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Original Article

Monitoring of peri-distal gastrectomy carbohydrate antigen 19-9 level in gastric juice and its significance

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Abstract: Gastric carcinoma is one of the most common and deadly malignancies nowadays, and carbohydrate antigen 19-9 (CA 19-9) in gastric juice has been rarely studied. To compare peri-distal gastrectomy (DG) gastric juice and serum CA 19-9 and reveal its significance, we selected 67 patients diagnosed with gastric carcinoma who underwent DG, and collected their perioperative gastric juice whose CA 19-9 was detected, with serum CA 19-9 monitored as a comparison. We found that: gastric juice CA 19-9 pre-gastrectomy was significantly correlated with tumor TNM classification, regarding tumor size, level of gastric wall invaded, differentiated grade and number of metastatic lymph nodes as influencing factors, while serum CA 19-9 revealed little information; gastric juice CA 19-9 was significantly correlated with radical degree, and regarded number of resected lymph nodes and classification of cutting edge as impact factors; thirteen patients whose gastric juice CA 19-9 rose post-DG showed features indicating poor prognosis; the difference of gastric juice CA 19-9 between pre- and post-gastrectomy was correlated with tumor TNM classification and radical degree, and regarded tumor size, number of resected metastatic and normal lymph nodes, sum of distances from tumor to cutting edges and classification of cutting edge as influential factors. We conclude that peri-DG gastric juice CA 19-9 reveals much information about tumor and radical gastrectomy, and may indicate prognosis; while serum CA 19-9 has limited significance.

Keywords: Gastric carcinoma, distal gastrectomy, perioperative, gastric juice, carbohydrate antigen 19-9

Introduction

Gastric carcinoma (GC) is one of the most common and deadly malignancies nowadays [1]. Its incidence ranks fourth all over the world [2] and it has a mortality of about 10%, only second to lung cancer [3]. Surgery is the major and effective treatment, and D2 gastrectomy is applied most frequently in East Asia due to its assurance of relatively high survival and low recurrent rates [4]. GC sufferers can hope to live significantly longer and enjoy a better quality of life post-surgery with an ideal overall survival rate of over 90% if they are lucky enough to be screened in early stage and dealt with immediately and adequately, while the prognosis of those detected in advanced stage is desperate even with their stomach resected [5, 6]. This common and tough medical problem raises great concerns for gastroenterologists.

Although there are many relatively sensitive imaging and pathologic methods applied for diagnosing and monitoring GC, tumors of diverse biological features can't always be easily perceived by our senses or those assistant techniques. Researchers are still trying hard to unearth body liquid biomarkers aiming at screening the existence, evaluating the progress and predicting the prognosis of the lesion [7-9].

Malignancies secrete many kinds of substances to its surroundings and body liquids, and part of them with considerable specificity are considered tumor markers and used in clinical assay within discrepant samples [10]. Scholars hope to clarify their clinical values and have analyzed a great many of them, some of which with relatively satisfying sensitivity like carbohydrate antigen 19-9 (CA 19-9) is usually applied to detect gastrointestinal neoplasm [11, 12]. Up till now, many researchers have reported their studies on CA 19-9 in blood, tissue, effusions and so on, among which serum CA 19-9 is

Table 1. General clinical features of the patients enrolled (continuous data in $\bar{X} \pm SD$)

Item	Value
Number of patients enrolled	67
Gender (Male/Female)	47/20
Smoke (Yes/No)	32/35
Alcohol (Yes/No)	34/33
Pathological general stage (Early/Advanced)	21/46
Age (y)	62.16 ± 10.21
Body Mass Index (kg/m^2)	21.08 ± 3.29
Hemoglobin (g/L)	123.48 ± 20.67
Lymphocyte (10^9/L)	1.55 ± 0.53
Albumin (g/L)	40.15 ± 3.28
Prealbumin (mg/L)	241.27 ± 53.23
Days of getting out of bed post-operation (d)	1.12 ± 0.33
Anal exhaust time post-operation (d)	3.27 ± 0.69
Serum CEA (μg/L)	3.81 ± 3.64
Serum AFP (μg/L)	2.83 ± 3.24
Serum CA 125 (U/mL)	11.86 ± 10.21

CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; CA 125, cancer antigen 125.

most widely discussed. However, its sensitivity and specificity is limited, and its diagnostic, indicative and prognostic significances remain controversial [13-24].

Malignant tissue releases GC biomarkers directly into gastric juice, which has been scarcely looked into and requires further investigation. Reports on CA 19-9 in gastric juice are mainly focused on its diagnostic values before gastric is removed [13-15, 25]. To our knowledge, only two researches on perioperative serum CA 19-9 tried to reveal possible clinical values for gastric and pancreatic cancer respectively [19, 26], and we haven't found any article on detection of CA 19-9 in gastric juice post-gastrectomy and comparison of perioperative gastric juice CA 19-9 between pre- and post-surgery home and abroad, while it could be clinically meaningful and useful.

In this study, we monitored and compared perioperative CA 19-9 in gastric juice and serum among patients suffering from GC pre- and post-distal gastrectomy (DG), analyzed correlations between different parameters using univariate analysis and factors affecting CA19-9 in different samples using multivariate analysis, trying to uncover possible clinical significances.

Material and methods

Patients and specimens

All patients selected in our study were diagnosed with GC pathologically without metastasis, in need of DG. Their overall conditions were relatively fine (Hb>90 g/L, albumin>30 g/L), and they were free of severe malfunction of important organs or systematic unfits including dyscrasia and refractory ascites. Moreover, we confirmed that there weren't any other diseases like carcinoma that might potentially influence CA 19-9 with them, neither were there severe psychiatric abnormalities. We gained written informed consent from every enrolled individual and obtained permission from Ethics Committee of the First Affiliated Hospital of Anhui Medical University before implementing our research, which was in accordance with Declaration of Helsinki [27].

The enrolled patients hadn't received any gastroenterological surgery, nor had they been treated with any chemo-, radio-, or interventional therapy before. Those undergoing multivisceral resection or having other gastroenterological diseases were excluded from our study. Drainage samples collected were not polluted by blood, remnant food or reflux, and we had detailed information of each of them.

A total of 77 patients undergoing DG plus Billroth I reconstruction in the First Affiliated Hospital of Anhui Medical University from July 5th, 2012 to May 17th, 2013 were regarded eligible for our study. Apart from 10 individuals who quit the pilot half-way or were affected greatly by irrelevant factors or whose samples or data went against our standards, 67 patients' drainage and blood samples were available eventually (**Table 1**).

Samples collection and detection

Before surgery, the selected patients were forbidden from food, drink, cigarettes and alcohols for more than 12 hours, and had only some liquid food the night before. At 7:00 on the morning of the surgery day, the patients were required to lie in a quiet circumstance, and a nasogastric tube was put into his/her digestive tract until the end reached the gastric

mucoid pools [28]. Then we aspirated about 10 mL gastric fluid with a syringe, and wrote down the depth the tube had been pushed in. We also collected approximately 5 mL fasting peripheral venous blood from each patient enrolled.

The tube was fixed to the same depth as that pre-operation after surgery. Patients were all fed with parenteral nutrition, and we changed the suction disc at 7:00 pm the 5th day post-surgery, and collected about 10 mL fluids again inside the disc at 7:00 am the 6th day post-operation. We labeled the samples, centrifuged them (4000 g, 15 min) at room temperature right after we got them, and absorbed the supernatant.

Analysis of samples was completed on the day we obtained them. As gastric juice pH of patients suffering from GC of discrepant classifications differs greatly [29], which affects antibody binding kinetics and contents of CA 19-9 detected [13-15, 25], pH of samples were adjusted to 7.0 before detection. Then we tested the concentration of CA 19-9 (original reagent used) using Automated Immunoassay Analyzer provided by Roche, Germany (type: Cobase 601) with method of electrochemiluminescence (Serum CA 19-9 was considered normal when it's less than 34.0 U/mL according to the instructions). We preserved rest of the samples in refrigerators of -80°C.

Surgical management

The same group of operators (A.M.X., L.H., W.X.H. and Z.J.W.) performed uniform and standard open radical DG (D2) with Billroth I reconstruction for all patients. Gastroduodenostomy was conducted with anastomosis after distal part of the gastric and lymph nodes were removed standardly. We cut the gastric branch of vagus while preserving the hepatic and celiac ones.

Statistical analyses

Statistical management was conducted with the SPSS 16.0 package. The correlation of two groups of normally distributed variables was evaluated using univariate analysis with Pearson related coefficient r calculated. The correlation between CA 19-9 and TNM stage was quantified by Spearman test with rank correlation coefficient r_s calculated. Factors affecting CA 19-9 in different samples were estimated using multiple linear regression with partial regression coefficient b and standardized partial regression coefficient b' calculated. Independent-samples t-test was applied to compare means from two identical measurement data samples. Continuous data were in mean ± standard deviation. P-values of less than 0.05 and 0.01 were considered to indicate significant and very significant differences respectively.

Results

CA 19-9 in gastric juice and serum before DG

Content of gastric juice CA 19-9 was 260.44 ± 75.97 U/mL and significantly higher among patients in advanced stages than that among patients in early stages (275.78 ± 80.84 U/mL vs 226.69 ± 51.00 U/mL, t'=2.941, P=0.005), while there weren't significant differences of CA 19-9 in gastric juice between patients who smoked and those who didn't (t=-0.427, P=0.671), or between patients who drank alcohol and those who didn't (t=0.494, P=0.140).

Content of serum CA 19-9 was 23.03 ± 13.84 U/mL, but we didn't find significant differences of serum CA 19-9 between patients in advanced and early stages (t=0.718, P=0.475). The difference between patients who smoked and who didn't was not significant (t=1.319, P=0.192), while patients who drank alcohol had significantly higher level of CA 19-9 in serum than those who didn't (26.85 ± 15.41 U/mL vs 18.95 ± 10.75 U/mL, t=2.363, P=0.021).

Concentration of CA19-9 in gastric juice was significantly higher than that in serum (t'=24.597, P=0.000), and there existed a weak correlation between them (r=0.375, P=0.002).

Gastric juice CA 19-9 was significantly correlated with tumor TNM classification (r_s=0.720, P=0.000) and regarded tumor size, level of gastric wall invaded, differentiated grade and number of metastatic lymph nodes as significant influencing factors, while the coefficients of patients' age, gender and tumor location were not statistically significant (**Table 2**) (levels of gastric wall invaded and classification of cutting edge as R0, R1 and R2 were both based on the TNM Classification System by AJCC (the 7th edition), and the differentiated grade of adenocarcinoma was in accordance with Japanese grading system [30]).

Table 2. Result of multiple linear regression of factors potentially impacting gastric juice CA 19-9 pre-DG

	b	*b'*	*t*	*P*
Gender	2.019	0.012	0.134	0.894
Age	-0.299	-0.041	-0.442	0.660
Tumor size	1.579	0.525	6.252	0.000**
Tumor location	3.992	0.082	0.982	0.331
Level of gastric wall invaded	6.188	0.210	2.241	0.029*
Differentiated grade	17.398	0.216	2.668	0.010*
Number of metastatic lymph nodes	3.533	0.211	2.387	0.020*

CA 19-9, carbohydrate antigen 19-9; DG, distal gastrectomy; *b,* partial regression coefficient; *b'*, standardized partial regression coefficient; *P<0.05, indicating significant result; **P<0.01, indicating very significant result.

Table 3. Result of multiple linear regression of factors potentially impacting serum CA 19-9 pre-DG

	b	*b'*	*t*	*P*
Gender	-5.718	-0.190	-1.318	0.193
Age	0.307	0.228	1.576	0.121
Tumor size	0.015	0.028	0.213	0.832
Tumor location	-1.500	-0.168	-1.281	0.205
Level of gastric wall invaded	0.351	0.065	0.441	0.661
Differentiated grade	2.448	0.167	1.304	0.198
Number of metastatic lymph nodes	1.027	0.336	2.410	0.019*

CA 19-9, carbohydrate antigen 19-9; DG, distal gastrectomy; *b,* partial regression coefficient; *b'*, standardized partial regression coefficient; *P<0.05, indicating significant result.

Serum CA 19-9 was also significantly correlated with tumor TNM classification, but with a much smaller coefficient (r_s=0.443, P=0.000). It only regarded number of metastatic lymph nodes as a significant impact factor, while the coefficients of patients' age, gender, tumor size, location, levels of gastric wall invaded and differentiated grade were all not statistically significant (**Table 3**).

CA 19-9 in gastric juice after DG

It's 159.16 ± 69.10 U/mL, which was significantly lower than that pre-DG (t=7.890, P=0.000), while there wasn't significant difference between patients in advanced stages and those in early stages (t'=0.360, P=0.722).

It's not correlated with tumor TNM classification (r_s=0.110, P=0.385), but significantly correlated with radical degree (classified as A, B and C [31]) (r_s=0.545, P=0.000), and regarded number of resected normal lymph nodes and classification of cutting edge as significant influencing factors, while the coefficients of patients' age, gender, number of resected metastatic lymph nodes and the sum of distances from the tumor to the two cutting edges were not statistically significant (**Table 4**).

There were 13 individuals in total whose CA 19-9 in gastric juice rose post-DG. These patients were all suffering from GC in advanced stages (2 IIIa, 4 IIIb, 7 IIIc according to TNM classification system (the 7th edition) [30]), among whom 8 had their gastric walls invaded by tumor to the serosa level, 5 out of serosa to the nearby tissue. Moreover, among them the sum of distances from the tumor to the two cutting edges was all less than 4 cm, and 8 patients' cutting edges were classified to be R1 (there were no R2 cutting edges in our study). Ten of them underwent DG with radical degrees of C, the rest three B. As for differentiated grade, eleven malignancies were differentiated poorly, the other two undifferentiated.

Difference of CA 19-9 in gastric juice between pre- and post-DG (pre- minus post-)

Patients in advanced stages tended to have greater changes than those in early stages (t=2.001, P=0.05). The difference was significantly correlated with tumor TNM classification with relatively smaller coefficient compared with that pre-DG (r_s=0.436, P=0.000), as well as radical degree (r_s=-0.659, P=0.000), but negatively, and regarded tumor size, number of resected metastatic and normal lymph nodes, the sum of distances from the tumor to the two cutting edges and classification of cutting edge as significant influencing factors, while the coefficients of patients' age, tumor location, levels of gastric walls invaded and differentiated grade were not statistically significant (**Table 5**).

Discussion

CA19-9 is a kind of glycoprotein which scarcely exists in normal gastric epithelia, and elevates significantly when malignancy occurs [13, 15]. When detected continuously, it may indicate

Table 4. Result of multiple linear regression of factors potentially influencing gastric juice CA 19-9 post-DG

	b	*b'*	*t*	*P*
Gender	-6.010	-0.040	-0.389	0.699
Age	1.007	0.150	1.275	0.207
Number of resected metastatic lymph nodes	0.764	0.050	0.490	0.626
Number of resected normal lymph nodes	-8.568	-0.391	-2.959	0.004**
Sum of distances from tumor to two cutting edges	-1.029	-0.073	-0.597	0.553
Classification of cutting edge	51.670	0.362	3.218	0.002**

CA 19-9, carbohydrate antigen 19-9; DG, distal gastrectomy; *b,* partial regression coefficient; *b'*, standardized partial regression coefficient; **$P<0.01$, indicating very significant result.

Table 5. Result of multiple linear regression of factors potentially influencing the difference of gastric juice CA 19-9 between pre- and post-DG

	b	*b'*	*t*	*P*
Gender	9.044	0.039	0.518	0.607
Age	-1.754	-0.167	-2.119	0.039*
Tumor size	0.967	0.226	3.263	0.002**
Tumor location	-7.314	-0.105	-1.538	0.130
Level of gastric wall invaded	-3.355	-0.080	-1.030	0.308
Differentiated grade	9.978	0.087	1.327	0.190
Number of resected metastatic lymph nodes	4.322	0.181	2.510	0.015*
Number of resected normal lymph nodes	7.446	0.218	2.480	0.016*
Sum of distances from tumor to two cutting edges	6.109	0.277	3.390	0.001**
Classification of cutting edge	-68.925	-0.309	-4.087	0.000**

CA 19-9, carbohydrate antigen 19-9; DG, distal gastrectomy; *b,* partial regression coefficient; *b'*, standardized partial regression coefficient; *$P<0.05$, indicating significant result; **$P<0.01$, indicating very significant result.

progress of carcinogenesis, surgical outcome, prognosis and occurrence. Serum is most commonly applied in clinical essay of CA 19-9 which has been widely studied and whose diagnostic and prognostic values still remains controversial [13, 19, 24, 32]. Later on, the existence of CA 19-9 in gastric juice directly released by tumor was noticed [15, 25]. Researchers reported diverse positive rates of serum and gastric juice CA 19-9 among patients suffering from GC with different threshold set and higher diagnostic value if assays of two samples are combined [13, 14, 25]. CA 19-9 in gastric juice isn't significantly correlated with prognosis, but it may serve as a method to detect people at high risk and early gastric cancer, while the diagnostic value is limited [13-15, 25]. However, up till now reports concerned with gastric juice are still rare and all about patients with an intact stomach showing limited clinical values [13-15, 25], and research about perioperative CA 19-9 in gastric juice both pre- and post-gastrectomy and the comparison of gastric juice CA 19-9 between pre- and post-operation hasn't been found. Only one study we've obtained on perioperative CA 19-9 among patients suffering from GC showed diverse clinical significances for the lesion in different stages, but was based on the sample of blood [19]. In this study, we analyzed and compared CA 19-9 in gastric juice and serum between pre- and post-DG from a different aspect unlike the only four articles involving gastric juice CA 19-9, and since more pathological information is available and applied in our analyses after the removal of gastric, we are making a further investigation aiming at unearthing possible significances, which appears to be novel and may be useful for gastroenterologists to evaluate and deal with GC sufferers both pre- and post-surgery wisely.

Regardless of tissue grading, GC can produce CA 19-9 and transfer it to the surrounding and distant, and gastric juice CA 19-9 significantly elevates among patients suffering from gastric malignancy [15, 25]. Biomarkers detected in tumor tissue, gastric juice and other body liquids may be decided by following factors: tumor burden, growth rate, polarity of tumor cells secretion, venous and lymphatic channels, blood transportation and liver metastasis [33]. Based on simultaneous monitoring of CA 19-9 in peripheral and portal venous blood, Tabuchi revealed that CA 19-9 released by tumor was drained into the lymphatic instead of portal system before entering circulatory [34]. Circulating CA 19-9 mainly depends on the following three factors: amount of tumor cells secretion, ability of malignancy releasing CA 19-9 into transporting channels and metabolic function of the liver. The more CA 19-9 enters blood stream

through lymphatic without being obviously eliminated by liver, the higher serum CA 19-9 is with the assistance of lymph nodes. CA 19-9 may also be affected by immune recognition and destruction, and as tumors grow, it rises [13]. Gastric juice is one of the body liquids nearest to the tumor and contacts it closely, and CA 19-9 inside is directly released by the tumor without liver elimination, thus revealing more accurate information about the lesion to us.

According to our study, gastric juice CA 19-9 is significantly higher than that in serum, and CA 19-9 in gastric juice and serum correlates weakly with each other. We also find that patients suffering from GC in advanced stages have higher CA 19-9 in gastric juice, and that the later stage according to TNM classification is, the larger amount of gastric juice CA 19-9 there exists, which may be because as malignancies progress, all potential impact factors contribute to greater secretion of CA 19-9 by the lesion. We further reveal that CA 19-9 in gastric juice with gastric complete may suggest much information about tumor and its invasiveness (tumor size, levels of gastric wall invaded, differentiated grade and number of metastatic lymph nodes), while patients' general characteristics like age and gender plays no significant roles. Although serum CA 19-9 is also correlated with tumor TNM classification with a relatively small coefficient, it indicates rather limited specific information, showing deficient value in assisting assessment. Tocchi [13] and Duraker [14] reported similar results of CA 19-9 in gastric juice among GC sufferers with a complete gastric compared with ours. Harrison [25] and Duraker [14] also reported a higher level of gastric juice CA 19-9. Tochhi [13] found no correlation between CA 19-9 in two samples which challenges our result, possibly due to the discrepancy in ability of liver resulted from diversity of included population. Tocchi's [13] finding that positive rate of gastric juice CA 19-9 rises when tumor invade beyond the subserosa is in accordance with our conclusion, and Farinati [15] also declared no significant influence of patients' general features on gastric juice CA 19-9. Gastric juice CA 19-9 may contribute to early detection and screening people at high risk as shown by other scholars [13-15, 25]. Besides, lots of the information revealed by gastric juice CA 19-9 may not be obtained through pathology and imaging techniques preoperation without intruding and penetrating into the lesion itself (even imaging equipment with high resolution may fail to tell us how large the lesion is and how many lymph nodes have been intruded by tumor cells, and we've no idea of the level invaded by the malignancy), and we can even get more data about the malignancy if assays of gastric juice CA 19-9 and those detection techniques are combined, which contributes to more precise classification of tumor stage pre-operation and wiser decision of comprehensive management, thus may be of great values to improve patients' prognosis. Besides, it's economical and convenient, and we can get gastric juice when patients are undergoing gastroscopy, so it's clinically feasible.

With early postsurgical activities, effects of anesthesia, stress, and psychological factors die away. The overall condition of the patient and environment inside remnant gastric reach a relatively steady condition gradually with the recovery of gastrointestinal motility, rectification of internal environment, stabilization of neurohormonal factors and rehabilitation of important organs. A significant decrease of CA 19-9 in gastric juice was noticed by us after detection of each studied individual again after removal of their distal gastric which may be due to the elimination of producing source, and the difference complied with discrepant tumor stages and classification disappears in the face of the strong interfering force of surgical intervention. We further uncovered that it's significantly correlated with radical degree and that it takes number of resected metastatic lymph nodes and classification of cutting edge as significant influential factors, which may serve as a great assistance to post-surgical pathological diagnosis, and evaluation of satisfaction of radical operation and prognosis, since cutting edged classified as R1 with more remnant tumor cells may lead to higher rate of recurrence, and potential malignant cells left in the lymph nodes are also great hazards [35].

The 13 patients with their gastric juice CA 19-9 rising after DG were all suffering from poorly differentiated GC in relatively late stages with their gastric walls invaded by tumor to serosa or beyond to nearby tissues, and for all of them sums of distances from tumor to two cutting edges are less than 4 cm, which is really risky taking into account the standard distance of 5 cm from cutting edge to the tumor for more malignant cells may possibly preserve [36].

Moreover, eight of the pathological tissues were found to have remnant tumor cells invaded at the cutting edge (classified as R1) via microscopic observation, leading to sharp deteriorations in radical degree from an ideal A to doom C and greater risk of recurrence. All these indicate a terrible outcome [37, 38]. Thus the increase of CA 19-9 in gastric juice may be a signal of bad prognosis and serve as a sensitive indicator of pathologically undetected metastasis or remnant tumor cells, complimentary to post-operative biopsy. Though both Tocchi [13] and Duraker [14] reported limited prognostic values of the positive rate of gastric juice CA 19-9, their conclusion was based on individuals with a complete gastric and dichotomous data lack of abundant information from original continuous outcomes, while gastrectomy may influence the outcome greatly. We are keeping track of all these patients hoping to further uncover the significance.

We also found that CA 19-9 in gastric juice has a tendency to decrease more sharply among patients in later stages and that the difference of gastric juice CA 19-9 between pre- and post-gastrectomy is significantly correlated with both tumor TNM classification (positively, with a relatively smaller coefficient) and radical degree (negatively). The difference took tumor size, number of resected metastatic and normal lymph nodes, the sum of distances from tumor to two cutting edges and classification of cutting edge as significantly influential according to our study. Particularly, the fact that the difference correlates with resected lymph nodes may be because the lymphatic system is the major path draining CA 19-9 produced by tumor [34]. So we may judge the overall condition of the tumor and perfection of radical gastrectomy to an ideal degree through the difference as well as postsurgical CA 19-9 in gastric juice before the pathological results come out, which may also serve as an important assistance to pathological diagnosis especially in those places where medical technology is not so developed and pathologists are less qualified, and an indication for prognosis as well.

In conclusion, CA 19-9 in gastric juice pre- and post-gastrectomy can provide us with much information about tumor and radical gastrectomy, while serum CA 19-9 has limited significance. CA 19-9 in gastric juice post gastrectomy, the difference of CA 19-9 in gastric juice between pre- and post-gastrectomy and a rise of gastric juice CA 19-9 post-surgery may indicate prognosis.

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Disclosure of conflict of interest

All authors declare no conflict of interest.

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