

## Review Article

# Meta-analysis of the correlation between recurrence of atrial fibrillation and serum uric acid level after radiofrequency ablation

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**Abstract:** Objective: To systematically evaluate the level of serum uric acid in patients with postoperative recurrence of atrial fibrillation, and explore the evidence-based medical basis for serum uric acid and postoperative recurrence. Methods: The literature on serum uric acid levels in patients with postoperative recurrence of atrial fibrillation was collected using keywords in PubMed, Embase, Web of Science, Cochrane Library, CNKI, World Wide Web, Chinese Biomedical Literature and other publicly published databases. The literature was collaboratively screened by one scholar based on pre-established inclusion and exclusion criteria. Then, we extracted the data in the literature, evaluated the quality of the literature and used RevMan software for statistical analysis. Results: This meta-analysis included 14 research papers, involving 2046 clinical patients, and analyzed serum uric acid levels in the postoperative recurrence group and non-recurrence group. Combining the analysis of the serum uric acid levels in the patients in each study, we found that the serum uric acid levels of the patients in the recurrence group (WMD = 40.79 [27.62, 53.95],  $P < 0.001$ ) were significantly higher than those of the non-recurrence group. Also, the recurrence rate of patients in the high uric acid group (OR = 2.21 [1.73, 2.83],  $P < 0.001$ ) was significantly higher than that of the low uric acid group. Conclusion: The level of serum uric acid is closely related to the recurrence of atrial fibrillation after radiofrequency ablation, and patients with high serum uric acid level have a higher risk of postoperative recurrence.

**Keywords:** Atrial fibrillation, radiofrequency ablation, uric acid

## Introduction

Clinically, atrial fibrillation is a relatively common arrhythmia, and its incidence is related to age. Economically, it brings a substantial burden to society [1]. Due to its high efficiency and convenience, radiofrequency ablation has become the primary method for the treatment of atrial fibrillation. Large-scale cohort studies have found, however, that patients after radiofrequency ablation still have a high risk of recurrence. Therefore, exploring the risk factors affecting recurrence after radiofrequency ablation has become a hot spot in clinical research [2, 3]. In order to explore the factors associated with the recurrence of atrial fibrillation after radiofrequency ablation, this meta-analysis included randomized control trials (RCTs) from multiple countries, and used subgroup analysis and regression analysis to determine whether

high serum uric acid level of patients was associated with postoperative recurrence.

Uric acid is a product of purine metabolism. Studies have found that uric acid can promote the response of related inflammatory factors, leading to inflammation, thereby triggering electrical remodeling and structural remodeling of the atrium [4], which is of great significance in postoperative recurrence. This meta-analysis of relevant published clinical literature explores the association between serum uric acid levels and the recurrence of atrial fibrillation after radiofrequency ablation.

## Materials and methods

### General materials

We searched PubMed, Embase, Web of Science, Cochrane Library, Chinese Biomedical

Literature, CNKI and Wanfang Database. The time range is from the establishment of the database to March 2022. The search strategy was to combine subject keywords with free words. Keywords in Chinese include atrial fibrillation, recurrence after radiofrequency ablation and serum uric acid. Keywords in English include 'serum uric acid/UA/SUA', 'recurrence paroxysmal atrial fibrillation', 'catheter ablation', 'serum uric acid and catheter ablation and recurrence', 'serum uric acid in recurrence paroxysmal atrial fibrillation with catheter ablation' and 'serum uric acid or SUA and recurrence paroxysmal atrial fibrillation and catheter ablation'.

### *Inclusion and exclusion criteria*

*Inclusion criteria:* The included articles were all randomized controlled trials (RCTs). The study population was patients with atrial fibrillation after radiofrequency ablation; the key event observed in the study was recurrence; serum uric acid levels were detected in both the recurrence group and the non-recurrence group.

*Exclusion criteria:* We excluded duplicate published literature, reviews, conference reports, books, case reports and letters, as well as articles from which data could not be extracted or were insufficient.

### *Literature screening and data extraction*

First, Yuan Chen and Yucheng Wu read the title and abstract of the retrieved articles and initially obtained the legal research according to the pre-established inclusion and exclusion criteria. Second, the full text was read for further screening. When there were different opinions, the inclusion was discussed with Xin Chu to obtain a final decision. Third, the extracted data were independently processed and cross-checked by two researchers and reviewed by the third researcher. The data of included studies included year of publication, author, country, patient sample size, publication time, study site, intervention measures and outcome variables.

### *Literature quality assessment*

The quality of the included literature was independently assessed by two investigators according to the Newcastle-Ottawa Scale (NOS)

score, which included the selection of the study population, comparability between groups and outcome measurement. Articles with a score of 6 points or more were included in this meta-analysis. Different opinions were discussed within the group to obtain a final decision.

### *Statistical methods*

RevMan software was used for systematic analysis. For enumerated data, the OR value and its confidence interval were used to express. For measured data, weighted mean difference (WMD) and confidence interval were used. A difference of  $P < 0.05$  was considered significant. The heterogeneity among studies was assessed by  $I^2$  test and  $P$  value.  $I^2 > 50$  or  $P < 0.1$  indicates significant heterogeneity among the studies, and a random effect model was used for the study results. Otherwise, a fixed effect model was used. Furthermore, the funnel plot test was used to evaluate the publication bias between different studies, and the test level was  $\alpha = 0.05$ .

## Results

### *Literature search results*

Through database retrieval, we obtained a total of 325 papers and removed 66 duplicate papers. After reading the titles and abstracts of the articles, we found that 192 items did not meet the inclusion criteria. Among them, 63 studies were unavailable for clinical data, and 129 were reviews, case reports, conference abstracts or monographs. We reviewed the full text of the remaining 67 articles, 6 articles had no study endpoint, 37 articles were excluded due to insufficient data, 10 articles had NOS scores lower than 6 points, and in the end 14 articles were included in the study, involving a total of 2046 patients. The literature screening process and results are shown in **Figure 1**. The basic characteristics of the included literature are shown in **Table 1**.

### *Meta-analysis of serum uric acid levels in different groups*

All 14 studies provided the test results of serum uric acid in patients. Combining with the serum uric acid level and postoperative recurrence of patients in each study group, this meta-analy-

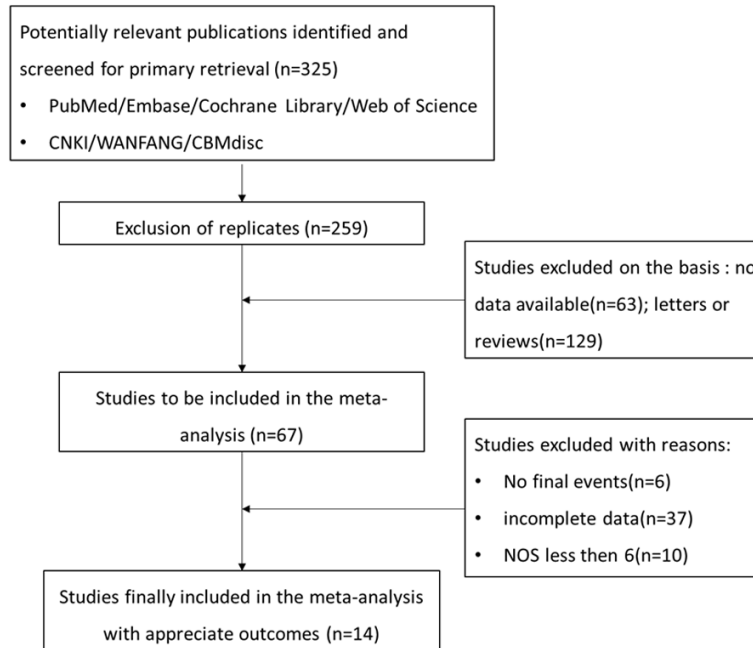


Figure 1. Literature screening process.

sis found that there was significant heterogeneity among the studies ( $I^2 = 61\%$ ,  $P < 0.001$ ), so a random effect model was used to conduct a joint analysis of serum uric acid. The analysis results showed that the serum uric acid level in the recurrence group was higher than that in the non-recurrence group (WMD = 40.79 [27.62, 53.95],  $P < 0.001$ ), and the difference was statistically significant (Figure 2).

#### Meta-analysis of recurrence rate

In 7 studies, the patients were divided into a low uric acid group and a high uric acid group according to the serum uric acid level, and the recurrence rate of each group was calculated. Meta-analysis found that there was no significant heterogeneity among the results of each study ( $I^2 = 0\%$ ,  $P = 0.45$ ), so a fixed-effect model was used to conduct a joint analysis of the recurrence rate. The analysis results showed that the recurrence rate in the high serum uric acid group was higher than that of the low serum uric acid group (OR = 2.21 [1.73, 2.83],  $P < 0.001$ ) (Figure 3).

#### Post offset

A funnel plot analysis was performed on the included research papers, and it was found that the scattered points in the figure were basically symmetrically distributed, indicating

that the included studies had no obvious publication bias (Figure 4).

#### Sensitivity and heterogeneity analysis

Sensitivity analysis was performed by Stata software, and each study was excluded in turn to observe its influence on the total effect. The results showed that after excluding Canpolat's or Ercan's study, the combined effect size changed significantly, suggesting that the results may have a certain degree of heterogeneity, and subgroup analysis was required. See Figure 5.

Ercan's and Canpolat's studies were excluded from the meta-analysis, and no significant heterogeneity was observed.

Heterogeneity in serum uric acid levels was possibly due to different laboratory measurements. See Figure 6.

Meta-regression analysis showed that the number, age, and sex of patients in each study were not associated with postoperative recurrence, and high serum uric acid level was a high-risk factor for postoperative recurrence. See Table 2.

#### Discussion

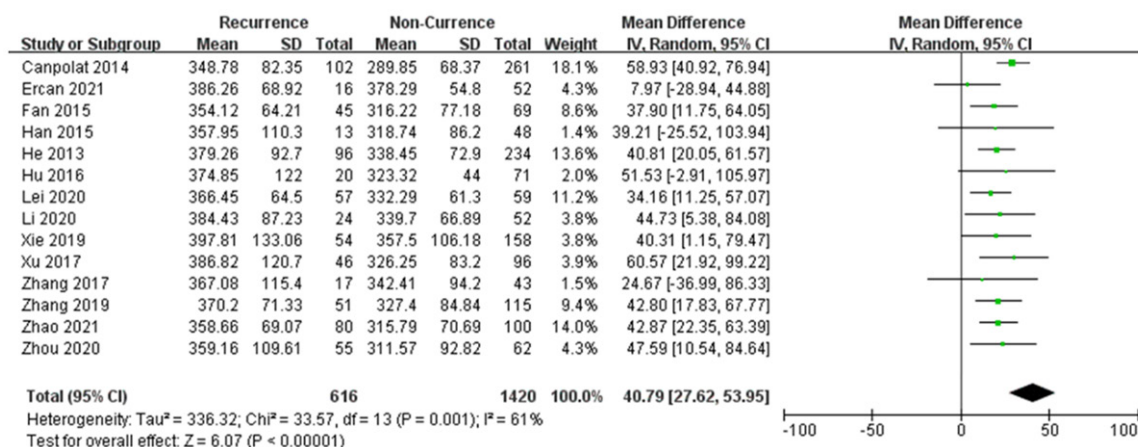
The clinical treatment of early atrial fibrillation is mainly based on drugs, but radiofrequency ablation is used due to the significant side effects of drugs. In recent years, radiofrequency ablation has become an effective means for treating atrial fibrillation. Radiofrequency ablation guides the electrode catheter into the patient's heart through the venous route. Electrophysiologic mapping technology is used to find abnormal electrical conduction channels or ectopic beat points in the heart. The cardiomyocytes are dried and necrotic to achieve the purpose of rapid treatment for arrhythmia [19]. Although radiofrequency ablation has a rapid treatment effect, as a clinical invasive operation, there is still a severe recurrence problem in patients with postoperative atrial fibrillation. There are clinical studies finding that the postoperative recurrence rate of atrial fibrillation

# Correlation between atrial fibrillation recurrence and uric acid after radiofrequency ablation

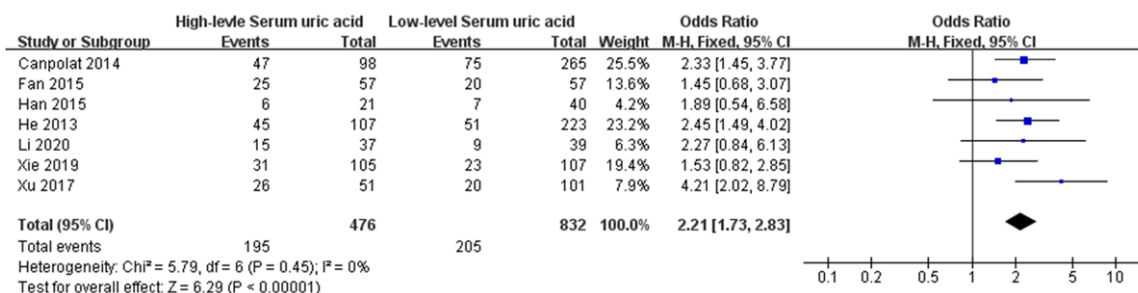
**Table 1.** General characteristics of included studies

Author and publication year	Country	Male/Female	Age	Recurrence group	Non-recurrence group	NOS score
Xie 2019 [5]	China	33/99	40-80	54	158	7
Han 2015 [6]	China	6/25	55-75	13	48	6
Hu 2016 [7]	China	14/47	50-70	20	71	6
Fan 2015 [8]	China	15/42	39-77	45	69	8
Lei 2020 [9]	China	15/33	45-70	27	59	7
Zhao 2021 [10]	China	22/67	50-80	50	100	6
Zhou 2020 [11]	China	35/39	45-65	55	62	7
Zhang 2019 [12]	China	30/69	55-80	51	115	8
Li 2020 [13]	China	15/30	45-75	24	52	7
He 2013 [14]	China	51/123	50-75	96	234	8
Canpolat 2014 [15]	Turkey	72/96	52-80	102	261	6
Ercan 2021 [16]	Italy	11/21	55-75	16	52	7
Xu 2017 [17]	China	25/50	45-75	46	96	8
Zhang 2017 [18]	China	13/29	50-75	17	43	6

NOS: Newcastle-Ottawa Scale.



**Figure 2.** Meta-analysis of serum uric acid levels.

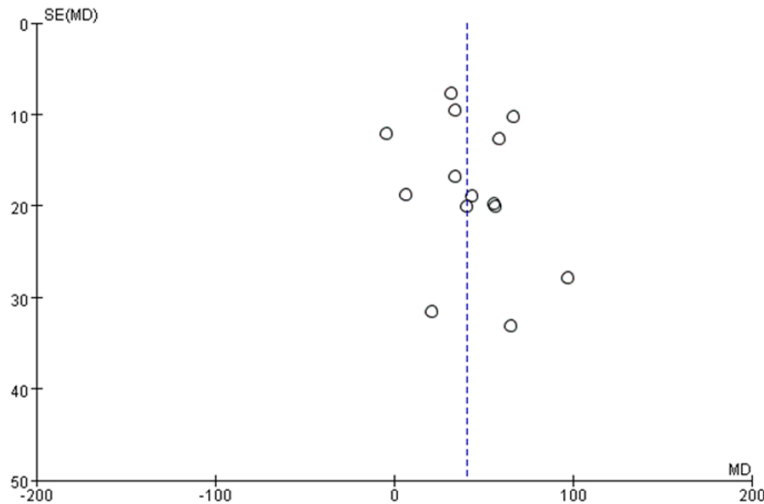


**Figure 3.** Meta-analysis of recurrence rate.

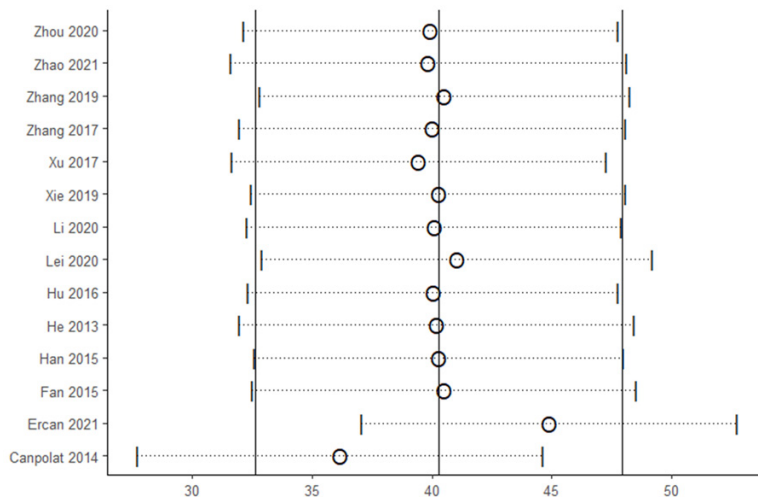
after radiofrequency ablation was as high as 45%. The postoperative recurrence of such patients may be related to the level of serum

uric acid. High uric acid in serum can activate oxidative stress and inflammatory responses in the body, leading to calcium overload in cells,

## Correlation between atrial fibrillation recurrence and uric acid after radiofrequency ablation



**Figure 4.** Publication bias analysis.



**Figure 5.** Sensitivity and heterogeneity analysis.

which in turn reduces the activity of sodium ion channels, thereby triggering electrical remodeling. In addition, oxidative stress can also aggravate myocardial cell damage, which in turn leads to atrial remodeling [20]. Several studies have also reported that high uric acid level is a risk factor for recurrence after radiofrequency ablation in patients with atrial fibrillation [21]. Therefore, this study selected patients with atrial fibrillation to conduct a correlation analysis on serum uric acid levels, aiming to explore the relationship between serum uric acid levels and postoperative recurrence of atrial fibrillation, so as to provide evidence-based information for postoperative recurrence of atrial fibril-

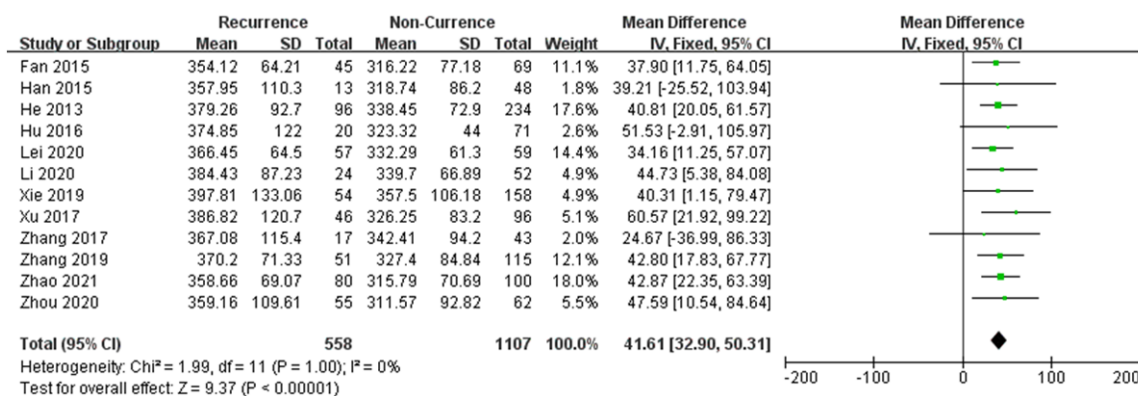
lation and serum uric acid levels.

On the one hand, high uric acid in patients is related to vascular endothelial dysfunction, systemic inflammatory response, and oxidative stress [22]. On the other hand, the remodeling of atrial structure is the pathologic basis for atrial fibrillation, and the clinical manifestations are mainly atrial irregularity in patients-enlargement and fibrosis [23]. Therefore, in atrial structural remodeling, the inflammatory response induced by serum uric acid may play a key role in atrial fibrillation [24]. Marchant et al. believed that serum uric acid levels were related to inflammatory markers, such as c-reactive protein, IL-6, and TNF- $\alpha$ , and the inflammatory state in patients could promote intra-atrial thrombosis, atrial cell apoptosis and atrial fibrosis [25]. Possible mechanisms by which inflammation promotes atrial structural and electrical remodeling include atrial fibrosis, gap junction regulation and abnormal intracellular calcium handling [26]. In addition, uric acid can enter cells through the uric acid transporter protein and

act as a pro-oxidant to activate the NF- $\kappa$ B pathway and induce cells to release inflammatory response mediators (such as IL-6 and TNF- $\alpha$ ). These inflammatory factors activate NF- $\kappa$ B through positive feedback, which amplifies the inflammatory response, leading to fibrosis, apoptosis and cardiomyocyte death [27]. Therefore, reducing the level of uric acid in the serum of patients is beneficial to reduce the risk of postoperative recurrence [28].

The results of this meta-analysis showed that the serum uric acid level in the postoperative recurrence group was significantly higher than that of the non-recurrence group. Further

## Correlation between atrial fibrillation recurrence and uric acid after radiofrequency ablation



**Figure 6.** Heterogeneity was observed after Ercan's and Canpolat's studies were excluded.

**Table 2.** Statistical analysis of basic patient information

	Coefficient	SE	P value
N	0.189	0.042	0.382
Age	0.293	0.056	0.234
Sex	-0.376	0.108	0.472
Serum uric acid	1.274	0.587	0.029

grouped analysis found that the postoperative recurrence rate in the high uric acid group was significantly higher than that of in the low uric acid group, implying that the high uric acid level was significantly related to the postoperative recurrence. However, this study also has certain limitations. First, some data derived from the article may be different from the original data. Second, most of the published literature included are in Chinese, and only 2 are in English, so the generality of the analysis results may be affected. Third, this systematic review is subject to the defects and possible biases of the original research. Last, there are not a lot of data available, so the reliability of the findings need to be verified by large-sample clinically relevant studies. Nevertheless, from the results of this study, the serum uric acid level of patients with atrial fibrillation treated with radiofrequency ablation is closely related to postoperative recurrence, and patients with high serum uric acid levels have a higher risk of postoperative recurrence.

### Disclosure of conflict of interest

None.

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### References

- [1] Liu HY and Xue YM. Aging and atrial fibrillation. *Chin J Card Pacing Electrophysiol* 2021; 35: 120-123.
- [2] Sha YJ, Hu Q, Zhou Y, Li LN, Li SJ, Wang T and Yue QX. The study of left atrial strain and mechanical dispersion in predicting the recurrence of patients with atrial fibrillation after radiofrequency catheter ablation. *Chin J Cardiovasc Res* 2022; 20: 62-68.
- [3] Nuo Z and Dai NE. Meta-analysis of factors influencing recurrence after radiofrequency ablation of atrial fibrillation. *Clin Focus* 2019; 267-272.
- [4] Miao CL, Zhuang JQ, Jin MD, Chen SH, Wu SL, Hong J and Xin AJ. Relationship of hyperuricemia with all-cause mortality in patients with atrial fibrillation. *Clin Med China* 2021; 37: 31-38.
- [5] Xie DJ, Zhou JH, Yuan XY and Liu W. Risk factors for recurrence of atrial fibrillation after first radiofrequency ablation. *Jilin Med J* 2019; 40: 950-954.
- [6] Han YL, Chen CJ, Yi Z, Zhang M and Jin WH. Correlation of serum uric acid and N-terminal probrain natriuretic peptide (NT-pro BNP) levels with atrial fibrillation recurrence after radiofrequency ablation. *Chronic Pathematology J* 2015; 16: 146-149.
- [7] Hu X, Zhang J and Ding ZJ. Relationship between serum uric acid level and recurrence of patients with paroxysmal atrial fibrillation after radiofrequency ablation. *Chin Gen Pract* 2016; 19: 2275-2278.
- [8] Fan JH, Xie J, Zou C, Jiang B, Chen D, Hui J, Song JP, Li X and Yang XJ. Correlation of serum

## Correlation between atrial fibrillation recurrence and uric acid after radiofrequency ablation

- uric acid and recurrence of paroxysmal atrial fibrillation after radiofrequency ablation. *Jiangsu Med J* 2015; 41: 273-275.
- [9] Lei ZB and Huang GR. The serum uric acid in predicting the recurrence of nonvalvular atrial fibrillation after radiofrequency ablation. *Chin J Integrat Med Cardio-Cerebrovasc Dis* 2020; 18: 4022-4025.
- [10] Zhao SJ. Risk factors of recurrence after catheter radiofrequency ablation of paroxysmal atrial fibrillation. *Med Innovation China* 2021; 18: 129-133.
- [11] Zhou L, Tang SP and Sun XL. Factors of recurrence of paroxysmal atrial fibrillation after radiofrequency ablation. *Chin J Clin Healthcare* 2014; 17: 533-535.
- [12] Zhang LZ, Wu XP, Liu SZ, Song HL, Li BY and Wan DG. Clinical study on early recurrence of paroxysmal atrial fibrillation after catheter ablation. *J Pract Med* 2019; 35: 3798-3802.
- [13] Li L, Liu GJ and Wu FX. Risk factors for recurrence of paroxysmal atrial fibrillation after radiofrequency ablation. *Pract Clin J Integr Tradit Chin West Med* 2020; 20: 117-118.
- [14] He XN, Li SN, Zhan JL, Xie SL, Zhang ZJ, Dong JZ, Yu RH, Long DY, Tang RB and Ma CS. Serum uric acid levels correlate with recurrence of paroxysmal atrial fibrillation after catheter ablation. *Chin Med J* 2013; 126: 860-864.
- [15] Canpolat U, Aytémir K, Yorgun H, Şahiner L, Kaya EB, Çay S, Topaloğlu S, Aras D and Oto A. Usefulness of serum uric acid level to predict atrial fibrillation recurrence after cryoballoon-based catheter ablation. *Europace* 2014; 16: 1731-1737.
- [16] Vizzardi E, Curnis A, Latini MG, Salghetti F, Rocco E, Lupi L, Rovetta R, Quinzani F, Bonadei I, Bontempi L, D'Aloia A and Dei Cas L. Risk factors for atrial fibrillation recurrence: a literature review. *J Cardiovasc Med (Hagerstown)* 2014; 15: 235-253.
- [17] Xu HX, Lu Q, Huang YH, Gu ZS, Chen ZW and Mou JJ. Predictor analysis in patients of paroxysmal atrial fibrillation recurrence after radiofrequency ablation. *Chin Circ J* 2017; 32: 1203-1207.
- [18] Zhang BH and Wang J. Effect of NT-proBNP and SUA on arrhythmia recurrence after radiofrequency ablation of atrial fibrillation. *J Guangxi Med Univ* 2017; 34: 1348-1350.
- [19] Xie LM, Yu YF, Yang PW, Chen XZ, Sun YM, Li W and Yan JF. Study on the success rate and short-term recurrence rate of radiofrequency ablation after electrical cardioversion of persistent atrial fibrillation. *Chin J Cardiovasc Res* 2015; 13: 917-920.
- [20] Li T, Zhu TQ, Fang ST, Ouyang JY, Xiang HF, Chen SZ, Wang YT, Yao YH and Huang CX. Effect of pueraria isoflavones on inflammation and stress response in hyperuricemia mice. *Pract J Card Cereb Pneumal Vasc Dis* 2022; 30: 75-80.
- [21] Zhang ZP, Liu JY and Gao LJ. Research progress on risk factors of atrial fibrillation recurrence after catheter ablation. *J Pract Electrocardiol* 2016; 25: 442-446.
- [22] Chen Y, Xia Y, Han X, Yang Y, Yin X, Qiu J, Liu H, Zhou Y and Liu Y. Association between serum uric acid and atrial fibrillation: a cross-sectional community-based study in China. *BMJ Open* 2017; 7: e019037.
- [23] Correa S, Curtis KA, Waikar SS and Mc Cauland FR. Serum myeloperoxidase, uric acid, and the risk of atrial fibrillation in chronic kidney disease. *Circ Arrhythm Electrophysiol* 2021; 14: e009483.
- [24] Hong M, Park JW, Yang PS, Hwang I, Kim TH, Yu HT, Uhm JS, Joung B, Lee MH, Jee SH and Pak HN. A mendelian randomization analysis: the causal association between serum uric acid and atrial fibrillation. *Eur J Clin Invest* 2020; 50: e13300.
- [25] Hidru TH, Tang Y, Liu F, Hui S, Gao R, Li D, Yang X and Xia Y. Does serum uric acid status influence the association between left atrium diameter and atrial fibrillation in hypertension patients? *Front Cardiovasc Med* 2020; 7: 594788.
- [26] Kuwabara M and Hisatome I. Gender difference in the association between uric acid and atrial fibrillation. *Circ J* 2018; 83: 27-29.
- [27] Ono K. How is uric acid related to atrial fibrillation? *Circ J* 2019; 83: 705-706.
- [28] Wang XD, Liu J, Zhang YC, Wang Y, Wang Y and Ma D. Correlation between the elevated uric acid levels and circulating renin-angiotensin-aldosterone system activation in patients with atrial fibrillation. *Cardiovasc Diagn Ther* 2021; 11: 50-55.