drinking pattern differs.<sup>[16]</sup> In China, people often drink spirits,<sup>[17]</sup> and the proportion of drinking is much higher in men than women.<sup>[17]</sup> However, the proportion of drinkers in women is increasing with the recent changes in lifestyle.<sup>[18]</sup> We recently conducted an atrial fibrillation screening study in elderly community dwellers in Shanghai.<sup>[19–21]</sup> In the present analysis, we investigated the association between alcohol consumption and the risk of incident atrial fibrillation in men and women of this elderly population sample.

# METHODS

#### **Study Population**

Our study participants were elderly ( $\geq 65$  years) residents from five community health centers in the urban areas of Shanghai, who participated in a randomized controlled trial for systemic atrial fibrillation screening in the community. The study protocol of the trial had been published in detail previously.<sup>[19-21]</sup> Briefly, all residents aged 65 years or older were invited for the possible participation in the trial. Those without atrial fibrillation history and atrial fibrillation rhythm, and without serious life-threatening diseases, such as, cancer, and severe cardiac, cerebral, liver, and kidney diseases who might not manage to attend follow-up were eligible for inclusion in the study, and followed up for two years. The study was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine and conducted in accordance with the principles of the Declaration of Helsinki. Informed written consent was obtained from all study participants at the screening clinic visit.

A total of 8,741 residents attended the community health clinics from April 17, 2017 to June 26, 2018. After exclusion of 214 residents who declined to participate and 287 individuals with electrocardiography (ECG)-confirmed previously unknown atrial fibrillation (n = 38), ECG-confirmed known atrial fibrillation (n = 133), and known atrial fibrillation in sinus rhythm (n = 116), 8,240 subjects free of atrial fibrillation history and atrial fibrillation rhythm were enrolled and followed up for the detection of atrial fibrillation till October 30, 2020. From the present analysis, we excluded 1,569 participants because they withdrew their consent (n = 868) or did not attend any follow-up visit (n = 566), or because information on alcohol intake was not collected (n =135). We further excluded all past drinkers (n = 53) because none of them had atrial fibrillation during follow-up. Thus, the total number of participants included in the present analysis was 6,618.

#### Systemic Screening for Atrial Fibrillation

A questionnaire was administered and an ECG recorded at baseline and during follow-up (annually, quarterly or quarterly plus weekly for the first month after randomization) for the detection of atrial fibrillation. A single-lead (lead I) ECG was recorded for 30 s with a handheld ECG device (Alive-Cor<sup>®</sup> Heart Monitor, now Kardia Mobile<sup>®</sup>, Mountain View, CA, US). Each ECG rhythm strip was reviewed by a cardiologist from the research team at the screening visit. The ECGs were classified into three groups: sinus rhythm, atrial fibrillation and uninterpretable. Participants with an uninterpretable single lead ECG were referred for 12-lead ECGs, which were reviewed by a second cardiologist. Both atrial fibrillation and atrial flutter diagnosed by ECG were identified as cases of atrial fibrillation. Participants with a documented history of atrial fibrillation in their medical records from qualified hospitals or with atrial fibrillation recorded on any prior ECG but in sinus rhythm on the singlelead ECG were defined as 'known atrial fibrillation in sinus rhythm'. We excluded those participants with atrial fibrillation at baseline from the present analysis.

#### Data Collection on Alcohol Consumption

A questionnaire was administered for the collection of information on alcohol consumption. Participants were asked to indicate the quantity and volume of the consumed beer, wine, rice aperitif and spirits in the past 12 months. For the calculation of the amount of alcohol consumption, it was assumed that 100 mL of wine, 500 mL of beer, 100 mL of yel-

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low or white rice aperitif, or 50 mL of spirits contained 20 g of ethanol.<sup>[22]</sup> Average alcohol consumption (in grams per day) was computed by multiplying frequency and amount of the alcoholic beverages consumed. Individuals were classified as never drinkers and current light-to-moderate (< 40 g/day) and heavy drinkers ( $\geq$  40 g/day).

#### **Other Data Collections**

With the questionnaire, we also collected information on medical history, cigarette smoking and use of medications. Body weight was measured with light indoor clothes and without shoes. Body mass index was calculated as the body weight in kilograms divided by the body height in meters squared.

Blood pressure was measured three times consecutively by experienced physicians using a validated Omron 7051 oscillometric blood pressure monitor (Omron Healthcare, Kyoto, Japan), after the participants had rested for at least 5 min in the sitting position. These three blood pressure readings were averaged for the definition of hypertension (systolic  $\geq$  140 mmHg or diastolic  $\geq$  90 mmHg, or the use of antihypertensive medication). A followup questionnaire and ECG recording were administered by the research cardiologist.

#### **Statistical Analyses**

For database management and statistical analysis, we used SAS software (Version 9.4; SAS Institute, Cary, NC, US). Means and proportions were compared by the student *t*-test and the chi-square test, respectively. The log-rank test was used to compare the cumulative incidence of atrial fibrillation between various groups with the Kaplan-Meier survival function to show the time to incidence of atrial fibrillation. Because the systemic screening during follow-up was on annually or quarterly basis, we performed logistic regression in adjusted analyses to compute odds ratios (ORs) and 95% confidence intervals (CIs) for the association between alcohol intake and atrial fibrillation. The sex-specific analyses were adjusted for age, body mass index, cigarette smoking, history of heart failure, history of stroke or myocardial infarction, hypertension and diabetes mellitus. The analyses in men combined with women were additionally adjusted for sex. For all analyses, a two-sided *P* value < 0.05 was considered statistically significant.

# RESULTS

# Characteristics of the Study Participants at Baseline

The 6,618 study participants without atrial fibrillation at baseline (2,849 [43.0%] men) had a mean age of 71.4 ± 6.2 years and included 3,687 (55.7%) hypertensive patients and 1,351 (20.4%) diabetic patients. Men and women differed significantly ( $P \le$ 0.04) in the proportions of current alcohol drinking (25.9% *vs.* 1.4%), current smoking (30.9% *vs.* 0.9%), and the history of stroke or myocardial infarction (15.0% *vs.* 20.9%). Nonetheless, men and women had similar ( $P \ge 0.29$ ) body mass index (24.5 kg/m<sup>2</sup>), prevalence of hypertension (55.7%) or diabetes mellitus (20.4%), use of antihypertensive drugs (52.3%) and proportions of patients with a history of heart failure and (0.5%) and valvular heart disease (0.03%, Table 1).

Within each sex, male drinkers (n = 739) and nondrinkers (n = 2110) differed ( $P \le 0.0003$ ) in current smoking (47.4% vs. 25.1%), and the history of stroke or myocardial infarction (10.8% vs. 16.4%); female drinkers (n = 54) and non-drinkers (n = 3715) differed ( $P \le 0.04$ ) in the prevalence of diabetes mellitus (9.3% vs. 20.4%) and current smoking (18.5% vs. 0.6%).

# Incidence of Atrial Fibrillation According to Alcohol Consumption

During a median follow-up of 2.1 years (interquartile range, 2.0–2.2 years), 73 incident cases of atrial fibrillation were documented, including 60 (31 men and 29 women) in never drinkers (n = 5,825) and 13 (6 men and 7 women) in current drinkers (n = 793).

The overall incidence rate of atrial fibrillation was 1.10%; it was slightly but non-significantly higher in men than women (1.30% vs. 0.96%, P = 0.19), and in current drinkers than never drinkers (1.64% vs. 1.03%, P = 0.12). There was interaction between sex and current alcohol intake in relation to the incidence of atrial fibrillation (P < 0.0001). Current drinkers had a significantly higher incidence rate of atrial fibrillation than never drinkers in women (12.96% [7/54] vs. 0.78% [29/3715], P < 0.0001), but not men (0.81% [6/739] vs. 1.47% [31/2110], P = 0.17, Table 2). Kaplan-Meier survival curve showed a signific-

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Variable	All ( <i>n</i> = 6,618)	Men ( <i>n</i> = 2,849)	Women ( <i>n</i> = 3,769)
Age, yrs	71.4 ± 6.2	$71.2 \pm 5.8$	71.5 ± 6.5
Body mass index, kg/m <sup>2</sup>	$24.5 \pm 3.4$	$24.5 \pm 3.1$	$24.5 \pm 3.5$
Alcohol consumption category			
Never drinker	5825 (88.0%)	2110 (74.1%)	3715 (98.6%)
Current drinker	793 (12.0%)	739 (25.9%)	54 (1.4%)
< 40 g/day	518 (7.8%)	470 (16.5%)	48 (1.3%)
≥40 g/day	275 (4.2%)	269 (9.4%)	6 (0.2%)
Systolic blood pressure, mmHg	$137.6\pm18.8$	$136.8\pm18.0$	$138.2\pm19.3$
Diastolic blood pressure, mmHg	$74.3 \pm 9.5$	$75.6\pm9.7$	$73.3 \pm 9.3$
Pulse rate, beats/min	$73.4\pm10.9$	$73.0 \pm 11.2$	$73.7 \pm 10.7$
Current smoking	912 (13.8%)	879 (30.9%)	33 (0.9%)
Hypertension	3687 (55.7%)	1580 (55.5%)	2107 (55.9%)
Use of antihypertensive drugs	3464 (52.3%)	1470 (48.4%)	1994 (52.9%)
Calcium channel blockers	1520 (23.0%)	648 (22.7%)	872 (23.1%)
Angiotensin converting-enzyme inhibitors/angiotensin receptor blockers	1 208 (18.3%)	462 (16.2%)	746 (19.8%)
Diuretics	11 (0.2%)	9 (0.3%)	2 (0.1%)
β-Blockers	111 (1.7%)	56 (2.0%)	55 (1.5%)
Other antihypertensive drugs	614 (9.3%)	295 (10.4%)	319 (8.5%)
Diabetes mellitus	1351 (20.4%)	590 (20.7%)	761 (20.2%)
History of heart failure	32 (0.5%)	13 (0.5%)	19 (0.5%)
History of stroke or myocardial infarction	1214 (18.3%)	426 (15.0%)	788 (20.9%)
History of valvular heart disease	2 (0.03%)	1 (0.04%)	1 (0.03%)

Table 1 Baseline characteristics of the study participants.

Values are mean  $\pm$  SD or n (%).

antly higher cumulative incidence rate of atrial fibrillation in current drinkers than never drinkers in women (log-rank test, P < 0.0001), but not men (logrank test, P = 0.16, Figure 1). In spite of smaller number of incident cases of atrial fibrillation, the incidence rate in women increased with the increasing amount of alcohol intake from 10.42% (5/48) in light-to-moderate drinkers to 33.33% (2/6) in heavy drinkers.

# Adjusted Analyses on the Association Between Alcohol Intake and Incidence of Atrial Fibrillation

After adjustment for age, body mass index, current smoking, prevalence of hypertension and diabetes mellitus, history of heart failure, and the history of myocardial infarction or stroke, the interaction between sex and current alcohol intake in relation to the incidence of atrial fibrillation remained statistically significant (P < 0.0001). The adjusted OR for the incidence of atrial fibrillation in current drinkers versus never drinkers was 10.21 (95% CI: 3.53-29.53, P < 0.0001) in women and 0.62 (95% CI: 0.25-1.51, P = 0.29, Table 2) in men. In women, the adjusted OR of atrial fibrillation in the current light-to-moderate and heavy drinkers versus never drinkers was 9.45 (95% CI: 3.06-29.16, P < 0.0001) and 18.83 (95% CI: 1.92-184.78, P = 0.01, Table 3), respectively.

# DISCUSSION

Our study showed a significant association between current alcohol intake and the incidence of atrial fibrillation in elderly Chinese women but not men. In women, heavy drinking, compared with light-to-moderate drinking, conferred even greater risk of incident atrial fibrillation. Considering the fast-increasing alcohol drinking in Chinese women, our study may have immediate important clinical

Participants	Never drinkers	Current drinkers
All ( <i>n</i> = 6,618)		
Number of participants	5,825	793
Number of incident cases	60	13
Incidence rate	1.03%	1.64%
Age and sex adjusted OR (95% CI)	1	1.57 (0.81–3.05)
Multivariate adjusted OR (95% CI)	1	1.50 (0.76-3.00)
Men ( <i>n</i> = 2,849)		
Number of participants	2,110	739
Number of incident cases	31	6
Incidence rate	1.47%	0.81%
Age adjusted OR (95% CI)	1	0.59 (0.25–1.43)
Multivariate adjusted OR (95% CI)	1	0.62 (0.25–1.51)
Women ( <i>n</i> = 3,769)		
Number of participants	3,715	54
Number of incident cases	29	7
Incidence rate	0.78%	12.96%
Age adjusted OR (95% CI)	1	19.15 (7.83–46.84)
Multivariate adjusted OR (95% CI)	1	10.25 (3.54–29.67)

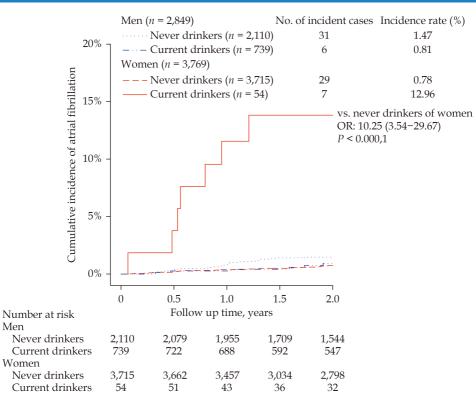
Table 2 Risk of incident atrial fibrillation according to alcohol intake status.

The multivariate analyses were adjusted for age, body mass index, cigarette smoking, history of heart failure, history of stroke or myocardial infarction, hypertension and diabetes mellitus in sex-specific analyses and additionally for sex in the analysis in all participants. CI: confidence interval. OR: odds ratio.

implications in cardiovascular prevention. Female drinkers may have to seriously consider alcohol restriction and screening for atrial fibrillation.

There is no previous study that has shown sexspecific association between alcohol intake and atrial fibrillation in women. However, several previous studies did show significant association between alcohol intake and atrial fibrillation either in women alone<sup>[12]</sup> or in both sexes combined.<sup>[8,11,23,24]</sup> In the Women's Health Study (*n* = 34,715), women consuming two or more drinks per day (n = 1359) was associated with a significantly higher risk of incident atrial fibrillation (HR = 1.60, 95% CI: 1.13-2.25) than nondrinking women (n = 15,370) after multivariable adjustment.<sup>[12]</sup> In a Korea nationwide study (n = 9,776,956), both women and men who drank every day (n = 139,635), compared with those who drank twice per week (n = 1,271,588), had an increased risk of new-onset atrial fibrillation (*n* = 139,635, HR = 1.42, 95% CI: 1.38–1.46).<sup>[23]</sup> In an European cohort study in 48,354 men and 51,738 women, even modest habitual alcohol intake of one drink (12 g) per day was associated with an increased risk of atrial fibrillation both before (HR = 1.16, 95% CI: 1.11–1.22) and after adjustment for classical cardiovascular risk factors (HR = 1.18, 95% CI: 1.12–1.25), compared with never drinkers (0 g/day).<sup>[11]</sup>

The observed high risk of incident atrial fibrillation in drinking women is incompletely understood. Women are known vulnerable to develop alcohol-related health problems at even lower levels of alcohol intake. For example, women are more susceptible to supraventricular arrhythmia, neurotoxic effects, severe alcoholic liver diseases, and alcohol induced cardiomyopathy.<sup>[25]</sup> On the other hand, alcohol is causally linked with other risk factors of atrial fibrillation, such as hypertension, obstructive sleep apnea, obesity and left ventricular dysfunction.<sup>[26,27]</sup> In a north Sweden cohort study (n =109,230), the risk of atrial fibrillation was associated with obesity (body mass index  $\geq$  30 kg/m<sup>2</sup>), history of hypertension, diabetes mellitus, or smoking in women.<sup>[28]</sup> In addition, women had a higher risk of stroke<sup>[29]</sup> and cardiovascular disease<sup>[30]</sup> and death<sup>[30]</sup> among individuals with atrial fibrillation.<sup>[29,30]</sup>



**Figure 1** Kaplan-Meier survival curve for incidence rate of atrial fibrillation in men and women according to alcohol consumption status. The number of participants and incident cases of atrial fibrillation and the incidence rate of atrial fibrillation are given for each category of alcohol intake. The *P* value for log-rank test and odds ratio for multiple logistic regression analysis are also given.

In contrast to the results of several previous studies,<sup>[11,27,31,32]</sup> our study did not show significant association between alcohol intake and incidence of atrial fibrillation in men. In a meta-analysis of nine prospective studies (n = 249,496), high levels of alcohol intake were associated with an increased risk of atrial fibrillation in men as well as women (in men and women combined, HR = 1.34, 95% CI: 1.20-1.49).<sup>[32]</sup> However, moderate levels of alcohol intake were associated with an elevated risk of atrial fibrillation only in men (HR = 1.26, 95% CI: 1.04–1.54) but not women (HR = 1.03, 95% CI: 0.86-1.25). Low levels of alcohol intake up to 1 standard drink per day were not associated with the risk of atrial fibrillation (HR = 0.95, 95% CI: 0.85-1.06).<sup>[32]</sup> Compared to this meta-analysis<sup>[32]</sup> and previous studies such as the abovementioned European cohort study,<sup>[11]</sup> our study had a relatively small number of participants and incident cases of atrial fibrillation and short follow-up time, and hence probably had insufficient power to show mildly or moderately increased risks of atrial fibrillation in men.

We tried to control as many confounding factors as possible by adjusting for the baseline characteristics of the study participants. Previous studies identified older age,<sup>[33-35]</sup> female sex,<sup>[33,34]</sup> overweight/obesity,<sup>[33,34]</sup> cigarette smoking,<sup>[35]</sup> and various cardiovascular and metabolic diseases such as hypertension,<sup>[33-35]</sup> diabetes mellitus,<sup>[35]</sup> heart failure,<sup>[33,35]</sup> stroke<sup>[34]</sup> and myocardial infarction<sup>[34]</sup> as risk factors of incident atrial fibrillation. Although it was not the focus of the present analysis, we found that the risk of incident atrial fibrillation was significantly associated with older age, overweight/ obesity and heart failure in men and older age and cigarette smoking in women (data not shown).

The mechanisms for alcohol consumption as a possible causal risk factor for incident atrial fibrillation may involve both acute and chronic physiological and pathological processes. Acute alcohol consumption may induce various electrophysiological changes in atrial cells characterized by shortening of the atrial effective refractory period and slowing intra-atrial conduction.<sup>[26,27]</sup> These changes can be shown by ECG P-wave prolongation. Acute alcohol

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Participants	Never drinkers	Light-to-moderate	Heavy
All ( <i>n</i> = 6618)			
Number of participants	5,825	518	275
Number of incident cases	60	8	5
Incidence rate	1.03%	1.54%	1.82%
Age and sex adjusted OR (95% CI)	1	1.41 (0.64–3.09)	1.96 (0.74-5.19)
Multivariate adjusted OR (95% CI)	1	1.37 (0.62-3.03)	1.83 (0.67-5.05)
Men ( <i>n</i> = 2849)			
Number of participants	2,110	470	269
Number of incident cases	31	3	3
Incidence rate (%)	1.47	0.64	1.12
Age adjusted OR (95% CI)	1	0.45 (0.14–1.48)	0.88 (0.26-2.91)
Multivariate adjusted OR (95% CI)	1	0.46 (0.14-1.52)	0.97 (0.28-3.35)
Women ( <i>n</i> = 3,769)			
Number of participants	3,715	48	6
Number of incident cases	29	5	2
Incidence rate (%)	0.78%	10.42%	33.33%
Age adjusted OR (95% CI)	1	13.89 (5.03-38.39)	128.96 (21.44-775.74)
Multivariate adjusted OR (95% CI)	1	9.45 (3.06-29.16)	18.83 (1.92-184.78)

 Table 3
 Risk of incident atrial fibrillation according to the quantity of alcohol consumption.

The multivariate analyses were adjusted for age, body mass index, cigarette smoking, history of heart failure, history of stroke or myocardial infarction, hypertension and diabetes mellitus in sex-specific analyses and additionally for sex in the analysis in all participants. CI: confidence interval. OR: odds ratio.

consumption may also predispose to atrial fibrillation directly via cardiac toxicity,<sup>[36]</sup> or indirectly via changes in the autonomic nervous tone.<sup>[26,27]</sup> In addition, it is known that chronic alcohol consumption may cause left atrial remodeling<sup>[37]</sup> and in turn incident atrial fibrillation.

Our study should be interpreted within the context of its limitations. First, the sample size of our study was relatively small, especially with regard to the number of female drinkers. Second, the followup time was short. This short duration of follow-up makes it difficult to show any long-term health consequences of alcohol intake even in the elderly. Third, although we repeatedly administered questionnaires and recorded ECGs during follow-up, Holter monitoring was not performed in this community-based study. Thus, some of patients with paroxysmal atrial fibrillation might have been missed.

In conclusion, our study in an elderly Chinese population showed a higher risk of incident atrial fibrillation in current female drinkers. Our findings require confirmation by future studies with a larger sample size and longer follow-up time and hence a larger number of incident cases of atrial fibrillation.

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# CONFLICT OF INTEREST

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# AUTHORS' CONTRIBUTIONS

JGW and BF designed and supervised the study. WZ, YC, and CYM coordinated the study and data collection. DW, QFH, CSS and YL participated in the recruitment of patients and data management. XFY together with JGW, performed statistical analyses, interpreted the data, verified the underlying data and prepared the first draft of the manuscript. All authors were involved in data interpretation, reviewed and revised the manuscript, and approved the final version for submission.

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