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Original Article

Combination of Serum Test and Questionnaire in Early Gastric Cancer Screening

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Abstract

Background: We aimed to analyze the predictive role of serum test and questionnaire in Early Gastric Cancer in The First Affiliated Hospital of Xingtai Medical College, Hebei Province from 2019 to 2020.

Methods: In this prospective study, 280 medical examiners underwent questionnaire, serum test and gastroscopy. They were divided into Gastric cancer (GC) and Non-Gastric cancer (NGC) group. NGC group was divided into Low-grade intraepithelial neoplasia (LGIN), Chronic atrophic gastritis (CAG) and Non-chronic atrophic gastritis (NCAG) group.

Results: Age, drinking, sex and Gastrin-17(G-17) was respectively independent risk factors for GC. Age, drinking and G-17 was independent risk factors for GC in men. G-17 of GC group was higher than that of LGIN and NCAG group ($P<0.05$). Pepsinogen I/II ratio (PGR) of GC was lower than that of NCAG group ($P<0.05$). There was no significant difference between Pepsinogen I (PGI) and Pepsinogen II (PGII) in the four groups. *Helicobacter pylori*-immunoglobulin G antibodies (*H. pylori*-IgG) of LGIN group was significantly higher than that of CAG and NCAG group in gastritis group ($P<0.008$). G-17≥42.95 pmol/L, age≥69years, male and drinking can predict GC.

Conclusion: Older, drinking, men and high G-17 could respectively predict GC. Especially in men, older, drinking and high G-17 could affect the occurrence of GC. G-17, age, drinking and sex used respectively to screen high-risk populations for GC were more efficient than combined screening. GC had a higher serum G-17 and a lower PG than other gastric diseases.

Keywords: Gastrin-17; *Helicobacter pylori*; Immunoglobulin G; Pepsinogen; Early gastric cancer

Abbreviation: Gastric cancer(GC); non-gasric cancer(NGC); Early gastric cancer(EGC); Gastrin-17(G-17); Pepsinogen(PG); Pepsinogen I(PGI); Pepsinogen II (PGII); PGR(pepsinogen I/II ratio); H.pylori-immunoglobulin G antibodies (*H. pylori*-IgG); low-grade intraepithelial neoplasia(LGIN); High-grade intraepithelial neoplasia (HGIN); Chronic atrophic gastritis(CAG); atrophic gastritis(AG); non-atrophic gastritis(NAG). Standard error (SE). Confidence intervals(CI)

Introduction

Gastric cancer (GC) ranks the 5th and 4th in the global cancer incidence and death spectrum respectively. GC occurs mainly in Asia, including China, Japan, and South Korea. EGC has no specific symptoms and is easily overlooked (1-3). Most of them have reached advanced when clinical symptoms appear.

In 2016, the Japanese government decided to introduce endoscopic screening for GC in order to increase the efficiency of screening (4). If gastroscopy screening were used to screen the main method for "healthy people" in China, it may cause waste of medical resources because the large population of China, and the discomfort caused by gastroscopy, most people are unwilling to accept it.

Our study analyzed the feasibility of hematology examination with questionnaires in screening EGC.

Methods

Clinical data

This study was conducted at the First Affiliated Hospital of Xingtai Medical College, Hebei Province from 2019 to 2020. The inclusion criteria were as follow: 1) Age ≥18 years old, 2) No proton pump inhibitors or other acid-suppressing drugs were taken within 2 weeks before gastroscopy; Patients were excluded: 1)Patients had severe heart, liver and other organ diseases, 2)Patients cannot cooperate with the examination, 3) Patients with previous gastric surgery and active upper gastrointestinal bleeding, etc. (5,6). Overall, 280 eligible cases were enrolled into the study. They were divided into GC and NGC group according to the results of gastroscopy. The GC group included adenocarcinoma and HGIH. The NGC group included LGN, CAG and NAG group (Table 1).

Table 1: General information

Group	*Sex (case)*		*Age*		*Pathological type (case)*		
	Men	Women	Interval	average			
GC	19	1	52~88	72±8	GC (15)	HGIN (5)	
NGC	158	103	40~86	66±15	LGIN(33)	CAG(124)	NAG(103)

Questionnaire

Including gender, age, discomfort symptoms in daily life, etc. (Table 2). The frequent occurrence of abdominal pain, bloating, acid reflux, heartburn, nausea, vomiting, hiccups, belching and other discomforts in daily life for more than 6 months as positive symptoms. Occasionally and the above -mentioned symptoms that have never occurred as negative. Smoking and drinking refer respectively to those who >10 cigarettes per day and lasting >6 months. Like hot drinks as positive symptoms.

Gastroscopy and pathological diagnosis

The pathological diagnosis of chronic gastritis adopts the visual analog scoring method. If the gastric mucosa performs abnormal, the biopsy requirements were carried out (7).

Clinical evaluation

This study analyzed the relationship between each item in the questionnaire, serum, combination of serum and questionnaire for GC.

Table 2: Univariate analysis affecting the occurrence of GC

Influencing factors	*Partial regression coefficient*	*SE*	*Wald Bangla*	*P*	*OR*	*95% CI OR*	
						Lower	Upper
Sex	2.507	1.034	5.880	0.015	12.266	1.617	93.042
age	0.102	0.031	10.978	0.001	1.108	1.043	1.177
G-17	0.025	0.010	6.529	0.011	1.025	1.006	1.045
PGI	0.000	0.002	0.023	0.880	1.000	0.997	1.004
PGII	0.015	0.018	0.679	0.410	1.015	0.980	1.051
PGR	-0.008	0.025	0.099	0.753	0.992	0.945	1.042
H. pylori	-0.344	0.473	0.529	0.467	0.709	0.281	1.792
Bloating	0.439	0.541	0.657	0.418	1.551	0.537	4.481
Heartburn	-0.348	0.577	0.365	0.546	0.706	0.228	2.185
Acid reflux	-0.446	0.576	0.599	0.439	0.640	0.207	1.980
Nausea	0.125	0.582	0.046	0.830	1.133	0.362	3.544
Vomit	-0.249	0.646	0.149	0.700	0.779	0.220	2.766
Hiccup	-0.432	0.766	0.318	0.573	0.649	0.145	2.912
Belching	1.059	0.680	2.421	0.120	2.882	0.760	10.937
Eating discomfort	0.551	0.662	0.694	0.405	1.735	0.474	6.350
stomach ache	0.379	0.586	0.418	0.518	1.461	0.463	4.605
Smoking	0.405	0.476	0.726	0.394	1.500	0.590	3.811
Drinking	1.585	0.538	8.662	0.003	4.878	1.698	14.012
Hot diet	-0.116	0.579	0.040	0.841	0.890	0.286	2.768
Eating too fast	-0.225	0.578	0.152	0.697	0.798	0.257	2.477
Passive smoking	0.160	0.653	0.060	0.807	1.173	0.326	4.216
Missing teeth	0.032	0.474	0.005	0.946	1.033	0.408	2.614
Anemia	0.613	0.591	1.078	0.299	1.847	0.580	5.880
Family history of upper GC	-1.240	1.040	1.420	0.233	0.289	0.038	2.224

Statistical analysis

SPSS-24.0 (IBM Corp., Armonk, NY, USA) was performed for statistical analysis. The measurement data first passed $P<0.1$ to detect normality. If it does not conform to the normal distribution, use Mann-Whitey U test. The count data uses X^2 test. Univariate analysis used logistic regression. Multivariate analysis was the logistic regression for variables with $P < 0.1$ in univariate analysis. The diagnostic performance evaluation of a single measurement data adopted ROC. Multiple measurement data combined application diagnostic performance evaluation used firstly Logistic regression to calculate the P of the combined diagnosis. The specific evaluation index of diagnostic performance was the specificity, sensitivity, positive predictive value, negative predictive value, and so on obtained through ROC and four-grid table method. $P<0.05$ was considered statistically significant.

Results

Risk factors of GC in the whole group of patients

Male, older, drinking and G-17 respectively were more likely to develop GC in univariate analysis ($P<0.1$, Table 2). Multivariate analysis found that gender, age, drinking and G-17 have been independent risk factors that affect the occurrence of GC ($P<0.05$, Table 3).

Table 3: Multivariate analysis influencing the occurrence of GC and male GC

Influencing factors	*Partial regression coefficient*		*SE*		*Wald Bangla*		*P*		*OR*		*95% CI OR*			
											Lower		Upper	
		Male		Male		Male		Male		Male		Male		Male
Sex	2.474		1.095		5.106		0.024	0	11.871		1.389		101.499	
Age	0.125	0.121	0.037	0.034	11.705	12.62	0.001	0.017	1.133	1.128	1.055	1.056	1.218	1.206
G-17	0.034	0.026	0.012	0.011	8.554	5.651	0.003	0	1.034	1.026	1.011	1.005	1.058	1.048
Drinking	2.168	2.534	0.689	0.666	9.916	14.487	0.002	0	8.745	12.604	2.268	3.418	33.721	46.473

Risk factors for GC in male patients

Age, G-17 and drinking were more likely to develop GC in univariate analysis (P<0.1, Table 4). Age, G-17and heavy drinking were independent risk factors affecting the occurrence of GC in multivariate analysis (P<0.05, Table 3).

Table 4: Univariate analysis of influencing male and female GC

Influencing factors	*Partial regression coefficient*		*SE*		*Wald Bangla*		*P*		*OR*		*95% CI OR*			
											Lower		Upper	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Age	0.089	0.201	0.033	0.15	7.14	1.802	0.008	0.179	1.093	1.222	1.024	0.912	1.166	1.639
G-17	0.025	3.582	0.01	5.068	5.923	0.5	0.015	0.48	1.026	35.946	1.005	0.002	1.047	--
PGI	0	-0.027	0.002	0.026	0.013	1.049	0.908	0.306	1	0.973	0.996	0.924	1.003	1.025
PGII	-0.001	0.147	0.021	0.105	0.004	1.953	0.948	0.162	0.999	1.158	0.959	0.943	1.04	1.423
PGR	-0.001	-1.512	0.022	2.052	0.001	0.543	0.972	0.461	0.999	0.22	0.957	0.004	1.043	12.308
H. pylori	-0.242	-17.252	0.491	5684.145	0.244	0	0.622	0.998	0.785	0	0.3	0	2.055	
Bloating	0.74	-16.833	0.568	8380.814	1.7	0	0.192	0.998	2.096	0	0.689	0	6.378	
Heartburn	-0.206	-16.912	0.592	7463.647	0.121	0	0.728	0.998	0.814	0	0.255	0	2.597	
Acid reflux	-0.273	-16.954	0.591	7105.18	0.213	0	0.644	0.998	0.761	0	0.239	0	2.425	
Nausea	0.129	-16.76	0.598	9748.227	0.047	0	0.829	0.999	1.138	0	0.352	0	3.675	
Vomit	-0.049	-16.821	0.665	8569.17	0.005	0	0.941	0.998	0.952	0	0.259	0	3.503	
H. pylori	-0.318	-16.749	0.782	10048.24	0.166	0	0.684	0.999	0.727	0	0.157	0	3.368	
Belching	1.021	-16.628	0.709	17974.84	2.073	0	0.15	0.999	2.775	0	0.692	0	11.136	
Stomach ache	0.794	-16.808	0.619	8770.825	1.647	0	0.199	0.306	2.212	0	0.658	0	7.434	1.025
Eating discomfort	0.657	-16.681	0.689	12710.13	0.91	0	0.34	0.999	1.929	0	0.5	0	7.437	
Smoking	0.04	-16737	0.492	10377.78	0.007	0	0.936	0.998	1.041	0	0.397	0	2.729	
Heavy drinking	1.102	0	0.546	0	4.07	0	0.044	0	3.011	0	1.032	0	8.786	
Missing teeth	-0.233	17.648	0.502	4910.353	0.215	0	0.643	0.997	0.792	46156424	0.296	0	2.12	
Eating too fast	-0.137	-16.859	0.593	8038.594	0.053	0	0.818	0.998	0.872	0	0.273	0	2.79	
Anemia	0.861	-16.737	0.621	10377.78	1.922	0	0.166	0.999	2.367	0	0.7	0	8.001	
Family history of upper GC	-1.121	-16.76	1.052	9748.227	1.135	0	0.287	0.999	0.326	0	0.041	0	2.563	
Passive smoking	0.791	17.945	0.831	4610.45	0.906	0	0.341	0.997	2.206	62133648	0.433	0	11.243	

Risk factors for GC in female patients

The occurrence of GC had nothing to do with age, bloating, heartburn and other factors (Table 4).

Evaluation of G-17, age, sex, drinking and combined predict GC

ROC of G-17 and age predict the occurrence of GC had been 0.670(0.549, 0.791) and 0.735 (0.627, 0.843), cut-off value was 42.95 pmol/L and 69 years, sensitivity was 45% and 80.0%, and specificity was 83.5% and 59.6% respectively (Fig. 1). Gender and drinking respectively predict the occurrence of GC, sensitivity was 95% and 80%, specificity was 39.6% and 91.9%, positive predictive value was 10.7% and 50.0%, and negative predictive value was 99.0% and 98.3%.

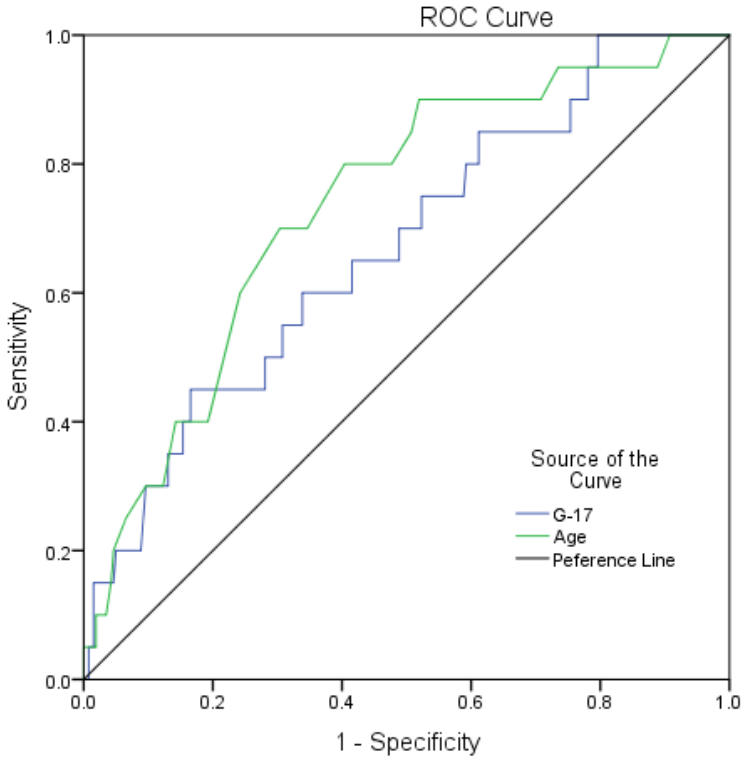

Fig. 1: ROC Curve of serum G-17, Age alone Screening for Gastric Cancer

G-17≥42.95pmol/L, age≥69 years, male and drinking were regarded as positive predictors of GC. The combined detection of these 4 items predicts sensitivity, specificity, positive predictive value, negative predictive value and accuracy of GC (Table 5). Although the combination of four, three and two indicators had high specificity, but its sensitivity was greatly reduced, therefore it was easy to miss the screen.

Specificity (True Negative Rate): reflects the ability of the screening test to determine that there was no GC; Sensitivity (True Positive Rate): reflects the ability of the screening test to determine GC. Positive predictive value: reflects the possibility of actually suffering from GC in the screening test; Negative predictive value: reflects the possibility of actually not suffering from GC in the screening test. Accuracy = true positive + true negative / total number of cases.

Table 5: G-17, age, sex and drinking combined respectively predict GC

Variable	*Gastroscopy diagnosis(cases)*		*Sensitivity (%)*	*Specificity (%)*	*Positive predictive value(%)*	*Negative predictive value(%)*	*Accuracy(%)*
	NGC	GC					
G-17+Age+Sex+Drinking							
NGC	259	19	5	92.50	43.20	93.20	93
GC	1	1					
G-17+Sex+Drinking							
NGC	259	18	10%	99.62	66.67	93.50	93.21
GC	1	2					
Age+Sex+Drinking							
NGC	254	16	20%	97.69	40	94.07	92.14
GC	6	4					
Sex+Drinking							
NGC	260	14	30%	100	100	94.89	95
GC	0	6					

ROC of the combined of G-17 and age in GC screening were 0.758 (0.662, 0.855), sensitivity and specificity were respectively 85.5% and 52.7% (Fig. 2). Therefore, G-17, age, and combined detection were certain reference value for predicting GC (AUC>0.5, P<0.05). ROC of the combined test was higher than that of a single indicator, but there was a crossover between 95%CI, indicating that the difference was not statistically significant, so predictive value of the combined test was low (Table 6).

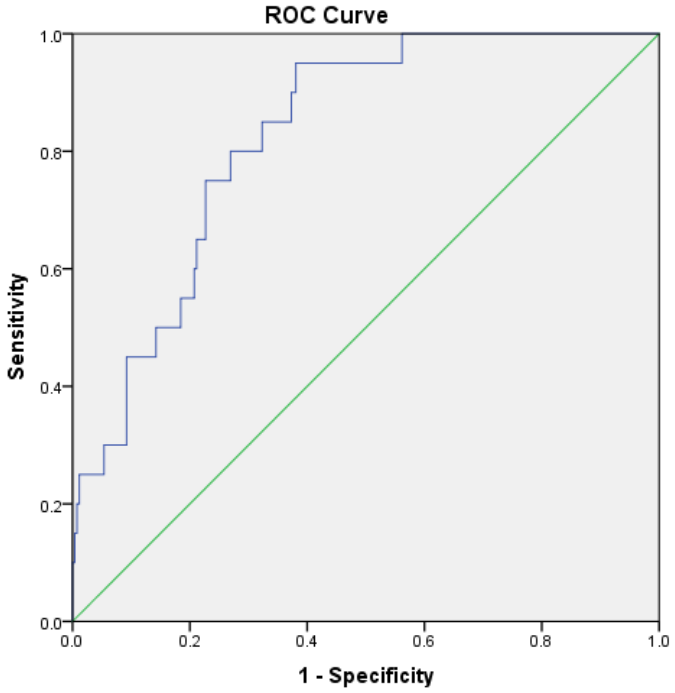

Fig. 2: ROC Curve of Age and serum G-17 combined to predict Gastric Cancer

Table 6: ROC parameters of G-17, Age, G-17 and Age in the diagnosis of GC

Variable	*AUC*	*95%CI*	*P*	*Optimal threshold*	*Sensitivity (%)*	*Specificity (%)*
G-17	0.670	0.549~0.791	0.011	42.95	45.00	83.50
Age	0.735	0.627~0.843	0	69.00	80.00	59.60
G17+Age	0.758	0.662~0.855	0		85.50	52.70

Comparison of different serological indexes in gastric diseases

In comparison of four groups, G-17 (22.73±54.02)pmol/L in GC group was higher than LGIN (5.64±12.35) pmol/L and CAG group (9.17±37.53) pmol/L (*P*<0.05 Table 7). PGR of GC group was (4.88±6.70) pmol/L was lower than NCAG group (11.48±10.50) pmol/L (*P*<0.05). PGI and PGII had not significant differences among the four groups (Table 7). The positive rate of *H. pylori*.IgG in LGIN group significantly higher than CAG and NCAG group (*P*<0.008, Table 7). The G-17 was not completely the same in GC, LGIN, CAG and NCAG groups (Table 7).

Table 7: Comparison of the contents of G-17, PGR, PGII, PGI and *H. pylori* positive rate in four groups (M±QR) pmol/L

Group	*Cases*	H. pylori *positive(cases)*	H. pylori *positive rate(%)*	*G-17*	*PGR*	*PGII*	*PGI*
GC	20	8	40	(22.73±54.02) *&	(4.88±6.70) &	(13.35±13.7)	(102.27±134.34)
LGIN	33	24	72.7*#	(5.64±12.35)	(9.34±7.37)	(13.5±9.37)	(153.06±90.55)
CAG	124	57	46	(9.17±37.53)	(9.76±13.15)	(11.31±13.1)	(126.91±140.71)
NAG	103	45	43.7	(8.29±22.89)	(11.48±10.5)	(11.98±12.5)	(153.06±90.55)

Compared to 2 groups *P*<0.05 was*, Compared to 3 groups *P*<0.05 was#,
Compared to 4 groups *P*<0.05 was &

Discussion

The development process of GC is generally: long-term stimulation by adverse factors→chronic inflammation→atrophic gastritis→CAG with IN →IN→EGC →advanced GC, in which IN is classified as LGI and HGIN. Some HGIN are similar to EGC due to their biological behavior (8).Early intervention during the evolution of gastric mucosal epithelium will reduce the incidence of GC (9).

In our study, gender, age, drinking, and G-17 could predict the occurrence of GC. A research found that males and older increase the risk of cardiac cancer (10). *H. pylori* infection and drinking were related to the incidence of GC (11). 327 cases of GC diagnosed by 109,530 subjects who underwent gastroscopy screening at Asan Medical Center. The seropositivity rate of *H. pylori* and drinking is independent positive risk factor for GC (12). There were an association between alcohol consumption and GC risk (13). Different from our study, hot food intake, family history of tumors, gastric disease and other factors were related to the occurrence of GC (12,13). We have analyzed that questionnaire was filled out mainly based on the subjective feelings of the patients, there may be deviations.

The 2020 Global Cancer Statistics Report shows that incidence and mortality of GC in men are higher than those in women (3). Our study also found that men are more likely to develop GC than women. Some studies have shown that the level of estrogen in the body may be negatively correlated with the occurrence of GC. A literature found that there was a negative correlation between hormone replacement therapy regulating the level of estrogen in the body and the incidence of GC (14).

However, many studies (15-17) attribute to men than women that are more likely to be affected by GC. Men are mainly caused by drinking alcohol. Our research also found that drinking is an independent risk factor affecting the occurrence of GC. A meta-analysis found a significant correlation between alcohol consumption and increased GC risk (18). There was a lack of correlation between moderate drinking and the risk of GC, but there was a correlation between heavy drinking (≥4 glasses per day) and the risk of GC (19).

The level of G-17 in GC group was higher than that in LGIN and CAG group, so G-17 was a good predictive value for GC. Our study was consistent with other research results (20-22). GC is higher than that of dysplasia and CAG. It may be because GC is mainly caused by the transformation of gastric mucosal epithelial cells into cancer cells, which loses the original gastric acid secretion function, and the body maintains normal functions. Lower gastric acid levels negatively stimulate G cells to secrete G-17, so G-17 compensatory increases in blood. Some studies have found that the elevated G-17 binding to gastrin receptors can promote tumor proliferation and metastasis (23).

Compared with CAG group, PGI and PGR levels of AG and EGA group were significantly reduced, and G-17 level was significantly increased ($P<0.05$) (24). A study of GC screening population in East China found that PGII and G-17 levels in patients with gastric IN and GC were significantly increased, and PGR were significantly reduced. The combined use of different serological markers can improve the diagnostic efficiency, G-17 combined with PGR had the highest diagnostic accuracy (25). Serological indicators also have certain significance in predicting and diagnosing CAG (26, 27). Our study found that PGR level in GC and severe dysplasia group was lower than NCAG group, but there was no significant difference between PGI and PGII. PGR with GC and severe dysplasia were low in our study. Compared with the change of a single index, it is of greater significance in the early screening of GC and dysplasia.

Our study found that *H. pylori* positive rate in LGIN group was significantly higher than AG and NCAG group, but *H. pylori* positive rate in the GC group had been low. This was different from previous study (28). It may be related to the relatively small number of GC patients included in this study. A retrospective cohort study that collected information from patients diagnosed with *H. pylori* infection in the Veterans Health Administration. The incidence of GC were 0.37%, 0.5%, and 0.65%, respectively after *H. pylori* infection 5, 10 and 20 years. Eradication of *H. pylori* can reduce the risk of GC (29). The molecular mechanism of *H. pylori*-induced GC has not yet been concluded. *H. pylori* infection is related to changes in PG levels (30). *H. pylori* may play a role in the PI3K-AKT signaling pathway that occurs in GC (31,32).

Conclusion

Older, drinking, men, and high G-17 are independent risk factors for GC. Especially in men, it is found that older, drinking, and high G-17 affect the occurrence of GC. G-17, age, drinking, and sex used alone to screen high-risk populations for GC are more efficient than combined screening. Compared with other gastric diseases, GC has a higher serum G-17 and a lower PG.

Ethics Journalism considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission,

redundancy, etc.) have been completely observed by the authors.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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