Serum Uric Acid Levels in Relation to Atrial Fibrillation: A Case-Control Study

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Conflict of interest: None declared

Background: Although serum uric acid (SUA) levels have been reported to be associated with atrial fibrillation (AF), the specific associations remain unclear. The purpose of this study was to investigate the potential relationship of serum uric acid levels to atrial fibrillation.

Material/Methods: We retrospectively analyzed clinical data of 970 consecutive hospitalized patients (M/F, 519/451; age, 64.78±13.49 years). The study included 478 patients with AF, and 492 age-matched patients with sinus rhythm and no history of arrhythmia as a control group. The t test, ANOVA, chi-squared test, or Fisher exact test were performed to analyze clinical baseline data.

Results: Compared with the control group, patients with AF exhibited higher SUA levels (5.66±1.90 vs 5.35±1.55 mg/dL, P=0.006), especially women (P<0.001). Pearson correlation analysis showed SUA was influenced by A/G, PAB, and APOA1 in patients with AF. Logistic regression analysis showed SUA was associated with AF (total: OR=1.002, 95% CI: 1.000-1.003; women: OR=1.005, 95% CI: 1.003-1.007). After adjustment for clinical related factors for AF, SUA was still associated with AF (total: OR=1.004, 95% CI: 1.002-1.006; women: OR=1.005, 95% CI: 1.002-1.009). Also, elevated SUA was positively correlated with A/G and PAB and negatively correlated with APOA1. There were no significant differences in SUA levels in AF subtypes and complications.

Conclusions: Elevated SUA levels were associated with AF, but the independent association was significant only in women. Elevated SUA may promote other AF-related factors and participate in the pathological process of AF.

Keywords: Risk • Gender Identity • Atrial Fibrillation • Accident Prevention

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/934007
Background

Atrial fibrillation (AF) is an increasingly common arrhythmia, which has a considerable impact on patient health and socioeconomic factors. Currently, AF affects 33 million people worldwide [1], and this rate is predicted to increase [2], which also means there will be an increased risk of ischemic stroke, systemic embolism, and heart failure [3-5]. Although ablation approaches and antiarrhythmic drugs are widely used as effective therapies for AF, the recurrence and mortality rates still remain high. In addition, evidence suggests that the present long-term outcome of catheter ablation of AF is not ideal, particularly for patients with paroxysmal atrial fibrillation, with single-procedure success rates of only 66.6% [6] and a 5-year success rate of less than 30% after a single procedure [7]. Given the increasing risk of AF, its morbidity and mortality, and its significant health and socioeconomic impact, the prevention and treatment of AF cannot be ignored.

Although the pathological mechanism of AF can be an inconclusive measurement, inflammatory and oxidative stress have been shown to play an important role in the pathological progress of AF. Serum uric acid (SUA) is a byproduct of purine catabolism and is catalyzed by xanthine oxidoreductase [8]. Several studies have demonstrated that elevated SUA levels are associated with activated pro-inflammatory and oxidative stress pathways [9,10], and xanthine oxidoreductase is generally considered to be an important link in this process. Regardless of the predictor or causative factor, an increasing data have demonstrated the positive association between increased SUA levels and AF [11-13]. Nevertheless, in most instances, the pathological progression of AF and SUA levels can be influenced by multiple parameters, including drugs and diseases, and in particular, patient sex [14,15]. From the clinical standpoint, the associations between SUA levels and AF appear to be ambiguous and create ongoing controversy.

In the present study, we aimed to understand the pathological process of AF by investigating the potential relationship between SUA levels and AF.

Material and Methods

Data Source and Study Design

This was a case-control study. Data were obtained from the electronic medical record database of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine from January 2019 to May 2021. We retrospectively analyzed the clinical data of 970 consecutive hospitalized patients (male/female, 519/451; age, 62.17±15.48 years). The sample included 478 patients with AF aged 31 to 85 years old, and 492 age- and sex-matched patients with sinus rhythm and no history of arrhythmia served as a control group. Inclusion criteria were as follows: patients with AF, regardless of paroxysmal or permanent, and complete clinical data. Exclusion criteria were as follows: valve diseases, structural heart disease, cardiac surgery, heart failure, hepatic or renal dysfunction, hyperthyroidism, malignant tumor, uric acid lowering drugs, diuretics, allopurinol, and pregnancy. We collected and analyzed baseline data, including AF categories, age, sex, complications, medication, and laboratory data, from a medical record review. Patients with AF were divided into 6 groups according to SUA levels and sex as follows: men (low level group: SUA <5.5 mg/dl; middle level group: 5.5≤SUA≤6.5 mg/dl; and high level group: SUA >6.5 mg/dl) and women (low level group: SUA <4.2 mg/dl; middle level group: 4.2≤SUA≤5.0 mg/dl; and high level group: SUA >5.0 mg/dl). This study was approved by the Ethics Committee on Medical Research of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine and was performed according to the principles of the Declaration of Helsinki. Informed consent was waived.

Definition of AF

According to guidelines [16], AF was considered to be an arrhythmia lasting long enough for a 12-lead electrocardiogram to be recorded, or lasting for at least 30 s. In addition, paroxysmal AF was specifically defined as AF that terminated spontaneously or with intervention within 7 days of initiation. Permanent AF was defined as the presence of recognized AF and sinus rhythm that would not be further restored or maintained.

Definition of Hyperuricemia

The measurements of SUA were reported in μmol/L and converted as 1 mg/dL=59.48 μmol/L. SUA levels were measured by the uricase method. Hyperuricemia was defined as an SUA level >7.0 mg/dL in men and an SUA level >5.7 mg/dL in women [17].

Screened Indicators

We screened basic indicators, including age, sex, blood pressure, complications, and medication and biochemical indicators, including serum creatinine (Scr), fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALT/AST, serum apolipoprotein A1 (APOA1), APOB (serum apolipoprotein B), albumin (ALB), Ig, A/G, prealbumin (PAB), and lipoprotein (a) (Lp [a]) in all participants.

Statistical Analysis

Analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism software (version 9.0.0).
Continuous variables were expressed as mean±standard deviation or median (interquartile range [IQR]). Categorical variables were presented as percentages or ratios. The comparisons of parametric and nonparametric continuous variables were performed by ANOVA or the t test and Mann-Whitney U test, respectively. The comparison of categorical variables was performed by the chi-squared test or Fisher exact test. Pearson correlation analyses were performed to distinguish interrelationships. Multivariate regression analysis was performed to screen the independent risk factor for AF. The P value <0.05 was considered statistically significant, and statistically testing was 2-sided.

Results

Baseline Characteristics of the Study Population

A total of 478 patients were included in the AF group: 253 (52.9%) were men and the mean age was 64.87±10.75 years; 492 participants without AF were included in the control group: 266 (54.1%) were men and the mean age was 64.69±15.72 years. The AF group had more patients with hyperuricemia than did the control group (n=142 vs 102, P=0.001; men: 70 vs 66, women: 72 vs 36, P=0.017, Table 1). Patients with AF had significantly higher SUA levels (5.66±1.90 vs 5.35±1.55 mg/dL, P=0.006, Table 1 and Figure 1; women: 5.33±1.88 vs 4.58±1.21 mg/dL, P<0.001, Table 1 and Figure 2), Scr (78.23±55.15 vs 66.95±34.43 μmol/L, P<0.001, Table 1), and ALT/AST (1.28±0.55 vs 1.15±0.51, P<0.001, Table 1) than did controls. In addition, patients with AF had significantly lower ALB (37.75±4.59 vs 40.30±4.04 g/L, P<0.001, Table 1), APOA1 (1.08±0.25 vs 1.22±0.25 g/L, P<0.001, Table 1), APOB (0.81±0.48 vs 1.00±0.25 g/L, P<0.001, Table 1), A/G (1.35±0.24 vs 1.46±0.22, P<0.001, Table 1), and PAB (190.63±60.78 vs 227.69±52.68 mg/L, P<0.001, Table 1) than did controls. Obviously, the AF group was more prone to have a history of hypertension, diabetes, and coronary heart disease (all P<0.001, Table 1) and to take β-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEI/ARBs), and statins (all P<0.001, Table 1). We also observed that SUA levels were positively correlated with A/G (r=0.318, P=0.046, Figure 3A), PAB (r=0.138, P=0.002, Figure 3B) and negatively correlated with APOA1 (r=-0.201, P<0.001, Figure 3C) in the AF group.

Association Between SUA Levels and AF

To check the association between SUA levels and AF using logistic regression analysis, we adjusted for sex, hypertension, diabetes, coronary heart disease (CHD), β-blockers, CCBs, ACEI/ARB, and statins (OR=1.002, 95% CI: 1.000-1.004, P=0.004). After adjusting for Scr, AST, ALT/AST, ALB, APOA1, APOB, A/G, and PAB, SUA levels remained a significant factor correlated with AF (OR=1.003, 95% CI: 1.002-1.005, P=0.001). After further adjustment for all these factors, SUA remained a significant indicator for AF (OR=1.004, 95% CI: 1.002-1.006, P=0.014). Furthermore, the independent association was significant in women (P<0.05) but not in men (P>0.05) (Table 2, Figure 4).

Association of SUA Levels and AF by Subtypes and Complications

As shown in Table 3, the SUA levels in patients with paroxysmal AF and permanent AF were 5.54±1.95 vs 5.73±1.87 mg/dL, respectively (P=0.290). The SUA levels in patients with AF with hypertension, diabetes, and CHD were 5.71±1.91 vs 5.40±2.13 vs 5.61±1.86 mg/dL, respectively (P=0.292). There were no significant differences between subtypes and complications in patients with AF.

Association of SUA Levels and Metabolic Indicators in Patients with AF by Sex

As shown in Table 4, regardless of sex, patients with higher SUA levels had higher Scr (75.20±34.22 vs 79.79±16.35 vs 89.49±31.89 μmol/L, P=0.005) and ALB (36.44±4.90 vs 39.28±4.75 vs 37.77±4.47 mg/L, P<0.001. In male patients with AF, those with higher SUA levels had higher PAB (169.78±60.93 vs 205.28±65.03 vs 209.18±64.06 mg/L, P<0.001).

Discussion

In the present study, we observed that elevated SUA levels were associated with AF and that the independent association was significant only in women (P<0.05). SUA level was positively correlated with A/G and PAB and negatively correlated with APOA1. SUA levels showed no significant difference by subtypes and complications of AF. In addition, SUA levels were independently associated with Cre and ALB in patients with AF and independently associated with PAB only in men.

SUA is the final product of purine of purine metabolism catalyzed by xanthine oxidase in humans and is produced in the liver and muscles and is mainly excreted by the kidneys [18,19]. Overproduction and insufficient excretion can promote elevated SUA levels. Because of the uricosuric effect of estrogen, although SUA levels increase after menopause, SUA levels in men are higher than those in women throughout life [20,21]. In general, normal serum SUA levels are 6.5 to 7 mg/dL for men and 6 to 6.5 mg/dL for women [22]. The recommended goal is a concentration below 5 mg/dL in patients with higher cardiovascular risk [23,24].
Table 1. Demographic and clinical characteristics of control and atrial fibrillation group.

| Variable           | Control group (n=492) | AF group (n=478) | P value |
|--------------------|-----------------------|------------------|---------|
| SUA, mg/dL         | 5.35±1.55             | 5.66±1.90        | 0.006   |
| Male, mg/dL        | 6.05±1.56             | 6.15±1.99        | 0.385   |
| Female, mg/dL      | 4.38±1.21             | 5.33±1.88        | <0.001  |
| Hyperuricemia      | 102 (20.7)            | 142 (20.7)       | 0.001   |
| Male, n (%)        | 66 (64.7)             | 70 (49.3)        | 0.017   |
| Female, n (%)      | 36 (35.3)             | 72 (50.7)        |         |
| Age, years         | 64.69±15.72           | 64.87±10.75      | 0.835   |
| Male, n (%)        | 266 (54.1)            | 253 (52.9)       | 0.723   |
| Hypertension, n (%)| 172 (35.0)            | 315 (65.9)       | <0.001  |
| Diabetes, n (%)    | 82 (16.7)             | 135 (28.2)       | <0.001  |
| CHD, n (%)         | 146 (29.7)            | 443 (72.7)       | <0.001  |
| Scr, μmol/L        | 66.95±34.43           | 78.23±55.15      | <0.001  |
| FBG, mmol/L        | 5.97±1.80             | 6.10±1.97        | 0.284   |
| ALT, U/L           | 17 (12-25)            | 16 (12-24)       | 0.424   |
| AST, U/L           | 18 (15-23)            | 19.5 (16-25)     | 0.001   |
| ALT/AST            | 1.15±0.51             | 1.28±0.55        | <0.001  |
| APOA1, g/L         | 1.22±0.25             | 1.08±0.25        | <0.001  |
| APOB, g/L          | 1.00±0.25             | 0.81±0.48        | <0.001  |
| ALB, g/L           | 40.30±4.04            | 37.75±4.59       | <0.001  |
| Ig, g/L            | 28.10±3.99            | 28.48±4.35       | 0.156   |
| A/G                | 1.46±0.22             | 1.35±0.24        | <0.001  |
| PAB, mg/L          | 227.69±52.68          | 190.63±60.78     | <0.001  |
| Lp (a), mg/L       | 14 (6.3-27.9)         | 14.5 (7.85-28.78)| 0.160   |
| β-blockers, n (%)  | 109 (22.2)            | 367 (76.8)       | <0.001  |
| CCBs, n (%)        | 102 (20.7)            | 162 (33.9)       | <0.001  |
| ACEI/ARB, n (%)    | 104 (21.1)            | 284 (59.4)       | <0.001  |
| Statins, n (%)     | 128 (26.0)            | 308 (64.4)       | <0.001  |

Data are presented as mean±standard deviation (SD), median (interquartile range [IQR]), or n (%). AF – atrial fibrillation; CHD – coronary heart disease; Scr – serum creatinine; FBG – fasting blood glucose; ALT – alanine aminotransferase; AST – aspartate aminotransferase; AST/ALT – aspartate aminotransferase/alanine aminotransferase; APOA1 – serum apolipoprotein A1; APOB – serum apolipoprotein B; ALB – albumin; Ig – immunoglobulin; A/G – albumin/globulin; PAB – prealbumin; Lp (a) – lipoprotein (a); CCBs – calcium channel blockers; ACEI/ARB – angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
To date, although the pathogenesis of AF is still challenging, inflammation and oxidative stress have been demonstrated to play important roles in the occurrence and development of AF [25,26]. In this regard, hyperuricemia-induced AF, occurring through an inflammatory pathway, has been receiving attention [27]. Evidence has indicated that the formation of free radical superoxide anion and oxidative stress contribute to the electrical remodeling of the left atria, and SUA plays an important role in this process [28,29]. Moreover, the release of pro-inflammatory cytokines and local activation of the renin-angiotensin system are also associated with SUA levels [30,31]. Notably, inflammation also promotes the production of SUA through augmented cell destruction [21]. In addition, chronic inflammation promotes the activation of the Janus kinase/signal transducer and activator of transcription pathway, which also plays an important role in left atrial electrical remodeling [32,33]. Studies have identified that hyperuricemia is associated with paroxysmal or persistent AF as well as with the risk of AF in patients undergoing surgery [34].

Clinical evidence has shown that SUA level is associated with an increased risk for future AF in both sexes [21]. Indeed, to date, the effects of sex on the association between SUA and AF are still controversial. In a cohort study of 7155 patients, regardless of sex, SUA levels significantly increased the crude prevalence of AF (P<0.001), and after adjustment for multiple related factors for AF, the effect of SUA on AF was independent only in women [35]. In a cross-sectional study involving 11 956 participants, SUA was positively associated with the prevalence of AF. However, the independent association was significant only in men (P<0.05) [36]. Consistent with a previous report, after adjustment for clinical related factors for AF, in the present study, we observed that elevated SUA levels were associated with AF, but the independent association was significant only in women (P<0.05). Nevertheless, a clinical study also indicated that SUA levels are associated with AF in both sexes [21]. Accordingly, further studies are needed to determine the effect of sex on the association between SUA and AF.

Furthermore, in the present study, we observed a difference in the association of SUA with AF by subtypes and complications. However, few studies tested the association of SUA with AF by subtypes and complications. In a cross-sectional study of 45 patients with paroxysmal AF, 41 patients with permanent AF and 48 controls were tested, and the results indicated that a significant difference in SUA level was evident between patients with paroxysmal AF (5.7 mg/dL), patients with permanent AF (6.7 mg/dL), and control participants (5.1 mg/dL) (P<0.001), and there was an association between SUA and permanent AF [27]. Nevertheless, no statistically significant differences were found in the present study, which may have been due to its small sample size.

Multiple parameters, including drugs and diseases, can influence AF. In the present study, we observed that SUA, sex, hypertension, diabetes, CHD, β-blockers, CCBs, ACEI/ARBs, statins, SCR, AST, ALT/AST, ALB, APOA1, APOB, A/G, and PAB were associated with AF. After further analysis, we found that SUA level was
Table 2. Association between serum uric acid levels and atrial fibrillation.

| Model   | OR 95% CI       | P value | OR 95% CI       | P value | OR 95% CI       | P value |
|---------|------------------|---------|------------------|---------|------------------|---------|
| Model 1 | 1.002 (1.000-1.003) | 0.006   | 1.000 (0.999-1.002) | 0.783   | 1.005 (1.003-1.007) | <0.001 |
| Model 2 | 1.002 (1.000-1.004) | 0.004   | 1.001 (0.999-1.004) | 0.402   | 1.004 (1.001-1.007) | 0.008   |
| Model 3 | 1.003 (1.002-1.005) | 0.001   | 1.002 (1.000-1.005) | 0.043   | 1.006 (1.003-1.009) | <0.001 |
| Model 4 | 1.004 (1.002-1.006) | 0.014   | 1.003 (1.001-1.007) | 0.054   | 1.005 (1.002-1.009) | 0.005   |

Model 1: Crude, no adjustment. Model 2: Adjusted for sex, hypertension, diabetes, CHD, β-blockers, CCBs, ACEI/ARB, and statins. Model 3: Adjusted for Scr, AST, ALT/AST, ALB, APOA1, APOB, A/G, and PAB. Model 4: Adjusted for all these factors. AF – atrial fibrillation; CHD – coronary heart disease; Scr – serum creatinine; FBG – fasting blood glucose; AST – aspartate aminotransferase; ALT/ALT – aspartate aminotransferase/alanine aminotransferase; APOA1 – serum apolipoprotein A1; APOB – serum apolipoprotein B; ALB – albumin; A/G – albumin/globulin; PAB – prealbumin; CCBs – calcium channel blockers; ACEI/ARB – angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
| Variable                      | Male AF patients (n=253) | Female AF patients (n=225) | P value |
|-------------------------------|--------------------------|---------------------------|---------|
|                               | <5.5 mg/dL | 5.5-6.5 mg/dL | >6.5 mg/dL | <4.2 mg/dL | 4.2-5.0 mg/dL | >5.0 mg/dL |         |
| Number, n                     | 98          | 67           | 88         | 63         | 52          | 110       |         |
| Cre, μmol/L                   | 75.20±34.22 | 79.79±16.55  | 89.49±31.89 | 0.005      | 57.75±10.44 | 67.37±40.95 | 87.82±99.70 | 0.025 |
| AST, U/L                      | 21.29±10.10 | 26.88±23.86  | 44.14±139.10 | 0.160      | 21.56±9.52  | 21.12±7.38  | 24.75±24.52 | 0.378 |
| ALT/AST                       | 1.22±0.46   | 1.14±0.47    | 1.17±0.59  | 0.595      | 1.41±0.55   | 1.41±0.57   | 1.39±0.58   | 0.966 |
| ALB, g/L                      | 36.44±4.90  | 39.28±4.75   | 37.77±4.47 | <0.001     | 36.67±4.53  | 38.08±4.26  | 38.44±4.10  | 0.030 |
| APOA1, g/L                    | 1.05±0.27   | 1.02±0.19    | 0.99±0.24  | 0.238      | 1.17±0.27   | 1.16±0.23   | 1.13±0.24   | 0.547 |
| APOB, g/L                     | 0.83±0.93   | 0.74±0.23    | 0.83±0.28  | 0.590      | 0.76±0.20   | 0.85±0.28   | 0.82±0.25   | 0.125 |
| A/G                           | 1.32±0.25   | 1.40±0.24    | 1.37±0.23  | 0.097      | 1.31±0.29   | 1.33±0.25   | 1.37±0.21   | 0.269 |
| PAB, mg/L                     | 169.78±60.93| 205.28±65.03 | 209.18±64.06| <0.001     | 180.68±58.79| 187.52±54.40| 192.61±52.99| 0.390 |

Data are presented as mean±standard deviation (SD). AF – atrial fibrillation; SCr – serum creatinine; AST – aspartate aminotransferase; AST/ALT – aspartate aminotransferase/alanine aminotransferase; APOA1 – serum apolipoprotein A1; APOB – serum apolipoprotein B; ALB – albumin; A/G – albumin/globulin; PAB – prealbumin.
positively correlated with A/G and PAB and negatively correlated with APOA1. Meanwhile, SUA levels were independently associated with SCR and ALB in patients with AF and independently associated with PAB only in men. Inflammation and oxidative stress have been proposed as the important mechanisms contributing to the occurrence of AF [38,39]. Serum albumin exerts anti-inflammatory and anti-oxidative functions in physiological conditions [40,41]. A/G, the indicator of measuring nutritional status, has been confirmed to be involved in the systemic inflammatory process [42]. Generally, low A/G represents poor nutritional status and chronic inflammation. Many studies have suggested that low A/G is inversely associated with cardiovascular events [42,43]. A previous study demonstrated that serum albumin level is independently and inversely related to AF [44]. Furthermore, evidence supports that the alteration of A/G may contribute to sympathovagal imbalance, which is closely related to the onset of AF [45,46]. PAB is also an indicator that reflects the body’s nutritional and immune status. Generally, PAB suggests low levels in inflammatory states and impaired heart function [47], and low PAB is associated with cardiovascular risk [48]. ApoA1, the major apolipoprotein of high-density lipoprotein (HDL), mediates the antiatherogenic and cardioprotective functions of HDL [49]. A previous study, based on patients with AF treated with oral anticoagulation, reported that higher ApoA1 levels were independently related with a lower risk of ischemic cardiovascular outcomes. Therefore, it is speculated that ApoA1 may mediate the ischemic outcome of AF [50]. Additionally, APOA1 can exert anti-inflammatory and anti-oxidant effects through related enzymes [51,52]. A study demonstrated that compared with levels in a healthy population, ApoA1 levels were significantly lower in patients with AF [53]. Another small study also showed that compared with that in a healthy population, patients with AF had an approximately 30% lower expression of ApoA1. Further studies are needed to determine their causality and effects on AF.

We conducted a retrospective case-control study to investigate the potential relation of SUA levels to AF and the effects of sex on the association between SUA and AF. Moreover, we evaluated the associations between SUA and other clinical parameters in patients with AF. These findings may contribute to the understanding of the pathological process for AF. However, this study had several potential limitations. First, the small sample size was the largest limitation. Second, patients with persistent AF were not observed, and several asymptomatic patients with AF may have been ignored. Accordingly, results cannot be generalized to all patients with AF. Third, this was a single-center retrospective study, and we only investigated associations and not causalities. Fourth, markers of inflammation and oxidative stress were not included. Lastly, due to the retrospective nature of this study, there may still be potential confounding factors. Further prospective studies should focus on confirming our results and elucidating the specific associations between SUA levels and AF.

Conclusions

In conclusion, elevated SUA levels were associated with AF in the present study; however, the independent association was significant only in women. We also observed that elevated SUA levels were positively correlated with A/G and PAB and negatively correlated with APOA1. Nevertheless, there were no significant differences found between subtypes and complications of AF. The findings may be useful in understanding the pathological progress of AF and may contribute to its prevention.

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Statement

The funding bodies had no role in the research design, data collection, analysis, interpretation, manuscript writing, or submission.

Declaration of Figures’ Authenticity

We declare that all figures submitted are created by the authors, who confirm that these images are original with no duplication and have not been previously published in whole or in part.

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