Prognostic Significance of the Preoperative Ratio of C-Reactive Protein to Albumin in Patients with Colorectal Cancer

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Abstract. *Background: Inflammation has been reported to play an important role in cancer progression, and several inflammatory markers, such as the neutrophil to lymphocyte ratio (NLR) and modified Glasgow prognostic score (mGPS), have been reported to be prognostic markers. The aim of this retrospective study was to evaluate the prognostic significance of the ratio of C-reactive protein to albumin (CRP/ALB ratio) in patients with colorectal cancer who undergo potentially curative surgery. Patients and Methods: A total of 705 patients who underwent potentially curative surgery for colorectal cancer were enrolled. The CRP/ALB ratio was calculated form the preoperative samples by dividing the serum C-reactive protein level by the serum albumin level. We evaluated the correlation between the CRP/ALB ratio and survival. Furthermore, we compared the accuracy of the CRP/ALB ratio as a predictor for survival with the mGPS. Results: We set 0.0271 as the cut-off value for the CRP/ALB ratio according to a receiver operating characteristic curve analysis. Based on the cut-off value of 0.0271, 347 patients were classified into the low CRP/ALB ratio group and 358 patients were classified into the high CRP/ALB ratio group. The group with high CRP/ALB ratio had significantly worse relapse-free survival (p=0.0003) and cancer-specific survival (p=0.0026) rates than those of the low CRP/ALB ratio group. According to a multivariate analysis, the CRP/ALB ratio was identified as an independent prognostic factor for relapse-free survival (p=0.025) and cancer-specific survival (p=0.045). Moreover, even in a sub-analysis limited to patients with an mGPS of 0, the high CRP/ALB ratio group had significantly worse relapse-free survival (p=0.0015) and cancer-specific survival (p=0.0131) rates than the low CRP/ALB ratio group. Conclusion: The preoperative CRP/ALB ratio is a useful prognostic marker in patients with colorectal cancer who undergo potentially curative surgery. Moreover, the CRP/ALB ratio may be superior to the mGPS for predicting survival.*

Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide (1). Despite recent advances in surgical procedures and adjuvant chemotherapy, a large number of patients experience relapse after curative surgery. Although the Union for International Cancer Control (UICC) TNM classification is useful to select the appropriate strategy for patients with colorectal cancer (2), the TNM staging system alone cannot predict a patient's prognosis. Therefore, it is important to define new biomarkers for selecting subgroups of patients who are most likely to have a poor prognosis.

Inflammation has been correlated with cancer progression (3), and several inflammatory markers, such as the neutrophil to lymphocyte ratio (NLR), Glasgow prognostic score (GPS) and modified GPS (mGPS), have been reported as prognostic markers in patients with various types of cancer, including CRC (4-7). Recently, the ratio of C-reactive protein to albumin (CRP/ALB ratio), which has been used for the purpose of predicting mortality in patients with sepsis, has been reported to correlate with survival in patients with hepatocellular carcinoma (8), esophageal squamous cell carcinoma (9) and small cell lung cancer (10). However, to the best of our knowledge, there has been no report regarding the prognostic significance of the CRP/ALB ratio in patients with CRC.

The aim of this retrospective study was to evaluate the prognostic significance of the preoperative CRP/ALB ratio and to compare the accuracy of the CRP/ALB ratio with that of the mGPS, which is also based on the serum CRP and ALB levels, as a prognostic marker in patients with CRC who undergo potentially curative surgery.

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Key Words: Colorectal cancer, prognosis, C-reactive protein to albumin ratio.

Materials and Methods

Patients. A total of 705 cases of colorectal cancer were enrolled in this study. All patients underwent potentially curative surgery for colorectal cancer at the Department of Surgical Oncology of Osaka City University between 2002 and 2009. Patients who received preoperative therapy and underwent emergency surgery for perforation/obstruction were excluded from this study.

The patient characteristics are listed in Table I. A total of 411 males and 294 females were included in this study. The median age of the patients at the initial surgery was 68 years (range=26-90 years). Four hundred and twelve patients had primary tumors located in the colon and 293 had primary tumors located in the rectum. The resected specimens were pathologically classified according to the seventh edition of the UICC TNM classification of malignant tumors (2). All patients were followed-up regularly with physical and blood examinations, including measurements of the levels of tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), and mandatory screening using colonoscopy and computed tomography until December 2014 or death.

Blood sample analysis. Preoperative blood samples were obtained at the time of diagnosis before surgery. The serum CRP and ALB concentrations were measured using a chemiluminescent immunoassay (Wako, Osaka, Japan) according to the manufacturer's protocol. The CRP/ALB ratio was calculated from the preoperative blood samples by dividing the serum CRP level by the serum ALB level. We defined the mGPS as described by a previous report (7) using the combination of the serum CRP and ALB levels. Patients with CRP <1.0 mg/dl were allocated a score of 0. Patients with both CRP ≥1.0 mg/dl and ALB ≥3.5 g/dl were allocated a score of 1. Patients with CRP ≥1.0 mg/dl and ALB <3.5 g/dl were allocated a score of 2.

Statistical analysis. Firstly, we performed an analysis of the receiver operating characteristic (ROC) curve to determine the appropriate cut-off value for the CRP/ALB ratio. All patients were classified into two groups according to the preoperative CRP/ALB ratio. The significance of the correlation between the preoperative CRP/ALB ratio and the clinicopathological characteristics was analyzed using the χ^2 test and *t*-test. The duration of the survival was calculated according to the Kaplan–Meier method. Differences in the survival curves were assessed with the log-rank test. A multivariate analysis was performed according to the Cox proportional hazards model. All statistical analyses were performed using the SPSS software package for Windows (SPSS Japan, Tokyo, Japan). Statistical significance was set at a value of $p<0.05$.

Ethical consideration. This research conformed to the provisions of the Declaration of Helsinki in 1975. All patients were informed of the investigational nature of this study and provided their written informed consent. This retrospective study was approved by the Ethics Committee of Osaka City University (approved no. 926).

Table I. *Patients' characteristics*.

Characteristic	Value
Gender, n	
Male	411
Female	294
Median age (range), years	68 (26-90)
Median serum CRP (range), mg/dl	0.10 (0.01-13.99)
Median serum albumin (range), g/dl	4.0 (2.0-4.8)
Median tumor diameter (range), cm	4.0 (0.2-14.0)
Location of primary tumor	
Colon	412
Rectum	293
Tumor depth	
T1-3	517
T4	186
Histological type, n	
Well, moderately	641
Poorly, mucinous	53
Lymphatic involvement, n	
Negative	278
Positive	413
Venous involvement, n	
Negative	588
Positive	103
Lymph node metastasis, n	
Negative	474
Positive	231
Stage, n	
I	219
II	255
III	231

CRP: C-Reactive protein.

Results

The median preoperative CRP/ALB ratio was 0.0278, with a range of 0.0022-4.2394. We used the continuous variable CRP/ALB ratio as the test variable and the 5-year survival as the state variable. When we investigated the cut-off value for the preoperative CRP/ALB ratio using ROC curve analysis, we found the appropriate cut-off value for the preoperative CRP/ALB ratio to be 0.0271 (sensitivity of 65.8%, specificity of 50.9%) (Figure 1). According to the cut-off value of 0.0271, 347 patients were classified into the low CRP/ALB ratio group and 358 patients were classified into the high CRP/ALB ratio group.

The correlations between the preoperative CRP/ALB ratio and clinicopathological parameters are shown in Table II. The preoperative CRP/ALB ratio exhibited significant relationships with tumor depth, tumor diameter and lymph node metastasis.

The correlations between the preoperative CRP/ALB ratio and the mGPS are shown in Table III. All patients with a mGPS of 1 and 2 were classified into the high-CRP/ALB ratio group. Of 629 patients with a mGPS of 0, 347 patients (55.2%) were classified into the low CRP/ALB ratio group and 282 patients (44.8%) into the high CRP/ALB ratio group.

The relapse-free survival rate was significantly worse in the group with a high CRP/ALB ratio ($p=0.0003$) (Figure

Table II. *Correlations between the preoperative C-reactive protein to albumin (CRP/ALB) ratio and clinicopathological factors.*

Factor	CRP/ALB ratio		*p*-Value
	Low	High	
Median tumor diameter (range), cm	3.0 (0.2-9.0)	4.9 (0.3-14.0)	<0.001
Tumor depth			<0.001
T1-3	278	239	
T4	69	117	
Histological type			0.317
Well, moderately	317	324	
Poorly, mucinous	22	31	
Lymphatic involvement			0.698
Negative	138	140	
Positive	198	215	
Venous involvement			0.523
Negative	289	299	
Positive	47	56	
Lymph node metastasis			0.045
Negative	246	228	
Positive	101	130	

Table III. *Correlation between the preoperative C-reactive protein to albumin (CRP/ALB) ratio and the modified Glasgow Prognostic Score (mGPS).*

	CRP/ALB ratio	
	Low, n	High, n
mGPS, n		
0	347	282
1	0	45
2	0	31

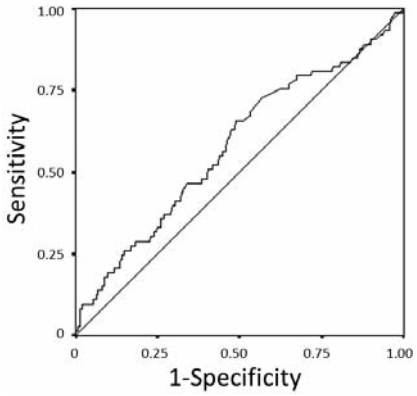

Figure 1. *A receiver operating characteristic curve analysis of the C-reactive protein/albumin (CRP/ALB) ratio in patients with colorectal cancer who underwent potentially curative surgery. Area under the curve=0.578, 95% confidence interval=0.506-0.649, p=0.030.*

2A). Moreover, the cancer-specific survival rate was also significantly worse in this group than in the group with a low CRP/ALB ratio (p=0.0026) (Figure 2B).

As with previous reports, close relationships between the mGPS and the prognosis of the patients were recorded in this study. The mGPS tended to be associated with the relapse-free survival rate (p=0.0530) and was significantly associated with cancer-specific survival (p=0.0343) (Figure 3). Because there was no significant difference between the survival rates of patients with an mGPS of 1 and those with an mGPS of 2, we combined these patients into one single group for further analyses. The relapse-free survival rate was significantly worse in patients with an mGPS of 1 or 2 than in those with a mGPS of 0 (p=0.0391) (Figure 4A). Moreover, the cancer-specific survival rate was significantly worse in patients with an mGPS of 1 or 2 than in those with a mGPS of 0 (p=0.0240) (Figure 4B).

We then performed a sub-analysis limited to patients with an mGPS of 0. Among these patients, the relapse-free survival rate was significantly worse in the group with a high CRP/ALB ratio than in that with a low CRP/ALB ratio (p=0.0015) (Figure 5A), and the cancer-specific survival rate was similarly significantly worse (p=0.0131) (Figure 5B).

The correlations between relapse-free survival and various clinicopathological factors are shown in Table IV. According to a univariate analysis, relapse-free survival exhibited significant relationships with increasing tumor depth and diameter, poorer histological type, lymphatic involvement, venous involvement, lymph node metastasis and increasing preoperative CRP/ALB ratio. In addition, a multivariate analysis indicated that lymphatic involvement, venous involvement, lymph node metastasis and the preoperative CRP/ALB ratio were independent risk factors for poor relapse-free survival. The correlations between cancer-specific survival and various clinicopathological factors are shown in Table V. According to a univariate analysis, cancer-specific survival exhibited significant relationships with increasing tumor depth and diameter, lymphatic involvement, venous involvement, lymph node metastasis and increasing preoperative CRP/ALB ratio. In addition, a multivariate analysis indicated that lymph node metastasis and the preoperative CRP/ALB ratio were independent risk factors for poor cancer-specific survival.

Discussion

In this study, we investigated the prognostic significance of the preoperative CRP/ALB ratio as a marker for predicting the survival in patients with CRC who undergo potentially curative surgery.

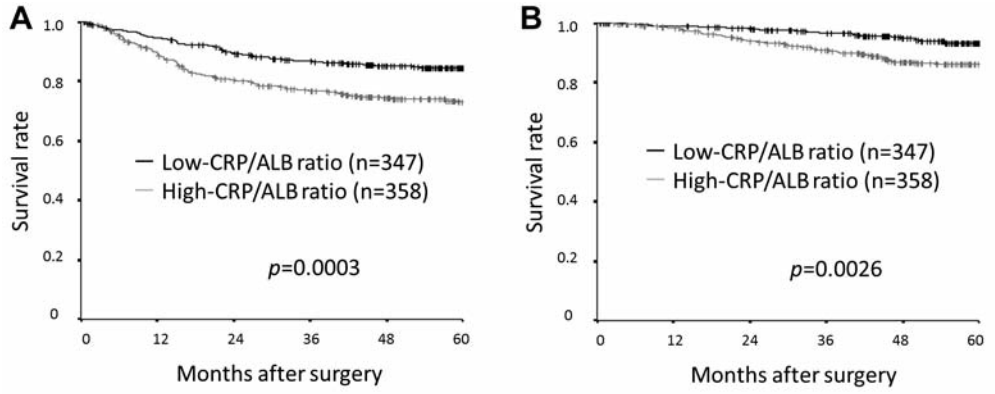

Figure 2. *Kaplan–Meier survival curves for relapse-free (A) and cancer-specific (B) survival according to the preoperative C-reactive protein/albumin (CRP/ALB) ratio. Both the relapse-free survival rate (p=0.0003) and the cancer-specific survival rate (p=0.0026) was significantly worse in the group with a high CRP/ALB ratio than in that with a low CRP/ALB ratio.*

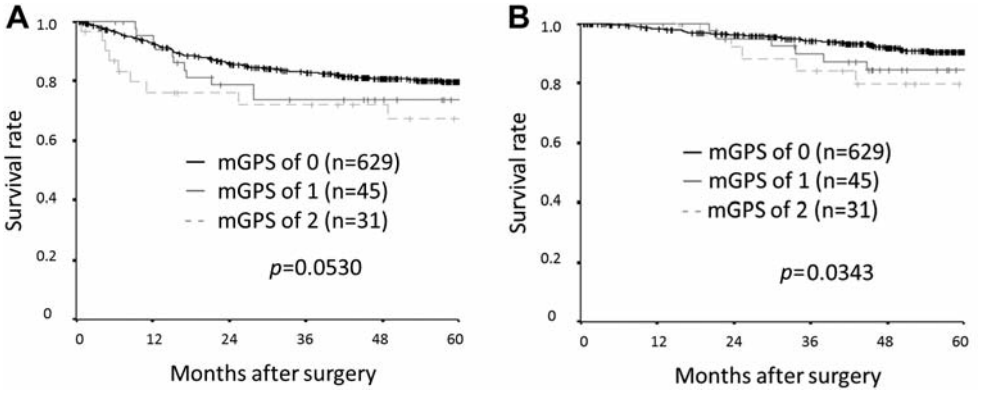

Figure 3. *Kaplan–Meier survival curves for relapse-free (A) and cancer-specific (B) survival according to the modified Glasgow Prognostic Score (mGPS). A high mGPS tended to have a detrimental effect on both relapse-free (p=0.0530) and cancer-specific (p=0.0343) survival.*

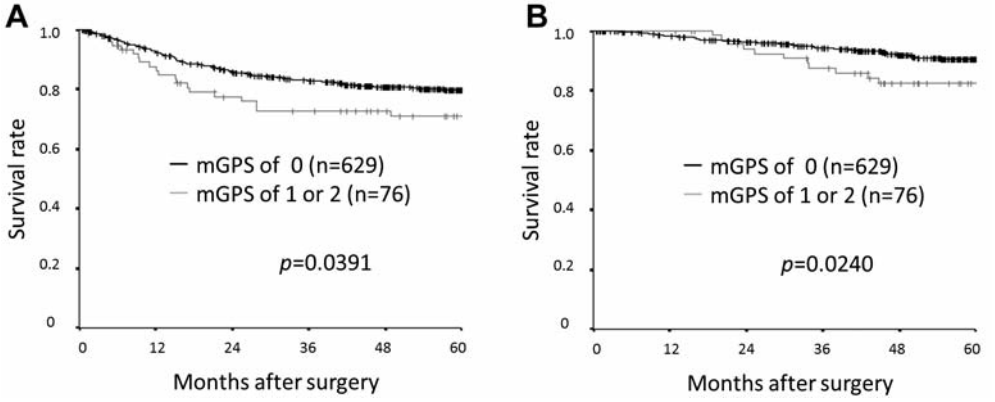

Figure 4. *Kaplan–Meier survival curves for the relapse-free (A) and cancer-specific (B) survival according to the modified Glasgow Prognostic Score (mGPS). The relapse-free survival rate was significantly worse in patients with an mGPS of 1 or 2 than in those with an mGPS of 0 (p=0.0391), as was the cancer-specific survival rate (p=0.0240).*

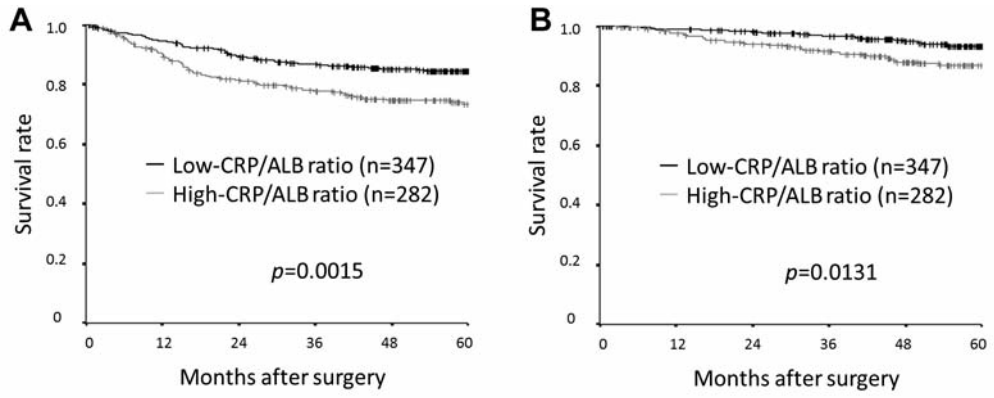

Figure 5. *Kaplan–Meier survival curves for relapse-free (A) and cancer-specific (B) survival in an analysis limited to patients with a modified Glasgow Prognostic Score (mGPS) of 0. The relapse-free survival rate was significantly worse in the group with a high CRP/ALB ratio than in that with a low CRP/ALB ratio (p=0.0015), as was the cancer-specific survival rate (p=0.0131).*

Table IV. *Correlations between the relapse-free survival and various clinicopathological factors.*

	Univariate analysis			Multivariate analysis		
Factor	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Tumor depth (T4 *vs*. T1-3)	2.678	1.922-3.729	<0.001	1.289	0.896-1.854	0.171
Tumor diameter (>5 cm *vs*. ≤5 cm)	2.428	1.742-3.385	<0.001	1.356	0.952-1.931	0.092
Histological type (poorly, mucinous *vs*. well, moderately)	1.919	1.170-3.147	0.010	1.117	0.674-1.853	0.667
Lymphatic involvement (positive *vs*. negative)	4.726	2.689-6.799	<0.001	2.212	1.328-3.682	0.002
Venous involvement (positive *vs*. negative)	2.861	1.998-4.096	<0.001	1.644	1.119-2.415	0.011
Lymph node metastasis (positive *vs*. negative)	4.472	3.166-6.317	<0.001	2.705	1.856-3.941	<0.001
Preoperative CRP/ALB ratio (>0.0027 *vs*. ≤0.0027)	1.857	1.319-2.614	<0.001	1.503	1.054-2.143	0.025

CI: Confidence interval, CRP/ALB ratio: C-reactive protein to albumin ratio.

Table V. *Correlations between cancer-specific survival and various clinicopathological factors.*

	Univariate analysis			Multivariate analysis		
Factor	Hazard ratio	95% CI	*p*-Value	Hazard ratio	95% CI	*p*-Value
Tumor depth (T4 *vs*. T1-3)	2.239	1.410-3.555	0.001	1.152	0.695-1.908	0.584
Tumor diameter (>5 cm *vs*. ≤5 cm)	2.303	1.452-3.652	<0.001	1.297	0.793-2.120	0.300
Histological type (poorly, mucinous *vs*. well, moderately)	1.266	0.580-2.760	0.554			
Lymphatic involvement (positive *vs*. negative)	2.880	1.608-5.159	<0.001	1.373	0.717-2.630	0.339
Venous involvement (positive *vs*. negative)	2.381	1.434-3.954	0.001	1.553	0.904-2.688	0.111
Lymph node metastasis (positive *vs*. negative)	5.335	3.234-8.801	<0.001	3.912	2.274-6.736	<0.001
Preoperative CRP/ALB ratio (>0.0027 *vs*. ≤0.0027)	2.070	1.276-3.357	0.003	1.672	1.012-2.764	0.045

CI: Confidence interval, CRP/ALB ratio: C-reactive protein to albumin ratio.

An increasing number of studies suggest a close relationship between inflammation and cancer. Cancer growth can induce a tissue inflammatory response (3). Moreover, inflammation is also induced by inflammatory cytokines which are produced by cancer cells themselves or other cells in the cancer microenvironment (11). These inflammatory cytokines also lead to tumor growth, invasion and metastasis (3, 12). Some peripheral inflammatory markers, including the serum levels of CRP and ALB, have been reported to correlate with the prognosis in patients with

various types of malignancies (13-17). CRP is an acute-phase protein that is synthesized in hepatocytes, and its serum levels are regulated by proinflammatory cytokines such as interleukin (IL)-1, IL6 and tumor necrotic factor (TNF)-α (18). The serum ALB concentration is not only an objective parameter of the nutritional status but is also associated with chronic inflammation. Under conditions of inflammation, the production of ALB by hepatocytes is suppressed due to the activation of inflammatory cytokines, including IL1, IL6 and TNFα (19-21).

The mGPS has been reported to be a useful prognostic marker in various types of cancers. The mGPS is a simple scoring system which is easy to calculate and is based on the serum CRP and ALB concentrations. However, its disadvantage is that the absolute value is less likely to be reflected (*e.g.* patients with CRP of 1.5 mg/dl and those with CRP of 5.0 mg/dl are classified into the same group). The CPR/ALB ratio is an improvement upon the mGPS by the use of the ratio of these two parameters. The CRP/ALB ratio was reported to be a more accurate prognostic marker than the mGPS in patients with hepatocellular carcinoma and esophageal squamous cell carcinoma (8-9). Although the mGPS is an excellent prognostic marker for patients with cancer, the majority of patients are classified into the group with mGPS of 0, which is the group with better prognosis . In this study, approximately 90% of the patients were classified as having an mGPS of 0. However, it was possible to classify these patients by the CRP/ALB ratio into two groups and significant differences in survival between these two groups were observed. Moreover, no patient with an mGPS of 1 or 2 was classified into the low CRP/ALB group, which is the better-prognosis group. As mentioned above, the CRP/ALB ratio might be more accurate than the mGPS as a prognostic marker for patients with cancer and may detect patients with a poor prognosis who are not detected by the mGPS.

The CRP/ALB ratio was significantly associated with tumor progression, such as higher tumor depth and lymph node metastasis, and remained a significant prognostic factor according to multivariate analysis. This indicates that the CRP/ALB ratio does not simply reflect cancer progression and might be an independent prognostic factor reflecting the status of the patient. Therefore, the combination of the TNM staging system and the CRP/ALB ratio may contribute to predicting the prognosis and decisions regarding the selection of therapeutic strategies (*e.g.* adjuvant chemotherapy) more accurately.

There are some possible limitations associated with this study. Firstly, we evaluated a relatively small number of patients and the study design was retrospective. Secondly, potential confounding factors, such as infection, ischemia or acute coronary disease, which may affect serum CRP/ALB levels, were not assessed. Thirdly, we did not examine underlying diseases of the patients which could affect the serum ALB level, such as liver cirrhosis and chronic renal failure. Fourthly, the optimum cut-off value for the preoperative CRP/ALB ratio is unknown, although we set it at 0.0271 in this study using the ROC analysis. Therefore, a large prospective study should be performed to evaluate our findings.

In conclusion, the preoperative CRP/ALB ratio is a useful prognostic marker in patients with CRC who undergo potentially curative surgery. Moreover, the CRP/ALB ratio may be superior to the mGPS for predicting survival.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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