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Correlation analysis of FT3/FT4 and frailty in elderly patients with coronary heart disease

Jiling Qu[1], Siqi Ji[2]*, Ting Zhou[3], Chuntao Wang[1], Yongbing Liu[2]*

[1]*Jiangsu Vocational College of Medical, Yancheng, Jiangsu, China*
[2]*School of Nursing and School of Public Health, Yangzhou University, Yangzhou City, Jiangsu Province, China*
[3]*Sir Run Run Hospital Nanjing Medical University, Nanjing city, Jiangsu Province, China*
**These authors are co-first authors with equal contributions.*

Abstract

Introduction: In previous studies on thyroid hormones and frailty, most of the target population were elderly, and there were relatively few studies on elderly patients with coronary heart disease (CHD). Inflammation, oxidative stress, and haemodynamic instability in cardiovascular disease (CVD) can influence fluctuations in thyroid hormone (TH) levels and increase the incidence of frailty. The purpose of the present study was to explore the effect of TH on the risk of frailty in elderly patients with CHD.

Material and methods: The Fried scale was used to assess the frailty of participants. The predictive value of TH for frailty was determined using the patient's operating characteristic curve. Multivariate logistic regression model was utilised to analyse the relationship between TH and frailty.

Results: A total of 277 elderly patients with CHD were included in the study, of whom 29.96% were in a state of frailty. Free triiodothyronine (FT3)/free thyroxine (FT4) predicted frailty with the largest area under the curve of 0.634. Unordered multinomial logistic regression analysis showed that a lower T3 level was a risk factor for pre-frailty ($p < 0.05$). Lower levels of T3, FT3, and FT3/FT4 were risk factors for frailty ($p < 0.05$) after adjusting for demographic variables and blood indexes.

Conclusion: The predictive value of FT3/FT4 for frailty was more accurate than that of a single index. Moreover, T3 ≤ 1.095 nmol/L, FT3 ≤ 4.085 pmol/L, and FT3/FT4 ≤ 0.336 were shown to be the influencing factors of frailty, while T3 ≤ 1.095 nmol/L is an independent risk factor pre-frailty. Clinicians should focus on timely identification of the risk of frailty in order to improve patient quality of life and to reduce the risk of complications. **(Endokrynol Pol 2024; 75 (5): 510–516)**

Key words: *coronary heart disease; frailty; thyroid hormone; FT3/FT4*

Introduction

Cardiovascular disease (CVD) is the leading cause of premature death worldwide, and it is expected to remain a global threat due to population expansion, ageing, and epidemiological changes [1]. Among CVDs, coronary heart disease (CHD) is the most common cause of death and morbidity and a major healthcare burden [2]. CHD, also known as coronary atherosclerotic heart disease, refers to a CVD caused by atherosclerosis of the coronary artery, which results in narrowing or obstruction of the coronary artery lumen or microvessels, followed by myocardial ischaemia and necrosis [3]. CVD is the most common cause of death in China. A recent report on CVD [4] shows that there are 11.39 million patients with CHD in China, and this trend is on the rise.

The functional status of CHD has a great impact on its treatment and prognosis, and frailty is the main manifestation of a decline in functional status [5]. Frailty is a nonspecific state in which older adults experience reduced physical reserves, increased vulnerability, and a reduction in the body's ability to resist stress [6]. One study [7] found that participants with CHD and frailty demonstrated an accelerated development of geriatric syndrome during a 6-year follow-up, suggesting that frailty is a risk factor for accelerating the development of adverse health outcomes in elderly CHD patients.

Hormone secretion is constantly changing over the life course, and the endocrine system has a clear role in regulating muscle growth, development, and metabolism. Endocrine and broader metabolic dysregulation is evident in skeletal muscle loss and frailty [8]. The tyroid is the body's largest endocrine gland. Thyroid follicular cells under the stimulus of thyroid-stimulating hormone (TSH) will release thyroxine (T4) and triiodothyronine (T3). Only a small amount of free thyroxine is active in its free form (FT3 and FT4) plays a role in circulation [9]. The FT3/FT4 ratio reflects the transformation process of FT4 to FT3 and can be used to evaluate the activity of deiodinase, which is considered a better representation of the thyroid function compared to FT3 and FT4.

Jiling Qu, Jiangsu Vocational College of Medical, Yancheng, Jiangsu, China, tel: 19551529059; e-mail: 1450868213@qq.com

There is growing evidence that frailty is characterised by a "metabolic signature" [9], in which thyroid hormone (TH) is a key regulator of metabolism. Therefore, it is important to clarify the relationship between TH and frailty.

In recent years, several studies have shown that thyroid hormones are associated with frailty. In the study of Bano et al. [10], 9640 elderly people were included for frailty assessment (average age 649 years); TSH, FT4, and thyroid peroxidase antibodies (TPOAbs) were measured, and the results showed that TSH and FT4 had U-shaped association with frailty, followed by follow-up (median follow-up time was 10.1 years, interquartile range was 57 to 108 years). Reassessment of frailty in 6416 participants revealed that FT4 levels were positively correlated with frailty at follow-up and change in frailty over time. Bertoli et al. [11] evaluated frailty and detected TSH, FT3, and FT4 in 112 patients, indicating that low FT3 levels were associated with increased risk of frailty, while TSH and FT4 were not associated with frailty. In the Bano study, thyroid function was assessed by measuring TSH, FT4, and thyroid peroxidase antibodies (TPOAbs), while Bertoli et al. chose to measure TSH, FT3, and FT4 in their study, but the results were completely different. Yangcheng [12] found that the decline of T3 was an independent risk factor for frailty in the elderly. Pasqualetti et al. [13] demonstrated a strong association between reduced FT3/FT4 ratio and frailty. Furthermore, even in patients with normal FT3 values, the FT3/FT4 ratio value became an independent marker of survival. Given the results of previous studies, in this study, relatively accurate results can be obtained by measuring T3, FT3, T4, FT4, TSH, and FT3/FT4 while guessing.

In previous studies on thyroid hormones and frailty, most of the target population were elderly [14], and there were relatively few studies on elderly patients with CHD. Inflammation, oxidative stress, and haemodynamic instability in CVD can influence fluctuations in TH levels and increase the incidence of frailty [15]. Therefore, it is necessary to understand the correlation between TH and frailty in patients with CHD, to provide a theoretical basis for preventing the occurrence and development of frailty.

The purpose of the present study was to investigate the prevalence of frailty in elderly patients with CHD, to observe the differences in TH levels according to frailty status, to explore the association between TH and frailty, and to provide new ideas for its prevention and treatment in elderly patients with CHD.

Material and methods

Study population

The convenience sampling method was used to select subjects for a cross-sectional survey at the cardiology ward of a hospital between August 2020 and May 2021. Participants were included if they were over 60 years old, had good communication skills, met the American Heart Association diagnostic criteria for coronary atherosclerotic heart disease, provided informed consent, and voluntarily participated in the study. Participants with acute or terminal stage of the disease, serious cardiopulmonary and renal insufficiency, hypothalamus, pituitary, and thyroid gland dysfunction, those taking medications that affect thyroid function, and those with a diagnosis of hypothyroidism or hyperthyroidism were excluded from the study.

General information questionnaire

The study used a self-made general data questionnaire, which included information regarding gender, age, body mass index (BMI), income level, living conditions, cultural degree, smoking status, alcohol consumption, family history, hypertension, diabetes, hyperlipidaemia, angina pectoris, acute coronary syndrome, heart failure, ventricular fibrillation, myocardial infarction, CVD, and multiple drug use. BMI was calculated using the following formula: BMI = weight (kg)/height (m)^2. Multiple medication use was evaluated with the following question: How many medications have you been taken at home for a long time in the last 3 months?

Peripheral blood parameters

The hospital's electronic medical records system was used to extract information about levels of white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, red blood cells, haemoglobin, platelet distribution width, albumin, alanine aminotransferase, glucose, creatinine, uric acid, cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. On the second day after admission, 6 ml of fasting peripheral venous blood was collected from all the enrolled patients, 4 ml of which was injected into the biochemical test tube, and the serum was separated. The levels of T3, T4, FT3, FT4, and TSH were detected by an automatic chemiluminescence immunoassay analyser provided by Beckman Coulter Trading Co., Ltd. The value of FT3/FT4 was calculated.

Frailty phenotype scale

The Fried frailty phenotype scale proposed by Fried et al. was used for frailty assessment [16]. The scale has 5 items: weight loss, fatigue, decline in grip strength, slow walking speed, and decreased physical activity. A score ≥ 3 points indicates frailty, a score of 1–2 points shows pre-frailty, and a score of zero points is assigned to no frailty.

Quality control

The research team consisted of one chief physician, one attending physician, 2 chief nurses, and 5 graduate students from the Department of Cardiology. Team members were trained uniformly before the survey and patients were evaluated using uniform assessment tools.

The inpatients filled out the questionnaire anonymously after signing the informed consent form. The survey was conducted through one-on-one and face-to-face interviews. The researchers checked the questionnaires once they were completed. If there were omissions or obvious errors, researchers helped the patients to correct them.

Statistical methods

SPSS (version 26.0, Chicago, U.S.) software was used for data input and analysis after the data were checked by 2 individuals.

The receiver operating characteristic curve (ROC) was used to analyse the predictive value of TH for frailty in elderly patients with CHD and its optimal cut-off value. TH values were divided into higher and lower groups according to the optimal truncation value.

The measurement data conforming to the normal distribution were expressed as mean ± standard deviation. The T test was used to compare the mean between the 2 groups, and analysis of variance was used to compare the mean between 3 or more groups. Median and quartile spacing [M (P_{25}, P_{75})] were used for measurement data that did not conform to the normal distribution, and nonparametric tests were used for comparison between groups. The statistical data were expressed via frequency and composition ratio, and the chi-square test was used to analyse differences between groups.
Frailty was considered to be the dependent variable, and unordered multinomial logistic regression analysis was used for multivariate analysis.
$p < 0.05$ was considered statistically significant.

Results

A total of 295 questionnaires were issued in the present study. A total of 277 valid questionnaires with an effective recovery of 93.90% were included in the analysis (excluding 18 invalid questionnaires) including 132 males (48.4%), 126 patients (45.5%) aged 70~79 years, and 84 patients (30.0%) with frailty. General demographic characteristics of elderly patients with CHD is shown in Supplementary Materials — Table S1. Thyroid hormone levels in elderly patients with CHD are shown in Supplementary Materials — Table S2.

Frailty in elderly patients with CHD

The median frailty score was 1 (0, 3), with 84 patients (30.32%) in a non-frailty state, 110 patients (39.71%) in a pre-frailty state, and 83 patients (29.96%) in a frailty state. The frailty scale for elderly patients with CHD is shown in Figure 1.

Optimal truncation of TH in frailty in elderly patients with CHD

Patients who met 3 or more frailty criteria were included in the frailty group, and the rest were considered to be in the non-frailty group. Frailty was considered to be the state variable, and the optimal critical values of T3, T4, TSH, FT3, FT4, and FT3/FT4 were determined using ROC curve analysis. The results showed that T3, FT3, FT4, and FT3/FT4 had statistical significance in predicting frailty ($p < 0.05$). The optimal truncation value for TH in frailty in elderly patients with CHD is shown in Table 1.

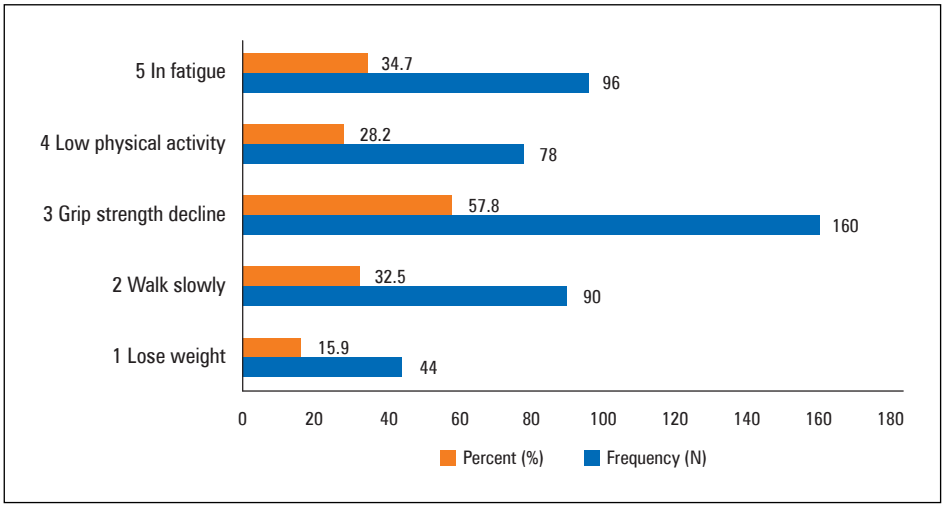

Figure 1. *Frailty scale for elderly patients with coronary heart disease (CHD)*

Table 1. *Optimal truncation value for thyroid hormones (TH) in frailty in elderly patients with coronary heart disease (CHD)*

Items	AUC	p	Youden index	Sensitivity	Specificity	Optimal truncation value
T3 [nmol/L]	0.612	0.003	0.210	0.494	0.716	1.095
T4 [nmol/L]	0.553	0.166	0.118	0.711	0.407	104.00
TSH [mIU/L]	0.559	0.122	0.167	0.373	0.794	3.115
FT3 [pmol/L]	0.577	0.042	0.176	0.434	0.742	4.085
FT4 [pmol/L]	0.601	0.008	0.181	0.578	0.603	11.855
FT3/FT4	0.634	< 0.001	0.230	0.446	0.784	0.336

AUC — area under the curve; T3 — triiodothyronine; T4 — thyroxine; TSH — thyroid-stimulating hormone; FT3 — free triiodothyronine; FT4 — free thyroxine

Univariate analysis of general data and frailty in elderly patients with CHD

The univariate analysis results for general data and frailty in elderly patients with CHD are shown in Supplementary Materials — Table S3.

Univariate analysis of blood parameters and frailty in elderly patients with CHD

Univariate analysis results for blood parameters and frailty in elderly patients with CHD are shown in Supplementary Materials — Table S4.

Univariate analysis of TH and frailty in elderly patients with CHD

The results showed that there were statistically significant frailty differences in elderly patients with CHD in T3, T4, TSH, FT3, FT4, and FT3/FT4 levels ($p < 0.05$). The univariate analysis of TH and frailty in elderly patients with CHD is shown in Table 2.

Unordered multinomial regression analysis of TH and frailty in elderly patients with CHD

Unordered multinomial logistic regression analysis was performed with frailty grade as the dependent variable and T3, T4, TSH FT3, FT4, and FT3/FT4 as independent variables. Age, BMI, education level, alcohol consumption, family history of CHD, diabetes, hyperlipidaemia, heart failure, multiple medication use, monocyte level, red blood cell level, haemoglobin level, red blood cell distribution width, albumin level, cholesterol level, triglyceride level, and low-density lipoprotein level were covariates. The results showed that T3 ≤ 1.095 nmol/L (odds ratio [OR] = 4.136, 95% confidence interval [CI] = 1.674~10.215, p = 0.002) was a risk factor for pre-frailty. T3 ≤ 1.095 nmol/L (OR = 4.328, 95% CI = 1.608~11.650, p = 0.004), FT3 ≤ 4.085 pmol/L (OR = 2.843, 95% CI = 1.100~7.350, p = 0.031), and FT3/FT4 ≤ 0.336 (OR = 2.984, 95% CI = 1.063~8.380, p = 0.038) were risk factors for frailty. Multivariate logistic regression analysis of TH and frailty in elderly patients with CHD is shown in Table 3.

Discussion

Frailty in hospitalised elderly patients with CHD

As the world's elderly population increases, so does the number of frail elderly people[16]. Frailty is an increasingly important concept in both clinical care and aging research. The incidence of frailty was 29.96% in the present study of 277 patients with CHD, which is consistent with the research by Ping et al. [17]. Previous studies have shown a short-term upward trajectory of frailty [18, 19]. Moreover, some measures can delay or even reverse this tendency [20]. This suggests that clinical workers should pay close attention to patients with frailty and actively take intervention measures to slow down the occurrence of frailty and improve patient quality of life.

In terms of the frailty indicators, the greatest effect was represented by 160 cases of decline in grip strength, accounting for 57.8% of the total number of patients, which was consistent with the results of previous studies [21]. The main reason for this observation may be related to the aging of the elderly, accompanied by a decline in muscle strength. Grip strength is one of the most direct and simple objective indicators that reflects the decline in muscle strength, which is the core factor of frailty [16]. A prior study showed that reduced

Table 2. ***Univariate analysis of thyroid hormones (TH) and frailty in elderly patients with coronary heart disease (CHD)***

Items	Classify	Number of cases (%)			X^2	p
		Non-frailty (n = 84)	Pre-frailty (n = 110)	Frailty (n = 83)		
T3	Lower	14 (14.6)	41 (42.7)	41 (42.7)	20.301	< 0.001
	Higher	70 (38.7)	69 (38.1)	42 (23.2)		
T4	Lower	42 (40.8)	37 (5.9)	24 (23.3)	8.929	0.012
	Higher	42 (24.1)	73 (42.0)	59 (33.9)		
TSH	Lower	66 (32.0)	88 (42.7)	52 (259.2)	8.587	0.014
	Higher	18 (25.4)	22 (31.0)	31 (43.7)		
FT3	Lower	19 (22.1)	31 (36.0)	36 (41.9)	9.100	0.011
	Higher	65 (34.0)	79 (41.4)	47 (24.6)		
FT4	Lower	59 (38.8)	58 (38.2)	35 (23.0)	13.623	0.001
	Higher	25 (20.0)	52 (41.6)	48 (38.4)		
FT3/FT4	Lower	12 (15.2)	30 (38.0)	37 (46.8)	18.932	< 0.001
	Higher	72 (36.4)	80 (40.4)	46 (23.2)		

T3 — triiodothyronine; T4 — thyroxine; TSH — thyroid-stimulating hormone; FT3 — free triiodothyronine; FT4 — free thyroxine

Table 3. *Multivariate logistic regression analysis of thyroid hormones (TH) and frailty in elderly patients with coronary heart disease (CHD)*

Items	Pre-frailty						Frailty					
	B	SE	Wald	P	OR	95% CI	B	SE	Wald	P	OR	95% CI
T3 ≤ 1.095 nmol/L	1.420	0.461	9.470	0.002	4.136	1.674～10.215	1.465	0.505	8.412	0.004	4.328	1.608～11.650
T4 ≤ 104.00 nmol/L	–0.426	0.377	1.282	0.257	0.653	0.312～1.366	–0.595	0.445	1.792	0.181	0.551	0.231～1.318
TSH ≤ 3.115 mIU/L	0.062	0.456	0.018	0.893	1.064	0.435～2.601	–0.817	0.491	2.774	0.096	0.442	0.169～1.155
FT3 ≤ 4.085 pmol/L	0.410	0.446	0.846	0.358	1.507	0.629～3.608	1.045	0.485	4.651	0.031	2.843	1.100～7.350
FT4 ≤ 11.855 pmol/L	–0.510	0.386	1.745	0.186	0.601	0.282～1.279	–0.673	0.452	2.218	0.136	0.510	0.210～1.237
FT3/FT4 ≤ 0.336	0.497	0.488	1.037	0.309	1.644	0.632～4.277	1.093	0.527	4.306	0.038	2.984	1.063～8.380

SE — standard error; OR — odds ratio; CI — confidence interval; T3 — triiodothyronine; T4 — thyroxine; TSH — thyroid-stimulating hormone; FT3 — free triiodothyronine; FT4 — free thyroxine

grip strength is an independent predictor of frailty [22]. Therefore, medical staff should pay attention to the grip strength test of the elderly patients to prevent frailty as soon as possible.

Relationship between TH and frailty in hospitalised elderly patients with CHD

As an important hormone, TH plays a significant role in muscle maintenance. T3 is an important factor regulating muscle function, and it is involved in muscle contraction, metabolism, myogenesis, and repair [8]. FT3 and FT4 are the main physiological components of TH, and most of FT3 is transformed by liver deiodinase and kidney FT4 [23]. A previous study [24] suggested that measuring FT3 values can help to identify frailty in elderly subjects. This may be due to many pre-existing factors, such as the nutritional status of a patient with fracture, sarcopaenia, disability, and comorbidities, which characterise and influence the pathogenesis of the condition and are closely related to FT3 values. On one hand, a reduction in FT3 level depends on the same factors that cause frailty, and frailty may in turn be worsened by a lower FT3 level. On the other hand, lower FT3 levels can lead to frailty development. In our study, logistic regression analysis showed that a lower T3 level is a risk factor for early frailty in elderly patients with CHD. Lower T3 and FT3 levels are independent risk factors for frailty in elderly patients with CHD.

A previous prospective study found a U-shaped association between TSH and FT4 at baseline and frailty index. TSH was not associated with frailty after 10.1 years of follow-up, and only patients with higher FT4 levels were more likely to experience frailty. The results suggest that using FT4 as a potential marker of deteriorating health may have some impact on predicting and preventing frailty [25]. When analysing only those with a normal thyroid function, FT4 was associated with fatigue and weight loss, and high FT4 levels were independent predictors of frailty in older men [26]. In addition, some studies have found no significant correlation between FT4 and frailty [27]. These findings may be inconsistent due to differences in study population, race, methodology, and disease status. The present study results showed that FT4 had a predictive value for frailty, although multivariate logistic regression analysis did not determine whether a lower FT4 level was an independent protective factor for pre-frailty and frailty.

The ROC curve analysis of this study found that FT3/FT4 had the largest area under the curve for frailty, and that the Youden index was the largest, indicating that FT3/FT4 had the highest predictive value for frailty. Logistic regression showed that a lower FT3/FT4 was an independent risk factor for frailty in elderly patients with CHD. This is consistent with the results of some previous studies [23]. The FT3/FT4 ratio could be an expression of 5 -deiodinase (D1) activity. Subjects with a relatively high FT3/FT4 ratio are probably able to preserve D1 activity. In these subjects a decline in serum T3 levels, observed during aging, could be balanced by a compensatory increase in D1 activity. This adaptive ability, aimed at maintaining an adequate local production of active T3, could allow preservation of thyroid hormones signalling [23].

Studies about the effect of TSH on frailty have been inconsistent. A lower TSH concentration was not found to be a protective factor for frailty in the present study, which is consistent with the results of several other studies [26, 28, 29]. Some prior studies have also found that high TSH concentrations are associated with frailty. Veronese et al. [9] found that a higher TSH concentration was associated with frailty in both men and women in a cross-sectional analysis, while a lower TSH concentration was associated with increased risk of frailty in a longitudinal analysis in women only. Higher TSH levels can increase triglyceride levels and lead to an increased incidence of CVD, which is a frailty-related disease [30].

There are some limitations to the study. First, this was a cross-sectional study that could only explain the association between TH and frailty in patients with CHD, but it could not prove causality. Second, the study had a small sample size and was conducted in a tertiary hospital in China, and the results may not be representative. A multi-centre, large-sample, longitudinal study should be carried out in the future to explore the causal relationship between TH and frailty. Third, this study did not explore the role of gender differences in the effects of TH on frailty. The prevalence of thyroid dysfunction and frailty varies between men and women and these differences need to be investigated.

Conclusion

There is a correlation between TH and frailty in elderly patients with CHD. The study results demonstrated that the predictive value of FT3/FT4 for frailty is more accurate than that of a single index. Moreover, T3 ≤ 1.095 nmol/L, FT3 ≤ 4.085 pmol/L, and FT3/FT4 ≤ 0.336 were shown to be the influencing factors of frailty, while T3 ≤ 1.095 nmol/L is an independent risk factor pre-frailty. The study provided more evidence of the influence of TH level on frailty, suggesting new ideas for the prevention and treatment of frailty in elderly patients with CHD.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethics statement

The present study was reviewed by the Ethics Committee of the School of Nursing of Yangzhou University (Ethics batch no. YZUHL20200012). In this study, informed consent and confidentiality principles were strictly observed. If the elderly patients with CHD agreed to participate in the study, they signed the informed consent form.

Author contributions

Y.B.-L. and J.L.-Q. designed and directed the project. J.L.-Q., S.Q.-J., T.-Z., C.T.-W., and Y.B.-L. collected and input the data. J.L.-Q. analysed the data. J.L.-Q. and S.Q.-J. drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that they have no conflict of interest.

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