Original Article

Causal associations between atrial fibrillation and esophageal cancer: a two-sample Mendelian randomization study

Jinsong Lei[1#], Longjun Yang[2#], Gongming Wang[1], Qianwen Liu[1], Guangran Guo[1]

[1]Department of Thoracic Surgery, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China; [2]Department of Thoracic Surgery, Cancer Hospital of Shandong First Medical University, Jinan, China

Contributions: (I) Conception and design: G Guo; (II) Administrative support: Q Liu; (III) Provision of study materials or patients: L Yang; (IV) Collection and assembly of data: G Wang; (V) Data analysis and interpretation: J Lei; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Qianwen Liu, PhD; Guangran Guo, PhD. Department of Thoracic Surgery, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, No. 651 Dongfeng Road East, Yuexiu District, Guangzhou 510060, China. Email: liuqw@sysucc.org.cn; guogr@sysucc.org.cn.

Background: Previous studies indicated that atrial fibrillation (AF) patients had a significantly higher esophageal cancer (EC) risk. However, influencing by confounding factors, the causal effect is uncertain. In this study, we aimed to validate the causal relationship between AF and EC by Mendelian randomization (MR) analysis.

Methods: An observational analysis was conducted using the data from the National Health and Nutrition Examination Survey (NHANES) and UK Biobank. Then a two-sample MR method was employed to assess the causal effect of AF on EC. The exposure of AF was collected from publicly available genome-wide association studies (GWASs). Meanwhile, the EC outcome data were derived from the UK Biobank and the FinnGen consortium. A set of 108 single-nucleotide polymorphisms (SNPs) served as instrumental variables (IVs). The effect estimates were calculated using the inverse variance weighted (IVW) method.

Results: Genetically predicted AF was associated with an increased risk of EC [odds ratio (OR), 1.73; 95% confidence interval (CI): 1.01–1.73; P=0.04]. The similar results could be found by sensitivity analyses and no any evidence of horizontal pleiotropy was observed.

Conclusions: This two-sample MR analysis suggested that AF was causally associated with an increased risk of EC.

Keywords: Atrial fibrillation (AF); esophageal cancer (EC); Mendelian randomization (MR)

Submitted Oct 28, 2024. Accepted for publication Jan 14, 2025. Published online Mar 10, 2025.
doi: 10.21037/tcr-24-2107
View this article at: https://dx.doi.org/10.21037/tcr-24-2107

Introduction

The global prevalence of atrial fibrillation (AF) has increased substantially over the past three decades, concerning approximately 60 million cases (1). AF is associated to morbidity and mortality due to systemic embolic complications and heart failure (2). In addition to cardiovascular complications, cancer also accounts for approximately 11% of all deaths in AF patients (3). Owing to rapid population aging and the increasing global burden seen in both diseases, more work needs to answer whether AF is a risk factor for cancer.

A comprehensive nationwide cohort study revealed that individuals diagnosed with AF exhibited a markedly increased risk of developing cancer compared to the general population. Notably, patients with newly onset AF faced the greatest cancer risk during the initial year post-diagnosis,

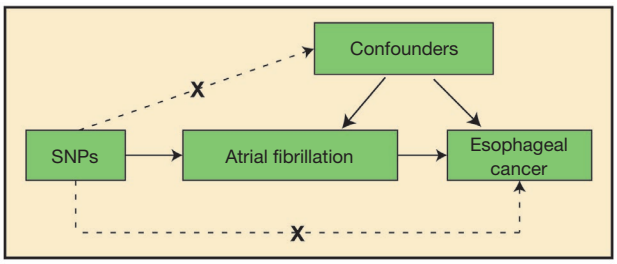

Figure 1 The schematic view of the study design with three assumptions: (I) the genetic variants are robustly associated with AF; (II) the genetic variants are not associated with other confounders; and (III) the genetic variants are associated with the clinical outcome only through AF. AF, atrial fibrillation; SNP, single-nucleotide polymorphism.

and this elevated risk continued to be evident even after 10 years (4). Recently, another research based on 25,964,447 Chinese patients revealed that AF was associated with 1.41-fold increased prevalence of esophageal cancer (EC) (5). However, it remains unclear whether AF and EC will interact and the causal relationship of AF and EC deserves further confirmation.

As a matter of fact, an increase of AF incidence among EC patients was also reported (6). Traditional observational studies, including well-designed prospective studies frequently encounter limitations due to residual confounding and reverse causality. Mendelian randomization (MR) is a method using genetic variants as instrumental variables (IVs) for exposures to evaluate the potential causality between various exposures and clinical outcomes. Since genetic variations are established at conception and occur before the development of disease, MR analysis can address reverse causation bias and minimize the impact of potential unmeasured confounders (7). In this research, we aimed to explore the potential causal link between AF and EC using the two-sample MR analysis. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2107/rc).

Highlight box

Key findings

- This study confirmed the causal relationship between atrial fibrillation (AF) and esophageal cancer (EC) by Mendelian randomization analysis.

What is known and what is new?

- Previous observational studies indicated that AF may increase the risk of EC.
- The causal associations those two diseases have been not elucidated yet.

What is the implication, and what should change now?

- AF patients need to pay attention to possible EC-related syndrome and consult for more medical help.

Methods

Study design and data sources

In our study, we used a two-sample MR approach to evaluate the causal relationship between AF and EC, with the study design depicted schematically in *Figure 1*. The rationale of our MR design is based on three specific criteria: firstly, the genetic variants are strongly associated with AF; secondly, the absence of associations between these genetic variants and other confounding variables; and thirdly, the genetic variants influence the clinical outcome exclusively through AF. For this analysis, we obtained genome-wide association study (GWAS) summary statistics for AF from the resource based on six contributing studies (8) to explore the association between AF and single-nucleotide polymorphisms (SNPs). The genetic data for EC (n=218,792) were obtained from the UK Biobank (https://www.ukbiobank.ac.uk) and the FinnGen consortium (https://www.finngen.fi/en). All GWAS statistics used were publicly available and ethical approval was not required for this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Two public databases were used to investigate the incidence correlation between AF and EC. We utilized data from the National Health and Nutrition Examination Survey (NHANES) for the years 1999 to 2023, with a total of 58,744 individuals aged 18 years and older, and data from the UK Biobank, which included 467,627 participants from 2006 to 2010, aged between 37 and 73 years. Data on age, gender, education, smoking, alcohol consumption, and the status of EC and AF were extracted from the two databases.

Selection and validation of SNPs

We pinpointed 108 independent SNPs linked to AF by adhering to three criteria. Firstly, SNPs were chosen based on a genome-wide significance threshold, where P values were less than 5×10^{-8}. The second criterion involved using paired linkage disequilibrium to ensure the

Table 1 Characteristics of the cohort studies

Variables	NHANES		UK Biobank	
	AF (n=1,525)	Control (n=57,219)	AF (n=8,356)	Control (n=459,271)
Age (years)	67 [60–79]	49 [34–64]	64 [59–67]	57 [49–63]
Gender				
Female	815 [53]	29,679 [52]	2,530 [30]	257,218 [56]
Male	710 [47]	27,540 [48]	5,826 [70]	202,053 [44]
Education				
College degree	645 [42]	28,561 [50]	2,312 [27.7]	149,955 [32.7]
Others	880 [58]	28,658 [50]	6,044 [72.3]	309,316 [67.3]
Smoke				
Yes	747 [49]	24,489 [43]	4,512 [54]	202,597 [44.1]
No	34 [2.2]	1,128 [2.0]	3,844 [46.0]	256,674 [55.9]
Unknown	744 [49]	31,602 [55]	–	–
Drink				
Yes	169 [11]	7,066 [12]	7,985 [95.6]	438,662 [95.5]
No	12 [0.8]	730 [1.3]	371 [4.4]	20,509 [4.5]
Unknown	1,344 [88]	49,423 [86]	–	–
EC	3 [0.2]	33 [<0.1]	33 [0.4]	983 [0.2]

Data are presented as median [IQR] or n [%]. AF, atrial fibrillation; EC, esophageal cancer; IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey.

independence of selected SNPs. SNPs with r^2>0.001 within a clumping window of 10,000 kb were discarded if they were correlated with more SNPs or had higher P values. Lastly, we confirmed the strength of individual SNPs using the *F* statistic, considering SNPs as sufficiently strong to reduce potential bias if their *F*-statistics exceeded ten. Aata-harmonization steps were also conducted before performing the MR analysis.

Statistical analysis

For the primary analysis, we utilized random effect inverse variance weighted (IVW) MR methods, which presumes that all SNPs serve as valid instruments and calculates the effect of each variant using first-order weights. To assess horizontal pleiotropy among the selected SNPs, we subsequently applied the MR-Egger method and weighted median analysis. MR-Egger method allows for directional pleiotropy and the MR-Egger intercept estimates the average pleiotropic effect across all SNPs. If the MR Egger intercept deviates from zero, directional pleiotropy is present. Similarly, funnel plots can also identify directional pleiotropy if there is asymmetry. The Q statistic was employed to test for heterogeneity among SNPs in the IVW analysis. We also performed a leave-one-out sensitivity analysis to determine if any single SNP disproportionately influenced the overall estimates. The effects of AF on EC were reported as odds ratios (ORs) with 95% confidence intervals (CIs). All statistics were carried out using the "Two-Sample MR" package in R 4.2.0. For the significant causal associations in the univariable MR analysis, the multivariable MR (MVMR) analysis was performed using the MVMR-IVW method, aiming to adjust for potential confounding factors including smoking, alcohol, education (9) as well as obesity (Table S1).

Results

Firstly, we compared the incidence rate of EC between AF patients and normal people. The incidence was higher in AF patients compared with the general population (*Table 1*). To confirm the causal relationship between the two diseases, we selected SNPs and then estimated the effect of genetically predicted AF on EC.

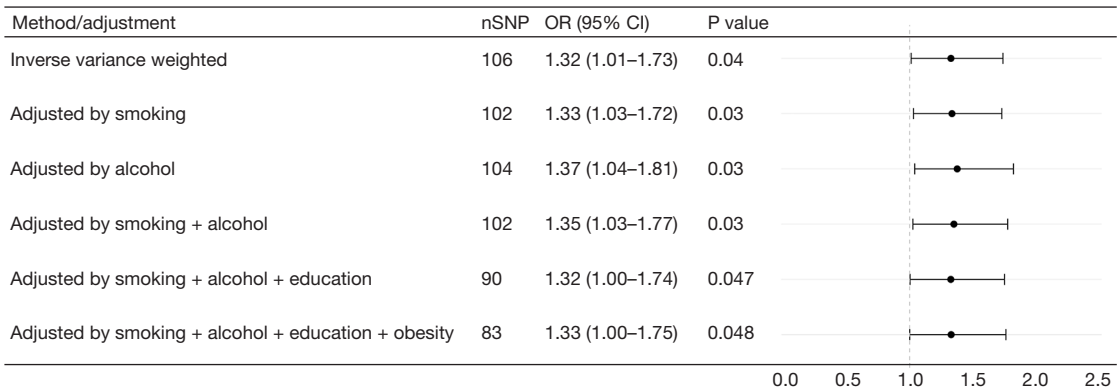

Figure 2 Associations of AF with EC. AF, atrial fibrillation; CI, confidence interval; EC, esophageal cancer; nSNP, number of SNP; OR, odds ratio; SNP, single-nucleotide polymorphism.

Table 2 Sensitivity analyses of the genetic association between AF and EC risk

Sensitivity analyses	Value	P value
MR-Egger		
OR (95% CI)	1.24 (0.74–2.07)	0.41
Weight median		
OR (95% CI)	1.21 (0.72–2.03)	0.47
Heterogeneity test		
Cochrane Q	96.26	0.72
Pleiotropy test		
Intercept	0.006	0.77

AF, atrial fibrillation; CI, confidence interval; EC, esophageal cancer; MR, Mendelian randomization; OR, odds ratio.

We identified 108 independent SNPs associated with AF (Table S2). Then we applied random-effects IVW models, and the two-sample MR analyses based on these SNPs demonstrated a causal effect of genetically predicted AF on the risk of EC (OR, 1.32; 95% CI, 1.01–1.73; P=0.04). Even after adjusting for smoking, alcohol, education as well as obesity, the causal effect of AF on EC still existed (*Figure 2*). The results of MR-Egger and weighted median are consistent with the IVW models but of low precision. No evidence of directional pleiotropy and heterogeneity were detected (*Table 2*).

The funnel plots in *Figure 3* revealed no evidence of directional pleiotropy. The scatter plots illustrating the association between AF and EC are presented in Figure S1, revealing similar results. The leave-one-out sensitivity analysis confirmed that the association was not significantly driven by any individual SNP (Figure S2). In addition, Figure S3 provides details on the associations of each variant with AF and the risk of EC.

Discussion

Given the lengthened life expectancy in the general population, the coexistence of AF and cancer has also increased pervasively, and AF may present an additional factor affecting the prognosis of malignant diseases (10). A large initially healthy cohort showed that women with new-onset AF had an elevated cancer risk beyond 1 year of AF diagnosis (11). Yet, limited research has been done to confirm the potential causality relationship between AF and EC. To our knowledge, this is the first MR analysis to reveal the causal relationship between AF and EC.

Previous studies have indicated a close association between AF and EC. Firstly, postoperative AF is frequently observed in EC patients undergoing esophagectomy with an increased risk of death (12). For EC therapy, radiation (13) and anticancer agent like fluorouracil (14) also increases AF risk. Even for cancer patients without active treatment are still associated with a 20% increased risk of AF (15). One nationwide population-based study revealed that AF risk varies depending on the cancer type, and EC patients show the highest AF risk among all the solid cancers (16). In addition, patients with cancer and new-onset AF showed a 2-fold increased risk of thromboembolism and a 6-fold increased risk of heart failure (17). However, the potential

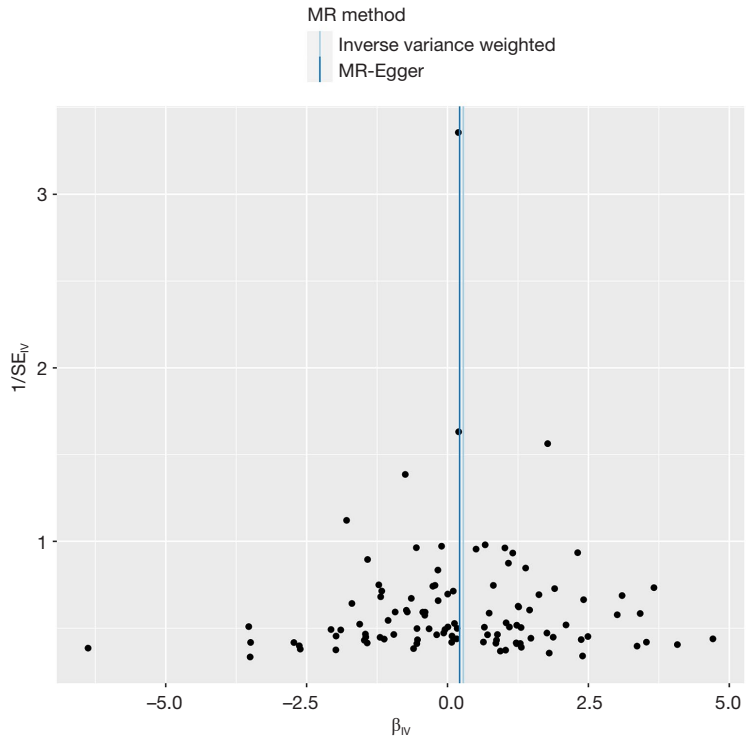

Figure 3 Funnel plot of the associations between AF and EC. AF, atrial fibrillation; EC, esophageal cancer; IV, instrumental variable; MR, Mendelian randomization; SE, single equation.

causality role of AF on EC still remains unknown. Few studies showed that AF patients had a higher risk of EC (5) and suggested that AF may be a risk and predictor of EC (4). If the causal relationship is established, AF patients need to pay attention to possible EC-related syndrome.

In our study, we uncovered the causal effect of AF on EC by two-sample MR analysis using large-scale GWAS data, inferring the higher risk of EC among AF patients comparing to the normal people.

It remains unclear why AF patients are associated with increased prevalence of EC, and some factors may be responsible for the increased risk. First, some common risk factors such as smoking, alcohol use, and obesity are shared by both diseases (18). It has also been reported that higher educational attainment has a protective effect on EC (19). However, causality relationship between AF and EC still existed based on MR analysis even after adjustment for these factors, suggesting that another mechanism may involve. Considering that inflammation promotes the progress of the two diseases, inflammation may be another possible mechanism. Indeed, remodeling and increased energy demand during AF lead to oxidative stress (20), which could cause the esophageal injury indirectly (21). It has been proven that during the Barrett's esophagus-dysplasia-EC sequence, esophageal cells are under a tremendous burden of accumulating reactive oxygen species oxidative stress (22). In addition, the STAT3/NF-κB signaling increases AF vulnerability (23) as well as involvement in tumorigenesis (24). NF-κB modulates EC tumor microenvironment and is linked to poor prognosis (25). Furthermore, remodeling of the extracellular matrix (ECM) has been identified as a significant factor contributing to the pathophysiology of both AF and EC. Fibroblasts control the composition and structure of ECM and play a central role in stabilizing the reentrant drivers that maintain the arrhythmia (26). In EC, cancer-associated fibroblasts can also promote tumorigenesis, metastatic dissemination, and therapeutic resistance (27).

Recent study has shown that EC-related gene-4 (ECRG4) is implicated in the pathogenesis of AF. Downregulation of ECRG4 expression level correlates with myocardial injuries and arrhythmias as well as EC (28). ECRG4 may be used in the treatment of arrhythmias and tumors in this regard.

However, there are some unique challenges for therapeutic decision-making in AF patients with cancer. As a matter of fact, the use of anticoagulants for reducing the high risk of AF-associated thromboembolism may increase the risk of bleeding in EC, especially for those who have received treatment (29). Considering the heterogeneity in cancer patients, risk assessments should also take into account cancer stage, treatment response, and overall prognosis (30). Furthermore, the immune checkpoint inhibitors (ICIs) have revolutionized the treatment paradigm for EC (31), while ICI-associated myocarditis may contribute to higher risk of atrial arrhythmias (32). Understanding the relationship between AF and EC may result in improved prevention and treatment strategies for both diseases.

This study is the first MR analysis to uncover the causal effects of AF on EC. Comparing to traditional observational studies, MR analyses are well suited to overcome confounding by unmeasured factors. Additionally, the role of inflammation among AF on EC and their potential mechanism deserve further study. Despite the findings, there are several limitations to consider. Firstly, the GWAS data were derived from individuals of European ancestry, potentially limiting the generalization of our results to other population. Then, in the period following AF diagnosis, there are more interactions with healthcare, and thus providing more opportunities to find asymptomatic EC. Moreover, children are susceptible to AF but have a low probability of suffering EC, the age-specific relationships between AF and EC should be further clarified in the future.

Conclusions

In conclusion, this two-sample MR analysis identified causal relationships between AF and EC. Furthermore, additional research is necessary to clarify the underlying mechanisms that mediate the association between these two diseases.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2107/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2107/prf

Funding: The study was supported by the Guangzhou Science and Technology Program (No. 2024A04J4411).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-2107/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Elliott AD, Middeldorp ME, Van Gelder IC, et al. Epidemiology and modifiable risk factors for atrial fibrillation. Nat Rev Cardiol 2023;20:404-17.
2. Wilke T, Groth A, Mueller S, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace 2013;15:486-93.
3. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, et al. Causes of Death in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol 2016;68:2508-21.
4. Hung YP, Hu YW, Liu CJ, et al. Risk and predictors of subsequent cancers of patients with newly-diagnosed atrial fibrillation - A nationwide population-based study. Int J Cardiol 2019;296:81-6.
5. Chen M, Li C, Zhang J, et al. Cancer and Atrial Fibrillation Comorbidities Among 25 Million Citizens in Shanghai, China: Medical Insurance Database Study. JMIR Public Health Surveill 2023;9:e40149.

6. Mery B, Guichard JB, Guy JB, et al. Atrial fibrillation in cancer patients: Hindsight, insight and foresight. Int J Cardiol 2017;240:196-202.
7. Richmond RC, Davey Smith G. Mendelian Randomization: Concepts and Scope. Cold Spring Harb Perspect Med 2022;12:a040501.
8. Nielsen JB, Thorolfsdottir RB, Fritsche LG, et al. Biobank-driven genomic discovery yields new insight into atrial fibrillation biology. Nat Genet 2018;50:1234-9.
9. Loh PR, Kichaev G, Gazal S, et al. Mixed-model association for biobank-scale datasets. Nat Genet 2018;50:906-8.
10. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. J Am Coll Cardiol 2014;63:945-53.
11. Conen D, Wong JA, Sandhu RK, et al. Risk of Malignant Cancer Among Women With New-Onset Atrial Fibrillation. JAMA Cardiol 2016;1:389-96.
12. Schizas D, Kosmopoulos M, Giannopoulos S, et al. Meta-analysis of risk factors and complications associated with atrial fibrillation after oesophagectomy. Br J Surg 2019;106:534-47.
13. Miller ED, Wu T, McKinley G, et al. Incident Atrial Fibrillation and Survival Outcomes in Esophageal Cancer following Radiotherapy. Int J Radiat Oncol Biol Phys 2024;118:124-36.
14. Moriyama S, Yokoyama T, Irie K, et al. Atrial fibrillation observed in a patient with esophageal cancer treated with fluorouracil. J Cardiol Cases 2019;20:183-6.
15. O'Neal WT, Lakoski SG, Qureshi W, et al. Relation between cancer and atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke Study). Am J Cardiol 2015;115:1090-4.
16. Yun JP, Choi EK, Han KD, et al. Risk of Atrial Fibrillation According to Cancer Type: A Nationwide Population-Based Study. JACC CardioOncol 2021;3:221-32.
17. Hu YF, Liu CJ, Chang PM, et al. Incident thromboembolism and heart failure associated with new-onset atrial fibrillation in cancer patients. Int J Cardiol 2013;165:355-7.
18. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
19. Zhang X, Yang X, Zhang T, et al. Association of educational attainment with esophageal cancer, Barrett's esophagus, and gastroesophageal reflux disease, and the mediating role of modifiable risk factors: A Mendelian randomization study. Front Public Health 2023;11:1022367.
20. Mason FE, Pronto JRD, Alhussini K, et al. Cellular and mitochondrial mechanisms of atrial fibrillation. Basic Res Cardiol 2020;115:72.
21. Song S, Guha S, Liu K, et al. COX-2 induction by unconjugated bile acids involves reactive oxygen species-mediated signalling pathways in Barrett's oesophagus and oesophageal adenocarcinoma. Gut 2007;56:1512-21.
22. Peng D, Zaika A, Que J, et al. The antioxidant response in Barrett's tumorigenesis: A double-edged sword. Redox Biol 2021;41:101894.
23. Hsu YJ, Chang GJ, Lai YJ, et al. High-phosphate diet causes atrial remodeling and increases atrial fibrillation vulnerability via STAT3/NF-κB signaling and oxidative stress. Acta Physiol (Oxf) 2023;238:e13964.
24. Sharma T, Gupta A, Chauhan R, et al. Cross-talk between the microbiome and chronic inflammation in esophageal cancer: potential driver of oncogenesis. Cancer Metastasis Rev 2022;41:281-99.
25. Gu L, Sang Y, Nan X, et al. circCYP24A1 facilitates esophageal squamous cell carcinoma progression through binding PKM2 to regulate NF-κB-induced CCL5 secretion. Mol Cancer 2022;21:217.
26. Meulendijks ER, Al-Shama RFM, Kawasaki M, et al. Atrial epicardial adipose tissue abundantly secretes myeloperoxidase and activates atrial fibroblasts in patients with atrial fibrillation. J Transl Med 2023;21:366.
27. Dunbar KJ, Wong KK, Rustgi AK. Cancer-Associated Fibroblasts in Esophageal Cancer. Cell Mol Gastroenterol Hepatol 2024;17:687-95.
28. Zhang Z, Wang W, Zhang Y, et al. A potential link between aberrant expression of ECRG4 and atrial fibrillation. Front Oncol 2023;13:1031128.
29. Boriani G, Lee G, Parrini I, et al. Anticoagulation in patients with atrial fibrillation and active cancer: an international survey on patient management. Eur J Prev Cardiol 2021;28:611-21.
30. Madnick DL, Fradley MG. Atrial Fibrillation and Cancer Patients: Mechanisms and Management. Curr Cardiol Rep 2022;24:1517-27.

31. Nagata Y, Yamamoto S, Kato K. Immune checkpoint inhibitors in esophageal cancer: Clinical development and perspectives. Hum Vaccin Immunother 2022;18:2143177.

32. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol 2018;71:1755-64.

Cite this article as: Lei J, Yang L, Wang G, Liu Q, Guo G. Causal associations between atrial fibrillation and esophageal cancer: a two-sample Mendelian randomization study. Transl Cancer Res 2025;14(3):1849-1856. doi: 10.21037/tcr-24-2107