

# Association of Estimated Glomerular Filtration Rate (eGFR) and High-Sensitivity C-Reactive Protein (Hs-CRP) with the Risk of New-Onset Atrial Fibrillation in Patients with Diabetes

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**Background:** Both renal function decline and systemic inflammation may synergistically increase the risk of atrial fibrillation (AF). This study investigates the association between estimated glomerular filtration rate (eGFR) and high-sensitivity C-reactive protein (hs-CRP) levels with the risk of new-onset AF in patients with diabetes mellitus.

**Methods:** We included diabetic patients without AF who participated in physical exams in the Kailuan Study from 2006 to 2010. Participants were categorized into four groups based on baseline eGFR and hs-CRP levels: 1) high eGFR ( $\geq 60$  mL/min/1.73m<sup>2</sup>) and low hs-CRP ( $< 3$  mg/L) (n=6,915), 2) high eGFR and high hs-CRP ( $\geq 3$  mg/L) (n=3,154), 3) low eGFR ( $< 60$  mL/min/1.73m<sup>2</sup>) and low hs-CRP (n=4,638), 4) low eGFR and high hs-CRP (n=1,809). We employed multivariable Cox regression analysis to evaluate the relationships between eGFR, hs-CRP, and new-onset AF, adjusting for confounders including smoking status, alcohol consumption, blood pressure, fasting blood glucose (FBG), heart rate, lipid levels, body mass index (BMI), and medication usage. Competing risk analysis was also performed.

**Results:** Among 16,516 patients, 222 developed new-onset AF over a mean follow-up of 12.6 years. After adjusting for confounders, elevated hs-CRP and reduced eGFR were significantly associated with higher risk of new-onset AF compared to the high eGFR/low hs-CRP group. These findings remained consistent after excluding AF cases within the first 2-year. No significant interaction between eGFR and hs-CRP was observed ( $P=0.227$ ). Subgroup analysis revealed that the combination of eGFR and hs-CRP had predictive value primarily in males under 60 years of age, individuals with FBG  $< 9$  mmol/L, hypertension, and those not on hypoglycemic medications.

**Conclusion:** In diabetic patients, decreased eGFR and elevated hs-CRP were independently linked to an increased risk of new-onset AF, emphasizing the importance of monitoring these factors for early detection and prevention of AF.

**Keywords:** estimated glomerular filtration rate, high-sensitivity C-reactive protein, atrial fibrillation, diabetes mellitus

## Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia, associated with severe complications such as stroke, heart failure, cognitive impairment, and cardiac arrest, which lead to increased morbidity and mortality, significantly



affecting patients' quality of life.<sup>1</sup> Moreover, AF contributes to rising healthcare expenses.<sup>2</sup> Diabetes mellitus is a well-established independent risk factor for the development of AF.<sup>3</sup> Chronic hyperglycemia and related metabolic disorders result in structural and electrophysiological remodeling of cardiac tissue, thereby increasing susceptibility to arrhythmias.<sup>4</sup>

Impaired renal function is also recognized as an independent predictor of AF.<sup>5</sup> This underscores the critical role of renal dysfunction in the pathogenesis of AF, particularly in diabetic patients. Deterioration of glomerular filtration, as evidenced by reduced eGFR, is directly linked to higher rates of all-cause mortality and cardiovascular mortality.<sup>6</sup> Thus, it is essential to acknowledge that impaired kidney function is not just a complication but a significant and independent risk factor for the development of AF.

Inflammation further contributes to the pathogenesis of AF in diabetes.<sup>7</sup> High-sensitivity C-reactive protein (hs-CRP), a common systemic inflammation marker, is associated with an increased risk of AF across different populations.<sup>8</sup> However, it is crucial to note that while hs-CRP may enhance the risk of inflammation-related AF risk, it is less specific compared to true disease markers like the decline in glomerular filtration. Animal study suggests that inflammation plays a role in AF induced by chronic kidney disease (CKD).<sup>9</sup>

Given the complex relationship among kidney function, inflammation, and AF, this study aims to investigate the impact of varying stratifications of eGFR and hs-CRP on the risk of incident AF in diabetic patients. By elucidating the independent predictive role of impaired renal function, this study seeks to provide valuable insights into the stratification of AF risk in this vulnerable population and contribute to developing targeted prevention strategies.

## Methods

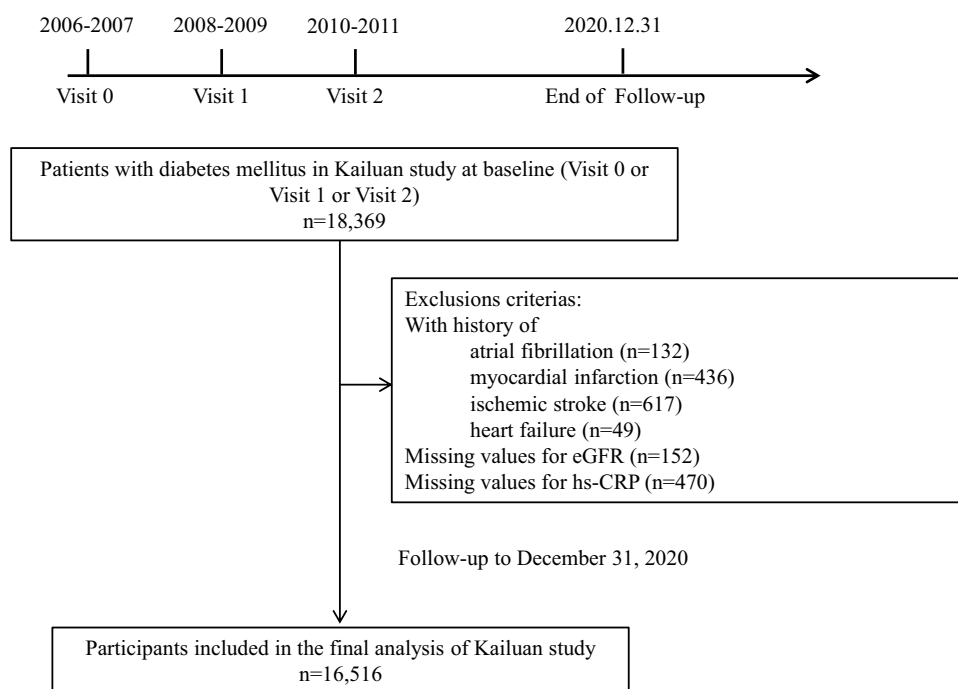
### Study Population

The study received approval from the Ethics Committee of Kailuan General Hospital, and informed consent was obtained from all participants. Data for this research were derived from the Kailuan Study, a prospective cohort study conducted in northern China. The detailed study design has been described previously.<sup>10</sup> The Kailuan study was approved by the Ethics Committee of the Kailuan General Hospital and complies with the Declaration of Helsinki (trial registration number ChiCTR-TNRC-11001489). All participants signed written informed consent forms. Participants completed questionnaires and underwent clinical follow-up every two years. The current analysis included 18,369 diabetic participants who completed at least one consecutive survey between 2006 and 2011 and had no missing data on eGFR and hs-CRP. After excluding individuals with a history of AF, myocardial infarction, stroke, and heart failure, a final total of 16,516 participants were included (Figure 1).

### Assessment of eGFR and Hs-CRP

The eGFR was calculated using a modified 4-variable Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula adjusted with a coefficient of 1.1 for the Chinese population.<sup>11</sup> The formula is as follows:  $eGFR (CKD-EPI) = 141 \times \min(SCr/\kappa, 1)^\alpha \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{\wedge}Age \times 1.018$  (if female)  $\times 1.1$ , where SCr represents serum creatinine,  $\kappa$  is 0.7 for females and 0.9 for males,  $\alpha$  is  $-0.329$  for females and  $-0.411$  for males, and "min" and "max" refer to the minimum and maximum of SCr/ $\kappa$  or 1, respectively. Hs-CRP levels were assessed using a high-sensitivity nephelometry assay (Cias Latex CRP-H, Kanto Chemical Co. Inc., Tokyo, Japan), which has a detection limit of 0.1 mg/L.

Based on previous studies,<sup>12–14</sup> we categorized patients into four groups according to their levels of hs-CRP and eGFR, using cut-off values of 3 mg/L for hs-CRP and 60 mL/min/1.73 m<sup>2</sup> for eGFR. The categorization is as follows: 1) high eGFR ( $\geq 60$  mL/min/1.73 m<sup>2</sup>) and low hs-CRP ( $< 3$  mg/L), 2) high eGFR ( $\geq 60$  mL/min/1.73 m<sup>2</sup>) and high hs-CRP ( $\geq 3$  mg/L), 3) low eGFR ( $< 60$  mL/min/1.73 m<sup>2</sup>) and low hs-CRP ( $< 3$  mg/L), and 4) low eGFR ( $< 60$  mL/min/1.73 m<sup>2</sup>) and high hs-CRP ( $\geq 3$  mg/L).



**Figure 1** Flow chart of study population selection.

**Abbreviations:** eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein.

## Ascertainment of Outcome

The primary outcome of this study was new-onset AF. AF cases were identified through comprehensive data sources, including questionnaires, discharge records from 11 affiliated hospitals, and information from municipal social insurance institutions. Each participant underwent a 10-second, 12-lead electrocardiogram (ECG) at every visit. The diagnosis of AF was based on established ECG criteria, which include: (1) irregular R-R intervals, (2) absence of repeating P waves, and (3) irregular atrial activity.<sup>15</sup> In cases of suspected AF, a panel of three physicians reviewed all relevant data to confirm the diagnosis. Mortality data were acquired from provincial demographic records and updated annually. Participants were followed from the time of the third survey until death, onset of AF, or December 31, 2020.

## Statistical Analysis

Continuous variables with a normal distribution are expressed as mean  $\pm$  standard deviation (SD), while continuous variables with a skewed distribution are reported as medians and interquartile ranges. Categorical variables are presented as frequency and percentages. Comparisons of continuous variables were performed using analysis of variance, and categorical variables were compared using the  $\chi^2$ -test. Details of missing values are provided in [Table S1](#). Multiple imputation was employed to address missing values. The incidence of AF was calculated as the number of new cases per 1,000 person-years of follow-up. The Cox regression model was utilized to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between different groups and the risk of AF. Likelihood tests for multiplicative interaction terms were conducted to evaluate the multiplicative scales. Several sensitivity analyses were performed to assess the robustness of the findings, including: (1) exclusion of participants with less than two years of follow-up, (2) exclusion of participants with baseline hypertension, (3) exclusion of participants who developed myocardial infarction during follow-up, and (4) exclusion of participants who developed cardiovascular diseases during follow-up. The Fine-Gray model was applied to account for the competing risk of death. All statistical analyses were conducted using SAS version 9.4 (SAS Institute; Cary, NC), with two-sided tests and a significance threshold set at  $P < 0.05$ .

## Results

### Baseline Characteristics

The baseline characteristics of participants categorized by eGFR and hs-CRP are summarized in Table 1. The participants had a mean age of 55.71 ( $\pm$  10.48) years, with 83.2% of them being male. Compared to high eGFR/low hs-CRP group, individuals in low eGFR/low hs-CRP, low eGFR/ high hs-CRP and high eGFR/high hs-CRP groups were significantly older and exhibited a higher prevalence of hypertension, as well as increased systolic and diastolic blood pressure, fasting blood glucose levels, and body mass index (BMI). Additionally, levels of high-density lipoprotein cholesterol (HDL-C) were lower in these groups.

### Associations of Hs-CRP and eGFR with Risk of AF in Patients with Diabetes

Kaplan-Meier survival curves revealed significant differences in the risk of AF among the various groups, with participants in low eGFR/low hs-CRP, low eGFR/ high hs-CRP and high eGFR/high hs-CRP groups exhibiting markedly higher risks of AF compared to those in the high eGFR/low hs-CRP group (Figure 2) ( $P=0.001$ ). The relationship between group classification and AF risk is detailed in Table 2. Over a mean follow-up period of 12.6 years, a total of 222 participants were diagnosed with new-onset AF.

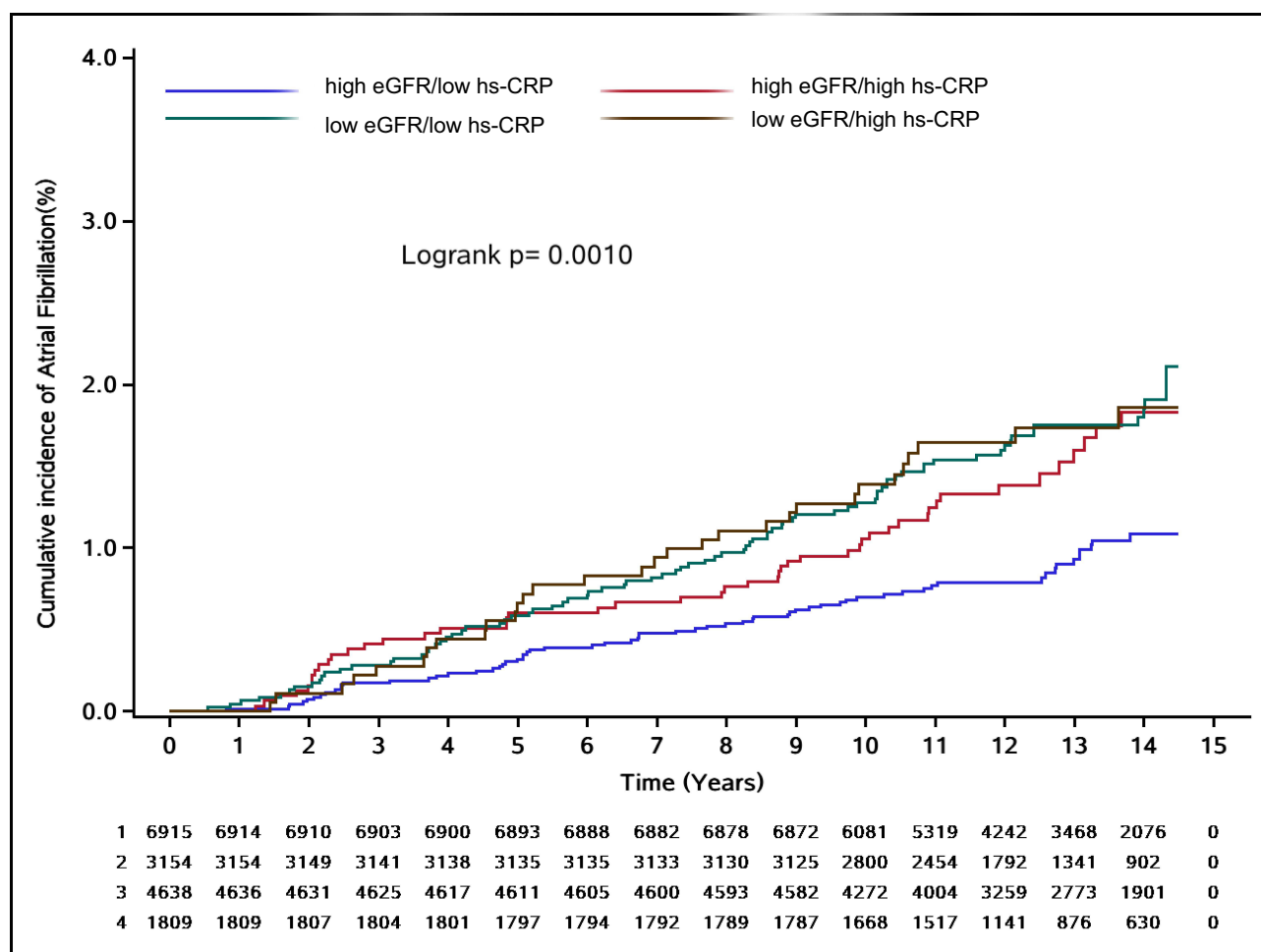
After adjusting for confounding factors, including smoking status, alcohol consumption, hypertension, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), heart rate, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), body mass index (BMI), and the use of lipid-lowering medications, hypotensive and hypoglycemic medications, the high eGFR/high hs-CRP, low eGFR/ low hs-CRP and low eGFR/ high hs-CRP groups showed significantly higher risks of AF compared to the high eGFR/ low hs-CRP group. The adjusted hazard ratios (aHRs) for these groups were 1.641 (95% CI: 1.080–2.495), 1.595 (95% CI: 1.017–2.503), and 1.759 (95% CI: 1.090–2.838), respectively.

**Table 1** Baseline Characteristics of the Participants Based on Different eGFR and Hs-CRP Groups

Variables	Total (N=16,516)	High eGFR/Low hs-CRP (N=6,915)	High eGFR/High hs-CRP (N=3,154)	Low eGFR/Low hs-CRP (N=4,638)	Low eGFR/High hs-CRP (N=1,809)	P value
Age, mean $\pm$ SD, years	55.71 $\pm$ 10.48	53.53 $\pm$ 9.76	55.53 $\pm$ 9.97	57.39 $\pm$ 10.77	60.08 $\pm$ 11.13	<0.0001
Current smoker (%)	5,187 (31.4)	2,250 (32.5)	839 (26.6)	1,557 (33.6)	541 (29.9)	<0.0001
Current alcohol drinker (%)	2,515 (15.2)	1,052 (15.2)	352 (11.2)	847 (18.3)	264 (14.6)	<0.0001
Hypertension (%)	10,457 (63.3)	4,025 (58.2)	2,017 (64.0)	3,102 (66.9)	1,313 (72.6)	<0.0001
SBP, mean $\pm$ SD, mmHg	139.03 $\pm$ 21.13	136.43 $\pm$ 20.62	138.88 $\pm$ 20.95	141.31 $\pm$ 21.09	143.35 $\pm$ 22.10	<0.0001
DBP, mean $\pm$ SD, mmHg	87.13 $\pm$ 11.87	86.16 $\pm$ 11.56	86.74 $\pm$ 11.69	88.08 $\pm$ 12.02	89.06 $\pm$ 12.53	<0.0001
FBG, mean $\pm$ SD, mmol/L	8.89 $\pm$ 2.81	8.68 $\pm$ 2.69	8.97 $\pm$ 2.71	9.04 $\pm$ 2.90	9.16 $\pm$ 3.08	<0.0001
HR, mean $\pm$ SD, bpm	77.12 $\pm$ 11.30	77.18 $\pm$ 11.29	77.44 $\pm$ 11.36	76.50 $\pm$ 10.96	77.95 $\pm$ 11.96	0.0002
TC, mean $\pm$ SD, mmol/L	5.27 $\pm$ 1.40	5.30 $\pm$ 1.24	5.35 $\pm$ 1.54	5.19 $\pm$ 1.44	5.23 $\pm$ 1.62	<0.0001
LDL-C, mean $\pm$ SD, mmol/L	2.62 $\pm$ 1.19	2.64 $\pm$ 1.08	2.50 $\pm$ 1.70	2.65 $\pm$ 0.91	2.63 $\pm$ 1.13	<0.0001
HDL-C, mean $\pm$ SD, mmol/L	1.52 $\pm$ 0.47	1.56 $\pm$ 0.49	1.50 $\pm$ 0.47	1.51 $\pm$ 0.42	1.47 $\pm$ 0.53	<0.0001
UA, mean $\pm$ SD, umol/L	284.24 $\pm$ 87.38	276.42 $\pm$ 84.70	277.56 $\pm$ 84.67	291.57 $\pm$ 87.35	307.01 $\pm$ 96.27	<0.0001
Serum creatinine, mean $\pm$ SD, umol/L	91.75 $\pm$ 42.78	75.76 $\pm$ 13.68	74.25 $\pm$ 15.20	117.91 $\pm$ 54.39	116.27 $\pm$ 64.37	<0.0001
eGFR, mean $\pm$ SD, mL/min/1.73m <sup>2</sup>	69.88 $\pm$ 24.71	83.15 $\pm$ 18.55	85.65 $\pm$ 25.48	47.80 $\pm$ 9.27	48.28 $\pm$ 9.12	<0.0001
Hs-CRP, median (IQR), mg/L	1.50 (0.68–3.53)	1.00 (0.50–1.70)	5.60 (3.90–8.90)	0.90 (0.41–1.60)	5.40 (3.90–8.50)	<0.0001
Log(hs-CRP), mean $\pm$ SD, mg/L	0.40 $\pm$ 1.34	-0.23 $\pm$ 1.03	1.87 $\pm$ 0.66	-0.26 $\pm$ 1.00	1.87 $\pm$ 0.68	<0.0001
BMI, mean $\pm$ SD, kg/m <sup>2</sup>	26.20 $\pm$ 3.50	25.89 $\pm$ 3.43	26.83 $\pm$ 3.82	26.01 $\pm$ 3.25	26.79 $\pm$ 3.56	<0.0001
Hypotensive medications (%)	2,996 (19.1)	1,186 (17.9)	613 (21.0)	819 (18.4)	378 (22.6)	<0.0001
Lipid-lowering medications (%)	287 (1.74)	117 (1.69)	54 (1.71)	78 (1.68)	38 (2.10)	<0.0001
Hypoglycemic medications (%)	3,189 (20.8)	1,359 (20.9)	543 (19.0)	953 (21.8)	334 (20.5)	0.0791

**Notes:** high eGFR: eGFR $\geq$ 60 mL/min/1.73m<sup>2</sup>; low eGFR: eGFR<60 mL/min/1.73m<sup>2</sup>; high hs-CRP: hs-CRP $\geq$ 3 mg/L; low hs-CRP: hs-CRP<3 mg/L. BMI is weight in kilograms divided by the height in meters squared.

**Abbreviations:** BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; UA, uric acid.



**Figure 2** Survival curves for cumulative incidence of new-onset AF in different eGFR and hs-CRP groups.

**Abbreviations:** AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein.

## Sensitivity Analyses

A series of sensitivity analyses were conducted (Table 3). The findings remained robust after excluding participants who experienced AF within the first two years of follow-up, as well as those with hypertension, myocardial infarction, or other cardiovascular diseases. In the competing risks model for mortality, after adjusting for multiple covariates, the high

**Table 2** Associations Between Different Groups and Atrial Fibrillation

	High eGFR/Low hs-CRP	High eGFR/High hs-CRP	Low eGFR/Low hs-CRP	Low eGFR/High hs-CRP
<b>Case/total</b>	63/6,915	47/3,154	81/4,638	31/1,809
<b>Incidence rate (per 1,000 persons-years)</b>	0.729 (0.570–0.933)	1.209 (0.908–1.609)	1.357 (1.092–1.688)	1.361 (0.957–1.936)
<b>HR (95% CI)<sup>a</sup></b>	1.000 (reference)	1.664 (1.141–2.428)	1.845 (1.328–2.565)	1.862 (1.211–2.863)
<b>HR (95% CI)<sup>b</sup></b>	1.000 (reference)	1.507 (1.017–2.233)	1.588 (1.120–2.250)	1.595 (1.017–2.503)
<b>HR (95% CI)<sup>c</sup></b>	1.000 (reference)	1.641 (1.080–2.495)	1.595 (1.017–2.503)	1.759 (1.090–2.838)

**Notes:** high eGFR: eGFR $\geq$ 60 mL/min/1.73m<sup>2</sup>; low eGFR: eGFR<60 mL/min/1.73m<sup>2</sup>; high hs-CRP: hs-CRP $\geq$ 3 mg/L; low hs-CRP: hs-CRP<3 mg/L. <sup>a</sup>Model was crude model, <sup>b</sup>Model was adjusted for smoking status, alcohol drinking status, hypertension, SBP, DBP, FBG, heart rate, LDL-C, HDL-C, UA, BMI, <sup>c</sup> Model was adjusted for smoking status, alcohol drinking status, hypertension, SBP, DBP, FBG, heart rate, LDL-C, HDL-C, UA, BMI, lipid-lowering medications, hypotensive medications, hypoglycemic medications. BMI is weight in kilograms divided by the height in meters squared.

**Abbreviations:** BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UA, urine acid.

**Table 3** Sensitivity Analysis

	Crude Model		Multivariable Adjusted Model	
	Case/Total	HR (95% CI)	Case/Total	HR (95% CI)
<b>*Excluding AF occurred within the first 2 years of follow-up (19 cases).</b>				
High eGFR/low hs-CRP	58/6,910	1.000 (reference)	58/6,910	1.000 (reference)
High eGFR/high hs-CRP	42/3,149	1.618 (1.088–2.407)	42/3,149	1.578 (1.011–2.462)
Low eGFR/low hs-CRP	74/4,631	1.825 (1.294–2.574)	74/4,631	1.508 (1.013–2.245)
Low eGFR/high hs-CRP	29/1,807	1.891 (1.211–2.953)	29/1,807	1.840 (1.124–3.015)
<b>†Excluding the participants with hypertension (10,457 cases).</b>				
High eGFR/low hs-CRP	18/2,890	1.000 (reference)	18/2,890	1.000 (reference)
High eGFR/high hs-CRP	9/1,137	1.309 (0.588–2.915)	9/1,137	1.470 (0.646–3.344)
Low eGFR/low hs-CRP	21/1,536	2.150 (1.146–4.036)	21/1,536	1.629 (0.799–3.318)
Low eGFR/high hs-CRP	7/496	2.274 (0.950–5.444)	7/496	1.993 (0.769–5.165)
<b>*Excluding the participants developing myocardial infarction during follow-up (530 cases).</b>				
High eGFR/low hs-CRP	60/6,747	1.000 (reference)	60/6,747	1.000 (reference)
High eGFR/high hs-CRP	46/3,042	1.732 (1.180–2.544)	46/3,042	1.713 (1.122–2.614)
Low eGFR/low hs-CRP	79/4,470	1.913 (1.367–2.676)	79/4,470	1.601 (1.091–2.347)
Low eGFR/high hs-CRP	30/1,727	1.939 (1.251–3.005)	30/1,727	1.788 (1.097–2.912)
<b>*Excluding the participants developing CVDs during follow-up (2,229 cases).</b>				
High eGFR/low hs-CRP	59/6,117	1.000 (reference)	59/6,117	1.000 (reference)
High eGFR/high hs-CRP	42/2,698	1.645 (1.107–2.443)	42/2,698	1.551 (1.003–2.399)
Low eGFR/low hs-CRP	75/3,966	1.886 (1.341–2.653)	75/3,966	1.577 (1.073–2.318)
Low eGFR/high hs-CRP	27/1,506	1.843 (1.169–2.906)	27/1,506	1.583 (0.951–2.636)
<b>*Competing risk model with the all-cause mortality as a competing risk.</b>				
High eGFR/low hs-CRP	63/6,915	1.000 (reference)	1,285/6,915	1.000 (reference)
High eGFR/high hs-CRP	47/3,154	1.699 (1.165–2.479)	706/3,154	1.657 (1.094–2.509)
Low eGFR/low hs-CRP	81/4,638	1.923 (1.383–2.673)	1,258/4,638	1.642 (1.120–2.406)
Low eGFR/high hs-CRP	31/1,809	2.071 (1.347–3.182)	658/1,809	1.927 (1.208–3.074)
<b>*Supplementing missing data with multiple imputation.</b>				
High eGFR/low hs-CRP	63/6,915	1.000 (reference)	63/6,915	1.000 (reference)
High eGFR/high hs-CRP	47/3,154	1.664 (1.141–2.428)	47/3,154	1.550 (1.058–2.270)
Low eGFR/low hs-CRP	81/4,638	1.854 (1.328–2.565)	81/4,638	1.728 (1.238–2.413)
Low eGFR/high hs-CRP	31/1,809	1.862 (1.211–2.863)	31/1,809	1.645 (1.062–2.546)

**Notes:** high eGFR: eGFR $\geq$ 60 mL/min/1.73m<sup>2</sup>; low eGFR: eGFR $<$ 60 mL/min/1.73m<sup>2</sup>; high hs-CRP: hs-CRP $\geq$ 3 mg/L; low hs-CRP: hs-CRP $<$ 3 mg/L\*) Multivariable adjusted model was adjusted for smoking status, alcohol drinking status, hypertension, SBP, DBP, FBG, heart rate, LDL-C, HDL-C, UA, BMI, hypotensive medications, lipid-lowering medications, hypoglycemic medications. †The model was adjusted for the variables mentioned above, excluding hypertension and hypotensive medications. BMI is weight in kilograms divided by the height in meters squared.

**Abbreviations:** BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UA, urine acid.

eGFR/high hs-CRP, low eGFR/low hs-CRP and low eGFR/ high hs-CRP groups also demonstrated significantly higher risks of AF compared to the high eGFR/low hs-CRP group. These groups exhibited adjusted hazard ratios of 1.657 (95% CI: 1.094–2.509), 1.642 (95% CI: 1.120–2.406), and 1.927 (95% CI: 1.208–3.074), respectively. Furthermore, after addressing missing data through multiple imputation, the results remained consistent with the primary analyses.

## Subgroup Analysis and Mediation Effect Analysis of eGFR and hs-CRP

Subgroup analysis, as presented in Table 4, revealed that among male diabetic individuals, the risk of AF was significantly elevated in low eGFR/low hs-CRP (aHR: 1.628 (95% CI: 1.082–2.449)) and low eGFR/ high hs-CRP (aHR: 1.716 (95% CI: 1.024–2.877)) groups compared to the high eGFR/low hs-CRP group. Conversely, no statistically significant differences in AF risk were found within the female diabetic individuals. In the hypertensive subgroup, participants in the high eGFR/high hs-CRP, low eGFR/low hs-CRP and low eGFR/ high hs-CRP groups exhibited a significantly greater risk of AF compared to those in the high eGFR/low hs-CRP group. Among individuals under 60 years old, only the low eGFR/low hs-CR group and the low eGFR/ high hs-CRP group demonstrated an increased risk of

**Table 4** Subgroup Analyses

Subgroups	Case/Total	Groups	Crude Model HR (95% CI)	Multi-Model HR (95% CI)
<b>*Gender</b>				
<b>Male</b>	184/13,751	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	1.518 (0.951–2.424)	1.536 (0.920–2.566)
		Low eGFR/low hs-CRP	1.903 (1.327–2.728)	1.628 (1.082–2.449)
		Low eGFR/high hs-CRP	1.845 (1.162–2.931)	1.716 (1.024–2.877)
<b>Female</b>	38/2,765	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	1.894 (0.974–3.685)	1.815 (0.842–3.909)
		Low eGFR/low hs-CRP	1.171 (0.155–8.828)	0(-)
		Low eGFR/high hs-CRP	3.334 (0.766–14.501)	3.346 (0.720–15.553)
<b>†Hypertension</b>				
<b>No</b>	55/6,059	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	1.309 (0.588–2.915)	1.470 (0.646–3.344)
		Low eGFR/low hs-CRP	2.150 (1.146–4.036)	1.629 (0.799–3.318)
		Low eGFR/high hs-CRP	2.274 (0.950–5.444)	1.993 (0.769–5.165)
<b>Yes</b>	167/10,457	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	1.700 (1.104–2.617)	1.656 (1.025–2.674)
		Low eGFR/low hs-CRP	1.650 (1.120–2.428)	1.598 (1.042–2.450)
		Low eGFR/high hs-CRP	1.606 (0.979–2.636)	1.775 (1.043–3.020)
<b>*Age, years old</b>				
<b>&lt;60</b>	103/11,494	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	2.081 (1.247–3.474)	2.270 (1.298–3.968)
		Low eGFR/low hs-CRP	1.743 (1.067–2.845)	1.371 (0.767–2.452)
		Low eGFR/high hs-CRP	2.093 (1.078–4.063)	2.128 (1.039–4.359)
<b>≥60</b>	119/5,022	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	1.108 (0.632–1.945)	0.973 (0.512–1.849)
		Low eGFR/low hs-CRP	1.401 (0.893–2.196)	1.314 (0.793–2.175)
		Low eGFR/high hs-CRP	1.113 (0.629–1.970)	1.079 (0.565–2.061)
<b>**FBG, mmol/L</b>				
<b>&lt;9</b>	154/11,050	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	1.447 (0.913–2.295)	1.512 (0.915–2.500)
		Low eGFR/low hs-CRP	1.854 (1.265–2.719)	1.615 (1.043–2.503)
		Low eGFR/high hs-CRP	1.643 (0.966–2.795)	1.558 (0.871–2.788)
<b>≥9</b>	68/5,466	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	2.331 (1.175–4.626)	1.894 (0.886–4.053)
		Low eGFR/low hs-CRP	1.923 (1.004–3.686)	1.351 (0.646–2.828)
		Low eGFR/high hs-CRP	2.540 (1.189–5.426)	2.201 (0.936–5.174)

(Continued)

**Table 4** (Continued).

Subgroups	Case/Total	Groups	Crude Model HR (95% CI)	Multi-Model HR (95% CI)
<b>††Hypoglycemic medications</b>				
<b>No</b>	151/12,145	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	1.751 (1.119–2.739)	1.681 (1.044–2.707)
		Low eGFR/low hs-CRP	1.689 (1.128–2.528)	1.568 (1.014–2.425)
		Low eGFR/high hs-CRP	1.972 (1.182–3.290)	1.712 (0.981–2.988)
<b>Yes</b>	50/3189	High eGFR/low hs-CRP	1.000 (reference)	1.000 (reference)
		High eGFR/high hs-CRP	1.779 (0.760–4.162)	1.419 (0.583–3.451)
		Low eGFR/low hs-CRP	2.077 (1.033–4.178)	1.685 (0.791–3.589)
		Low eGFR/high hs-CRP	2.473 (1.025–5.968)	2.044 (0.797–5.241)

**Notes:** high eGFR: eGFR $\geq$ 60 mL/min/1.73m<sup>2</sup>; low eGFR: eGFR<60 mL/min/1.73m<sup>2</sup>; high hs-CRP: hs-CRP $\geq$ 3 mg/L; low hs-CRP: hs-CRP<3 mg/L\*) Multivariable adjusted model was adjusted for smoking status, alcohol drinking status, hypertension, SBP, DBP, FBG, heart rate, LDL-C, HDL-C, UA, BMI, hypotensive medications, lipid-lowering medications, hypoglycemic medications. <sup>†</sup>The model was adjusted for the variables mentioned above, excluding hypertension and hypotensive medications. <sup>\*\*</sup>The model was adjusted for the variables mentioned above, excluding FBG. <sup>††</sup>The model was adjusted for the variables mentioned above, excluding hypoglycemic medications. BMI is weight in kilograms divided by the height in meters squared.

**Abbreviations:** BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UA, urine acid.

new-onset AF relative to high eGFR/low hs-CRP group. Furthermore, we did not observe a significant mediating effect between eGFR and hs-CRP.

## Discussion

### Main Findings

This study encompassed a total of 16,516 diagnosed diabetic patients, and after a mean follow-up duration of 12.6 years, 222 cases of new-onset AF were identified. Our analysis indicated that, after adjusting for potential confounders, the risk of new-onset AF was significantly higher in the high eGFR/high hs-CRP, low eGFR/low hs-CRP and low eGFR/ high hs-CRP groups when compared to the high eGFR/low hs-CRP group. Further analysis, which excluded cases of new-onset AF within the first two years of follow-up, as well as instances of myocardial infarction and cardiovascular disease during the study period, demonstrated consistent results. Additionally, multivariable competing risk analyses and multiple imputation for missing data demonstrated that increases in hs-CRP and decreases in eGFR, individually and in combination, were associated with an elevated risk of new-onset AF. Notably, no significant interaction effect was observed between eGFR and hs-CRP. Subgroup analyses suggested that the predictive value of these factors for new-onset AF was evident mainly in males under 60 years old, patients with FBG below 9 mmol/L, individuals without hypertension, and those receiving hypoglycemic medications. These findings emphasize the critical roles of renal function and systemic inflammation in the risk of AF among diabetic patients, underscoring the necessity for targeted management strategies that incorporate these factors.

### Increasing Prevalence of Atrial Fibrillation in Diabetic Patients

According to data published by the International Diabetes Federation (IDF) in 2021, diabetes has become one of the most significant public health challenges globally. With changing lifestyles and an aging population, the number of individuals with diabetes continues to rise, particularly in low-income and middle-income countries. China has emerged as the country with the highest prevalence of diabetes, a position expected to persist until 2045.<sup>16</sup> Patients with diabetes exhibit significantly elevated risks of cardiovascular conditions, including AF, which is increasingly recognized as a major complication associated with diabetes.<sup>17</sup> A meta-analysis by Huxley et al<sup>18</sup> indicated a 40% higher risk of developing AF in diabetic patients compared to non-diabetic individuals. AF, characterized by irregular heart rhythm, is more prevalent in patients with decompensated diabetes, surpassing occurrences of other arrhythmias such as atrial flutter and ventricular



tachycardia.<sup>19</sup> These findings raise critical implications for early identification and monitoring strategies within this patient population. Consequently, it becomes imperative to pinpoint specific clinical indicators that can predict the incidence of AF, facilitating timely interventions that may improve patient outcomes.

## Impact of eGFR on Atrial Fibrillation Risk in Diabetic Patients

The eGFR, a vital measure of kidney function, has gained attention for its relationship with cardiovascular risk, particularly AF. A decline in eGFR (eGFR < 60 mL/min/1.73 m<sup>2</sup>), frequently observed in type 2 diabetes patients, is significantly associated with increased AF incidence.<sup>12,13</sup> Thus, we designate the eGFR threshold at 60 mL/min/1.73 m<sup>2</sup>, aligning this criterion with the grouping utilized in most studies. Although our study did not categorize participants into multiple eGFR groups, the survival curves clearly illustrate that individuals with eGFR < 60 mL/min/1.73 m<sup>2</sup> exhibit a significantly higher risk of AF compared to those with eGFR ≥ 60 mL/min/1.73 m<sup>2</sup> (Figure 2). Furthermore, an analysis involving nearly 27,000 American adults revealed that CKD was associated with an increased prevalence of AF. Among patients with stage 4 or 5 CKD, the prevalence of AF was highest, and this association persisted even after multivariable adjustments across various subgroups.<sup>20</sup> Notably, individuals with advanced CKD demonstrate a notably high prevalence of AF, a finding that holds true even after adjusting for several confounding factors.<sup>6,21</sup> Our subgroup analysis indicates that the risk of AF significantly increases in diabetic patients, particularly among males and those with eGFR < 60 mL/min/1.73 m<sup>2</sup>. This finding suggests that sex may influence the incidence of AF in diabetic patients with renal impairment. Furthermore, the subgroup analysis indicates that a decline in eGFR and an increase in hs-CRP are associated with a higher risk of AF, but specifically within the hypertensive population. Hence, it can be concluded that the triad of hypertension, diabetes, and impaired renal function are independent predictors of cardiovascular events, so they will always be superimposed. However, further research is warranted to validate these conclusions and to better understand the underlying mechanisms by which gender influences AF risk in this specific population. Exploring these relationships could yield essential insights for the management and prevention of AF in diabetic patients with CKD.

The mechanisms contributing to the increased risk of AF in CKD patients may involve multiple factors. A decline in renal function can lead to hypertension, which in turn may result in ventricular hypertrophy and decreased compliance, ultimately influencing atrial structure and function.<sup>22</sup> A study suggested that, irrespective of diabetes severity, the cumulative burden of hypertension positively correlates with the risk of AF.<sup>23</sup> Our subgroup analysis aligns with this finding, showing that lower eGFR is associated with a higher risk of AF specifically in the hypertensive population. Therefore, it is crucial to develop a long-term comprehensive treatment strategy that focuses on the assessment and management of both diabetes and hypertension to mitigate the risk of AF in patients with a lengthy history of diabetes. Additionally, the activation of the endogenous renin-angiotensin-aldosterone system (RAAS) due to CKD has been recognized as a significant factor promoting AF. Dysregulation of RAAS may lead to atrial fibrosis, thereby creating an environment conducive to development of AF.<sup>24</sup> Concurrently, CKD may exacerbate the occurrence of AF by amplifying the risk of cardiovascular diseases and promoting sympathoadrenal overactivity.<sup>25</sup> The activation of the renin-angiotensin-aldosterone system (RAAS), frequently upregulated in CKD, further contributes to atrial remodeling, fostering an environment conducive to AF development.<sup>26</sup> Additionally, inflammation plays a crucial role in this intricate relationship, with elevated inflammatory markers, detectable even in early CKD, being implicated in the progression of renal dysfunction and the onset of AF.<sup>27,28</sup> Our results further indicate that within the population with eGFR < 60 mL/min/1.73 m<sup>2</sup>, individuals with exhibiting hs-CRP levels greater than 3 mg/L exhibit an increased risk of developing AF compared to those with hs-CRP levels below 3 mg/L. This finding underscores the potential role of inflammation, as indicated by elevated hs-CRP levels, as a contributory factor to the heightened incidence of AF in patients with renal impairment.

## The Role of Inflammation and High-Sensitivity C-Reactive Protein in Atrial Fibrillation Risk and Prognosis

Inflammation significantly contributes to the development and progression of AF.<sup>29</sup> Hs-CRP, an acute-phase reactant protein, is a widely accepted marker for assessing inflammation in clinical settings. Research indicates a strong

correlation between baseline hs-CRP levels and the recurrence of AF following various interventions, such as catheter ablation.<sup>30</sup> Previous studies have shown that long-term exposure to high levels of hs-CRP (hs-CRP  $\geq$  3 mg/L) is associated with an increased risk of cardiovascular diseases and myocardial infarction in a dose-dependent manner.<sup>14</sup> Furthermore, previous research from the Kailuan cohort has demonstrated a positive correlation between elevated serum hs-CRP levels (hs-CRP > 3 mg/L) and the new-onset AF, while Mendelian randomization studies have not supported a causal effect of CRP on AF.<sup>8</sup> This observation suggests that the elevation of hs-CRP may serve as a companion marker in the development of AF rather than a direct pathogenic factor. Elevated hs-CRP levels are recognized as independent predictors of all-cause mortality, stroke, and cardiovascular adverse events in patients with AF.<sup>31</sup> The results of this study are consistent with these prior findings, indicating that after adjusting for multiple factors, the risk of developing AF is heightened in the elevated hs-CRP and reduced eGFR group when compared to the high eGFR/low hs-CRP group. This further substantiates the predictive value of hs-CRP in assessing the risk of new-onset AF among diabetic patients. Among individuals under 60 years old, only those in the elevated hs-CRP group exhibited a significantly increased risk of AF compared to the high eGFR/low hs-CRP group. Therefore, enhanced attention should be directed towards diabetic patients exhibiting heightened systemic inflammatory responses, particularly among those under 60, to enhance early prevention and diagnosis of AF. Overall, hs-CRP plays a significant role in the occurrence and prognosis of AF, warranting regular monitoring in clinical practice. Consistent monitoring of hs-CRP levels may facilitate the evaluation of prognosis and recurrence risk of patients with AF, providing valuable data for clinical management. Moreover, inflammatory markers, including hs-CRP, IL-6, and IL-8, tend to show elevated levels in patients with AF compared to those in sinus rhythm.<sup>32</sup> Inflammation appears to exacerbate conditions frequently associated with AF, such as myocardial infarction and cardiac surgery.<sup>33</sup> However, Marott et al<sup>34</sup> cautioned that elevated hs-CRP levels may not directly increase AF risk, suggesting a complex and multifactorial role of hs-CRP in AF.

The interplay between inflammation and atrial structural changes is profound, inflammatory cytokines contributing to electrical remodeling and predisposition to AF. Elevated hs-CRP levels frequently coincide with immune cell infiltration in atrial tissue, specifically macrophages and lymphocytes, which release inflammatory cytokines that activate fibroblasts, leading to atrial fibrosis and heightened inflammation that escalates AF risk.<sup>35</sup> Furthermore, hs-CRP may promote atrial myocyte injury and apoptosis via inflammatory pathways, resulting in adverse electrical properties in the atrium. Inflammation is also associated with heterogeneity in atrial conduction and prolonged conduction times, while intracellular localization of hs-CRP in atrial tissue can significantly enhance inward L-type calcium currents in myocytes, potentially triggering AF.<sup>36,37</sup> A bidirectional relationship exists between inflammation and AF, as persistent AF can elevate hs-CRP levels, indicating that hs-CRP may induce myocyte damage through inflammatory mechanisms.<sup>38</sup> Although elevated hs-CRP levels correlate with increased AF risk, large-scale genetic studies indicate that genetic variations resulting in higher hs-CRP do not directly increase risk of AF, suggesting that elevated plasma hs-CRP might serve as a marker rather than a direct pathogenic factor.<sup>34</sup> Additionally, ethnic differences have been observed, with baseline hs-CRP levels significantly associated with risk of AF in Korean and Japanese populations, but showing variability among different ethnic groups.<sup>39,40</sup> In summary, hs-CRP likely plays a crucial role in the development of AF by facilitating electrical and structural remodeling of the atria, necessitating further investigation into its mechanisms related to atrial fibrosis, conduction heterogeneity, and myocardial cell injury.

## Interaction Between eGFR and Hs-CRP

Exploration of the interaction between eGFR and hs-CRP levels revealed that although both factors independently influence risk of AF, no significant interaction effect was identified. This observation suggests that eGFR and hs-CRP may operate through distinct biological pathways in influencing the pathogenesis of AF. Poor kidney function, as evidenced by a decline in eGFR, is associated with fluid imbalances and electrolyte disturbances, both of which are known risk factors for AF. Conversely, hs-CRP serves as an indicator of systemic inflammation and associated cardiovascular risks. Given that both factors contribute to AF independently, strategies focused on enhancing kidney function and mitigating inflammation may be critical in reducing risk of AF.<sup>41</sup>

## Clinical Significance and Future Perspectives

The findings of this study provide novel insights into the risk assessment of AF in diabetic patients, emphasizing the importance of a comprehensive evaluation of kidney function and inflammatory status. Clinicians managing diabetic patients should consistently monitor eGFR and hs-CRP levels to identify high-risk individuals and implement preventive measures effectively. Given the strong association between new-onset AF in diabetic patients and serious complications such as stroke and heart failure, the early identification and intervention for high-risk patients may help reduce the incidence of cardiovascular events, improve prognosis of patients, and decrease healthcare resource utilization. While this study offers preliminary evidence regarding the relationship between eGFR, hs-CRP, and new-onset AF, large-scale prospective studies are necessary to further substantiate these findings and explore potential mechanisms. Additionally, stratified analyses of patients by ethnicity, age, and gender will facilitate a better understanding of how these factors influence AF risk. Future research should concentrate on delineating the specific biological mechanisms by which decreased eGFR and elevated hs-CRP contribute to the occurrence of AF. Intervention studies testing the effects of improving kidney function and diminishing inflammatory markers on the incidence of AF are warranted. Furthermore, the development of individualized risk assessment models that integrate eGFR, hs-CRP, and other clinical characteristics will promote tailored preventive strategies. Furthermore, longitudinal studies should explore the dynamic relationships among these factors and their impact on patients' quality of life and long-term prognosis. Such a comprehensive approach would provide a more robust scientific basis for the prevention and management of AF in diabetic patients.

## Limitations

This study has several limitations. First, reliance on existing medical records may result in the underreporting of high-risk patients or early symptoms of new-onset AF, potentially affecting the representativeness of the sample. Additionally, variability in data quality and recording standards across different medical institutions may further compromise the reliability of the study results. Second, retrospective studies often encounter issues with missing data related to laboratory test results, medical history, and follow-up information. Although multiple imputation methods were employed, the potential impact of missing data on the results cannot be completely eliminated, and missing data may be associated with risk of AF, exacerbating study bias. While various potential confounding factors were accounted for, the influence of unmeasured confounders, such as patients' lifestyle and mental health status, on the AF occurrence cannot be ruled out and may impact the final outcomes. Furthermore, the concentration of the sample in specific populations or regions limits the external validity of the results. Differences in demographics, healthcare systems, and management practices in other regions or populations may yield distinct disease mechanisms and risk factors. Lastly, this study only investigated the relationship between a single measurement of eGFR and hs-CRP in relation to new-onset AF in diabetic patients, without examining the dynamic changes of these biomarkers concerning AF occurrence. These limitations may affect the interpretation and generalizability of the study findings.

## Conclusions

This study highlights the potential roles of eGFR and hs-CRP as important biomarkers for the risk of new-onset AF in diabetic patients. These findings underscore their clinical significance in risk assessment and management. Future prospective studies and intervention trials are necessary to elucidate their causal relationships and to develop new strategies for the prevention of AF in individuals with diabetes.

## Data Sharing Statement

The dataset generated during the current study is available upon reasonable request. Raw data are not publicly available due to privacy concerns but can be accessed through the research team. Please contact [liutong@tmu.edu.cn] for specific details on data access. All data will be shared in accordance with ethical guidelines, ensuring that individual participant privacy is maintained.

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## Disclosure

The authors declare they have no conflict of interest.

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