# Newly detected atrial fibrillation is associated with cortex-involved ischemic stroke

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## Abstract

**Background:** Both cortical and cortical-subcortical (cortex-involved) lesions are typically associated with embolic stroke, of which atrial fibrillation (AF) is the common cause. The aim of this study was to find out the associations between cortex-involved stroke, vascular risk factors, and the subtypes (discovery time and duration) of AF.

**Methods:** This was an imaging study of the China Atrial Fibrillation Screening in Acute Ischemic Stroke Patients (CRIST) trial. Between October 2013 and June 2015, 1511 acute ischemic stroke or transient ischemic attack (TIA) patients within 7 days after stroke onset at 20 Chinese hospitals were enrolled in this prospective, multicenter cohort, cross-sectional study. The final analysis of this sub-study included 243 patients with AF with required magnetic resonance imaging (MRI) sequences. AF was diagnosed by 6-day Holter monitoring and classified by duration of 24 h. Two stroke specialists blinded to the clinical information reviewed MRI (diffusion-weighted MRI). The third stroke specialists, also blinded to the clinical information, assessed the conflicts. Adjusted large artery atherosclerosis as confounding factor, the associations between cortex-involved lesions, vascular risk factors, and the subtype of AF were evaluated by univariate and multivariate regression analyses.

**Results:** Of 243 acute ischemic stroke patients with AF, 190 were known AF and 53 were newly detected AF. There were 28 patients with AF persistent >24 h and 25 persistent ≤24 h in newly detected AF. Patients with newly detected AF were likely to have a fewer history of stroke or TIA (16.98% *vs.* 36.31%, $P = 0.008$) and lower fasting blood glucose (5.91 ± 1.83 mmol/L *vs.* 6.75 ± 3.83 mmol/L, $P = 0.030$) than patients with known AF. Among these 243 patients, 102 (41.98%) patients were with cortex-involved lesions. Cortex-involved lesions were significantly related to newly detected AF persistent >24 h (odds ratio [OR]: 4.517, 95% confidence interval [CI]: 1.490–13.696, $P = 0.008$), proteinuria (OR: 3.431, 95% CI: 1.530–7.692, $P = 0.021$), and glycosylated hemoglobin (OR: 0.632, 95% CI: 0.464–0.861, $P = 0.004$).

**Conclusions:** Compared to previously known AF, newly detected AF persistent >24 h was associated with cortex-involved ischemic stroke.

**Clinical trial registration:** NCT02156765, https://clinicaltrials.gov/ct2/show/record/NCT02156765

**Keywords:** Atrial fibrillation; Ischemic stroke; Prolonged electrocardiograph monitoring; Magnetic resonance imaging

## Introduction

Diagnosis of atrial fibrillation (AF) after stroke is essential for secondary prevention of stroke. Previous studies demonstrated that oral anticoagulation is superior to aspirin for stroke prevention in patients with AF.[1,2] With prolonged cardiac monitoring by a variety of techniques, AF is newly detected in nearly a quarter of patients with stroke.[3] The China Atrial Fibrillation Screening in Acute Ischemic Stroke Patients (CRIST) trial, which recruited consecutive 1556 patients with ischemic and transient ischemic attack (TIA) within 7 days from October 2013 to June 2015, showed that prolonged monitoring evaluation (6 days) could increase AF detection to about 20% in China, of these 4.4% were newly detected AF.[4] However, the available evidence demonstrated no significant benefit of oral anticoagulation for stroke prevention in such patients.[5-7] Although AF is a well-known risk factor for cardioembolic stroke, it is not always directly responsible for the embolism.[8,9] No consensus has been reached about the embolization risk for different duration of AF.[3] It is crucial to evaluate whether the exact etiology of the stroke is related to the presence of AF.

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Neuroimaging may help distinguish the cause of stroke. Cardioembolic stroke was associated with the presence of cortex-involved lesions with territorial distribution or confluent lesion (>15 mm) with additional lesions involving multiple vascular territories.[10,11]

In this imaging study of China Atrial Fibrillation Screening in Acute Ischemic Stroke Patients (CRIST) trial, we aimed to investigate the associations between the cortex-involved lesion on diffusion-weighted image (DWI), which indirectly suggests embolism mechanism of the index event, and the characteristics of AF (before or after stroke, persistent more or less than 24 h).

## Methods

### Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Beijing Tiantan Hospital. Informed written consent was obtained from all subjects or their next of kin if the consent from the patient was unavailable.

### Study population

This was an imaging study of the CRIST trial. Between October 2013 and June 2015, 1511 acute ischemic stroke or TIA patients within 7 days after stroke onset at 20 Chinese hospitals were enrolled in this prospective, multicenter cohort, cross-sectional study. Initially, a total of 1556 patients were included in this study. Among them, 305 patients were diagnosed with AF by 6-day Holter monitoring. Those who were with required magnetic resonance imaging sequences ($n$ = 243) were enrolled in our study [Figure 1].

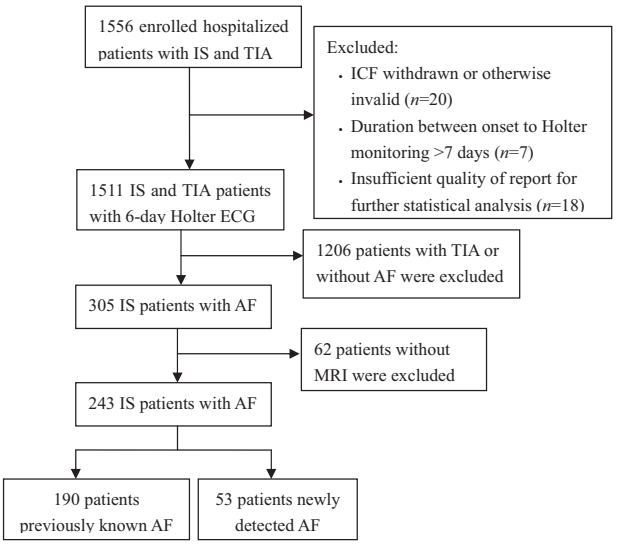


**Figure 1:** Flow chart of the study. IS: Ischemic stroke; TIA: Transient ischemic attack; ICF: Informed consent forms; ECG: Electrocardiograph; AF: Atrial fibrillation; MRI: Magnetic resonance imaging.

AF was diagnosed as ≥1 period of absolute arrhythmia without detectable P-waves (episodes >30 s duration interpreted by Holter and episodes <30 s required manual review of all possible AF events).[12] Previously known AF was diagnosed according to the medical history reported by the patients and the prior available medical records.

### Clinical information

Clinical information such as demographic information, stroke risk factors, detailed medical history, and treatments were assessed as previously described.[4]

The 6-day Holter monitoring initiated within 7 days after the index event using a commercially available 3-lead monitor device (iHolter, Yocaly Information Science & Technology Co., Ltd., Jinan, Shandong, China). Two investigators from central core laboratory analyzed the electrocardiograph (ECG) recordings blindly using dedicated analysis software (DoctorClient, Software version 1.5.0.16, Yocaly Information Science & Technology Co., Ltd.). All ECG recordings with suspected AF were subsequently evaluated by another independent observer. The first time and longest duration of bursts of AF for each patient were also recorded.

MRI was performed using a 1.5-T or a 3.0-T system. The cortex-involved lesion was defined as cortical or cortical-subcortical territorial hyperintense lesions.[13] Infratentorial cortex-involved lesion was defined as a lesion involving the cerebellar cortex. Two stroke specialists blinded to the clinical information reviewed the image; any disagreements were resolved by a third stroke specialist.

### Statistical analysis

Categorical and range variables were reported as absolute number and frequencies (%), and continuous variables were reported as mean ± standard deviation (SD) for normal distribution data and median (Q1, Q3) for abnormal distribution data. Intergroup differences were assessed using the Chi-squared test for categorical variables, and Student's $t$ test or Kruskal-Wallis test for continuous variables. Adjusted large artery atherosclerosis as confounding factor, the associations between cortex-involved lesions, vascular risk factors, and the subtype of AF were evaluated by univariate and multivariate regression analyses. In multivariate logistic regression, the odds ratios (ORs) and 95% confidence intervals (CIs) were used to calculate the probability values. A probability value of ≤0.05 was considered statistically significant. Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

## Results

Among 243 acute ischemic stroke patients with AF, 190 (78.19%) were known AF and 53 (21.81%) were newly detected AF. There were 28 (52.83%) with AF persistent >24 h and 25 (47.17%) persistent ≤24 h in newly detected AF [Figure 1]. Patients with newly detected AF were likely to have a fewer history of stroke or TIA (16.98% *vs.* 36.31%, $P$ = 0.008) and lower fasting blood glucose (5.91 ± 1.83 mmol/L *vs.* 6.75 ± 3.83 mmol/L, $P$ = 0.030) than

patients with known AF; other characteristics on baseline were similar between two groups (Table 1).

Comparison of demographic information, stroke risk factors, detailed medical history, and lab results between cortex-involved lesions and non-cortex-involved lesions are presented in Table 2. Among these 243 patients, 102 (41.98%) patients were with cortex-involved lesions. In these 102 patients with cortex-involved lesion, 38 (37.25%) were newly detected AF and further divided by duration of AF: 21 with AF persistent >24 h and 17 with AF ≤24 h. Compared with patients with non-cortex involved lesions, patients with cortex-involved lesions had more newly detected AF, either persistent >24 h ($P < 0.001$) or ≤24 h ($P = 0.008$). According to univariate regression analysis, patients with cortex-involved lesions presented more frequently with proteinuria (41.18% *vs.* 20.57%, $P < 0.001$), and less frequently with history of diabetes (13.73% *vs.* 27.66%, $P = 0.009$) and ischemic stroke or TIA (23.53% *vs.* 38.30%, $P = 0.015$). Patients with non-cortex-involved lesions had higher glycosylated hemoglobin (6.88 ± 1.88% *vs.* 6.04 ± 1.05%, $P < 0.001$), fasting blood glucose (7.18 ± 4.31 mmol/L *vs.* 5.72 ± 1.53 mmol/L, $P < 0.001$), and low-density lipoprotein (2.75 ± 0.79 mmol/L *vs.* 2.53 ± 0.88 mmol/L, $P = 0.036$).

We conducted the multivariate logistic regression analysis for cortex-involved lesions compared to non-cortex-involved lesions after adjusted confounding factor. Cortex-involved lesions were significantly related to newly detected AF persistent >24 h (OR: 4.517, 95% CI: 1.490–13.696, $P = 0.008$), proteinuria (OR: 3.431, 95% CI: 1.530–7.692, $P = 0.021$), and glycosylated hemoglobin (OR: 0.632, 95% CI: 0.464–0.861, $P = 0.004$; Table 3). The value of C statistic was 0.759.

## Discussion

A major finding of this study was that compared to known AF, newly detected AF, particularly those persistent >24 h, were significantly related to cortex-involved lesions, which exactly resulted in the latest stroke attack. AF is a widely recognized healthcare challenge with increasing prevalence across the world.[14,15] The development of continuous long-term monitoring improved detection of AF.[3,5,16,17] It is still a question that newly detected AF itself does cause

**Table 1: Clinical features of 243 acute ischemic stroke patients with AF.**

| Variables | Patients with newly diagnosed AF ($n = 53$) | Patients with previous known AF ($n = 190$) | Statistical values | *P* |
|---|---|---|---|---|
| Age (years) | 69.6 ± 10.6 | 70.8 ± 9.8 | 0.770* | 0.443 |
| Female | 17 (32.08) | 74 (38.95) | 0.840† | 0.361 |
| BMI (kg/m$^2$) | 23.8 ± 3.2 | 24.0 ± 3.4 | 0.410* | 0.680 |
| Current smoker | 21 (39.62) | 65 (33.16) | 0.770† | 0.382 |
| Over drink | 5 (9.43) | 13 (6.84) | 0.410† | 0.524 |
| Medical history | | | | |
| Hypertension | 30 (56.60) | 130 (68.42) | 2.570† | 0.109 |
| Diabetes | 11 (20.75) | 42 (22.10) | 0.040† | 0.833 |
| Hyperlipidemia | 5 (9.43) | 23 (12.11) | 0.290† | 0.590 |
| Ischemic stroke or TIA | 9 (16.98) | 69 (36.31) | 7.110† | 0.008 |
| Myocardial Infarct | 2 (3.77) | 7 (3.68) | 0.001† | 0.976 |
| Coronary heart disease | 8 (15.09) | 34 (17.89) | 0.230† | 0.633 |
| Peripheral arterial disease | 1 (1.89) | 7 (3.68) | 0.420† | 0.517 |
| Heart failure | 4 (7.55) | 22 (11.58) | 0.710† | 0.401 |
| Renal dysfunction | 1 (1.89) | 7 (3.68) | 0.420† | 0.517 |
| Lab examination | | | | |
| GHB (%) | 6.16 ± 1.26 | 6.56 ± 1.67 | 1.640* | 0.104 |
| FBG (mmol/L) | 5.91 ± 1.83 | 6.75 ± 3.83 | 2.190* | 0.030 |
| TG > 1.70 mmol/L | 24 (45.28) | 89 (46.84) | 0.089† | 0.766 |
| CHOL (mmol/L) | 4.46 ± 1.00 | 4.44 ± 0.98 | –0.120* | 0.903 |
| HDL (mmol/L) | 1.39 ± 0.96 | 1.23 ± 0.44 | –1.170* | 0.247 |
| LDL (mmol/L) | 2.66 ± 0.88 | 2.65 ± 0.82 | –0.060* | 0.951 |
| Cr (μmol/L) | 76.42 ± 30.60 | 80.18 ± 49.86 | 0.670* | 0.501 |
| Proteinuria | 17 (32.08) | 54 (28.42) | 0.270† | 0.605 |
| eGFR < 60 mL·min$^{-1}$·1.73 m$^{-2}$ | 5 (9.43) | 35 (19.42) | 2.380† | 0.123 |
| NIHSS score at admission | 5 (2, 10) | 4 (2, 9) | 0.220‡ | 0.823 |
| CHADS2 score | 1 (1, 2) | 2 (1, 3) | 2.340‡ | 0.310 |
| CHADS2_VASc score | 2 (2, 3) | 3 (2, 5) | 2.310‡ | 0.387 |

The data were shown as mean ± standard deviation, *n* (%), or median (Q1, Q3). * *t* test. † Chi-squared test. ‡ Kruskal-Wallis test. AF: Atrial fibrillation; TIA: Transient ischemic attack; BMI: Body mass index; GHB: Glycosylated hemoglobin; FBG: Fasting blood glucose; TG: Triglyceride; CHOL: Cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Cr: Creatinine; eGFR: Estimated glomerular filtration rate; NIHSS: National Institutes of Health Stroke Scale.

**Table 2: Clinical features of patients with and without cortex-involved lesions.**

| Variables | Cortex-involved lesions ($n = 102$) | Non-cortex-involved lesions ($n = 141$) | Statistical values | *P* |
|---|---|---|---|---|
| Age (years) | 70.9 ± 9.0 | 70.0 ± 11.1 | 0.670* | 0.486 |
| Female | 35 (34.31) | 56 (39.71) | 0.740† | 0.391 |
| BMI (kg/m$^2$) | 23.5 ± 3.4 | 24.3 ± 3.3 | 1.730* | 0.085 |
| Current smoker | 37 (36.27) | 47 (33.33) | 0.230† | 0.634 |
| Over drink | 7 (6.86) | 11 (7.80) | 0.080† | 0.783 |
| Medical history | | | | |
| Hypertension | 63 (61.76) | 97 (68.79) | 1.300† | 0.254 |
| Diabetes | 14 (13.73) | 39 (27.66) | 6.740† | 0.009 |
| Hyperlipidemia | 10 (9.80) | 18 (12.77) | 0.510† | 0.475 |
| Ischemic stroke or TIA | 24 (23.53) | 54 (38.30) | 5.920† | 0.015 |
| Myocardial Infarct | 4 (3.92) | 5 (3.55) | 0.020† | 0.878 |
| Coronary heart disease | 14 (13.73) | 28 (19.86) | 1.560† | 0.212 |
| Peripheral arterial disease | 3 (2.94) | 5 (3.55) | 0.070† | 0.794 |
| Heart failure | 12 (11.76) | 14 (9.93) | 0.210† | 0.648 |
| Renal dysfunction | 4 (3.92) | 4 (2.84) | 0.220† | 0.640 |
| Lab examination | | | | |
| GHB (%) | 6.04 ± 1.05 | 6.88 ± 1.88 | 3.590* | <0.001 |
| FBG (mmol/L) | 5.72 ± 1.53 | 7.18 ± 4.31 | 3.630* | <0.001 |
| TG > 1.70 mmol/L | 42 (41.18) | 71 (50.35) | 2.480† | 0.115 |
| CHOL (mmol/L) | 4.32 ± 1.02 | 4.53 ± 0.95 | 1.610* | 0.110 |
| HDL (mmol/L) | 1.30 ± 0.43 | 1.24 ± 0.70 | −0.810* | 0.419 |
| LDL (mmol/L) | 2.53 ± 0.88 | 2.75 ± 0.79 | 2.110* | 0.036 |
| Cr (μmol/L) | 76.29 ± 27.35 | 81.60 ± 56.26 | 0.970* | 0.335 |
| Proteinuria | 42 (41.18) | 29 (20.57) | 12.120† | <0.001 |
| eGFR < 60 mL·min$^{-1}$·1.73 m$^{-2}$ | 15 (14.71) | 25 (17.73) | 0.410† | 0.520 |
| NIHSS score at admission | 2 (2, 10) | 2 (2, 9) | −0.070‡ | 0.942 |
| CHADS2 score | 1 (1, 3) | 2 (1, 3) | 2.190‡ | 0.094 |
| CHADS2_VASc score | 3 (2, 4) | 3 (2, 5) | 2.090‡ | 0.557 |
| AF | | | | |
| Previously known AF >24 h | 56 | 90 | | |
| Previously known AF ≤24 h | 8 | 36 | 5.830† | 0.016 |
| Newly detected AF >24 h | 21 | 7 | 11.280† | <0.001 |
| Newly detected AF ≤24 h | 17 | 8 | 7.090† | 0.008 |

The data were shown as mean ± standard deviation, *n* (%), *n*, or median (Q1, Q3). * *t* test. † Chi-squared test. ‡ Kruskal-Wallis test. AF: Atrial fibrillation; TIA: Transient ischemic attack; BMI: Body mass index; GHB: Glycosylated hemoglobin; FBG: Fasting blood glucose; TG: Triglyceride; CHOL: Cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Cr: Creatinine; eGFR: Estimated glomerular filtration rate; NIHSS: National Institutes of Health Stroke Scale.

**Table 3: Multiple regression analysis of cortex-involved infarcts compared to non-cortex-involved lesions.**

| Risk factors | OR | 95% CI | *P* |
|---|---|---|---|
| New diagnosed AF >24 h | 4.517 | 1.490–13.696 | 0.008 |
| GHB | 0.632 | 0.464–0.861 | 0.004 |
| Proteinuria | 3.431 | 1.530–7.692 | 0.021 |

Adjusted variables: age, female, current smoker, over drink, body mass index, medical history, hypertension, diabetes, hyperlipidemia, myocardial infarct, coronary heart disease, peripheral arterial disease, heart failure, National Institutes of Health Stroke Scale score at admission, GHB, fasting blood glucose, triglyceride, cholesterol, high-density lipoprotein, low-density lipoprotein, creatinine, proteinuria, estimated glomerular filtration rate. GHB: Glycosylated hemoglobin; OR: Odds ratio; CI: Confidence interval.

embolism or rather is a marker of cardioembolic risk.[8,9] This doubt has raised concern about the actual clinical impact of newly detected AF in terms of death or dependence after stroke, and how it should be treated or prevented. The role of AF duration on stroke risk, however, is controversial. A pooled analysis confirmed the significant increased risk of stroke or TIA for AF ≥1 h compared with AF <1 h (HR: 1.89–2.09).[18] In a recently published analysis from the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), the increased stroke risk due to newly detected subclinical AF was seen clearly only among those patients whose longest episode of AF was at least 24 h in duration.[19] However, according to Ontario Stroke Registry, newly detected AF was related to a lower risk of ischemic stroke recurrence than known AF (7.0% *vs.* 9.6%).[20] All of these findings called into question that to what extent newly detected AF after stroke is the cause or a consequence.

Imaging pattern has received more and more attention to support etiologic classification[13,21] and predict recurrence after ischemic stroke or TIA.[22-24] Territorial

distribution of the infarcts involving cortex or subcortex was suggested to indicate cardioembolic stroke mechanism. The cardioembolic stroke infarctions were usually in both anterior and posterior circulation or bilateral circulation of different age.[11] According to the previous report, patients with newly detected AF had reduced risk of cardioembolic stroke compared to the patients with known AF (OR: 0.11, 95% CI: 0.03–0.36, $P < 0.001$),[25] which studied defined cardioembolic stroke as cortex-involved territorial lesion without relevant large artery diseases or multiple non-contiguous lesions in bilateral hemispheres or both anterior and posterior circulations. In our study, only 14 patients complied with the second standards above. We only chose cortex-involved lesions to analysis to reduce heterogeneity. It was worth noting that we only analyzed DWI lesions which represented the new attack of this stroke. We have found that newly detected AF persistent >24 h was more likely associated with new cortex-involved lesions. We could not provide information on the potential role of cortex damage (such as insular) in the development of newly detected AF, which may have been attributable to the small sample size. Although we could not elucidated the exact neurogenic pathophysiology in stroke patients with newly detected AF, we might provide some clues that newly detected AF after stroke or TIA may be causally linked to the occurrence of new lesions in some cases.

We also found that cortex-involved lesions were significantly related to proteinuria and glycosylated hemoglobin. Proteinuria, which is an important potentially modifiable measure of kidney function, has been linked to elevations in the risk of stroke and poor outcomes and death after stroke in populations with and without chronic kidney disease.[26,27] However, the relationship of proteinuria and etiologic classification is unclear. Growing evidences have suggested an independent association between the presence of proteinuria and new-onset AF.[28-30] The biologic role of proteinuria as a marker of endothelial dysfunction, sympathetic activation may explain the possible mechanisms of the elevated risk of vascular events and new-onset AF.[31,32] Previous studies reported different effects of the estimated glomerular filtration rate (eGFR) and proteinuria on the risk of AF.[27,28,30] In our study, we analyzed both eGFR and proteinuria and only proteinuria reached statistical significance. We did not see definite interaction between eGFR and proteinuria. This controversy need further study with more data on kidney dysfunction. Current stroke risk scoring systems for patients with AF include a diagnosis of diabetes mellitus.[33,34] The association between glycosylated hemoglobin, a measure of glycemia during the prior 3 months, and ischemic stroke among diabetes mellitus patients has been investigated in general populations[35] and patients with AF.[36] Metabolic changes of diabetes could lead to atrial structural remodeling, atrial electrical remodeling, atrial electromechanical remodeling, and atrial autonomic remodeling.[37] So diabetes was closely related to AF which usually caused embolic stroke. Therefore, the correlation between glycosylated hemoglobin and brain cortical embolism was support by previous studies.

There were several limitations in our study. First, the exact etiologic classification of stroke or TIA could not be obtained due to lack of imaging information on large artery diseases. The cortex-involved lesions were used to represent the etiologic classification of cardioembolism. However, it must be acknowledged that accurate etiologic classification of stroke may not be possible in every case of stroke even with advanced neuroimaging and vascular imaging techniques. Second, the paroxysmal AF or pre-existing AF might be included in patients with newly detected AF on account of the reality of insufficient screening for AF before stroke or TIA. Finally, the small sample size restricted to subdivide the duration of AF into shorter or longer hours which possibly affected on the risk of embolism. Although there are many unknowns, the findings merit attention and need further research.

In conclusion, although newly detected AF persistent >24 h was associated with cortex-involved lesions, which was highly suggestive of cardioembolism. Further studies are needed to question how isolated newly detected AF causes embolic events.

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## Conflicts of interest

This study was sponsored and funded by Bayer HealthCare Pharmaceuticals. Bayer HealthCare Pharmaceuticals took no part in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

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