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A report from the Guangzhou atrial fibrillation ablation registry

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Research paper

A U-shaped relationship of body mass index on atrial fibrillation recurrence post ablation: A report from the Guangzhou atrial fibrillation ablation registry



Hai Deng^{a,b}, Alena Shantsila^a, Pi Guo^c, Tatjana S. Potpara^d, Xianzhang Zhan^b, Xianhong Fang^b, Hongtao Liao^b, Yang Liu^b, Wei Wei^b, Lu Fu^b, Shulin Wu^b, Yumei Xue^{b,*,1}, Gregory Y.H. Lip^{a,e,f,*,1}

^a Institute of Cardiovascular Sciences, University of Birmingham, United Kingdom

^b Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Science, Guangzhou, China

^c Department of Public Health, Medical College of Shantou University, Shantou, China

^d Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia

^e Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

^f Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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ABSTRACT

Background: Obesity or overweight is related to worse outcomes in patients with atrial fibrillation (AF) following catheter ablation (CA). The role of being underweight in relation to recurrent arrhythmias post AF ablation is less certain. We conducted a retrospective study to investigate the association of body mass index (BMI) with arrhythmia outcomes in AF patients undergoing CA.

Methods: In a cohort of 1410 AF patients (mean age 57.2 ± 11.6 years; 68% male) undergoing single CA, the association between BMI and AF ablation outcome was analyzed using BMI as a continuous variable and by four BMI categories (<18.5 kg/m², 18.5–24 kg/m², 25–29 kg/m², and ≥ 30 kg/m²).

Result: We observed a positive association between a cut off value of BMI and risk of AF recurrence post AF ablation. BMI ≥ 26.36 kg/m² was related to more AF recurrence (c-statistic 0.55, 95%CI 0.51–0.58; $P < 0.01$) with 50% increased risk of AF recurrence (HR 1.50, 95% CI 1.22–1.86; $P < 0.01$). Recurrence rates in the four BMI categories were 33.3%, 23.2%, 27.2 and 41.8%, respectively ($P < 0.01$).

Kaplan–Meier analysis showed that BMI categories of <18.5 kg/m² and ≥ 30 kg/m² were all associated with more AF recurrence ($P = 0.01$). Both underweight (HR 1.85, 95%CI 1.12–3.08; $P = 0.02$) and obesity (HR 1.78, 95%CI 1.17–2.72; $P = 0.01$) significantly increased the risk of AF recurrence in a Cox proportional hazard model.

Conclusion: BMI had good predictive value for AF ablation outcomes with a cut off value of ≥ 26.36 kg/m². Apart from being obese/overweight, being underweight might also be a risk factor for AF recurrence post ablation.

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1. Introduction

Obesity/overweight has many adverse impacts on hemodynamics and cardiovascular structure or function [1]. For example, obesity may increase insulin resistance and the prevalence of hypertension, heart failure, coronary heart disease, obstructive sleep apnea (OSA) and atrial fibrillation (AF) is generally higher among obese compared to non-obese individuals [1,2]. The association between obesity and AF has attracted much attention. In the Framingham Heart Study, for example, every unit of increase in body mass index (BMI) was associated with a

4–5% increase in AF risk [3]. Furthermore, increased BMI was related to the development of persistent or permanent AF. The mechanism(s) of AF promotion induced by obesity are multifactorial, and have been related to endothelial dysfunction, increased systemic inflammation, a prothrombotic state, systolic and diastolic dysfunction, increased pericardial fat leading to structural remodeling as atrial stretch increase, atrial fibrosis and scar formation [4]. Obesity or overweight has been related to a worse ablation outcome in patients with AF [5,6]. Indeed, weight management has modified arrhythmia outcomes post AF ablation [7]; however, various studies have reported contradictory results [8]. Being underweight is also a risk factor for new onset AF [9] and has been related to worse cardiovascular outcomes post catheter ablation (CA) [10]. In this study, we investigated the association between BMI and arrhythmia outcomes in a cohort of 1410 AF patients undergoing single catheter ablation.

* Corresponding author.

** Corresponding author at: Institute of Cardiovascular Sciences, University of Birmingham Birmingham, United Kingdom.

E-mail address: g.y.h.lip@bham.ac.uk (G.Y.H. Lip).

¹ Joint senior authors.

Research in context*Evidence before this study*

Obesity or overweight is related to worse outcomes in patients with atrial fibrillation (AF) following catheter ablation (CA). The role of being underweight in relation to recurrent arrhythmias post AF ablation is less certain.

Added value of this study

We found that BMI of ≥ 26.36 kg/m² increased the risk of AF recurrence post ablation by 50% relative to lower BMI; in addition, being underweight was also associated with higher AF recurrence rates. Thus, the impact of BMI on ablation outcome appears to have a “U” shape relationship such that underweight or overweight was related to the arrhythmia recurrence post CA in AF patients.

Implications of all the available evidence

There may be different influences of BMI on AF recurrence in different cohorts with unique cut off values. Further research should identify population-specific optimal BMIs that would lead to improved outcomes post CA.

2. Materials and methods**2.1. Ethics**

The study protocol was approved by the Clinical Research Ethics Committee of Guangdong General Hospital. All patient signed written informed consent for the ablation procedure and follow up observation.

2.2. Study subjects

This retrospective study included 1410 consecutive symptomatic adult patients (mean age 57.2 ± 11.6 years; 68% male) with non-valvular AF who underwent single ablation procedure between June 2011 and August 2015 in Guangdong General Hospital. Baseline clinical data were collected from patients' medical records and the hospital patient database.

Underweight was defined as a BMI of <18.5 kg/m², while overweight and obesity were defined as a BMI of 24 kg/m²–29 kg/m² and BMI ≥ 30 kg/m², respectively. Patients were categorized into four groups with BMI ranges as follows: <18.5 kg/m², 18.5–24 kg/m², 25–29 kg/m² and ≥ 30 kg/m².

Paroxysmal AF (PAF) was defined as AF that terminated spontaneously or with intervention within 7 days, persistent AF (PeAF) as AF not terminating spontaneously (usually lasting ≥ 7 days), and longstanding PeAF (LSPeAF) as AF lasting >1 year [11]. The term “non-paroxysmal” AF (NPAF) included PeAF and LSPeAF.

2.3. Ablation strategy

All patients received anticoagulation therapy and underwent an ablation procedure according to the guideline recommendations [12]. Pre-procedural transoesophageal echocardiography (TEE) or left atrial computed tomography (CT) was used to exclude left atrial thrombi. Amiodarone was discontinued for >1 month and other antiarrhythmic drugs (AADs) were discontinued for ≥ 5 half-lives before the procedure. During the ablation procedure, modest sedation with fentanyl was used. Following the trans-septal puncture, intravenous infusion of

unfractionated heparin was initiated with the activated clotting time (ACT) maintained between 250 and 350 s. Circumferential pulmonary vein isolation (CPVI) was performed under the guidance of 3D mapping system (Carto2 or 3, Johnsons Med Company or Navi X Ensite Classic and Velocity, St Jude Medical). A cryoballoon catheter (Biosense Webster, Inc., Diamond Bar, California) was used to perform cryoballoon ablation, as previously described [13]. Pharmaceutical (ibutilide or aminodarone) or electrical cardioversion was performed when AF continued post ablation.

2.4. Follow-up

Patients were treated with oral anticoagulants and amiodarone or propafenone within the first three months post ablation (the blanking period). Thereafter, oral anticoagulation was continued in patients with a CHA₂DS₂-VASc score of ≥ 2 , while the AAD was continued in those with an atrial arrhythmia. Follow up visits including physical examination, 12 lead ECG and 24-h Holter ECG were performed at discharge, 1, 3, 6 months post ablation and every 6 months thereafter. Patients were encouraged to make contact in case of symptoms suggestive of a cardiac arrhythmia and then additional ECG or 24-h Holter monitoring was performed as needed. Patients without evidence of arrhythmia recurrence were followed up for a minimum of 12 months. Arrhythmia recurred post the first three month (blanking period) was the study endpoint. The study endpoint might be late recurrence (<12 month) or very late recurrence (>12 month).

2.5. Statistical analysis

Continuous variables were described as mean \pm standard deviation, and categorical variables were presented as number and percentage. The ANOVA least significant difference (LSD) test or Chi-square test was used to compared difference among the BMI groups. Cox multivariate regression analysis was used to determine the predictive ability of clinical characteristics for AF recurrence. The area under receiver operating characteristic curve (AUC) was used to test the predictive probability of BMI and its cut off value for AF recurrence. In addition to demographic and clinical factors, Cox proportional-hazards models were also adjusted for BMI (categorized as under or above 26.36 kg/m² cut-off value) to evaluate the impact of BMI on ablation outcomes. Kaplan-Meier analysis was used to test the difference in time-dependent outcome among the BMI groups (<18.5 kg/m², ≥ 18.5 kg/m²–24 kg/m², 25 kg/m²–29 kg/m² and ≥ 30 kg/m²). A two-sided P value of <0.05 was considered statistically significant. Analyses were performed using the SPSS software version 20.0 (IBM Corporation, Armonk, NY, USA) and statistical software R version 3.0.2 (R Core Team, 2013).

3. Results

Of 1410 AF patients (mean age 57.2 ± 11.6 years; 68% male) undergoing single catheter ablation, 960 (68.1%) were male. Patient clinical characteristics in relation to BMI categories are shown in Table 1. During a mean follow-up 20.7 ± 8.8 months, AF recurrence occurred in 365 (27.9%), including 203 with PAF (18.6%) and 162 with NPAF (50.5%).

AF recurrence occurred in 33.3%, 23.2%, 27.2% and 41.8% of patients with a BMI of <18.5 kg/m², 18.5–24 kg/m², 25–29 kg/m² and ≥ 30 kg/m², respectively ($P < 0.01$) showing a “U” shaped pattern (see Fig. 4).

As shown in Table 1, patients with higher BMI values were younger, more often male and more likely to have persistent/longstanding AF, prior cardioversion, hypertension or larger left atrial size (all $p < 0.01$). The underweight and obesity groups had higher serum BNP and required significantly more substrate ablations compared to other two groups (all $P < 0.01$).

On multivariable Cox regression analysis, age, AF types, BMI, congestive heart failure (CHF), left atrial diameter (LAD), glomerular filtration rate (eGFR) and early recurrence (ER) (all $P < 0.01$) were significantly

associated with AF recurrence (see Table 2). BMI was not an independent risk factor for AF recurrence, with a non-significant trend (Hazard Ratio [HR] 1.06, 95% Confidence Interval [CI] 0.98–1.10, $P = 0.066$). Receiver operating characteristic (ROC) curve analysis yielded a cut off BMI value of 26.36 kg/m² for AF recurrence (specificity 72.4%, sensitivity 37.2%). The area under curve (AUC) for BMI for recurrence prediction (categorized as under or above 26.36 kg/m² cut-off value) was 0.549 (95%CI 0.51–0.58; $P < 0.01$) (see Fig. 1).

Patients with a BMI of ≥ 26.36 kg/m² had higher recurrence rate ($P < 0.01$), with larger LAD ($P < 0.01$) and lower eGFR ($P < 0.01$), as well as higher prevalence of NPAF ($P < 0.01$), hypertension ($P < 0.01$) and diabetes mellitus ($P = 0.026$) at baseline, and more substrate ablations and cardioversion during the procedure (see supplementary Table w1).

On a Cox multivariate regression analysis, patients with a BMI of ≥ 26.36 kg/m² had a 50% increased risk of AF recurrence (HR 1.50, 95% CI 1.22–1.86, $P < 0.01$) relative to those with lower BMI (see Table 3). Kaplan-Meier analysis showed that patients with a BMI of ≥ 26.36 kg/m² had more arrhythmias compared to those with a BMI of < 26.36 kg/m² (Log Rank, $P < 0.01$) during follow-up (see Fig. 2).

Kaplan-Meier analysis showed that BMI < 18.5 kg/m² or ≥ 30 kg/m² with significantly more AF recurrence rates post-ablation ($P = 0.011$) (see Fig. 3). Using a Cox proportional hazards model, BMI < 18.5 kg/m² or ≥ 30 kg/m² significantly increased the risk of AF recurrence ($P < 0.05$) (see Table 4).

4. Discussion

In this large cohort of AF patients undergoing CA, our principal findings are as follows: (i) A BMI of ≥ 26.36 kg/m² increased the risk of AF

Table 2
Multivariate analysis of risk factors for AF recurrence post ablation.

^b Risk factor	Hazard Ratio ^a (95% confidence interval)	P value
Age	0.97(0.96–0.98)	<0.01
AF types	1.78(1.42–2.23)	<0.01
ER	3.77(3.02–4.72)	<0.01
CHF	1.33(1.13–1.57)	<0.01
LAD(mm)	1.07(1.04–1.09)	<0.01
eGFR(ml/min/1.73m ²)	0.97(0.96–0.97)	<0.01
BMI(kg/m ²)	1.06(0.98–1.10)	0.066

ER, early recurrence; CHF, prior history of contractive heart failure; LAD, left atrial diameter; eGFR, estimated glomerular filtration rate; BMI, body mass index.

^a Covariate categorical Cox regression analysis, forward conditional method, $P < 0.05$ means statistical significant.

^b Adjusted by age, gender, bundle branch block, AF duration, chronic obstructive pulmonary disease, alcohol consumption, smoking, hypertension, diabetes mellitus, stroke/transient ischemic attack, coronary artery disease, ejection fraction and vascular disease, early recurrence, left atrial size, and AF type.

recurrence post ablation by 50% relative to lower BMI; and (ii) being underweight was also associated with higher AF recurrence rates. The impact of BMI on ablation outcome appears to have a “U” shape.

Regardless of ethnicity, overweight/obesity has been reported as an independent risk factor for new onset AF, being associated with a 20% higher risk of AF compared to normal weight [14] [15]. Obesity has also been associated with higher risk of post-operative AF [10] and AF recurrences post CA of AF [16]. In the study by Winkle et al. [17], for example, among 2715 consecutive patients undergoing single or repeated ablation for symptomatic AF, a BMI of ≥ 35 kg/m² impacted on ablation outcomes was reported. Our study found a lower BMI cut off value

Table 1
Characteristics differences among groups with four BMI categories.

Characteristics	Total	Group 1	Group 2	Group 3	Group 4	P value
N (%)	1410 (100)	48 (3.4)	737 (52.3)	570 (40.4)	55(3.9) (40.4)	P value
Age, years	57.3 ± 11.5	57 ± 15.7*	58.5 ± 11.8	55.3 ± 11.6	55.3 ± 11.6	<0.01
Male	960 (68.1)	21 (43.8)	446 (33)	435 (30.9)	38 (69.1)	<0.01
Recurrence	365 (25.9)	16 (33.3) [†]	171 (23.2)	155 (27.2)	23 (41.8)*	<0.01
LAD,mm	36.9 ± 5.3	33.5 ± 4.9*	35.7 ± 5.0	38.2 ± 5.2	40.8 ± 5.5	<0.01
BNP, pg/ml	319 ± 465	481 ± 668 [†]	308 ± 454	306 ± 444	473 ± 568 [†]	<0.01
CRP, mg/dl	2.3 ± 3.8	2.3 ± 2.3	2.2 ± 3.3	2.5 ± 4.4	2.8 ± 2.9	0.39
eGFR, ml/min/1.73m ²	87 ± 22	91 ± 27	88 ± 24	86 ± 19	83 ± 25	0.054
EF, %	64.7 ± 6.1	66 ± 5.3	64.8 ± 6.3	64.6 ± 5.8	63.5 ± 7.3	0.22
Fu, months	20.7 ± 8.8	20.2 ± 8.4	20.8 ± 8.6	20.8 ± 9.2	18.2 ± 7.3	0.82
PeAF	320 (22.7)	7 (14.6)*	140 (19.0)	155 (27.2)	19 (34.5)	<0.01
BBB	94 (6.6)	5 (10.4)	51 (6.9)	31 (5.4)	7 (12.7)	0.12
COPD	9 (0.6)	1 (2.1)	5 (0.7)	3 (0.5)	0	0.56
Alcohol	75 (5.3)	0	28 (3.8)	44 (7.7)*	3 (5.5)	<0.01
Smoking	244 (17.3)	4 (8.3)	117 (15.9)	116 (20.4)*	7 (12.7)	0.04
HF	71 (5)	1 (2.1)	30 (4.1)	34 (6)	6 (10.9)	0.22
Hypertension	508 (36.1)	10 (20.8)*	248 (33.7)	221 (38.8)	29 (52.7)	<0.01
DM	143 (10.2)	3 (6.2)	70 (9.5)	61 (10.7)	9 (16.4)	0.30
Stroke	84 (6)	3 (6.2)	47 (6.4)	31 (5.4)	3 (5.5)	0.99
CAD	105 (7.5)	2 (4.2)	53 (7.2)	45 (7.9)	5 (9.1)	0.75
Cryoballoon	74 (5.3)	6 (12.6)	38 (5.2)	28 (4.9)	2 (3.6)	0.14
Smart touch	247 (17.5)	5(10.4)	131 (17.8)	96 (16.8)	15 (27.3)	0.14
ECV	157 (11.2)	3 (6.2)*	57 (7.8)	83 (14.6)	14 (25.9)	<0.01
Pharm CV	221 (15.7)	8 (16.7)	99 (13.4)	100 (17.5)	14 (25.5)*	0.04
CPVI	1394(99.3)	46(95.8)	726(98.8)	568(99.6)	54(98.1)	0.91
CFAE	35 (2.9)	3 (6.2)*	23 (3.1)	7 (1.2)	2 (3.6)	0.045
CTI	337 (24)	14 (29.2) [†]	157 (21.3)	144 (25.3)	22 (40)*	<0.01
SCVI	87(6.2)	2(4.2)	49(6.6)	33(5.8)	3 (5.6)	0.85
Linear	266 (18.9)	12 (25) [†]	112 (15.2)	125 (21.9)	17 (30.9)*	0.001
ER	317 (22.5)	9 (18.8)	164 (22.3)	128 (22.5)	16 (29.1)	0.62

Values are n (%) or mean ± SD. Chi-square test or ANOVA LSD test.

Group 1, BMI < 18.5 kg/m²; Group 2, BMI 18.5–24 kg/m²; Group 3, BMI 25–29 kg/m²; Group 4, BMI ≥ 30 kg/m²;

BBB, bundle branch block; BMI, body mass index; BNP, B-type natriuretic peptide; CAD, coronary artery disease; Cryoballoon, cryoballoon ablation; CRP, C reactive protein; CTI, cavo-tricuspid isthmus ablation; CFAE, complex fractionated atrial electrogram ablation; COPD, chronic obstructive pulmonary disease; CPVI, circumferential pulmonary vein isolation; DM, diabetes mellitus; ECV, electrical cardioversion; ER, early recurrence; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, history of congestive heart failure; HT, hypertension; LAD, left atrial diameter; Linear, linear ablation; PVI, pulmonary vein isolation; Pharm CV, pharmaceutical cardioversion; TIA, transient ischemic attack; SCVI, superior vena cava ablation; ST, smart touch ablation catheter.

* $p < 0.05$ vs. other groups.

[†] $p < 0.05$ vs. group 2 or 3.

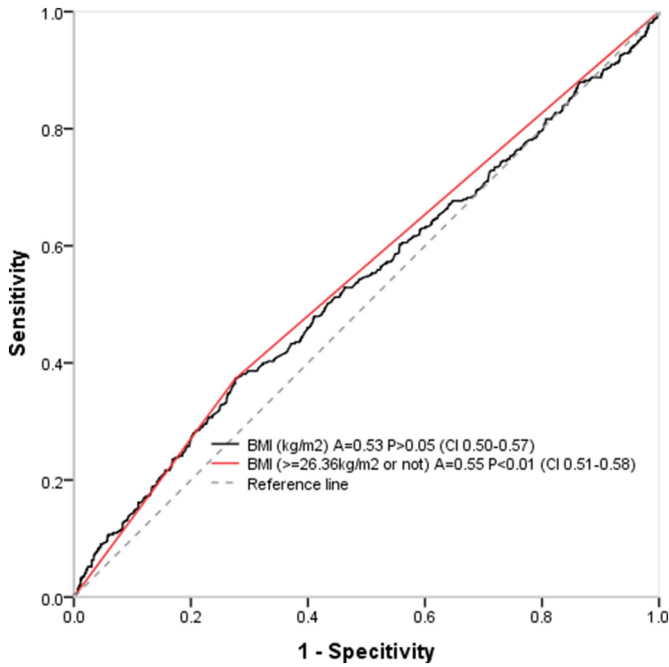


Fig. 1. Predictive ability analysis for AF recurrence post-catheter ablation in relation to BMI ≥ 26.36 kg/m². AUC, area under curve; ROC, receiver operating characteristic; BMI, body mass index. Red line, BMI ≥ 26.36 kg/m²; black line, BMI < 26.36 kg/m².

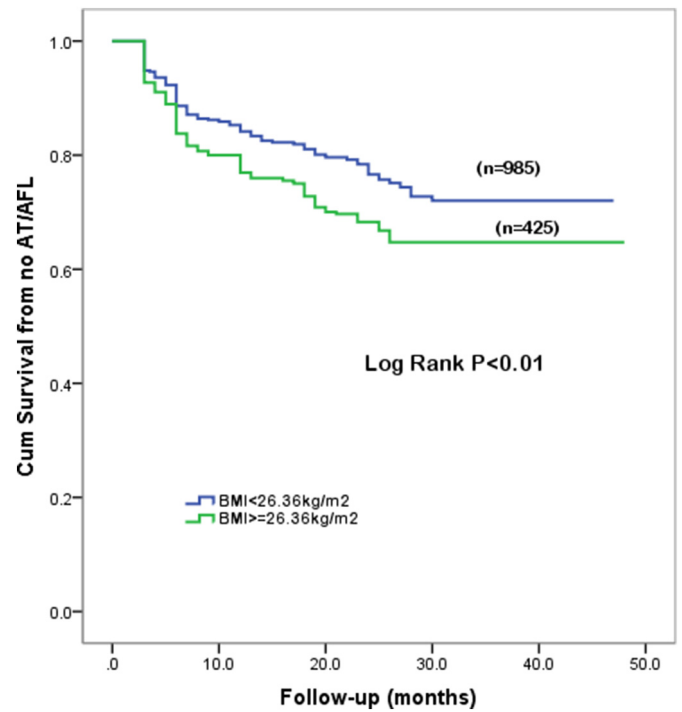


Fig. 2. Kaplan-Meier curve of freedom from AT/AFL in patients with BMI under or ≥ 26.36 kg/m². BMI, body mass index; AT/AFL, atrial tachycardia, atrial flutter or fibrillation. Log Rank test, statistical significant when $P < 0.05$.

(26.36 kg/m²) and we also divided patients into four groups based on accepted definitions of underweight, normal weight, overweight and obesity. Nevertheless, the proportion of obese patients in our cohort was small (3.9%) while there were 39% patients with BMI ≥ 30 kg/m² in the cohort by Winkle et al. [17].

Weight management provides more evidence of the association between obesity and AF. In the LEGACY Study [7], weight management was offered to patients with a BMI of ≥ 27 kg/m² and an average weight loss of $\geq 10\%$ was associated with over 6-fold increase in arrhythmia free survival. The result of the ARREST-AF study also showed that weight loss in AF patients with a BMI of ≥ 27 kg/m² improved the long-term outcome irrespective of single or multiple ablations [6]. The managed weight of these two studies was closed to findings in the present study (26.36 kg/m²).

The role obesity plays in the initiation and maintaining of AF is unclear. Obesity increases the percentage of epicardial adipose tissue (EAT) and increasing EAT might result in more extensive fatty infiltration in the myocardium leading to fibrosis or electrical remodeling [18]. Apart from obesity being related to left size enlargement and fibrosis, atrial inflammation and lipid infiltration, changes in atrial

electrophysiological properties have been observed in both animals and humans [19] [20] [21]. In our cohort, patients with obesity/overweight had larger left atrial size and required more additional ablation

Table 3
Multivariate analysis for AF Recurrence According to the cut off value of BMI.

^b Risk factor	Hazard Ratio ^a (95% confidence interval)	P value
Age	1.17(0.93–1.48)	0.18
CHF	1.43(1.27–1.61)	<0.01
Stroke/TIA	1.24(1.03–1.50)	0.02
BMI		
^c <26.36 kg/m ²	1.00	
≥ 26.36 kg/m ²	1.50(1.22–1.86)	<0.01

^a Covariate categorical Cox regression analysis, forward conditional method, $P < 0.05$ means statistical significant.

^b Adjusted by gender, age, bundle branch block, AF duration, ejection fraction, presence of coronary artery disease, heart failure, hypertension, diabetes mellitus, vascular disease, stroke or transient ischemic attack, bundle branch block, chronic obstructive pulmonary disease, alcohol consumption, and smoking.

^c Reference group.

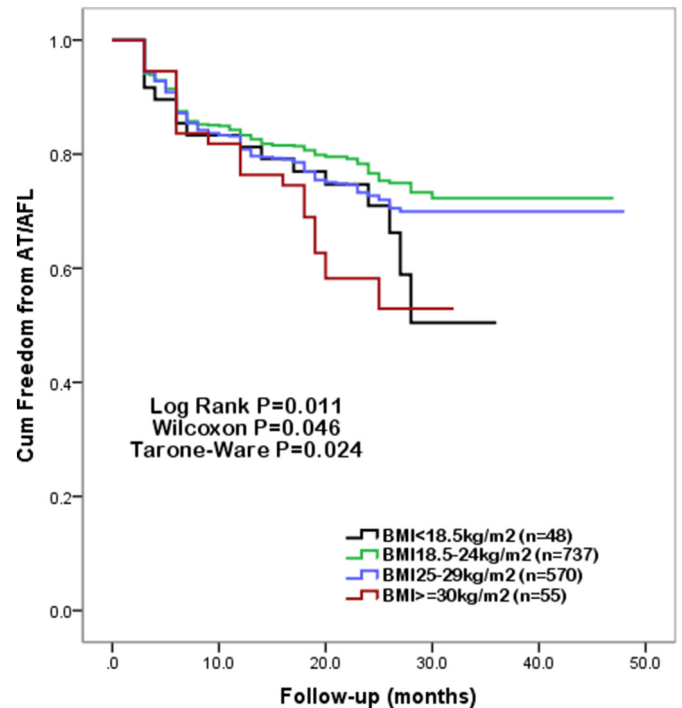


Fig. 3. Kaplan-Meier curve of four BMI categories. BMI, body mass index; AT/AFL, atrial tachycardia, atrial flutter or fibrillation. BMI categories: black line, BMI < 18.5 kg/m²; green line, BMI 18.5 kg/m²–24 kg/m²; blue line, BMI 25–29 kg/m²; red line, BMI ≥ 30 kg/m². Log Rank test, statistical significant when $P < 0.05$.

Table 4
Proportional Hazards of BMI categories for AF recurrence.

^b Risk factor	Hazard Ratio ^a (95% confidence interval)	P value
BMI cat1	1.85(1.12–3.08)	0.02
BMI cat4	1.78(1.17–2.72)	0.01
age	1.02(1.00–1.02)	0.01
AF type	1.79(1.43–2.25)	<0.01
CHF	1.36(1.17–1.59)	<0.01
LAD	1.06(1.04–1.08)	<0.01
ER	4.48(3.59–5.59)	<0.01

BMI, body mass index; CHF, prior history of contractive heart failure; LAD, left atrial diameter; ER, early recurrence.

^a Covariate categorical Cox regression analysis, forward conditional method, $P < 0.05$ means statistical significant.

^b Adjusted by gender, bundle branch block, AF duration, chronic obstructive pulmonary disease, alcohol consumption, smoking, hypertension, diabetes mellitus, stroke/transient ischemic attack, coronary artery disease, ejection fraction and vascular disease, early recurrence, left atrial size, AF type and BMI categories (cat 1, BMI < 18.5 kg/m²; cat 2, BMI 18.5–24 kg/m²; cat 3, BMI 25–29 kg/m²; cat 4, BMI ≥ 30 kg/m²).

^c Reference group.

or cardioversion during the procedure, which implies the presence of a more complicated AF substrate.

In a large observational Asian cohort, incident AF risk was increased in underweight, overweight and obesity individuals by 21%, 14% and 52%, when compared to those with normal weight; also, for those with normal weight, abdominal obesity was found an important risk factor for AF [22]. In a study of elderly outpatients with AF, being underweight has been related to worse outcomes [23]. In a report from a Korean nationwide population-based study, being underweight increased risk of AF onset by 13%, while obesity increased risk by 26%, suggesting a U-shape relationship of BMI and AF [9].

The association of underweight and AF recurrence post ablation has not been previously reported. In a study by Bunch et al. [24], underweight was defined as BMI ≤ 20 kg/m² but did not increase the recurrent risk post-CA, although those who were underweight experienced more cardiovascular events including stroke despite less AF burden.

5. Limitations

This is a single centre retrospective observational study. Arrhythmia outcome was acquired based on the clinical symptoms, 12-lead ECG or 24-h ECG recording and symptom driving ECG. Some asymptomatic AF recurrences might be missed by the follow-up tools we used, and ablation techniques and methods may have evolved during the study period. We have focused on evaluation of the predictive ability of *clinical factors* prior to a CA decision, and our objective was not to compare

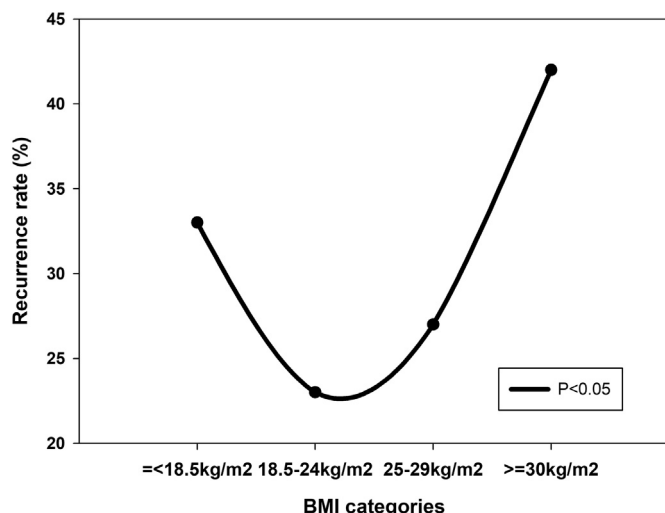


Fig. 4. Plot relationship between BMI categories and AF recurrence.

one catheter or ablation method to another in this ‘real world’ observational cohort. The relatively small number of patients in the underweight category is another limitation. Finally, our results were derived from a Chinese cohort with mean age < 60 years old and may not be generalizable to individuals with advanced age or a different ethnicity.

In conclusion, BMI had good predictive value of ablation outcome with a cut off value ≥ 26.36 kg/m². Apart from obesity/overweight, being underweight might also be another risk factor of AF recurrence post ablation.

Declaration of Interests

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

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Authors contributions

Idea and writing supervision: Gregory YH Lip, Yumei Xue.

Data collecting and assembly: Hai Deng, Lu Fu.

Ablation procedure and follow-up performance: Xianzhang Zhan, Yumei Xue, Xianhong Fang, Hongtao Liao, Hai Deng, Wei wei, Yang liu.

Data analysis and interpretation: Alena Shantsilla, Pi Guo.

Manuscript writing and revision: Hai Deng.

Manuscript comment: Gregory YH Lip, Tatijana S Potpara.

Final approval of manuscript: All authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ebiom.2018.08.034>.

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