



BMJ Open Resting heart rate and risk of atrial fibrillation in Chinese general population: Kailuan prospective cohort study

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ABSTRACT

Objective Previous research has shown an association of higher heart rate with an increased risk of atrial fibrillation (AF). However, the relationship between resting heart rate (RHR) and AF is unknown. The aim of this study was to investigate the association between RHR and AF in the general population of China.

Design Prospective observational cohort study.

Setting Community based.

Participants A total of 46 126 individuals from the Kailuan study who participated in the first three surveys (2006/2007, 2008/2009 and 2010/2011) and were followed up at 2-year intervals were enrolled.

Primary outcome measures The association between RHR and risk of incident AF was evaluated using Cox proportional hazards regression and restricted cubic spline models.

Results Two hundred and forty-one individuals (0.52%) developed AF during 7.5 years of follow-up. After adjustment for age, sex, low-density and high-density lipoprotein, physical activity, alcohol consumption, smoking status, body mass index, mean systolic blood pressure, and history of diabetes and hypertension, the HRs were 2.32 (95% CI 1.45 to 3.72) for an RHR <60 beats/min and 2.80 (1.13 to 6.94) for an RHR ≥100 beats/min in comparison with an RHR of 70–80 beats/min. Restricted cubic spline models revealed a U-shaped relationship between RHR and incident AF.

Conclusion These findings indicate that RHR and incident AF have a U-shaped relationship in the Chinese general population. Both lower and higher RHRs were associated with an increased risk of AF.

INTRODUCTION

Atrial fibrillation (AF) is one of the most common types of arrhythmia and is increasing in prevalence, with approximately 37 574 million people worldwide reported to have AF in 2017.¹ One study found that the prevalence of AF was 1.8% in the Chinese population in 2021.² AF is associated with higher cardiovascular and cerebrovascular morbidity and mortality rates, including a fivefold increase in risk of ischaemic stroke.^{3–7}

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study includes a large population with long-term follow-up.
- ⇒ Resting heart rate (RHR) values were obtained from ECGs recorded at three annual surveys.
- ⇒ The sex distribution in the RHR subgroups was not balanced.
- ⇒ The possibility that certain potentially relevant conditions (eg, thyroid disease, chronic obstructive pulmonary disease, anaemia) were not diagnosed cannot be excluded.
- ⇒ Cases of asymptomatic or undiagnosed atrial fibrillation cases may have been missed.

Therefore, it is necessary to determine the risk factors for AF and be able to identify individuals at increased risk of developing it.

Resting heart rate (RHR) has recently emerged as a risk factor for AF.^{8,9} However, there is no consensus regarding the patterns of association between RHR and the risk of AF. Previous reports on the relationship between RHR and AF have been inconsistent.^{7,10–12} A multicentre international randomised controlled trial that included individuals at high cardiovascular risk found that a low RHR (<60 beats/min) was independently associated with the risk of AF.¹² However, another study reported an association between a high RHR and incidence of AF in the general population aged 45–64 years.⁷ Moreover, the relationship between RHR and AF has not been investigated in the Chinese population. Therefore, the aim of this study was to investigate the association between RHR and AF at the general population level in China.

METHODS

Study population and collection of data

The Kailuan study is an ongoing prospective occupational cohort study conducted

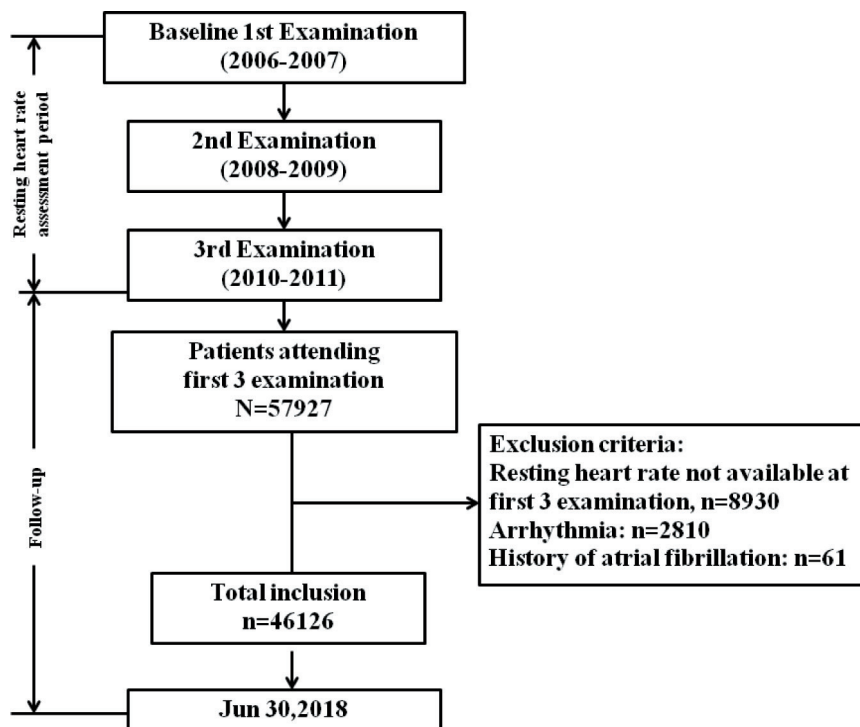


Figure 1 Flow chart of Kailuan cohort study.

in Tangshan, China. All employees and retirees aged 18–98 years old from the Kailuan Group were invited to participate in the study. Details of study design and procedures used have been published elsewhere.^{13 14} A total of 101 510 study participants were enrolled at any of 11 hospitals affiliated with the Kailuan Group between 2006 and 2007.

Participants were included in the present study if they completed the first three surveys (in 2006/2007, 2008/2009 and 2010/2011). A total of 57 927 individuals met this criterion. After exclusion of 8930 with missing heart rate date, 2810 with another physician-diagnosed type of arrhythmia (eg, atrial flutter, atrial premature beats, ventricular premature beats, ventricular tachycardia or atrioventricular block) and 61 with a history of AF, the study population included 46 126 individuals who had been followed up at 2-year intervals until 30 June 2018 (figure 1).

A questionnaire was sent to each study participant for completion and the responses were confirmed by trained medical staff members in a face-to-face interview to ensure the accuracy of the data collected.^{13–15} The questionnaire included items on sex, age, height, weight, complications, history of smoking and alcohol consumption, and physical exercise. Body mass index (BMI) was calculated as body weight divided by the square of height. Physical exercise was divided into sedentary/moderate activity (less than 3 times/week for ≥ 30 min/session) and high/intense activity (at least ≥ 3 times/week for ≥ 30 min/session). Physical activity was defined as aerobic exercise ≥ 3 times/week for ≥ 30 min/session. Antihypertensive medications include diuretics, β -blockers, calcium antagonists, ACE inhibitors, angiotensin receptor blockers and

combined preparations. Physical examination included blood pressure (BP), heart rate, an ECG and biochemical indices. All examinations were performed between 07:00 and 09:00. All participants were instructed to abstain from drinking alcohol or coffee, smoking and strenuous exercise for 30 min before the examination. RHR was measured by 12-lead ECG after a 5-minute rest period in a quiet environment.³ Lead II was used to calculate the R–R interval. We recorded five QRS wave groups continuously, measured the total R–R interval and calculated the average R–R value. Fasting blood samples were used to measure triglycerides (TGs), total cholesterol (TC), high-density (HDL-C) and low-density lipoprotein cholesterol (LDL-C), and fasting blood glucose (FBG).

Follow-up and assessment of outcomes

All participants completed a questionnaire and attended an interview, clinical and laboratory examinations at enrolment and were followed up at 2-year intervals from 2006 onwards. The follow-up assessments were performed by trained physicians who were blinded to the baseline data. Outcome information was confirmed by checking the discharge summaries from the 11 Kailuan hospitals and medical insurance records. Outcome information for participants with face-to-face follow-up was obtained from the Municipal Social Insurance Institution, which covers all study participants, the discharge registers of all 11 Kailuan hospitals and a questionnaire survey. For participants without face-to-face follow-up, the outcome information was obtained directly by checking death certificates from provincial vital statistics offices, discharge summaries and medical records.

The primary study outcome was the frequency of new-onset AF. Potential AF cases were identified by International Classification of Diseases, Tenth Revision codes. For suspected AF cases, a panel of three physicians reviewed the medical records and adjudicated these cases annually. In accordance with the 2006 European Society of Cardiology guidelines, AF was diagnosed if episodes of irregular R–R intervals with no discernible distinct P waves lasting at least 30s were observed on the ECG.¹⁶ During biennial interview, all participants underwent a 10-second 12-lead ECG examination.

Patient and public involvement

No patient involved.

Assessment of average RHR

RHR was recorded in all study participants at the first three surveys (2006/2007, 2008/2009 and 2010/2011). The calculation method of average RHR (AVE RHR) in our study was very similar to the average BMI in ‘Weight and weight change and risk of atrial fibrillation: the HUNT study’.

We denoted heart rate at three separate time points by the following terms: at survey I (2006–2007) as HR₀₆, at survey II (2008–2009) as HR₀₈ at survey III (2010–2011) as HR₁₀.

We designed the following equations for further analyses¹⁷:

$$\text{AVE RHR} = \frac{[(\text{HR}_{06} \times \text{Time}_{06-08}) + (\text{HR}_{08} \times \text{Time}_{08-10}) + (\text{HR}_{10} \times \text{Time}_{10-})]}{\text{Time} - \text{all}}$$

Time_{06–08}=time from survey I (2006–2007) to survey II (2008–2009)

Time_{08–10}=time from survey II (2008–2009) to survey III (2010–2011)

Time_{10–}=time from survey III (2010–2011) to the end of follow-up

Time–all=time from survey I (2006–2007) to the end of follow-up

We then divided the participants into six groups according to whether the AVE RHR was <60, 60–70, 70–80, 80–90, 90–100 or ≥100 beats/min.

Statistical analyses

The statistical analyses included the data for the 46126 individuals who underwent the first three surveys. Continuous variables are shown as the mean±SD and categorical variables as percentages and frequencies. Between-group differences in baseline characteristics were compared using analysis of variance for continuous variables and the X² test for categorical variables. Cox proportional regression models were used to assess the HRs and 95% CIs for AF according to AVE RHR (using AVE RHR 70–80 beats/min as the reference group) while considering age, sex, LDL-C and HDL-C, physical activity, alcohol consumption, smoking status, BMI, mean systolic BP (SBP), and history of diabetes and hypertension as confounders.¹⁸

Restricted cubic spline models were established to evaluate the association between RHR and the risk of incident AF. We respectively excluded the subsets of individuals who were on medication (β-blockers and calcium antagonists) and those with a history of cardiovascular disease from the sensitivity analysis to minimise their potential influence on the results. All statistical analyses were conducted using SAS V.9.3.

RESULTS

Baseline characteristics

The 46126 participants who completed the first three surveys were followed up until 2018. Baseline characteristics including age, sex, SBP, diastolic BP (DBP), TG, TC, HDL-C, LDL-C, BMI, FBG, smoking and drinking stage, the history of hypertension and diabetes, and use of anti-hypertensive agents are shown in table 1. There were more men than women in each of the six subgroups. With increasing AVE RHR, there was a rising trend in mean SBP, mean DBP, TG and FBG. The subgroup with AVE RHR ≥100beats/min had the highest rates of hypertension (68.10%) and diabetes (25.46%). Use of antihypertensive medication was significantly more common in individuals with AVE RHR of ≥100beats/min.

AVE RHR and risk of AF

During a median follow-up of 7.5 years, 241 individuals (0.52%) developed AF (table 2).

Both lower and higher AVE RHRs were associated with an increased risk of AF in comparison with AVE RHR of 70–80 beats/min. The incidence of new-onset AF in participants with AVE RHR <60beats/min and those with AVE RHR ≥100beats/min was 1.30% and 1.53%, respectively. After adjusting for age and sex, the HRs and 95% CIs for AVE RHR <60beats/min and AVE RHR ≥100beats/min were 2.62 (95% CI 1.29 to 3.27) and 3.23 (95% CI 1.31 to 7.93) compared with AVE RHR of 70–80 beats/min, respectively. Further, after adjusting for age, sex, SBP, BMI, LDL-C, HDL-C, history of smoking, alcohol consumption, diabetes and hypertension, the results were still consistent. The HRs and 95% CIs for AVE RHR <60beats/min and AVE RHR ≥100beats/min were 2.32 (95% CI 1.45 to 3.72) and 2.80 (95% CI 1.13 to 6.94) compared with AVE RHR of 70–80 beats/min, respectively. A multivariable Cox regression model with a restricted cubic spline found a U-shaped relationship between RHR and new-onset AF (figure 2).

Sensitivity analyses

Sensitivity analyses were then performed to exclude the effects of medication and cardiovascular disease on our results. We found that the association between AVE RHR and new-onset AF remained consistent after excluding participants who were using β-blockers (n=145 participants), those who were using β-blockers and calcium channel blockers (n=767 participants), and those with

Table 1 Baseline characteristics of the total study subjects

Variable	AVE RHR (bpm)						P value
	<60 (n=1776)	60-70 (n=13653)	70-80 (n=21820)	80-90 (n=6899)	90-100 (n=1652)	≥100 (n=326)	
Age, mean (SD), year	51.99 (11.84)	49.52 (11.56)	48.27 (11.40)	47.58 (11.85)	48.06 (11.71)	49.18 (11.49)	<0.05
Gender, n (%)	1458 (82.09)	10466 (76.66)	16788 (56.31)	5631 (81.62)	1363 (82.51)	275 (84.36)	<0.05
Mean SBP, mean (SD), mm Hg	126.60 (16.93)	127.26 (16.46)	129.80 (16.41)	133.69 (17.09)	137.78 (17.76)	144.16 (4.70)	<0.05
Mean DBP, mean (SD), mm Hg	80.60 (8.28)	82.10 (8.65)	83.95 (9.01)	86.25 (9.62)	88.22 (9.73)	90.74 (10.16)	<0.05
Mean HR, mean (SD), bpm	56.93 (2.83)	65.95 (2.71)	74.48 (2.75)	83.85 (2.77)	93.65 (2.62)	104.86 (4.70)	<0.05
TG, mean (SD), mmol/L	1.41 (1.05)	1.58 (1.25)	1.72 (1.42)	1.83 (1.55)	1.95 (1.59)	1.95 (1.47)	<0.05
TC, mean (SD), mmol/L	4.90 (1.14)	4.87 (1.11)	4.94 (1.13)	5.06 (1.16)	5.12 (1.21)	5.18 (1.09)	<0.05
HDL, mean (SD), mmol/L	1.55 (0.40)	1.55 (0.40)	1.55 (0.39)	1.56 (0.40)	1.59 (0.41)	1.64 (0.41)	<0.05
LDL, mean (SD), mmol/L	2.31 (0.91)	2.27 (0.95)	2.30 (0.88)	2.47 (0.92)	2.48 (0.87)	2.44 (0.83)	<0.05
BMI, mean (SD), kg/m ²	24.70 (3.18)	25.01 (3.34)	25.12 (3.47)	25.16 (3.58)	25.23 (3.72)	24.89 (3.81)	<0.05
FBG, mean (SD), mmol/L	5.12 (1.24)	5.21 (1.25)	5.41 (1.54)	5.71 (1.84)	5.98 (2.11)	6.18 (2.42)	<0.05
Hypertension, n (%)	731 (41.16)	5568 (40.78)	9940 (45.55)	3661 (53.07)	1009 (61.08)	222 (68.10)	<0.05
Use of antihypertensive, n (%)	351 (19.76)	2258 (16.54)	3860 (17.69)	1468 (21.28)	416 (25.18)	103 (31.60)	<0.05
Diabetes, n (%)	102 (5.74)	1052 (7.71)	2368 (10.85)	1004 (14.55)	349 (21.13)	83 (25.46)	<0.05
Drink, n (%)	890 (51.65)	5564 (42.32)	8639 (40.44)	3081 (45.36)	730 (44.92)	142 (43.69)	<0.05
Smoke, n (%)	751 (43.64)	5140 (39.11)	8296 (38.85)	3088 (45.49)	735 (45.23)	153 (46.93)	<0.05
High/intense activity, n (%)	419 (24.37)	2153 (16.43)	2687 (12.60)	788 (11.62)	215 (13.26)	43 (13.27)	<0.05

Values are mean±SD, n (%) or median (IQR).

AVE RHR, average resting heart rate; BMI, body mass index; bpm, beats per minute; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Table 2 HRs for atrial fibrillation by categories of average resting heart rate (AVE RHR)

AVE RHR (bpm)	Events, n (%)	HR (95% CI)*	HR (95% CI)†
<60 (n=1776)	23 (1.30)	2.06 (1.29, 3.27)**	2.32 (1.45, 3.72)**
60–70 (n=13653)	68 (0.50)	1.01 (0.73, 1.38)	1.06 (0.77, 1.46)
70–80 (n=21820)	99 (0.45)	1 (reference)	1 (reference)
80–90 (n=6899)	38 (0.55)	1.19 (0.81, 1.76)	1.14 (0.77, 1.68)
90–100 (n=1652)	8 (0.48)	1.10 (0.54, 2.27)	1.01 (0.49, 2.09)
≥100 (n=326)	5 (1.53)	3.23 (1.31, 7.93)*	2.80 (1.13, 6.94)*

*P<0.05, **p<0.01.
 *Adjusted for age and sex.
 †Adjusted for age, sex, low-density lipoprotein, high-density lipoprotein, physical activity, drinking, smoking, body mass index, mean systolic blood pressure, and history of diabetes and hypertension.
 bpm, beats per minute.

a history of cardiovascular disease (n=641 participants) (table 3).

DISCUSSION

In this prospective cohort study, we found that both lower and higher RHRs were associated with an increased risk of AF, indicating a U-shaped association between RHR and new-onset AF in the general population of China.

It is already widely accepted that RHR is an independent risk factor for AF. However, previous studies of the association between RHR and AF have yielded conflicting results. Our finding of a U-shaped relationship between AF and RHR is consistent with the results of the Copenhagen Electrocardiographic Study¹⁹ but not with those reported by the ONTARGET/TRANSCEND Studies, in which only a low AVE RHR was associated with an increased risk of AF.¹² Another study found that the risk of AF increased

by 1.14-fold with each 20 beats/min increment in RHR.²⁰ These conflicting reports may reflect differences between study populations. For example, the participants in the ONTARGET/TRANSCEND Studies were aged over 55 years and were at increased risk of cardiovascular disease,

Table 3 Sensitivity analysis of HRs for atrial fibrillation by categories of average resting heart rate (AVE RHR)

AVE RHR (bpm)	Event, n (%)	HR (95% CI)
Patients without β-blockers		
<60 (n=1763)	22 (1.25)	2.19 (1.36, 3.53)*
60–70 (n=13578)	68 (0.50)	1.07 (0.78, 1.46)
70–80 (n=21728)	98 (0.45)	1 (reference)
80–90 (n=6866)	37 (0.54)	1.15 (0.78, 1.70)
90–100 (n=1635)	8 (0.49)	1.04 (0.50, 2.15)
≥100 (n=321)	5 (1.56)	2.88 (1.16, 7.14)*
Patients without β-blockers and CCBs		
<60 (n=1736)	22 (1.27)	2.26 (1.40, 3.65)**
60–70 (n=13405)	67 (0.50)	1.08 (0.79, 1.49)
70–80 (n=21505)	96 (0.45)	1 (reference)
80–90 (n=6788)	37 (0.55)	1.18 (0.80, 1.75)
90–100 (n=1609)	8 (0.50)	1.07 (0.52, 2.22)
≥100 (n=316)	5 (1.58)	2.95 (1.19, 7.31)**
Patients without a history of cardiovascular disease		
<60 (n=1754)	23 (1.31)	2.33 (1.45, 3.73)**
60–70 (n=13472)	64 (0.48)	1.02 (0.74, 1.41)
70–80 (n=21511)	96 (0.45)	1 (reference)
80–90 (n=6796)	35 (0.52)	1.07 (0.71, 1.60)
90–100 (n=1629)	8 (0.49)	1.04 (0.50, 2.15)
≥100 (n=323)	5 (1.55)	2.85 (1.15, 7.07)**

Adjusted for age, sex, low-density lipoprotein, high-density lipoprotein, physical activity, drinking, smoking, body mass index, mean systolic blood pressure, and history of diabetes and hypertension.
 *P<0.05; **p<0.01.
 bpm, beats per minute; CCBs, calcium channel blockers.

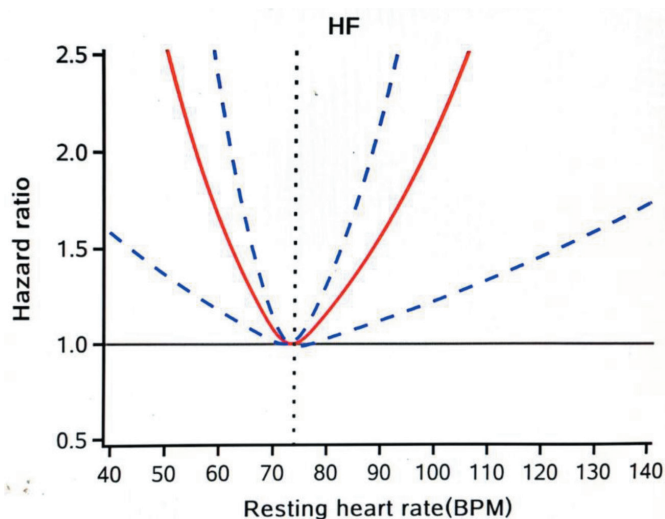


Figure 2 HRs of atrial fibrillation and average resting heart rate adjusted for age, sex, low-density lipoprotein, high-density lipoprotein, physical activity, drinking, smoking, body mass index, mean systolic blood pressure, and history of diabetes and hypertension. BPM, beats per minute; HF, heart failure.



whereas those in our study were drawn from the general population in China. Another possible reason for the lack of consistency between our present findings and the previous reports is that our study focused on long-term variability in RHR instead of single RHR.

RHR is a marker of the function of autonomic nervous system, which is involved in the development of AF.^{21 22} However, the mechanism underlying the relationship between RHR and the risk of AF in the general population remains unclear. Both lower and higher RHRs may represent subclinical dysfunction in the autonomic nervous system.^{19 23} Some potential explanations are as follows. First, regulation of heart rate is the result of the combined effect of vagal weakness and sympathetic activation.^{11 24 25} A lower RHR extends the time limit of vagal tone, leading to increased activation of vagal, which reduces the action potential duration of atria to mediate AF.^{26 27} Furthermore, a higher RHR may be associated with increased sympathetic activity, which could accelerate the automaticity of atrial muscle and shorten the atrial effective refractory period, leading to re-entrant excitation of the atria. Therefore, a higher RHR could promote onset of AF.^{11 28}

The results of this study indicate that an RHR <60 beats/min or ≥100 beats/min may be a marker of increased risk of new-onset AF. This finding provides a theoretical basis for management of RHR in the prevention of AF.

Strengths and limitations

This study has several strengths, including a longitudinal design, a large sample size and availability of detailed information on behavioural and biological variables. Furthermore, we used RHRs obtained by ECGs recorded on three separate occasions instead of a single RHR. The study has some limitations. First, the sex distribution in the RHR subgroups was not balanced, with most of the study participants being male. However, this is consistent with the distribution of the Kailuan study. Second, certain disease states that might affect heart rate could not be ascertained because of a lack of detailed information on medical diagnoses such as thyroid disease, chronic obstructive lung disease and anaemia. Nevertheless, we performed several sensitivity analyses to assess the robustness of our results. Third, we mainly ascertained cases of AF by hospital discharge codes. Therefore, asymptomatic or undiagnosed cases of AF may have been missed, which might have led to underestimation of the number of cases of new-onset AF. However, the incidence rate of AF in our study is comparable with that found by other studies in the Chinese population.^{29 30}

CONCLUSION

Our findings indicate that RHR and incident AF have a U-shaped relationship in the general population of China. Both lower and higher RHRs are associated with an increased risk of AF. Management of RHR may have an important role in the prevention of AF.

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Contributors Conception and design—ZH, MXZ, HX, SW. Acquisition, analysis and interpretation of data—ZH, MXZ, YS, SZ, SY, CW, MW, CY. Drafting of the manuscript—ZH, MXZ, HX. Critical revision of the manuscript for important intellectual content—ZH, MXZ, HX. Statistical analysis—MXZ, CW, YS. Administrative, technical or material support—ZH, MXZ, HX. ZH and MXZ contributed equally to this paper. HX as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and the Kailuan cohort study protocol was approved by the Ethics Committee of Kailuan General Hospital (KCS, clinical trial no. ChiCTR-TNRC-11001489). All patients provided signed informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study.

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