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Value of C-reactive protein/albumin ratio in predicting the development of preoperative oxygenation impairment in patients with Stanford type-B acute aortic dissection

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ABSTRACT

Objectives: We aimed to assess the predicting value of C-reactive protein (CRP)/albumin ratio (CAR) in the development of Oxygenation impairment (OI) in the patients with Stanford type-B acute aortic dissection (AAD).
Methods: This study included 133 patients (age = 58.8 ± 12.0 years, median age = 61 years, Male/Female = 117/16) diagnosed as Stanford type-B AAD accompanied by hypertension from July 2012 to May 2020. Clinical data were retrospectively extracted from the database. The patients in this study were divided into OI group (oxygenation index ≤ 200) and non-OI group (oxygenation index > 200). Clinical characteristics in both groups were compared, and predicting value of CAR in the development of OI was assessed.
Results: Patients in OI group had higher peak body temperature (37.94 ± 0.62 vs. 37.67 ± 0.51 ℃, P =.010), higher levels of serum CRP (41.74 ± 27.71 vs 15.21 ± 19.66 mg/L, P =.000) and plasma B-type natriuretic peptide (292.14 ± 251.11 vs 179.80 ± 241.27 ng/L, P =.016), lower levels of albumin (34.00 ± 5.14 vs 37.72 ± 5.24 g/L, P =.000), and higher CAR (1.27 ± 0.89 vs 0.41 ± 0.53, P =.000). In multivariate regression analysis, CAR (odds ratio: 5.215, 95 % CI: 2.682; 10.137, P =.000) and the peak body temperature (odds ratio: 2.905, 95 % CI: 1.255; 6.724, P =.013) could significantly predict the OI development. The AUC for CAR was 0.831 (95 % CI: 0.756–0.907). An optimal cutoff value for CAR for predicting OI was ≥ 0.70, with a sensitivity of 67.5 % and a specificity of 88.2 %.
Conclusions: Compared with CRP or albumin alone, the CAR might be a more accurate marker in predicting OI development in Stanford type-B AAD.

1. Introduction

Acute aortic dissection (AAD) is a life-threatening cardiovascular disease with a reported incidence of 15 cases per 100,000 per year.[1] It can cause several organs dysfunctions or even failures. Oxygenation impairment (OI) is frequently occurred in the patients with AAD due to pulmonary dysfunction, manifesting with low oxygenation index (PaO2/fraction of inspired oxygen ratio ≤ 200) indicated by blood gas analysis. The incidence was reported to be up to more than a half.[2,3] The development of OI may cause several adverse outcomes[4]: (1) The patients with OI frequently necessitate mechanical ventilation, resulting in ventilator-associated pneumonia and ventilator-associated lung injury; (2) It may cause surgery delay, leading to increasing risk for higher morbidity and mortality; (3) Some patients may refuse surgery worrying about the high risks caused by operation. We think that surgical intervention before the occurrence of OI should be necessary and effective. Hence, identification prior to the occurrence of OI in the patients who may be at risk for OI development is useful.

OI development is considered to be associated with systemic inflammatory reactions after aortic injury. [5–7] Several studies have been conducted to investigate the predictors for the development of OI in the patients with AAD. C-reactive protein (CRP) has been proposed as a valuable marker in predicting the occurrence of OI in Stanford type-B AAD.[3,5–7] Elevated peak levels of CRP and white blood cell count were indicated to be associated with the occurrence of OI in the patients with Stanford type-B AAD.[3,5–7] The levels of serum albumin may decrease in inflammatory states and many critically ill patients.[8] Recent studies showed that CRP/albumin ratio (CAR) might better

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reflect infection and inflammatory responses.[9–11] Although association between CAR and several cardiovascular clinical settings has been investigated[12–14], the value of CAR in predicting the development of OI in the patients with AAD has not been evaluated.

In this present study, we aim to assess the value of CAR in predicting the development of OI in the patients with AAD.

2. Methods

The study was approved by the medical ethics committee of the first affiliated hospital of Chongqing Medical University. All data were retrospectively collected from database, so written informed consent was not required. There is no financial support received for this study, and no conflicts of interest are declared.

2.1. Patients

At the first affiliated hospital of Chongqing Medical University (Chongqing, China), from July 2012 to May 2020, a total of 163 patients were diagnosed with AAD accompanied by hypertension. The age of the enrolled patients was 59.0 ± 11.7 years (range:55–74 years, median = 60 years). The patients consisted of 144 males (88.3 %) and 19 females (11.7 %). This study only investigated AAD in hypertensive patients and excluded other possible causes of AAD, such as: bicuspid aortic valve disease, Marfan syndrome, Turner syndrome and traumatic AAD, etc. We excluded the patients as below: (1) admission to hospital more than 24 h after the onset of symptoms ($n = 14$); (2) inadequate clinical records ($n = 1$); (3) patients receiving emergent operations ($n = 12$); (5) acute exacerbation of chronic obstructive pulmonary disease ($n = 1$), pneumonia ($n = 1$), and moderate to large pleural effusion ($n = 1$). After applying these exclusion criteria, a total of 133 patients were included in this present study. The age of the patients was 58.8 ± 12.0 years ranged from 54 to 74 years (median = 61 years). The patients consisted of 117 males (88.0 %) and 16 females (12.0 %).

2.2. Study protocols

Data regarding the patients' backgrounds, vital signs and laboratory findings were retrospectively extracted from the database. The patients' backgrounds included their gender, age, body mass index, current smoking and drinking habits, and elapsed time from onset of symptoms to hospital admission. Vital signs included body temperature, respiratory frequency, heart rate, blood pressure on arrival. Blood samples were obtained on admission and the following data were collected: platelet count, white blood cell count, neutrophil percentage, serum CRP, procalcitonin, D-dimer, albumin, serum creatinine, creatine kinase-muscle/brain, troponin, plasma B-type natriuretic peptide (BNP), and glucose. CRP and albumin were measured using an automatic biochemical analyzer (Modular DDP, Roche, Switzerland). The CAR was calculated by dividing the serum CRP level by the albumin level. The arterial oxygen tension (PaO2) was measured using an automatic blood gas analyzer system (5700, Instrumentation Laboratory, MA, USA). The oxygenation index was calculated, and OI was defined as oxygenation index ≤ 200 during monitoring and management in hospital. The patients in this study were divided into two groups: those with (OI group) and those without (non-OI group). Clinical variables were compared between the two groups, and the clinical variables especially CAR in predicting the development of OI were investigated.

2.3. Statistical analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables were expressed as percentage. Continuous variables were compared using Student *t* test. Categorical variables were compared using the chi-square test. Univariate and multivariate binary logistic regression analysis were performed to determine the independent predictors of OI. The receiver operating characteristics (ROC) curve analysis was performed to determine the cutoff value of CAR in prediction of OI. To rule out the possibility that CAR was confounded by other factors, the univariate and multivariate linear regression analysis were performed. The baseline variables for which a *P* value < 0.10 was found by univariate analysis were included in the multivariate analysis. Two-tailed *P* value < 0.05 was considered to be statistically significant. All statistical analysis was performed using the SPSS 21.0 software for windows (SPSS, Chicago, IL, USA).

3. Results

3.1. The demographic characteristics and clinical findings

The demographic characteristics and clinical findings of the patients

Table 1
Baseline demographic characteristics, clinical features, and laboratory results of the patients.

Variables	Total ($n = 133$)	OI group ($n = 40$)	Non-OI group ($n = 93$)	*P*
Age (years)	58.8 ± 12.0	57.1 ± 12.3	59.60 ± 11.9	0.283
Gender (male/female)	117/16	36/4	81/12	0.776
BMI	25.19 ± 2.97	25.68 ± 3.81	24.98 ± 2.53	0.293
Elapsed time after onset (hours)	10.17 ± 7.11	10.1 ± 6.0	10.2 ± 7.6	0.917
Current smoker	63.91 % (85)	65.00 % (26)	63.44 % (59)	0.864
Alcohol drinking	44.36 % (59)	50.00 % (20)	41.94 % (39)	0.634
Ta (℃)	36.56 ± 0.29	36.61 ± 0.29	36.54 ± 0.28	0.163
Tp (℃)	37.75 ± 0.56	37.94 ± 0.62	37.67 ± 0.51	0.010
The timing of Tp (days)	3.1 ± 1.5	3.4 ± 1.3	3.0 ± 1.6	0.163
Heart rate (beats per minute)	83.5 ± 16.1	87.0 ± 17.9	82.0 ± 15.1	0.101
Respiratory rate (breaths per minute)	20.0 ± 2.1	20.3 ± 2.2	19.9 ± 3.4	0.477
Systolic blood pressure (mmHg)	162.3 ± 28.6	168.8 ± 31.1	159.4 ± 29.2	0.082
Diastolic blood pressure (mmHg)	93.6 ± 17.6	97.2 ± 17.3	92.1 ± 17.6	0.121
Platelet count ($\times 10^9$/L)	170.1 ± 71.9	177.3 ± 66.6	167.0 ± 74.1	0.450
White blood cell count ($\times 10^9$/L)	12.14 ± 3.72	12.36 ± 4.00	12.04 ± 3.61	0.651
Neutrophil percentage (%)	85.28 ± 7.86	86.04 ± 7.58	84.95 ± 8.00	0.469
CRP (mg/L)	23.19 ± 25.40	41.74 ± 27.71	15.21 ± 19.66	0.000
Procalcitonin (ug/L)	0.50 ± 2.27	1.14 ± 4.06	0.22 ± 0.42	0.157
D-dimer (mg/L)	7.74 ± 11.63	7.99 ± 11.75	7.64 ± 11.64	0.875
Albumin (g/L)	36.60 ± 5.47	34.00 ± 5.14	37.72 ± 5.24	0.000
CRP/albumin	0.67 ± 0.77	1.27 ± 0.89	0.41 ± 0.53	0.000
Serum creatinine (umol/L)	89.05 ± 42.50	99.22 ± 53.08	84.67 ± 35.51	0.120
CK-MB (ug/L)	2.46 ± 6.22	2.97 ± 6.75	2.24 ± 6.00	0.537
Troponin (ug/L)	0.026 ± 0.10	0.020 ± 0.020	0.030 ± 0.12	0.687
BNP (ng/L)	213.58 ± 248.75	292.14 ± 251.11	179.80 ± 241.27	0.016
Serum glucose (mmol/L)	6.91 ± 2.12	6.90 ± 2.28	6.92 ± 2.06	0.959

Abbreviations: OI, oxygenation impairment; BMI, body mass index; Ta, body temperature on admission; Tp, the peak body temperature; CRP, C-reactive protein; CK-MB, creatine kinase-muscle/brain; BNP, B-type natriuretic peptide.

are summarized in Table 1. OI occurred in 40 (30.1 %) patients on hospital day 2.4 ± 1.4 on average. Twelve patients (38.6 %) in OI group necessitated mechanical ventilation, including 8 (20.0 %) patients with invasive mechanical ventilator and 4 (10.0 %) patients with non-invasive mechanical ventilator. No patients were prescribed with non-steroidal anti-inflammatory drugs or corticosteroids before or after admission.

3.2. Comparison of clinical characteristics between the two groups

Patients in OI group had higher peak body temperature than that in non-OI group (37.94 ± 0.62 vs. 37.67 ± 0.51 ℃, P =.010). In OI group, patients had higher levels of serum CRP (41.74 ± 27.71 vs 15.21 ± 19.66 mg/L, P =.000) and plasma BNP (292.14 ± 251.11 vs 179.80 ± 241.27 ng/L, P =.016). While albumin levels in OI group were significantly lower (34.00 ± 5.14 vs 37.72 ± 5.24 g/L, P =.000). The CAR in OI group was significantly higher than that in non-OI group (1.27 ± 0.89 vs 0.41 ± 0.53, P =.000). There were no significant differences in terms of other clinical characteristics between the two groups.

3.3. Regression analysis of clinical variables for OI development

Univariate regression analysis showed that the CAR (odds ratio: 6.815, 95 % CI: 3.069; 15.130, P =.000), peak body temperature (odds ratio: 4.005, 95 % CI: 1.418; 11.311, P =.009), procalcitonin (odds ratio: 1.665, 95 % CI: 0.928;2.950, P =.088) and BNP (odds ratio: 1.002, 95 % CI: 1.000;1.003, P =.026) were predictors for OI development (Table 2). In multivariate binary logistic regression analysis, CAR significantly predicted the OI development (odds ratio: 5.215, 95 % CI: 2.682; 10.137, P =.000). In addition, the peak body temperature was also found to be an independent predictor of OI development (odds ratio: 2.905, 95 % CI: 1.255; 6.724, P =.013).

In ROC curve analysis (Fig. 1), the CAR showed a similar curve with CRP. The AUC for CAR was 0.831 (95 % CI: 0.756–0.907), and the AUC for CRP was 0.825 (95 % CI: 0.748–0.902). Besides, the AUC for the peak body temperature was 0.630 (95 % CI: 0.524–0.737), and the AUC for albumin was 0.310 (95 % CI: 0.213–0.407). An optimal cutoff value for CAR for predicting OI was ≥ 0.70, with a sensitivity of 67.5 % and a specificity of 88.2 %.

3.4. Regression analysis of clinical variables for CAR

Univariate and multivariate linear regression analysis indicated that CAR was only determined by CRP (Coefficient = 0.029, t = 58.810, P =.000. 95 % CI: 0.028, 0.030) and albumin (Coefficient= - 0.022, t = -9.617, P =.000,95 %CI: −0.026, −0.017) (Table 3). The other clinical variables had no significant impact on CAR in this study.

Table 2
Independent predictors for OI development in univariate and multivariate binary logistic regression analysis.

Variables	Univariate OR, 95 CI %	*P*	Multivariate OR, 95 CI %	*P*
CRP/albumin ratio	6.815 (3.069–15.130)	0.000	5.215 (2.682–10.137)	0.000
The peak body temperature	4.005 (1.418–11.311)	0.009	2.905 (1.255–6.724)	0.013
Procalcitonin	1.655 (0.928–2.950)	0.088	1.236 (0.791–1.931)	0.353
BNP	1.002 (1.000–1.003)	0.026	1.002 (1.000–1.004)	0.056

Abbreviations: OI, oxygenation impairment; CRP, C-reactive protein; BNP, brain natriuretic peptide. CI, confidence interval; OR, odds ratio.

4. Discussion

In our study, a total of 40 patients (30.1 %) developed OI on hospital day 2.4 ± 1.4 on average, and 12 patients (38.6 %) in OI group necessitated mechanical ventilation. The high incidence of OI in the patients with AAD and risks with use of mechanical ventilation highlight the importance to predict this severe respiratory condition prior to the occurrence of OI. Our present study indicated that the CAR and the peak body temperature were independent predictors for OI development in the patients with AAD, and the CAR was a more accurate marker in predicting OI development compared with CRP or albumin alone.

It is considered that inflammation plays a great role in the pathogenesis of aortic dissection[15,16]. A great amount of cytokines and inflammatory cells were observed in the aortic wall of the patients with aortic dissection, and it was suggested that the imbalance between pro-inflammatory and anti-inflammatory system could contribute to aortic dissection.[16] Macrophages could secrete some pro-inflammatory substances, such as TNFα, IL-6, MCP-1 and IL-10, so macrophages were considered to be most closely related to aortic dissection among the numerous inflammatory cells.[15,16] When aortic dissection develops, the chronic inflammation in the aortic wall will rapidly develop to acute inflammatory reactions, especially around the site of aortic dissection, and some patients may worsen to develop systemic inflammatory reaction syndrome (SIRS) due to the uncontrolled inflammatory cascade.[17] In addition, impaired multiple organ perfusion in AAD can further aggravate SIRS apart from the effect of dissection in itself of the aortic wall.[18] Acute lung injury due to SIRS can cause fluid to leak across alveolar-capillary barrier resulting in enough alveolar edema, and dysfunction of pulmonary gas exchange causes the clinical manifestation of refractory hypoxemia.[19] A recent study indicated that acute lung injury complicated by AAD was closely related to the macrophages infiltrating the pulmonary interstitial tissue and released matrix metalloproteinases 9 in response to angiotensin II.[20] In our present study, the patients in OI group had higher peak body temperature, higher levels of CRP and lower levels of albumin. And the OI development was associated with CAR, procalcitonin and the peak body temperature in univariate analysis, suggesting the important role of inflammatory reactions in the development of OI and the possibility of inflammatory biomarkers in predicting the occurrence of OI in the patients with AAD.

CRP, a highly sensitive marker in inflammatory states, is an acute-phase protein induced by some pro-inflammatory cytokines, particularly IL-6[21], and it can reflect the severity of inflammatory reactions. It has been reported that systemic inflammatory reactions often occur in the patients with AAD and some inflammation-related markers, including CRP and cytokines, are significantly elevated.[22] Elevated level of serum CRP was considered to be an important risk factor and independently associated with in-hospital death in the patients with AAD.[21,23] Previous studies have been conducted to identify the predicting value of peak levels of CRP for the development of OI in the patients with AAD.[3,5–7] Our present study evaluated the impact of the combination of CRP and albumin in predicting OI development in the patients with AAD. We did not choose the peak level of CRP as a predictor of OI development, because our results showed that OI occurred in the very early few days after admission and the timing of peak CRP might be later than that of OI development. It decreased the value of peak CRP in predicting OI development. We hope that OI development can be predicted in the very early stage after admission, so we preferred the CRP on admission as the predictor of OI development.

Albumin is both an important nutritional indicator and an acute-phase protein involved in inflammatory response.[24] Its synthesis is stimulated by hormones and inhibited by pro-inflammatory substances, including IL-6.[25,26] Decreased serum albumin levels could be found in inflammatory states and critically ill patients.[8,27] Because albumin distribution alters from intravascular to extravascular compartments due to increased microvascular permeability in inflammatory states.[8,28] And increased depletion of albumin further leads to the negative

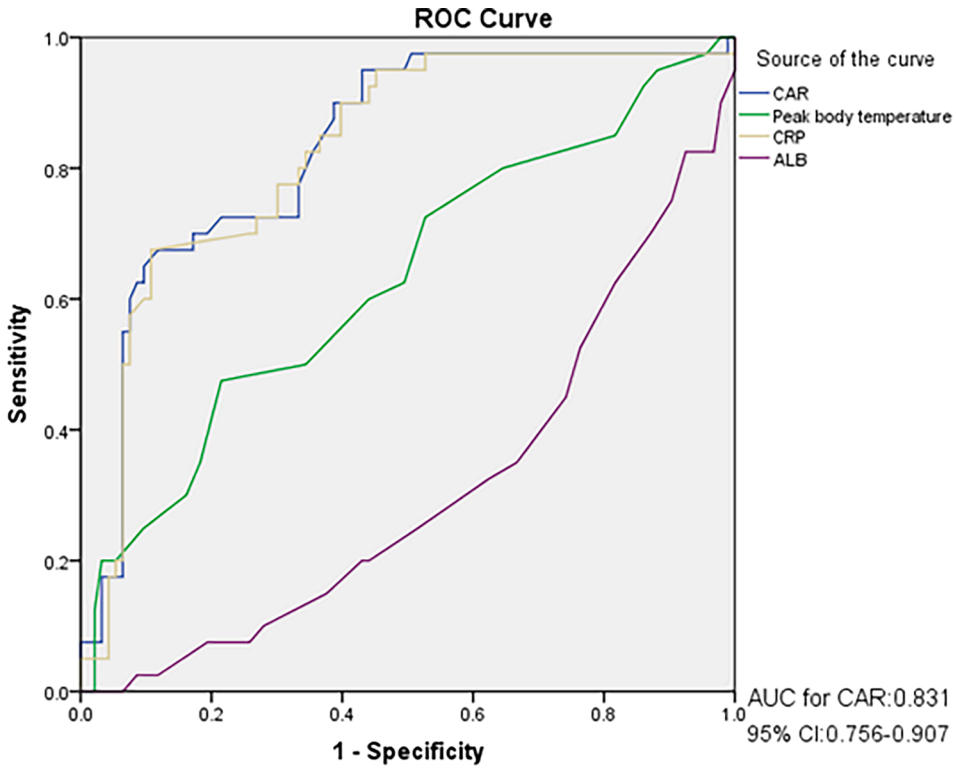

Fig. 1. Receiver operating characteristic (ROC) curves of C-reactive protein (CRP)/albumin ratio (CAR) and albumin for the development of oxygenation impairment in acute aortic dissection. The area under curve (AUC) for CAR was 0.831 (95% confidence interval [CI]: 0.756–0.907), and the AUC for CRP was 0.825 (95% CI: 0.748–0.902). The AUC for the peak body temperature was 0.630 (95% CI: 0.524–0.737), and the AUC for albumin was 0.310 (95% CI: 0.213–0.407).

Table 3
A multivariate linear regression analysis of the clinical variables associated with CAR.

CAR	Coefficient	Standard error	*t*	***P***	Coefficient, 95 % CI
CRP	0.029	0.000	58.810	0.000	0.028, 0.030
Albumin	−0.022	0.002	−9.617	0.000	−0.026, −0.017

Abbreviations: CAR, C-reactive protein/albumin ratio; CRP, C-reactive protein; CI, confidence interval.

albumin balance.[28] Decreased albumin levels have been found in some cardiovascular diseases, including heart failure and coronary heart disease.[29,30] However, this is the first time we introduce the value of albumin in predicting OI in the patients with AAD. We guess that lower levels of albumin in the patients with OI are perhaps due to more severe inflammatory reactions.

CAR has been investigated in various cardiovascular diseases. [12–14] Here we first assess the value of CAR in predicting the development of OI in the patients with AAD. We thought a combination of 2 biomarkers might have more accurate predicting value for OI development. In this study, we used 2 inflammatory biomarkers, CRP and albumin, and calculated the ratio of them. A significant increase in CAR can be indicated in severe inflammatory states, which may in turn predict the risk of OI development more reliably. Our study supported that CAR and the peak body temperature were independent predictors of OI development in patients with AAD. And we also found that CAR was a more accurate marker for OI development than CRP or albumin alone, because we found that CAR had a better sensitivity and specificity indicated by ROC curves. In this study, CAR was only determined by CRP and albumin levels and not significantly affected by other variables, especially age, BMI and comorbidities.

The use of CAR, a novel indicator of inflammatory states, has been investigated in many studies. It has been reported that CAR may be used to predict mortality in patients with spontaneous bacterial peritonitis and pancreatitis.[10,11] It has been demonstrated that CAR may be an easily accessible marker in assessing the development of stent stenosis in the patients with ischemic heart disease.[12,13] It has also been proposed that CAR is a marker of disease activity in Takayasu arteritis.[14] Seckin Setilmis et al also reported that CAR was a more accurate predictor for the occurrence of contrast-induced nephropathy compared with the single biomarker assessment of CRP and albumin in the patients with non-ST elevation myocardial infarction.[31] Currently, the value of CAR has not been investigated in predicting the occurrence of OI in the patients with AAD. Hence, we hypothesized that CAR should be used as a predictive marker in the development of OI. The results of our present study support this hypothesis. In multivariate analysis, CAR and the peak body temperature were both independent variables in predicting OI development in the patients with AAD. And ROC curves indicated that CAR had a better sensitivity and specificity compared to CRP or albumin alone. Although both CRP and albumin are non-specific, they are simple, widely available, and in-expensive tests. So CAR can be widely used as biomarkers in predicting OI in the patients with AAD.

This study has some limitations. Our study is a single-center retrospective design, and the sample size is relatively small. Because of retrospective nature of this study, we just analyzed some available clinical variables in medical records. We hope to establish a multicenter, large-sample prospective cohort study focusing on the prevention and management of OI in the patients with AAD.

5. Conclusions

AAD is frequently complicated with OI, which may necessitate mechanical ventilation. The incidence of OI development is relatively high, and it remains a great challenge in clinical practice because there are no effective modalities to prevent and manage this severe respiratory condition. It is considered that inflammatory reactions play an

important role in the pathogenesis of OI development. CAR and the peak body temperature were independent predictors for OI development in the patients with AAD. The optimal cutoff value for CAR was ≥ 0.70. The CAR was a more accurate marker in predicting OI development compared with CRP or albumin alone, because it had a better sensitivity and specificity. These findings will help identify the patients who are susceptible to have high risks of OI development, thereby leading to appropriate interventions to gain better prognosis.

CRediT authorship contribution statement

Xuemin Zhao: Data curation, Writing – original draft. **Mengjun Bie:** Formal analysis, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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