Rheumatoid arthritis and risk of atrial fibrillation: results from pooled cohort studies and Mendelian randomization analysis

Qiyuan Song[1], Luxiang Shang[2], Yujiao Zhang[2], Yansong Cui[3], Juanjuan Du[2]
Yinglong Hou[2]*

Affiliations:

1. Shandong First Medical University, The First Affiliated Hospital of Shandong First Medical University. Jinan, China.
2. Department of Cardiology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong Medicine and Health Key Laboratory of Cardiac Electrophysiology and Arrhythmia, Jinan, China;
3. The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Medical Integration And Practice Center, Shandong University. Jinan, China.

***Correspondence:**

Yinglong Hou, Ph.D., Email: yinglonghou@hotmail.com
Address: Department of Cardiology, The First Affiliated Hospital of Shandong First Medical University, No. 16766, Jingshi Road, Lixia Zone, Jinan, 250014, China.
Tel: +86 0531-89269217.

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Conflicts of interest: None.

Abstract

Observational research has shown that individuals diagnosed with rheumatoid arthritis (RA) face an elevated likelihood of developing atrial fibrillation (AF). A meta-analysis and Mendelian randomization (MR) analysis were used to explore the correlation and potential causal relationship between RA and AF. We searched PubMed, Embase, and Web of Science for cohort studies comparing AF risk among participants with and without RA. Quantitative synthesis of the adjusted risk ratio (RR) or hazards ratio was performed by the random-effects model. RA and AF were studied using a two-sample MR analysis. The Mendelian randomization (MR) analysis utilized the random-effects inverse variance weighted (IVW) method. We found patients with RA had a higher risk of AF than participants without RA [RR=1.32, 95% confidence interval (CI): 1.23-1.43, P < 0.0001]. Genetically predicted RA was not associated with a significantly higher risk of AF (odds ratio = 1.009, 95%CI: 0.986 - 1.032, P = 0.449). After adjusting for confounding factors of multifactorial MR, RA and AF still had no correlation. Sensitivity analyses yielded similar results, indicating the robustness of the causal association. Overall, RA is associated with increased risk of AF in our meta-analysis. However, genetically predicted RA may not be causal.

Keywords: Atrial fibrillation; Rheumatoid arthritis; Mendelian randomization; Meta-analysis; Causality.

Introduction

Atrial fibrillation (AF) is the most prevalent clinical arrhythmia worldwide [1]. The global prevalence rate of AF is around 59.7 million individuals based on estimation from the most recent Global Burden of Disease Study 2019 [2]. Furthermore, the lifetime risk of AF development has reached about one in three among Americans according to Framingham Heart Study and ARIC Study [3,4]. AF is widely recognized as a risk factor for conditions like heart failure, ischemic stroke, and cognitive decline. Furthermore, it is linked to increased rates of disability and mortality [5].Hence, AF imposes a tremendous burden on global health. Early control of risk factors and timely intervention for high-risk populations of AF is critical to public health.

Rheumatoid arthritis (RA) is a chronic, systemic, destructive autoimmune disease that involves primarily joints and can affect multiple organs, including cardiovascular systems [6]. Previous two meta-analyses [7,8] and several observational studies [9-11] have shown that patients with RA are at increased risk of AF relative to the general population. However, there are also studies reporting contradictory results. A matched study utilizing information from an extensive US commercial insurance plan revealed that RA was not linked to an increased risk of AF in the fully adjusted model [12]. The inconsistent results were likely due to the effects of confounding factors such as the use of RA medications, and the differences in the study design, study population, and sample size. Besides, since the publication of the lasted meta-analysis, new studies investigating this topic have emerged [9,11,13]. It is necessary to combine all available studies to achieve a more reliable result for addressing controversial findings. Thus, we intend to perform an updated meta-analysis to assess the association of RA and AF.

Observational studies may be subject to residual confounding, reverse causation, and measurement error, and thus cannot prove a causal relationship. The Mendelian randomization (MR) analysis can eliminate these limitations and has emerged as a powerful tool to identify more reliable associations than traditional observational studies by leveraging the random assortment of alleles during meiosis [14]. In this

present article, we further use the MR method to infer the causality between RA and AF.

Methods

Method for the systemic review and meta-analysis

The systemic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [15] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement [16]. The PRISMA 2020 checklist was presented in Table S1. This study was deemed exempt from ethical approval by the Medical Ethical Committee of our hospital because no individual patient-level data were analyzed.

Literature search strategy

The online literature search was conducted in PubMed, Embase, and the Web of Science. The detailed search strategies of the three databases are described in Table S2. Primary search terms included “atrial fibrillation” and “rheumatoid arthritis”. Two investigators (SQY and SLX) independently identified relevant studies published from inception to July 28th, 2023. We also screened the reference lists of eligible studies for cross-references.

Inclusion and exclusion criteria

The studies incorporated into this meta-analysis fulfilled the following criteria: (1) prospective or retrospective cohort studies comparing the AF risk in participants with and without RA; (2) reporting effect size [adjusted risk ratio (*RR*) or hazards ratio (*HR*)] and 95% confidence interval (CI); (3) original studies published in English.

We excluded case reports, editorials, letters, reviews, meta-analyses, and all non-full-length publications. Animal experiments and clinical studies with a cross-sectional or case-control design were also excluded.

Data extraction and risk of bias assessment

Two authors (SQY and SLX) independently extracted information and evaluated the quality of each eligible study. The disagreements were addressed and resolved

through consensus during a meeting involving a third investigator (ZYJ). Data on the first author, location, year of publication, study design and duration, numbers of participants enrolled, effect size, and adjusted variables were collected using a predesigned electronic form. The assessment of bias risk was conducted using the Newcastle–Ottawa Scale (NOS), a tool designed to evaluate the quality of nonrandomized studies [17]. A NOS score of 7 or higher was deemed indicative of high quality.

Methods for the MR analysis

We applied a two-sample MR analysis to estimate the causal effect size of genetic susceptibility to RA on AF following STROBE-MR guideline (Table S4) [18]. Figure 1 provides an overview of the MR design. The Medical Ethical Committee of our hospital considered this study exempt from ethical approval since it involves a secondary analysis of publicly accessible summary-level statistical data obtained from genome-wide association studies (GWAS).

Data sources

The summary-level GWAS data for RA was derived from FinnGen biobank round 9 (https://r9.finngen.fi/) with 9,243cases and 368,029controls [19]. The outcome dataset of AF was obtained from the largest GWAS meta-analysis of six studies (The Nord-Trøndelag Health Study, deCODE, the Michigan Genomics Initiative, DiscovEHR, UK Biobank, and the AFGen Consortium) and included 60,620 cases and 970,216 controls [20]. Heart failure and type 2 diabetes mellitus were included as confounding factors. The heart failure dataset is derived from 26 cohort studies within the HERMES consortium [21]. The type 2 diabetes dataset is derived from DIAbetes Genetics Replication And Meta-analysis (DIAGRAM), Genetic Epidemiology Research on Adult Health and Aging (GERA) and UKB [22]. Detailed information can be found in Table S5. Every participant granted written informed consent in accordance with the original description.

Selection of instrumental variables (IVs)

The selection of SNPs which were used as IVs was based on three main hypotheses of classical MR analysis. In the initial step, we chose independent SNPs

displaying a significant association with RA (P < 5×10-8). Subsequently, SNPs characterized by strong linkage disequilibrium (LD) with each other were eliminated (LD R2 ≥ 0.001, and a clump window size of 10,000 kb was employed). In the third stage, SNPs linked to the AF-related phenotype (P < 5×10-8) were excluded, leaving us with the remaining SNPs for subsequent analysis.

We calculated variance (R^2) and F statistics to evaluate the strength of the screened SNPs and avoid weak-tool bias [23]. The R^2 refers to the cumulative explained variance of the selected SNP during exposure. The F statistics was calculated using the formula: $R^2(N\text{-}K\text{-}1)/[K(1\text{-}R^2)]$, where K is the number of SNPs for the final analysis, and N is the sample size of the GWAS dataset of RA. Filtered out IVs unrelated to the outcome factor under the Bonferroni-corrected significance level (P > 0.05/SNPs). We conducted a PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) search for all known phenotypes associated with the IVs used in our analysis. SNPs associated with AF risk factors were excluded.

Multivariable MR (MVMR)

Considering heart failure and type 2 diabetes, often discussed as contributing risk factors for AF, we employed the MVMR-IVW method for MR analysis. Our aim is to ascertain if there's a causal relationship between RA and AF after adjusting for these potential confounders.

Statistical analysis and sensitivity analysis

The meta-analysis was performed using *R* version 4.2.1 for quantitative analysis. The *HR* used in cohort studies was considered as *RR* in this meta-analysis. The outcome was assessed by the random-effects model, and was expressed as polled *RR* with 95% CI. Cochran's Q and the I^2 statistic were used to investigate heterogeneity. A sensitivity analysis was performed using the leave-one-out method to assess the impact of each individual study on the overall pooled effect [24]. Publication bias was evaluated qualitatively by the asymmetry of the funnel plot and quantitatively by Egger's test.

The MR analysis was performed by R version 4.2.1 and TwoSampleMR package version 0.5.6. The random-effects inverse variance weighted (IVW) method was used as the main MR method, other methods (MR Egger, Weighted median, Simple mode, Weighted mode) were used as supplementary analyses. The results were presented as odds ratio (OR) with 95% confidence intervals (CIs). Sensitivity analyses including heterogeneity test, funnel plot, pleiotropy test, and leave-one-out sensitivity test were employed to evaluate the robustness of the results. Heterogeneity was assessed with the Cochran's Q test. Pleiotropy was accessed with the MR-PRESSO test. The power online analysis platform (https://shiny.cnsgenomics.com/mRnd/) was used to calculate power for MR.

A P value <0.05 was considered statistically significant.

Results

Literature search results

The flowchart of the study selection was shown in Figure 2. Six candidate articles yielded a total of 71,902 patients with RA and 4,567,067 controls were included in the quantitative synthesis [9,11,13,25-27]. The characteristics and information of the included studies was presented in Table 1. All articles were of high quality according to the NOS, as shown in Table S3.

Meta-analysis results

The random-effects model revealed that patients suffering from RA had a 31% higher risk of developing AF than individuals without RA (*RR*=1.32, 95%CI: 1.23-1.42, $P < 0.0001$, Figure 3A). The heterogeneity among studies was not significant ($I^2 = 38\%$, $P = 0.15$). A sensitivity analysis showed that no study from the pooled analysis changed the results significantly (Figure 3B). The funnel plot of all the studies was presented symmetrically, indicating a low risk of publication bias ($t = -1.350$, $P = 0.250$, Figure 3C).

Causal Effects of Genetic Predisposition to RA with AF risk

Excluding five SNPs (rs2476601, rs2013002, rs2395269, rs7453967, rs9268145) associated with potential confounding factors using the PhenoScanner database; detailed information can be found in Table S6.

Following a series of screenings, 24 SNPs were included in this MR analysis; detailed information is available in Table 2. All IVs were not significantly associated with AF at the Bonferroni adjusted significance level ($P > 0.00208$). These SNPs explain approximately 27.44% of the variation in RA patients. The F-statistic for the 24 SNP loci significantly exceeds the empirical threshold of 10, with a value of (50.563, 1769.424). The IV's F-statistic and the estimated power for all analyses are listed in Table S7 - 8.

The summary of MR analysis results is presented in Table 3 and Figure 4. The IVW method showed no statistically significant difference in the genetic predisposition risk for RA and AF (OR = 1.009, 95% CI: 0.986 ~ 1.032, $P = 0.449$). Further MR analyses using the weighted median and MR-Egger regression yielded similar results.

Sensitivity Analyses

Sensitivity analyses were performed to complement the main results of our MR analysis obtained with IVW. No significant heterogeneity in SNP effects was observed by Cochran's Q test ($P = 0.584$) and funnel plot (Figure S1, Table S9). The MR-Egger test (intercept = -2.546 × 10−3, SE = 3.348 × 10−3, $P = 0.455$) showed there is no detectable directional pleiotropy. No single SNP was found to strongly or reversely influence the overall effect of RA on AF in the leave-one-out analysis (Figure S2).

MVMR

In the MVMR analysis adjusting for heart failure and type 2 diabetes, there remains no significant association between RA and AF occurrence ($P = 0.465$). Refer to Table S10 for detailed information.

Discussion

In the present study, we made an updated meta-analysis of observational studies

and found that RA was associated with a statistically significant higher risk of developing AF. However, as opposed to the meta-analysis, the causality between genetically predisposed RA and AF risk was not supported by the MR analysis.

The correlation between RA and AF risk is inconsistent in previous epidemiological studies. The discordant results may be owing to the different genetic background, and differences in follow-up period, diagnosis methods for AF detection, and variables included in the multiple adjusted models. However, the general trend is that patients with RA is associated with increased risk of AF in either the Asian populations or Western populations. Our meta-analysis results, incorporating new observational study findings and expanding the sample size, remain consistent with the previous two meta-analyses [7,8], supporting RA as a risk factor for atrial fibrillation. In addition, RA was shown to be related to higher risk of AF recurrence after ablation [28]. The associations observed in cohort studies might be biased due to confounding factors. In the studies included in this meta-analysis, the research by Tilly MJ, et al.[11] indicated that RA patients had a higher risk of AF compared to non-RA patients. However, in subgroup analysis, male patients did not show a significant difference, suggesting that gender plays an important role in this association. Additionally, one study[26] adjusted for various risk factors such as diabetes, cardiovascular diseases, medications, and healthcare utilization, and found that the risk of AF did not increase in RA patients. In contrast, two other studies[10,27], even after adjusting for these risk factors, still observed an elevated risk. According to the United States National Inpatient Sample database, the prevalence of cardiac complications including AF, heart failure (HF), and acute myocardial infarction (AMI) in patients with RA was statistically significant increasing during the last decade [29]. Of which HF and AMI are well-recognized risk factors for AF. The association between RA and AF was perhaps mediated by these cardiovascular risk factors.

Our MR analysis did not uncover a causal relationship between genetically predicted RA and AF risk. Despite using only 24 SNPs as IVs, there was no evidence of directed pleiotropy among the genetic variants examined, indicating that the exclusion restriction hypothesis was not violated. Heterogeneity analysis indicated no

significant differences among the studied SNPs. Additionally, leave-one-out analysis suggested that the overall effect was not driven by individual SNPs, demonstrating the stability of our results. Furthermore, after correction for heart failure and type 2 diabetes, the results remained consistent, further supporting our MR analysis. Similarly, MR analysis may yield different results due to variations in data sources and statistical methods. Wang M, et al.'s research[30] reported outcomes that were concordant with our study findings. However, a recent study[31] by Rong JC et al. using MR analysis in an East Asian population showed a causal relationship between RA and AF (OR = 1.060; 95% CI, 1.028 ~ 1.092; P = 1.411 × 10-4). This suggests a potential AF risk in Asian RA patients to some extent. Nevertheless, given the complex pathophysiology of AF, the selected IVs can only explain partial genetic variations. Further research is needed to confirm the causal role of RA in AF.

The disparities between observational studies and MR analysis conclusions lead us to consider several potential reasons. First, both meta-analysis and MR analysis are based on secondary analyses, and the inherent limitations of each method cannot be entirely eliminated. This may impact the robustness of the results. Second, the association of RA and AF might be caused by the drugs for RA treatment. Evidence from a UK population-based cohort analysis showed that the cardiovascular risk was increased in patients with immune-mediated inflammatory diseases including RA who were taking glucocorticoid even at lower doses (<5 mg) [32]. Third, inflammation is generally thought to play a vital role in the pathology of RA-induced arrhythmias [33,34]. However, several recent MR studies investigating the association of inflammation and AF obtained similar conclusions to our MR result [35-37]. The genetically determined C-reactive protein[37] and monocyte chemoattractant protein-1 [36] were not significantly associated with AF. Meanwhile, another MR study did not support a causal role of inflammatory bowel disease, comprising ulcerative colitis, and Crohn's disease, with AF [35].

The results from studies included in this research are contradictory, making it challenging to draw definitive conclusions on the topic. Our inclination is that RA may carry a certain level of risk for AF. Li Y, et al.[38] discovered prolonged atrial

conduction time, unchanged atrial effective refractory period, atrial structural remodeling, and autonomic nerve remodeling in a collagen-induced RA rat model. This provides additional insights suggesting that RA may not directly lead to the occurrence of AF but could increase susceptibility to AF.

The major strength of our study is to provide a comprehensive and more reliable interpretation of the role of RA in AF since we integrate evidence from observational and genetics-driven studies to date. However, there were several limitations in our study. First, although we combined the adjusted *RR* value in the meta-analysis, different confounding factors may constitute potential confounding effect. Second, the genetic variants used in the MR analysis merely explained a part of variance of RA across individuals. Some unknown RA-related SNPs may also have important roles in the development of AF. Third, we cannot completely rule out the possibility that RA-related SNPs affect AF via other pathways. Although no horizontal pleiotropic effect was shown in MR-Egger test, suggesting no violation of the second MR assumption. Fourth, the sources of data for both meta-analysis and MR analysis may introduce potential biases into the results.

Conclusion

Observational studies indicated a positive association between RA and the occurrence of AF. However, the MR analysis did not provide evidence for a causal link between RA and AF. Additional research is needed to clarify the impact of RA on the development of AF.

Data Availability Statement

All data used in the current study were obtained from online publicly database.

Author Contributions

HYL, SQY, SLX: funds collection and study design; SQY, CYS, DJJ: data processing, statistical analysis and interpretation; SQY: wrote manuscript; All authors: critical review and approve the manuscript.

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Conflict of Interest

No commercial or financial relationships could be construed as a conflict of interest in the research.

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Figure legend

Fig 1. Illustrative diagram of Mendelian randomization assumptions.

Fig 2. Flow diagram for literature search and identification.

Fig 3. Meta-analysis of RA and risk of AF. A: Forest plot for the association of RA and AF; B: Sensitivity analysis of leave-one-out; C: Funnel plot of publication bias.

Fig 4. Scatter plot of SNPs associated with RA and their risk of AF.