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Incidence rate of postoperative cognitive dysfunction at different anesthetic depths and its correlation with serum levels of RAGE, NR2B, CREB, and NFL

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ABSTRACT

Background: Anesthetic depth may affect cognitive function, which is reflected by serum biomarker levels. We aimed to investigate the incidence rate of postoperative cognitive dysfunction (POCD) at different anesthetic depths and its correlations with levels of serum receptor for advanced glycation end product (RAGE), N-methyl-D-aspartate receptor 2B subunit (NR2B), cAMP response element-binding protein (CREB) and neurofilament light chain (NFL).

Methods: Elderly patients (n=273) undergoing general anesthesia from January 2022 to February 2024 were selected and assigned to a light anesthesia group [bispectral index (BIS): 60-70, n=98)], a moderate anesthesia group (BIS: 50-60, n=85) and a deep anesthesia group (BIS: 40-50, n=90). The serum levels of RAGE, NR2B, CREB and NFL were detected. Cognitive function was assessed by the Mini-mental State Examination to determine the occurrence of POCD. The correlations of POCD with RAGE, NR2B, CREB and NFL levels were explored by Spearman analysis. Their predictive efficiencies for POCD were evaluated using receiver operating characteristic curves.

Results: The levels of serum RAGE, NR2B, CREB and NFL had significant differences among groups, at each time point and at each interaction (p<0.05). At 7 d postoperatively, the CREB level rebounded in all groups, but it was still significantly lower in the deep anesthesia group than in the moderate and light anesthesia groups (p<0.05). The levels of serum RAGE, NR2B and NFL were positively correlated with the incidence rate of POCD (p<0.05), but the CREB level was negatively correlated with the rate (p<0.05). The areas under the curves (AUCs) of serum RAGE, NR2B, CREB and NFL for independently predicting POCD were 0.684, 0.807, 0.725 and 0.718, respectively (p<0.05), AUC of combination of the four biomarkers was 0.853 (p<0.05).

Conclusions: The levels of serum RAGE, NR2B, CREB and NFL are closely correlated with the incidence rate of POCD.

Keywords: cognitive dysfunction, depth, general anesthesia, incidence, serum biomarker

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a common postoperative syndrome mainly manifested as decline in memory, attention and information processing capability, and its incidence rate is especially high in elderly patients [1]. POCD not only affects the quality of life of patients but also may prolong the length of stay, increase medical costs, and lead to long-term cognitive impairment and even permanent cognitive dysfunction in severe cases [2]. Therefore, the prevention and treatment of POCD have become an important research field in anesthesiology and perioperative medicine. Anesthetic depth is considered an important factor affecting the incidence rate of POCD. Excessive anesthetic depth may raise the risk of POCD, while moderate control of anesthetic depth can help reduce the incidence of POCD [3]. However, the specific mechanism of different anesthetic depths influencing POCD remains unclear.

Growing evidence indicates that anesthetic depth may affect cognitive function, which is reflected by serum biomarker levels [4]. Receptor for advanced glycation end product (RAGE), N-methyl-D-aspartate receptor 2B subunit (NR2B), cAMP response element-binding

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protein (CREB) and neurofilament light chain (NFL) are cognitive function-associated biomarkers that have attracted much attention in recent years. RAGE is involved in inflammatory response and oxidative stress and is closely related to cognitive dysfunction [5]. NR2B is a subunit of the NMDA receptor, which is where the major excitatory neurotransmitter glutamate acts. It is implicated in learning and memory functions [6]. CREB is a transcription factor that plays a crucial role in neuroplasticity and memory formation [7]. NFL is a structural protein of neurons, and its elevated levels often indicate nerve damage [8]. The changes in these four biomarkers during anesthesia and surgery may have close relations to the incidence of POCD.

This study assessed the effect of different anesthetic depths on the incidence rate of POCD, and analyzed the correlations of POCD with levels of serum RAGE, NR2B, CREB and NFL, aiming to provide new ideas and basis for POCD prevention and anesthesia management.

METHODS

Subjects

This study was approved by the ethics committee of our hospital (approval No. YN2H202201005). Written informed consent was obtained from all enrolled patients after they were given detailed explanations regarding the three levels of anesthesia depth. Elderly patients (n=273) undergoing general anesthesia in our hospital from January 2022 to February 2024 were enrolled.

Inclusion criteria were as follows: 1) patients eligible for surgical treatment as confirmed by clinical evaluation, and 2) those suitable for general anesthesia, scheduled for elective surgery, and without preoperative cognitive dysfunction. Exclusion criteria were as follows: 1) patients diagnosed with cognitive dysfunction or mental illness preoperatively, 2) those with a history of nervous system diseases (stroke, Parkinson's disease, etc.), 3) those with serious complications (massive bleeding, cardiac arrest, etc.) intraoperatively, 4) those who failed to complete follow-up postoperatively or had incomplete data, 5) those who were using drugs that may affect cognitive function, or 6) those with preexisting conditions that may confound cognitive outcomes, such as active septic conditions, significant dysmetabolic imbalances, or a history of hypoxic encephalopathy.

These patients were assigned to a light anesthesia group [bispectral index (BIS): 60-70, n=98)], a moderate anesthesia group (BIS: 50-60, n=85) and a deep anesthesia group (BIS: 40-50, n=90) according to the anesthetic depth. The general data had no statistically significant differences among the three groups (p>0.05) (Table 1).

Anesthetic methods

First, all patients were deprived of food for 8 h and water for 6 h preoperatively. Midazolam 0.05 mg/kg was injected intravenously 30 min preoperatively for preoperative sedation. After the patient was sent to the operating room, vital signs such as ECG, pulse oxygen saturation (SpO2) and noninvasive blood pressure (NIBP) were routinely monitored, and the anesthetic depth was monitored using BIS. Propofol 2 mg/kg, remifentanil 0.3 μg/kg and cisatracurium 0.2 mg/kg were injected intravenously for anesthesia induction, followed by endotracheal intubation and mechanical ventilation using an anesthesia machine (respiratory rate: 12-16 bpm, tidal volume: 6-8 mL/kg) to maintain end-tidal carbon dioxide partial pressure (PaCO2) at 35-45 mmHg. Propofol and remifentanil were intravenously infused continuously for anesthesia maintenance via an infusion pump by target-controlled infusion, and their infusion concentrations were as follows: Propofol: 2.5-3.5 μg/mL in the light anesthesia group (BIS: 60-70), 3.5-4.5 μg/mL in the moderate anesthesia group (BIS: 50-60), and 4.5-5.5 μg/mL in the deep anesthesia group (BIS: 40-50). Remifentanil: 2-4 ng/mL in all groups. The infusion rates of propofol and remifentanil were adjusted intraoperatively according to the BIS, blood pressure and heart rate to maintain the target anesthetic depth and stable vital signs. During anesthesia maintenance, cisatracurium was supplemented according to the patient's condition to maintain adequate muscle relaxation.

Fifteen minutes before the end of the operation, the doses of propofol and remifentanil infusions were gradually reduced. Postoperatively, all anesthetic infusions were stopped, and 100% oxygen was given to increase the oxygen saturation and prevent hypoxia during the recovery phase. Mean arterial pressure (MAP) was main-

Table 1. General data (x ± s, n)

Anesthetic depth	Sex		Age (years)	Mean BMI (kg/m²)	ASA class (I/ II/ III)	Type of surgery (abdomen/ chest/ other)
	Male	Female				
Deep (n=90)	48	42	62.02 ± 4.84	23.51 ± 2.36	27/43/20	37/33/20
Moderate (n=85)	45	40	61.02 ± 4.91	23.50 ± 2.43	24/42/19	34/30/21
Light (n=98)	52	46	60.52 ± 5.21	23.53 ± 2.63	28/50/20	40/35/23
F/ Z/ χ^2	0.003		2.169	0.004	0.257	0.154
p value	0.999		0.116	0.996	0.992	0.997

tained within ±20% of baseline intraoperatively. Hypotension (decline in MAP ≥20%) was corrected by intravenous injection of 5-10 mg of ephedrine. Postoperatively, the patient was transferred to the recovery room and then returned to the general ward after fully waking.

Measurement of serum biomarkers

Fasting venous blood (5 mL) was drawn in the morning at three time points: one day before surgery, one day after surgery, and seven days after surgery. The blood was collected in an anticoagulant-free vacuum tube, left to stand at room temperature for 30 min, and centrifuged at 3000 rpm for 10 min. The serum separated was stored at a low temperature (-80°C) in enzyme-free EP tubes (Eppendorf, Germany) for testing. Then the levels of serum RAGE, NR2B, CREB and NFL were measured by enzyme-linked immunosorbent assay (ELISA) in strict accordance with the instructions of kits (Sangon Biotech, Shanghai). For RAGE: measuring range: 100-10000 pg/mL, limit of detection (LOD): 50 pg/mL, sensitivity: 20 pg/mL, intra-assay CV: ≤8%, and inter-assay CV: ≤10%. For NR2B: measuring range: 0.5-50 pg/mL, LOD: 0.2 pg/mL, sensitivity: 0.1 pg/mL, intra-assay CV: ≤6%, and inter-assay CV: ≤8%. For CREB: measuring range: 10-500 pg/mL, LOD: 3 pg/mL, sensitivity: 1 pg/mL, intra-assay CV: ≤5%, and inter-assay CV: ≤7%. For NFL: measuring range: 0.1-50 ng/mL, LOD: 0.05 ng/mL, sensitivity: 0.02 ng/mL, intra-assay CV: ≤10%, and inter-assay CV: ≤12%. The absorbance value (450 nm) was read using a microplate reader, and the standard curves were plotted, based on which the level of each biomarker was calculated. All measurements were performed by the same investigator to ensure the consistency and reliability of the results.

Assessment of cognitive function

The patients were assessed face-to-face by trained medical staff for cognitive function using the Mini-mental State Examination (MMSE) at 1 and 7 days postoperatively [9]. MMSE included 30 items covering orientation recognition, memory, attention and numeracy, recall, speech and visuospatial skills. The score ranged from 0 to 30 points, with lower scores indicating more severe cognitive dysfunction. The presence or absence of POCD was determined according to the change in the MMSE score at 7 days postoperatively (POCD: decline in the MMSE score ≥2 points at 7 days postoperatively vs. preoperatively).

Statistical analysis

All data were imported into SPSS 25.0 and MedCalc software for analysis. Measurement data were described by mean ± standard deviation (x ± s). Ranked data were compared by one-way analysis of variance among groups and by the q-test between two groups. Count data were compared by the χ^2 test. Continuous measurement data at different time points were compared between two groups by repeated measures analysis of variance (≥3 measurements). The correlations of POCD with levels of serum RAGE, NR2B, CREB and NFL were explored by Spearman analysis, and their predictive efficiencies for POCD were evaluated using receiver operating characteristic (ROC) curves. A value of $p<0.05$ was considered statistically significant.

RESULTS

MMSE scores and incidence rates of POCD

There was no significant difference in MMSE scores among the three groups preoperatively ($p>0.05$). At 7 d postoperatively, the MMSE score was the highest in the light anesthesia group, followed by the moderate anesthesia group and the deep anesthesia group ($p<0.05$).

The incidence rate of POCD was 47.78% (43/90) in the deep anesthesia group, 32.94% (28/85) in the moderate anesthesia group and 17.35% (17/98) in the light anesthesia group. It could be seen that the incidence rate of POCD in the deep anesthesia group was significantly higher than in the other two groups ($\chi^2=19.917$, $p<0.05$) (Table 2).

Levels of serum RAGE, NR2B, CREB and NFL

The levels of serum RAGE, NR2B, CREB and NFL had statistically significant differences among groups, at each time point and at each interaction ($p<0.05$). At 24h and 7 days postoperatively, the levels of serum RAGE, NR2B and NFL were the highest in the deep anesthesia group ($p<0.05$), followed by the moderate anesthesia group and light anesthesia group. At 24h postoperatively, the CREB level decreased in all groups, and it was significantly lower in the deep anesthesia group than in the moderate anesthesia group and the light anesthesia group ($p<0.05$). At 7 days postoperatively, the CREB level rebounded in all groups, but it was still significantly lower in the deep anesthesia group than in the moderate anesthesia group and the light anesthesia group ($p<0.05$) (Table 3 and Table 4).

Table 2. MMSE scores of patients [x ± s, n (%)]

Group	n	Preoperatively	7 days postoperatively	Incidence rate of POCD
Deep anesthesia	90	27.52±1.21	19.26±2.28	43 (47.78)
Moderate anesthesia	85	27.48±1.19	21.19±2.42*	28 (32.94)*
Light anesthesia	98	27.49±1.22	25.13±2.34*#	17 (17.35)*#
F/ χ^2		0.026	153.677	19.917
p value		0.974	<0.001	<0.001

Abbreviations: POCD- postoperative cognitive dysfunction. * $p<0.05$, comparisons of light and moderate anesthesia groups with deep anesthesia group; # $p<0.05$, comparisons between light and moderate anesthesia groups.

Table 3. Levels of serum RAGE and NR2B (x ± s)

Anesthetic depth	RAGE (pg/mL)			NR2B (pg/mL)		
	1 day preop.	24h postop.	7 days postop.	1 day preop.	24h postop.	7 days postop.
Deep (n=90)	123.16 ± 20.33	173.16 ± 42.50	143.20 ± 36.34	0.62 ± 0.23	1.22 ± 0.37	0.95 ± 0.11
Moderate (n=85)	124.21 ± 19.41	156.20 ± 36.43*	138.16 ± 21.50*	0.61 ± 0.19	0.96 ± 0.26*	0.76 ± 0.07*
Light (n=98)	123.64 ± 21.07	143.37 ± 28.21*#	126.20 ± 19.64*#	0.63 ± 0.20	0.84 ± 0.23*#	0.65 ± 0.06*#
Fintergroup/ Pintergroup		20.11 (p<0.001)			78.88 (p<0.001)	
Ftime/ Ptime		99.30 (p<0.001)			227.40 (p<0.001)	
Finteraction/ Pinteraction		6.76 (p<0.001)			21.89 (p<0.001)	

* p<0.05, comparisons of light and moderate anesthesia groups with deep anesthesia group; # p<0.05, comparisons between light and moderate anesthesia groups.

Table 4. Levels of serum CREB and NFL (x ± s)

Anesthetic depth	CREB (pg/mL)			NFL (ng/mL)		
	1 day preop.	24 h postop.	7 days postop.	1 day preop.	24 h postop.	7 days postop.
Deep (n=90)	118.50 ± 20.33	86.50 ± 16.45	97.15±15.24	2.52±0.53	5.72±1.66	3.92±1.46
Moderate (n=85)	120.14 ± 21.41	97.23 ± 18.63*	104.50±16.20*	2.46±0.47	4.51±1.43*	3.22±1.34*
Light (n=98)	121.20 ± 19.50	106.50 ± 20.10*#	116.50±18.62*#	2.43±0.51	3.62±1.37*#	2.82±1.22*#
Fintergroup/ Pintergroup		38.58 (p<0.001)			58.23 (p<0.001)	
Ftime/ Ptime		107.00 (p<0.001)			223.40 (p<0.001)	
Finteraction/ Pinteraction		6.52 (p=0.002)			16.23 (p=0.002)	

* p<0.05, comparisons of light and moderate anesthesia groups with deep anesthesia group; # p<0.05, comparisons between light and moderate anesthesia groups.

Correlations of POCD with serum levels of RAGE, NR2B, CREB and NFL levels

The results of Spearman correlation analysis revealed that the incidence of POCD displayed positive correlations with the levels of serum RAGE, NR2B and NFL (p<0.05), but a negative relation to the CREB level (p<0.05) (Table 5).

Table 5. POCD correlation with serum biomarkers

Serum biomarker	Correlation with POCD	
	r	p value
RAGE	0.325	<0.001
NR2B	0.364	<0.001
CREB	-0.426	<0.001
NFL	0.433	<0.001

ROC curve analysis for predicting POCD

With the presence or absence of POCD as a dependent variable (Presence=1, Absence=0), ROC curve analyses were carried out. It was found that the AUCs of serum RAGE, NR2B, CREB, and NFL for independently predicting POCD were 0.684, 0.807, 0.725, and 0.718, respectively (p<0.05 for all), and the AUC of the combination of the four biomarkers was 0.853, with sensitivity of 81.11% and specificity of 79.78% (p<0.05) (Table 6 and Figure 1).

DISCUSSION

As the BIS monitoring technology develops, accurate management of anesthetic depth has become possible [10]. BIS can be used to monitor the level of consciousness of patients in real-time by analyzing the spectrum of brain waves, providing an objective basis for individualized regulation of anesthetic depth [11]. BIS values range from 0 to 100, with lower values indicating deeper anesthesia. BIS values are usually controlled at 40-60 to maintain general anesthesia and reduce the incidence rate of intraoperative awareness [12]. However, the association between anesthetic depth and incidence rate of POCD remains unclear, especially that between serum biomarkers and POCD at different anesthetic depths.

In this study, cognitive function and incidence rate of POCD were compared among patients with different BIS values (light/moderate/deep anesthesia). The incidence rate of POCD may be related to many factors, including the anesthetic depth, the degree of central nervous system depression, and the inflammatory response and neuronal damage induced by surgery [13]. In addition, cultural differences, educational background, and

Table 6. Results of ROC curve analysis on serum RAGE, NR2B, CREB, and NFL for predicting POCD

Biomarker	AUC	SE	*p* value	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)
RAGE (pg/mL)	0.684	0.036	<0.001	0.625-0.738	8.69	38.90	93.40
NR2B (ng/mL)	0.807	0.038	<0.001	0.755-0.852	30.15	71.11	92.90
CREB (pg/mL)	0.725	0.031	<0.001	0.668-0.777	0.88	92.22	44.26
NFL (ng/mL)	0.718	0.033	<0.001	0.660-0.770	3.95	54.44	79.78
Combination	0.853	0.028	<0.001	0.805-0.893	-	81.11	79.78

emotional states all significantly affect cognitive performance [14]. In this study, the incidence rate of POCD was 47.78% in the deep anesthesia group, 32.94% in the moderate anesthesia group and 17.35% in the light anesthesia group. It could be seen that the incidence rate of POCD was significantly higher in the deep anesthesia group than in the other two groups, suggesting that too deep anesthesia may cause greater central nervous system depression and increase the risk of POCD, consistent with some previous findings [15].

The changes in levels of serum RAGE, NR2B, CREB and NFL were different in each group at 1 d preoperatively, and 24 h and 7 d postoperatively. At 24 h postoperatively, the levels of serum RAGE, NR2B and NFL increased in all groups, and they were significantly higher in the deep anesthesia group than in the moderate anesthesia group and the light anesthesia group, which may be attributed to acute stress, inflammatory response and neuronal damage induced by surgery and anesthesia. At 7 d postoperatively, the levels of serum RAGE, NR2B and NFL dropped but were still higher than those preoperatively. The elevation of RAGE, as a marker of inflammation and oxidative stress, is closely related to neuroinflammation and cognitive dysfunction [16,17]. Zhou et al. reported that RAGE played a crucial role in the acute inflammatory process of POCD, and blocking RAGE alleviated neuroinflammation and POCD [18]. Besides, NR2B is a key player in learning and memory, and its elevation may lead to neuronal excitotoxicity, thus impairing cognitive function [19]. The review of Guan et al. explored the influence of anesthetic administration, aging, pain, perioperative injury, and inflammation on NR2B-related pathophysiology of POCD [20]. Moreover, NFL is a sensitive biomarker of neuronal damage, and its elevation indicates neuronal structural damage [21]. Wiberg et al. found that only NFL measured at discharge was predictive of POCD [22]. In addition, the results of this study revealed that at 24 h postoperatively, the CREB level significantly decreased in the deep anesthesia group, followed by the moderate anesthesia group and the light anesthesia group. At 7 d postoperatively, the CREB level rebounded in all groups but did not reach the preoperative level, and it was still significantly lower in the deep anesthesia group. Decline in CREB, as a key factor involved in memory formation and neuroplasticity, indicates possible neuronal depression due to anesthesia, promoting the incidence of POCD [16]. Wang et al. reported that surgery reduced GDNF by suppressing

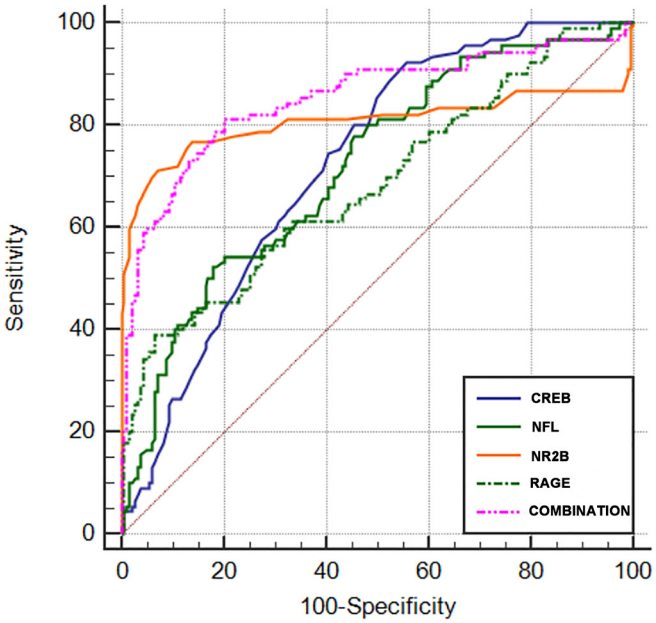

Figure 1. POCD prediction by serum biomarkers.

ERK-CREB signaling, which promoted the development of POCD [23]. Deep anesthesia not only causes acute inflammatory responses and nerve damage but also leads to long-term inhibition of neuroplasticity and cognitive function-related factors, contributing to the incidence of POCD [24,25]. In this study, the levels of serum RAGE, NR2B and NFL were positively correlated with the incidence of POCD. In contrast, the CREB level was negatively correlated with the incidence of POCD. The above results further verify the inhibitory and injurious effects of deep anesthesia on the nervous system. In contrast, a previous meta-analysis concluded that there was no significant correlation between the depth of anesthesia and POCD. The difference from our findings may be attributed to the study design, sample size, and control of confounding variables [26].

Moreover, ROC curve analyses showed that the AUCs of serum RAGE, NR2B, CREB and NFL for independently predicting POCD were 0.684, 0.807, 0.725 and 0.718, respectively, and the AUC of the combination of the four biomarkers was 0.853. It can be inferred that different pathological mechanisms of biomarkers may be implicated in the incidence of POCD, and combined detection can improve the predictive accuracy of POCD. Therefore, monitoring the postoperative changes in these biomarkers combined with the regulation of BIS values enables better prediction and prevention of POCD.

Nevertheless, this study is limited. The sample size is relatively small. Additionally, the assessment time of cognitive function is only 7 days. Hence, we will increase the sample size and extend the evaluation time in future studies. Moreover, we do not assess additional intraoperative factors that may influence POCD, such as variations in blood pressure, hemoglobin levels, and metabolic imbalances. Future studies should consider incorporating these cofactors into analysis to clarify their roles in POCD development and improve the accuracy of predictions regarding cognitive outcomes following surgery. Furthermore, only a small part of anesthetics are tested, so our findings need to be confirmed by evaluating the influence of other commonly used anesthetics.

CONCLUSIONS

In conclusion, different anesthetic depths have a significant influence on the incidence of POCD in elderly patients, and deep anesthesia may increase the risk of POCD. The incidence of POCD is closely correlated with the levels of serum RAGE, NR2B, CREB and NFL, and combined detection of these biomarkers has stronger predictive ability. Given the increased vulnerability of elderly patients to POCD, reasonable regulation of anesthetic depth and monitoring of relevant serum markers can help reduce the risk of POCD and guide safer anesthetic management in this population.

ABBREVIATIONS

AUC – area under the curve

BIS – bispectral index

BMI- body mass index

CREB – cAMP response element-binding protein

ELISA – enzyme-linked immunosorbent assay

MAP – mean arterial pressure

MMSE – Mini-mental State Examination

NFL – neurofilament light chain

NIBP – noninvasive blood pressure

NR2B – N-methyl-D-aspartate receptor 2B subunit

POCD – postoperative cognitive dysfunction

RAGE – receptor for advanced glycation end product

AUTHORS' CONTRIBUTION

XY – methodology

XL – conceptualization, supervision

QC – investigation, formal analysis

WZ – writing

CONFLICT OF INTEREST

None to declare.

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