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CORRELATION ANALYSIS OF SERUM FGF21 AND TSP2 LEVELS IN THE PROGNOSIS OF ELDERLY PATIENTS WITH CHRONIC HEART FAILURE

KORELACIONA ANALIZA SERUMSKIH NIVOA FGF21 I TSP2 U PROGNOZI KOD STARIJIH PACIJENATA SA HRONIČNOM SRČANOM INSUFICIJENCIJOM

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Summary

Background: Explore the connection between serum levels of fibroblast growth factor 21 (FGF21) and platelet response protein 2 (TSP2) and the prognosis of older people with chronic heart failure. Also, consider how useful it is to detect these two markers together for predicting clinical prognosis, providing a theoretical basis for risk stratification and personalised treatment of chronic heart failure.
Methods: A prospective cohort study design was adopted. Included were 210 senior patients (65 years of age or older) with chronic heart failure who were hospitalised in the cardiology department of a particular hospital. Based on the patients' serum levels of TSP2 and FGF21. Low FGF21 and low TSP2 groups, low FGF21 and high TSP2 groups, high FGF21 and low TSP2 groups, and high FGF21 and high TSP2 groups. Enzyme-linked immunosorbent assay (ELISA) was used to measure the patients' serum levels of FGF21 and TSP2. Major adverse cardiovascular events (MACE), such as worsening heart failure, myocardial infarction, stroke, and cardiovascular mortality, were documented over the two-year follow-up period for each patient. A receiver operating characteristic (ROC) curve was created to assess the predictive value, and the association between blood FGF21 and TSP2 levels and prognosis was examined using a Cox proportional hazards regression model.

Kratak sadržaj

Uvod: Cilj je bio da se ispita povezanost između serumskih nivoa fibroblastnog faktora rasta 21 (FGF21) i trombospondina 2 (TSP2) i prognoze kod starijih osoba sa hroničnom srčanom insuficijencijom. Takođe je procenjena klinička vrednost njihove kombinovane detekcije u predviđanju prognoze, kako bi se obezbedila teorijska osnova za stratifikaciju rizika i personalizovano lečenje hronične srčane insuficijencije.
Metode: Primenjen je prospektivni kohortni dizajn studije. Uključeno je 210 starijih pacijenata (≥65 godina) sa hroničnom srčanom insuficijencijom hospitalizovanih na kardiološkom odeljenju jedne bolnice. Na osnovu serumskih nivoa TSP2 i FGF21, pacijenti su podeljeni u četiri grupe: nizak FGF21 i nizak TSP2, nizak FGF21 i visok TSP2, visok FGF21 i nizak TSP2, te visok FGF21 i visok TSP2. Za određivanje serumskih nivoa FGF21 i TSP2 je korišćena metoda enzimski vezanog imunosorbentnog testa (ELISA). Tokom dvogodišnjeg perioda praćenja beleženi su veliki neželjeni kardiovaskularni događaji (MACE), uključujući pogoršanje srčane insuficijencije, infarkt miokarda, moždani udar i kardiovaskularni mortalitet. Za procenu prediktivne vrednosti je konstruisana ROC kriva, nakon što je povezanost između nivoa FGF21 i TSP2 u krvi i prognoze analizirana pomoću Cox-ovog proporcionalnog hazardnog regresionog modela.

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Results: Elderly patients with chronic heart failure had significantly higher serum levels of FGF21 and TSP2, which were positively linked with the NYHA cardiac function classification (P<0.05). The high FGF21 and high TSP2 groups had a considerably higher incidence of MACEs than the other three groups (P<0.05). Serum FGF21 and TSP2 levels were independent predictors of outcome in older individuals with chronic heart failure, as determined by multivariate Cox regression analysis (HR=2.38, 95% CI: 1.45–3.82, P<0.01; HR=1.91, 95% CI: 1.24–3.25, P<0.05). The area under the curve (AUC) for predicting the occurrence of MACEs by the combined detection of serum FGF21 and TSP2 was 0.86 (95% CI: 0.79–0.82), which was significantly better than that of single marker detection (P<0.05).
Conclusion: The prognosis and cardiac function status of elderly patients with chronic heart failure are strongly correlated with serum levels of FGF21 and TSP2. In addition to being a crucial biomarker for risk assessment and tailored care of older individuals with chronic heart failure, combined detection can improve the predictive value for adverse cardiovascular events in these patients.

Keywords: chronic heart failure, prognosis, cytokine-like domain-containing neurotrophic factor 2, thrombospondin 2

Rezultati: Stariji pacijenti sa hroničnom srčanom insuficijencijom su imali značajno više serumske nivoe FGF21 i TSP2, koji su bili pozitivno povezani sa NYHA klasifikacijom srčane funkcije (P<0,05). Grupa sa visokim FGF21 i visokim TSP2 je imala značajno veću incidenciju MACE u poređenju sa ostale tri grupe (P<0,05). Multivarijantna Cox regresiona analiza je pokazala da su serumski nivoi FGF21 i TSP2 nezavisni prediktori ishoda kod starijih osoba sa hroničnom srčanom insuficijencijom (HR=2,38, 95% CI: 1,45–3,82, P<0,01; HR=1,91, 95% CI: 1,24–3,25, P<0,05). Površina ispod ROC krive (AUC) za predikciju pojave MACE pri kombinovanoj detekciji FGF21 i TSP2 je iznosila 0,86 (95% CI: 0,79–0,82), što je bilo značajno bolje u odnosu na pojedinačne markere (P<0,05).
Zaključak: Prognoza i status srčane funkcije kod starijih pacijenata sa hroničnom srčanom insuficijencijom su snažno povezani sa serumskim nivoima FGF21 i TSP2. Kombinovana detekcija ovih biomarkera ne samo da predstavlja važan alat za procenu rizika i individualizovano lečenje, već i značajno unapređuje prediktivnu vrednost za nepovoljne kardiovaskularne događaje kod ovih pacijenata.

Ključne reči: hronična srčana insuficijencija, prognoza, neurotrofni faktor sa domenom sličnim citokinima 2, trombospondin 2

Introduction

Chronic heart failure (CHF) is a progressive clinical syndrome with high incidence and mortality worldwide, as it represents the terminal stage of various cardiovascular diseases (1). Ventricular remodelling is an important pathophysiological basis of CHF, further aggravating cardiac dysfunction and contributing to the increased mortality associated with CHF (2). Therefore, early prediction of ventricular remodelling and early adoption of treatment measures are crucial for delaying the progression of CHF and improving patient prognosis. Cytokine-like Domain-containing Neurotrophic Factor 2 (FGF21) is a secreted protein that can be induced by various stresses and plays important roles in cardiovascular and metabolic diseases (3). Studies have shown that FGF21 can affect the heart through autocrine/paracrine mechanisms, such as stimulating self-secreting FGF21 in the heart to prevent cardiac hypertrophy, infarction, and other cardiac damage in myocardial diseases (4). Thrombospondin 2 (TSP2) is a matrix protein that can interact with various ligands, such as extracellular matrix structural proteins, and is involved in the pathogenesis of cardiovascular diseases (5). Patients with type 2 diabetes and heart failure have higher serum TSP2 levels, and high levels of TSP2 are associated with early adverse left ventricular remodelling (6–8).

Therefore, in this study, the serum levels of FGF21 and TSP2 were measured in patients with CHF. Their relationships with ventricular remodelling, as well as their potential for early prediction of it, were explored to provide a reference for clinical treatment.

Materials and Methods

General information

The CHF group comprised 210 CHF patients admitted to our hospital between July 1, 2023, and July 1, 2025. Among them, 106 males and 104 females were included, with ages ranging from 60 to 76 (70.12±3.21) years.

At the same time, 200 healthy individuals whose ages and sex matched those of the CHF group were selected from our hospital as the control group. The Hospital's Ethics Committee gave its approval to this study [Research Approval: 2025-029].

Inclusion and exclusion criteria

Inclusion criteria: (1) met the diagnostic criteria for CHF and (2) provided informed consent from the patients and their families. Exclusion criteria: (1) acute myocardial infarction; (2) liver and kidney dysfunction or organic functional impairments such as heart and lungs; and (3) mental disorders.

Colour Doppler ultrasound examination

A Philips 7500 colour Doppler ultrasound imaging system equipped with a 4VC probe was used,

with a working frequency range of 1.7 to 3.5 MHz. Echocardiographic parameters, including left atrial diameter (LAD), left ventricular posterior wall thickness (LVPWT), and the left ventricular end-diastolic volume (LVEDV), were measured. After calculating the left ventricular mass index (LVMI), the CHF patients were split into two groups: one for ventricular remodelling (n=64) and another for nonventricular remodelling (n=146) (the normal value for females is 95 g/m^2, and for males is 115 g/m^2).

Measurement of serum FGF21 and TSP2 levels

Serum FGF21 and TSP2 levels were determined by enzyme-linked immunosorbent assay (ELISA). All patients had 5 millilitres of fasting venous blood collected within 24 hours after admission. The blood samples were collected using disposable vacuum blood collection tubes (manufacturer: BD Company, item number: 367820). The collected blood samples were left to stand at room temperature for 30 minutes, then centrifuged at 1000×g in a 4 °C centrifuge (model Eppendorf 5810R, manufacturer Eppendorf, Germany) for 20 minutes to separate the serum. The supernatant was immediately aliquoted into 0.5-millilitre sterile centrifuge tubes (manufacturer: Axygen Company, item number: PCR-2000-C), labelled with the patient's number and collection date, and stored at -80 °C in an ultra-low-temperature refrigerator (model: MDF-U53V, manufacturer: Sanyo Corporation of Japan) until the test.

Serum FGF21 levels were measured using the human FGF21 ELISA kit (item number: D711036-0096) from Shanghai Sangguo Biotechnology Co., Ltd., with a detection range of 15.6–1000 pg/ml and a sensitivity of 5 pg/mL. The serum TSP2 level was measured using the human TSP2 ELISA kit (RE1924H, Wuhan Rende Biotechnology Co., Ltd.), with a detection range of 31.2–2000 pg/mL and a sensitivity of 10 pg/mL. All ELISA experiments were carried out according to the instructions of the kits. The absorbance values were read at 450 nm using a Multiskan FC type microplate reader (manufacturer: United States Thermo Fisher Scientific Company, item number: 51119100).

Statistical methods

Software called SPSS 27.0 was used to do statistical analysis. A χ^2 test was performed on count data, which are expressed as frequencies and rates (cases (%) [n (%)]; an independent sample t test was performed on measurement data. The relationships between serum FGF21 and TSP2 levels and their associations with echocardiographic parameters were examined using Pearson correlation analysis. Using logistic regression, the variables affecting ventricular remodelling in CHF patients were examined, and receiver operating characteristic (ROC) curves were used to evaluate the predictive value of serum FGF21 and TSP2.

Results

Comparison of serum FGF21 and TSP2 levels between the CHF group and the control group

The CHF group's serum levels of TSP2 and FGF21 were considerably higher than those of the control group ($P<0.05$), see *Table I*.

Serum FGF21 and TSP2 levels were positively correlated with NYHA cardiac function classification, suggesting that these markers may reflect the severity of heart failure. The abnormal expression of FGF21 and TSP2 in patients with chronic heart failure may be involved in the pathological process of myocardial remodelling and decreased cardiac function.

Comparison of data between the ventricular remodelling group and the non-ventricular remodelling group

There were statistically significant differences ($P<0.05$) between the two groups for LAD, LVPWT, LVEDV, LVMI, FGF21, and TSP2, but no statistically significant differences ($P>0.05$) were found for age, sex, and CHF duration (see *Table II*).

Serum levels of FGF21 and TSP2 in patients with ventricular remodelling were significantly higher than in the non-ventricular remodelling group, suggesting that these two biomarkers may be closely

Table I Comparison of serum FGF21 and TSP2 levels between the CHF group and the control group ($\bar{x}\pm s$).

Group	n	FGF21 (pg/mL)	TSP2 (ng/mL)
Control group	200	100.33±13.74	9.21±3.16
CHF group	210	140.88±37.08	16.28±4.53
T value		10.296	12.818
P value		<0.001	<0.001

Table II Comparison of clinical data between L ventricular remodelling group and the non-ventricular remodelling group.

Group	n	Age (years, $\bar{x}\pm s$)	Gender [Cases (%)]		C H F course (months, $\bar{x}\pm s$)	LAD (mm, $\bar{x}\pm s$)	LVPWT (mm, $\bar{x}\pm s$)	LVEDV (mL, $\bar{x}\pm s$)	LVMI (g/m^2, $\bar{x}\pm s$)
			male	female					
Non-ventricular remodelling group	146	70.19± 3.16	70 (47.95)	76 (52.05)	16.99± 2.33	45.55± 4.21	50.95± 5.66	97.57± 10.22	105.95± 12.09
Ventricular remodelling group	64	70.21± 3.64	36 (56.25)	28 (43.75)	17.21± 2.81	48.76± 6.79	57.68± 7.28	112.61± 14.80	116.41± 13.57
χ^2/t value		0.175	0.617	0.609	2.931	5.154	6.026	3.970	
P value		0.866	0.436	0.549	0.007	<0.001	<0.001	<0.001	

Table III Correlation analysis between serum FGF21 and TSP2 and echocardiographic parameters in patients with ventricular remodelling.

Indicator	FGF21		TSP2	
	R value	P value	R value	P value
LAD	0.421	<0.001	0.459	<0.001
LVPWT	0.419	<0.001	0.462	<0.001
LVEDV	0.526	<0.001	0.500	<0.001
LVMI	0.477	<0.001	0.400	<0.001

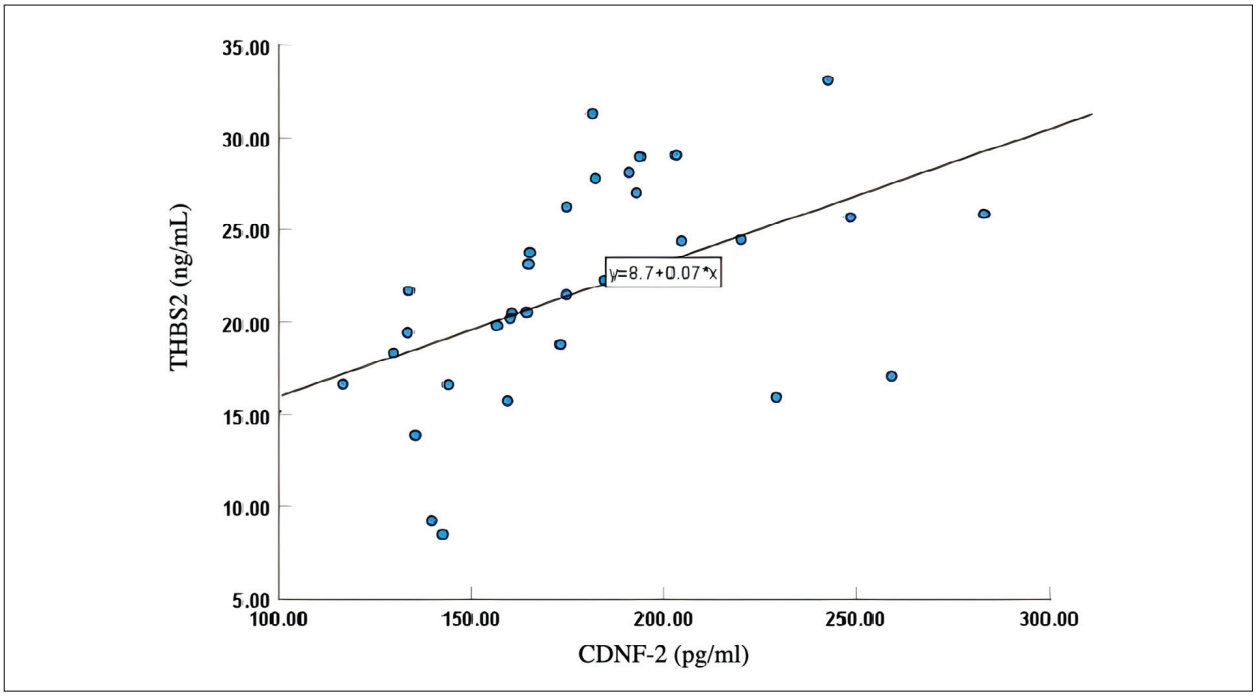

Figure 1 Correlation between serum FGF21 and TSP2 levels.

Table IV Multivariate logistic regression analysis of factors affecting ventricular remodelling in CHF patients.

Independent variable	β value	SE value	Wald x2 value	P value	OR value	95% CI
LAD	0.557	0.323	3.005	0.086	1.744	0.933~3.63
LVPWT	0.686	0.391	2.949	0.089	1.983	0.901~4.323
LVEDV	0.714	0.295	5.922	0.018	2.039	1.142~3.602
LVMI	0.635	0.342	3.270	0.073	1.884	0.942~3.721
FGF21	0.314	0.145	4.804	0.021	1.368	1.036~1.806
TSP2	0.487	0.197	6.219	0.016	1.625	1.102~2.375

Table V Predictive efficacy of serum FGF21 and TSP2 combined detection for ventricular remodelling in CHF patients.

Variable	AUC	Cutoff value	95% CI	Sensitivity (%)	Specificity (%)	Youden index
FGF21	0.826	155.07 pg/mL	0.730~0.894	75.03	80.85	0.551
TSP2	0.869	16.35 ng/mL	0.788~0.927	84.30	78.01	0.628
Unite	0.930	-	0.875~0.978	90.65	87.60	0.786

associated with the ventricular remodelling process. Ventricular remodelling, a key pathophysiological mechanism in the progression of chronic heart failure, involves extracellular matrix remodelling and inflammatory responses in the heart. FGF21 and TSP2, as important factors involved in these processes, can reflect the severity of ventricular remodelling.

Correlation analysis of serum FGF21 and TSP2 levels with echocardiographic parameters in patients with ventricular remodelling

Serum FGF21 and TSP2 levels were positively correlated with LAD, LVPWT, LVEDV, and LVMI ($P<0.05$; see *Table III*).

Serum FGF21 and TSP2 levels were positively correlated with echocardiographic parameters reflecting ventricular structure and function, suggesting that these markers may reflect the severity of ventricular remodelling. This correlation provides a new perspective on the molecular mechanism of ventricular remodelling in chronic heart failure. It offers potential serological indicators for assessing ventricular remodelling status and monitoring disease progression.

Correlation analysis of serum FGF21 and TSP2 levels in patients with ventricular remodelling

Serum FGF21 and TSP2 levels were positively correlated ($r=0.491$, $P<0.05$), see *Figure 1*.

Left ventricular remodelling is a crucial step in the progression of chronic heart failure. Its occurrence and development are accompanied by extracellular matrix remodelling in myocardial cells and by inflammatory responses. FGF21 and TSP2, as important factors involved in these processes, may reflect the severity of left ventricular remodelling through changes in their serum levels. The correlation between these two markers suggests they may have a synergistic effect during left ventricular remodelling.

Multivariate logistic regression analysis of the factors influencing ventricular remodelling in patients with CHF

To determine whether patients with CHF have ventricular remodelling as the dependent variable (yes = 1, no = 0), a logistic regression analysis was carried out using LAD, LVPWT, LVEDV, LVMI, FGF21, and TSP2 as independent variables. LVEDV, FGF21, and TSP2 were the factors influencing ventricular remodelling in patients with CHF ($P<0.05$; see *Table IV*).

Predictive efficacy of the combined detection of serum FGF21 and TSP2 for ventricular remodelling in patients with CHF

The results revealed that the area under the curve (AUC) values for predicting ventricular remodelling with serum FGF21 alone, TSP2 alone, and their combination were 0.826, 0.869, and 0.930, respectively. The combined prediction was superior to the individual predictions (Z combined - FGF21=2.909, $P=0.007$; Z combined -TSP2=2.194, $P=0.022$), as shown in *Table V*.

Discussion

In recent years, with the continuous advancement of medical technology, clinical research on the development of drugs for treating CHF and its related complications has achieved considerable success. For instance, sacubitril/valsartan, a neprilysin inhibitor and angiotensin receptor blocker, has a beneficial effect on ventricular remodelling and cardiac function in patients with CHF (9). Nevertheless, the overall efficacy of these drugs remains limited, and it is necessary to understand better other risk factors for CHF, which is crucial for developing novel CHF treatment approaches.

FGF21 is an endocrine regulatory factor that is synthesised and secreted mainly by the liver and adipose tissues. It plays a significant role in regulating glucose and lipid metabolism and related diseases (10). Previous studies (11) have shown that FGF21 treatment delays the onset of the first ventricular arrhythmia in mice with arrhythmia and reduces the duration of ventricular fibrillation. Consistent with these findings, in vitro studies also revealed that FGF21 can shorten the duration of action potential in cardiomyocytes treated with hydrogen peroxide. Changes in cardiac structure and electrophysiological properties resulting from ventricular remodelling are associated with the occurrence of ventricular arrhythmias (12). Other studies have reported that FGF21 activation can activate related signalling pathways (such as the SIRT1/PGC-1 /FGF21 signalling pathway), reduce oxidative stress, and promote autophagy in cardiomyocytes, thereby exerting protective effects on the hearts of patients with CHF (13). These findings indicate that FGF21 plays a positive role in CHF and is associated with ventricular remodelling. This study also revealed that FGF21 is highly expressed in the serum of CHF patients. Its level is significantly correlated with indicators of ventricular remodelling. These findings suggest that FGF21 is related to the occurrence of ventricular remodelling in CHF patients. The high expression level of FGF21 in the patient's serum may be a compensatory response to protect against ventricular remodelling. An evaluation of FGF21's ability to predict ventricular remodelling revealed that its AUC is 0.823, indicating that, in addition to being a possible target for CHF treatment, FGF21 can be utilised as a serum marker for the early prediction of ventricular remodelling in CHF patients.

TSP2 belongs to the platelet reaction protein family. It is widely distributed across several organs and tissues. It plays a role in a range of physiological and pathological processes, including inflammatory reactions, platelet aggregation, and cell migration and proliferation (14, 15). Studies have shown that TSP2 knockout mice have difficulty resisting increased cardiac load, leading to enhanced matrix metalloproteinase activity, disruption of myocardial cell matrix integrity, and triggering cardiomyopathy and cardiac rupture (16–18). Other studies have shown that TSP2-deficient mice are prone to senile dilated cardiomyopathy, which intensifies cardiac inflammation in myocarditis. Nonetheless, studies have shown that elevated TSP2 expression increases the likelihood of adverse cardiovascular events, and the mechanism may involve its role in cardiac remodelling and fibrosis, as well as its promotion of hypertension. The above studies show that the effects of TSP2 in cardiovascular diseases seem to contradict its mechanism of action. The results of this study are similar to those of previous studies. Patients with congestive heart failure (CHF) have significantly higher serum TSP2 levels, and this elevation correlates with ventricular remodelling (19). TSP2 activation may occur before CHF, and its high-level expression in the heart and circulation may represent an adaptive response to prevent the development of heart failure. In most patients with diagnosed cardiovascular disease, TSP2 has a compensatory protective effect against cardiac dysfunction, leading to increased serum TSP2 levels (20–22). Furthermore, serum TSP2 had 84.30% sensitivity and 78.01% specificity for predicting ventricular remodelling in CHF patients, suggesting that TSP2 is a potential biomarker for ventricular remodelling in these patients. Additionally, this study showed that there is a favourable correlation between the serum TSP2 level and the level of FGF21 in individuals with ventricular remodelling, and that the combined detection of the two can predict ventricular remodelling more accurately than either one alone, suggesting that they may jointly participate in the occurrence and development of CHF and ventricular remodelling through the same pathway, but the specific mechanism awaits further research.

However, this study has several limitations. The number of CHF patients with ventricular remodelling in this study was relatively small, which may have led to biased statistical results. There is a correlation between TSP2 and FGF21. The specific coordination mechanism between these processes in CHF and ventricular remodelling has not been fully studied. These deficiencies will be improved in the future to provide effective targets for clinical treatment.

Conclusion

Serum levels of TSP2 and FGF21 were significantly increased in CHF patients, and these changes were associated with ventricular remodelling. Moreover, the combination of these two indicators has greater clinical value for predicting ventricular

remodelling. It provides reliable biomarkers for CHF therapy and early clinical diagnosis.

Authors' contribution

Jiahao Chen and Wenwu Liu have made the same contribution to this work.

Ethical approval

This research has been approved by the Medical Research Ethics Committee of Suzhou Hospital of Traditional Chinese Medicine [No. 2025-029].

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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