Association of Multiple Tumor Markers with gastric cancer patients

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Abstract

Background

To explore the correlation between multiple tumor markers and gastric cancer.

Methods

We selected 268 newly-treated patients with gastric cancer and 209 healthy subjects for correlation research. The detection of multiple tumor markers was based on protein chip, and then the results were statistically analyzed by SPSS.

Results

(1)We concluded that gastric cancer was significantly related to gender, age, AFP, CEA, CA125, CA199, and CA242 (P 0.001). After CA199 and CA242 were stratified by gender, the OR of the male was 30.400 and 31.242 respectively, while the OR of the female was 3.424. After CA125 was stratified by age, among patients with gastric cancer over 54 years old, The risk of occurrence in the CA125-positive population was 16.673 times that in CA125-negative patient; and among patients less than or equal to 54 years old, CA125-positive was not a risk factor for gastric cancer(P=0.082); (2)AFP, CEA, CA125, CA199, CA242 in M1 stage were statistically significant compared with M0 stage and control group (P<0.001), but AFP (P=0.045) and CA125 (P=0.752) were not statistically significant compared with M0 stage and control group; (3)The combined detection sensitivity of multiple tumor markers were 41.79%.

Conclusions

Our research shows that gastric cancer is associated with age, gender, and the positive of AFP, CEA, CA125, CA199, and CA242. The positive of AFP and CA125 is related to the distant metastasis of gastric cancer; The combined detection of multiple tumor markers can be used for initial screening of gastric cancer to a certain extent.

Introduction

According to the 2019 State Council Development Research Center's research report on Cancer Incentives and Disease Burden in China, gastric cancer ranks second in incidence in China(1). Internationally, incidence and mortality rates of gastric cancer have been steadily declining over the last one-half century in most populations, but gastric cancer remains an important cancer worldwide and it is responsible for over one million new cases in 2020 and an estimated 769,000 deaths (equating to one in every 13 deaths globally), ranking fifth for incidence and fourth for mortality globally(2), exceeding 2/5 of the new cases occurred in China(1). Data show that the 5-year survival rate of gastric cancer confined to the mucosal layer of the gastric wall is higher than that of advanced patients. Due to the lack of typical clinical symptoms in the early stage of gastric cancer. Most patients are diagnosed as advanced as soon as they are diagnosed. The initial diagnosis rate is less than 10%. The 5-year survival rate is approximately 20%(3). Early detection and treatment are critical factors in the cure of gastric cancer, which can improve the survival rate of patients. Early non-specific symptoms coupled with objective factors such as the large population base in our country and the different medical standards in different regions, most patients are already in the middle and advanced stages when they are discovered, and the treatment effect is poor. The objectives of this paper is to study the relationship between gastric cancer and tumor markers, and further explore the possibility of early screening of tumor markers in gastric cancer.

Materials And Methods

Materials

A total of 268 newly-treated gastric cancer patients (aged 60.91±11.51) who were accepted by Sichuan Cancer Hospital from June 2018 to December 2019 were selected. Inclusion criteria: ①Gastric cancer group: in line with Guidelines for the Standardized Diagnosis and Treatment of Gastric Cancer(4) from the Chinese Medical Association, all diagnoses were performed by gastroscopy, CT, B-ultrasound, etc., and gastric cancer was confirmed by gastroscopy or postoperative pathological biopsy; no other primary sites cancer; no history of chemotherapy, radiotherapy or immunotherapy before collecting serum samples; age >18 years; M stage was collected according to the AJCC 7^{th} edition. ②Control group: 209 physical examination subjects who underwent physical examination in this hospital during the same period were selected as the control group (age 48.08±12.66). Healthy physical examination: No serious heart, brain, liver, lung, kidney, and other primary diseases in the past, relevant examinations are within the normal range; age> 18 years old. Exclusion criteria: accompanied by major organ dysfunction; combined with septic shock, hemorrhagic shock, myocardial infarction, and other diseases; pregnant and lactating female.

Methods

Equipment and reagents

Multi-tumor marker detection kit (Chaozhou Shukang Biotechnology Co., Ltd.), LU-07 biochip reader (Shanghai Mingyuan Shukang Biochip Co., Ltd.), biochip image analysis system software by Huzhou Shukang Biotechnology Co., Ltd.

Use a pyrogen-free and endotoxin test tube to draw 2ml of fasting venous blood, and collect serum samples without hemolysis after centrifugation. After the serum was antiquated, it was stored in a refrigerator at 4°C, and tested within 5 days, and equilibrated to room temperature before testing. Strictly follow the instructions of the biochip reader.

Statistics

The results were analyzed using SPSS26.0 statistical software (SPSS Inc., Chicago, Illinois, USA). The chi-square test was utilized to study clinical characteristics in two groups. The age value was established by the decision tree method. Gender and age stratification statistics were tested by CMH test. $P<0.010$ was considered statistically significant.

Results

The data distribution of tumor markers was shown in Table 1 and Fig 1. This article obtained the normal reference value depending on the upper limit of 95% reference values of its laboratory (Table 1).

Table 1. Distribution of Tumor Markers levels with Gastric cancer and Control

Tumor markers	Gastric Cancer (n=268)			Control (n=209)		
	Min	Max	Upper limit of 95% reference value	Min	Max	Upper limit of 95% reference value
AFP(ng/ml)	0.24	300.00	10.00	0.24	9.40	3.69
NSE(ng/ml)	1.26	57.47	6.83	1.32	8.00	4.33
FER(ng/ml)	2.21	519.46	412.3175	3.97	485.74	376.87
CEA(ng/ml)	0.23	60.00	50.38	0.20	10.88	3.18
CA125(U/ml)	1.43	500.00	231.31	1.70	147.25	20.46
CA153(U/ml)	1.08	176.79	23.06	1.46	75.00	24.46
CA199(U/ml)	2.00	455.13	384.08	0.56	46.00	24.23
CA242(U/ml)	1.00	200	143.67	1.00	24.61	7.61

AFP, alpha fetoprotein; NSE, neuron-specific enolase; FER, Ferritin; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153; CA199, carbohydrate antigen 199; CA242, carbohydrate antigen 242

Comparison of clinical characteristics between two groups

It could be seen from Table 2 and Table 3 that gastric cancer was significantly related to the gender and age of patients (P<0.001). Males accounted for 73.9% of the gastric cancer group, and the risk of the male suffering from gastric cancer was 3.329 times that of female; the age group over 54 years old in gastric cancer patients which accounted for 70.89%, and the risk of gastric cancer was 6.342 times that of the patient under 54 years.

It showed in Fig 2 that the positive of AFP, CEA, CA125, CA199, and CA242 was significantly correlated with gastric cancer (P<0.001). To further explore the impact of gender, and age on tumor markers, we conducted a group study based on gender and age.

*The chi-square test revealed a significant correlation between AFP, CEA, CA125, CA199, CA242 levels and these features of gastric cancer

The relationship between gastric cancer and multiple tumor markers stratified by gender.

It showed in Table 2 that the positive of AFP(OR=3.803), CEA(OR=6.633), CA125(OR=4.906), CA199, and CA242 was significantly correlated with gastric cancer (P<0.001). After CA199 was stratified by gender. In the male, the OR was 30.400, 95% CI was 4.127-223.928, P□0.001, the risk of CA199-positive was 30.4 times than that of CA199-negative suffering from gastric cancer. In the female, CA199-positive was also a risk factor for gastric cancer. The OR was 3.424, 95% CI was 1.420-8.257, P=0.004, the risk of

Table 2. The relationship between gastric cancer and multiple tumor markers stratified by gender.

Tumor markers	Gender	Gastric cancer(n=268)	Control(n=209)	χ^2	OR95%CI	P
/	Female	70	113			
/	Male	198	96	38.787	3.329(2.265-4.893)	0.001
AFP-	Female	60	105			
	Male	165	94			
AFP+	Female	10	8			
	Male	33	2	15.043	3.803(1.862-7.767)	0.001
NSE-	Female	62	110			
	Male	179	89			
NSE+	Female	8	3	4.592	2.229(1.054-4.717)	0.038
	Male	19	7			
FER-	Female	67	113			
	Male	185	86			
FER+	Female	3	0	4.924	/	0.054
	Male	13	10	1.330	0.604(0.255-1.433)	0.249
CEA-	Female	55	109			
	Male	146	90			
CEA+	Female	15	4	35.449	6.633(3.318-13.261)	0.001
	Male	52	6			
CA125-	Female	54	104			
	Male	161	95			
CA125+	Female	16	9	23.022	4.906(2.429-9.905)	0.001
	Male	37	1			
CA153-	Female	66	109			
	Male	191	90			
CA153+	Female	4	4	0.129	0.852(0.355-2.046)	0.719
	Male	7	6			
CA199-	Female	54	104			
	Male	150	95			
CA199+	Female	16	9	8.128	3.424(1.420-8.257)	0.004
	Male	48	1	25.057	30.400(4.127-	

					223.928)	0.001
CA242-	Female	54	104			
	Male	149	95			
CA242+	Female	16	9	8.128	3.424(1.644-4.446)	0.004
	Male	49	1	25.741	31.242(4.243-230.043)	0.001

OR: odds ratio; CI: confidence interval;

Table 3. The relationship between gastric cancer and multiple tumor markers stratified by age.

Variable	Age	Gastric Cancer (n=268)	Control (n=209)	χ^2	OR95%CI	P
/	≤54	78	151			
/	>54	190	58	87.571	6.342(4.245-9.474)	<0.001
AFP-	≤54	69	144			
	>54	156	55			
AFP+	≤54	9	7	15.074	3.803(1.862-7.767)	<0.001
	>54	34	6			
NSE-	≤54	73	141			
	>54	168	58			
NSE+	≤54	5	10	4.592	2.580(1.050-6.336)	0.032
	>54	22	0			
FER-	≤54	76	141			
	>54	176	58			
FER+	≤54	2	10	1.706	0.371(0.079-1.737)	0.229
	>54	14	0	4.529	1.330(1.235-1.431)	0.045
CEA-	≤54	67	146			
	>54	134	53			
CEA+	≤54	11	5	35.449	6.633(3.318-13.261)	<0.001
	>54	56	5			
CA125-	≤54	68	142			
	>54	147	57			
CA125+	≤54	10	9	3.181	2.32(0.901-5.974)	0.082
	>54	43	1	13.309	16.673(2.243-123.91)	<0.001
CA153-	≤54	75	142			
	>54	182	57			
CA153+	≤54	3	9	0.129	0.852(0.355-2.046)	0.719
	>54	8	1			
CA199-	≤54	66	144			
	>54	138	55			
CA199+	≤54	12	7	32.670	6.243(3.117-12.503)	<0.001
	>54	52	3			
CA242-	≤54	66	144			

	>54	137	55			
CA242+	≤54	12	7	33.589	6.372(3.184-12.753)	<0.001
	>54	53	3			

OR: odds ratio; CI: confidence interval;

CA199-positive was 3.424 times than that of CA199-negative suffering from gastric cancer; After CA242 was stratified by gender, in male, the OR was 31.242, 95% CI was 4.243-230.043, P<0.001, the risk of CA242-positive was 31.242 times than that of CA242-negative suffering from gastric cancer. In the female, CA242-positive was also a risk factor for gastric cancer. The OR was 3.424 and 95% CI was 1.420-8.257, P=0.004, the risk of CA242-positive was 3.424 times than that of CA242-negative suffering from gastric cancer.

The relationship between gastric cancer and multiple tumor markers stratified by age.

It could be seen from Table 3 that the positive of AFP (OR=3.803), CEA (OR=6.633), CA125, CA199 (OR=6.234), CA242 (OR=6.372) was significantly related to gastric cancer (P<0.001), After CA125 was stratified by age, patients with older than 54 years, the OR was 16.673, 95% CI was 2.243-123.91, P<0.001, that was, the risk of CA125-positive was 16.673 times than that of CA125-negative suffering from gastric cancer; While less than or equal to 54 years old people, CA125 positive was not a risk factor for the disease. The OR was 2.32, the 95% CI was 0.901-5.974, and P=0.082.

The relationship between gastric cancer distant metastasis and tumor markers.

We further studied the relationship between gastric cancer distant metastasis and tumor markers. From Table 4 and Fig 3, we could see that as the staging of gastric cancer was delayed, the proportion of positive tumor markers increased, and AFP, CEA, CA125, CA199, CA242 in the M1 stage were statistically significant compared with the M0 stage and control group ((P<0.001), but AFP (P=0.045) and CA125 (P=0.752) were not statistically significant compared with the M0 stage and control group.

*AFP, CA125 in the M1 stage were statistically significant compared with the M0 stage and the control group (P<0.001), but AFP (P=0.045) and CA125 (P=0.752) were not statistically significant compared with the M0 stage and control group.

Sensitivity, specificity, and accuracy of single and multiple serum tumor markers

The results in Table 5 showed that the sensitivity of AFP, CEA, CA125, CA199, and CA242 to detect gastric cancer was 16.04%, 25.00%, 19.78%, 23.88%, 24.25%, and the sensitivity of combined detection of multiple tumor markers was 41.79%, which the specific was 82.78% and the accuracy was 59.75%. In the M0 stage, the sensitivity of AFP, CEA, CA125, CA199, and CA242 to detect gastric cancer was 9.95%, 16.92%, 5.47%, 14.43%, 14.93%, and the sensitivity of combined detection of multiple tumor markers was 29.35%. While in the M1 stage, the sensitivity of AFP, CEA, CA125, CA199, and CA242 to detect gastric cancer was 34.33%, 49.25%, 62.69%, 52.24%, 52.24%, and the sensitivity of combined detection of multiple tumor markers was 79.1%.

Discussion

Gastric cancer is a malignant tumor disease with a high incidence. At the same time, the disease also is under a high fatality rate, and the threat to human health and life safety should

Table 4. Difference of tumor markers between M stage

Variable	AFP+	AFP-	CEA+	CEA-	CA125+	CA125-	CA199+	CA199-	CA242+	CA242-
Control	10	199	10	199	10	199	10	199	10	199
M0(201)	20	181	34	167	11	190	29	172	30	171
M1(67)	23	44	33	34	42	25	35	32	35	32
$\chi^2$1	4.031		15.739		0.100		11.069		11.967	
P1	0.045*		<0.001		0.752*		0.001		0.001	
$\chi^2$2	42.067		76.282		111.241		83.725		83.725	
P2	<0.001		<0.001		<0.001		<0.001		<0.001	
$\chi^2$3	22.169		28.027		103.680		39.521		38.083	
P3	<0.001		<0.001		<0.001		<0.001		<0.001	

$\chi^2$1, **P1 M0 vs control,** $\chi^2$2, **P2 M1 vs control,** $\chi^2$3, **P3 M0 vs M1**

* AFP (P=0.045) and CA125 (P=0.752) were not statistically significant compared with M0 stage and control group

Table 5. Sensitivity, specificity, and accuracy of single and multiple serum tumor markers

Tumor marker	Sensitivity (%)			Specificity (%)	Accuracy (%)
	M0+M1	M0	M1		
AFP	16.04(43/268)	9.95(20/201)	34.33(23/67)	95.22(199/209)	50.73(242/477)
CEA	25.00(67/268)	16.92(34/201)	49.25(33/67)	95.22(199/209)	55.77(266/477)
CA125	19.78(53/268)	5.47(11/201)	62.69(42/67)	95.22(199/209)	52.83(252/477)
CA199	23.88(64/268)	14.43(29/201)	52.24(35/67)	95.22(199/209)	55.14(263/477)
CA242	24.25(65/268)	14.93(30/201)	52.24(35/67)	95.22(199/209)	55.35(264/477)
Combination	41.79(112/268)	29.35(59/201)	79.10(53/67)	82.78(173/209)	59.75(285/477)

not be underestimated. Serum tumor markers refer to substances secreted by tumor cells in the -5process of tumor occurrence and development, including enzymes, oncogenes, protein antigens, hormones, glycoprotein antigens, etc., which have a vital role in tumor generation, change, development, and metastasis evolution. Such substances are generally expressed at low levels in normal physical examiners or patients with benign lesions. Below the detection threshold, the test results are often negative. However, when the body develops cancer cell proliferation, the serum tumor marker level rises high, it can be used for early screening of gastric cancer, and it can also play a certain auxiliary role in the prognostic evaluation and diagnosis of gastric cancer(5-9).

It is common practice in clinical practice to quote the reference values provided by literature or commercial kit, which is not appropriate because these reference values come from different laboratories, different regions, different populations, and different instruments(10, 11). Therefore, in the statistics of healthy people, we established our normal reference values in Table 1. This is of great significance for establishing normal reference values in the region and screening for gastric cancer.

The prevalence of gastric cancer increases with age, and male is larger than the female(2, 12-14). In this study, the number of male patients was much more than that of female patients, and the male-female sex ratio was 3.36:1. For patients aged less than or equal to 54 years and older than 54 years, the difference was statistically significant. The risk of gastric cancer older than 54 years was 6.342 times that of those younger than 54 years old people.

Alpha-fetoprotein (AFP) is a more sensitive tumor marker for primary liver cancer, but it can also be significantly increased in gastric cancer(15), and it is also widely used in the diagnosis of gastric cancer(16, 17). The results of our study showed that the sensitivity of serum AFP in the gastric cancer group was only 16.04%, AFP in the M1 stage was statistically significant compared with the M0 stage and control group ((P<0.001), but AFP (P=0.045) was not statistically significant compared M0 stage with the control group, This conclusion suggested that AFP may be related to the distant metastasis of gastric cancer. Some research has shown that AFP positive is associated with liver metastasis (18, 19). Carcinoembryonic antigen (CEA) is a broad-spectrum tumor marker. It is synthesized in small amounts in the gastrointestinal tract of adults and is excreted through the gastrointestinal tract without entering the blood system. When gastrointestinal tumors occur, the expression of CEA in serum can be significantly increased(17, 20, 21). Pang Fangning et al.(22) tested 3807 patients with gastric cancer and found 756 patients with positive CEA, with a sensitivity of 19.9% in patients with gastric cancer. The results of this study showed that the sensitivity of serum CEA in patients with gastric cancer was 25.00%, which directly confirmed that CEA was in high expression in patients with gastric cancer; Carbohydrate antigen (CA125) was initially used in the diagnosis and prognosis of ovarian cancer. Later studies have found that it has a clear connection to gastric cancer and has been widely used in the diagnosis of gastric cancer. Related studies have shown that the sensitivity of CA125 for gastric cancer is 34.3%(23), and the results of this study showed that the sensitivity was 19.78%. CA125 in the M1 stage was statistically significant compared with the M0 stage and the control group (P<0.001), but CA125 (P=0.752) was not statistically significant compared the M0 stage with control group. This conclusion suggested that CA125 might be related to the distant metastasis of gastric cancer. The CA125 levels had shown significant elevations with the presence of peritoneal carcinomatozis(24), and Tsutomu Namikawa(23) have shown that CA125 is a useful prognostic biomarker in patients with unresectable advanced or recurrent gastric cancer. The results of multiple studies have shown that CA125 is related to peritoneal metastasis.(9, 25-27), This research validates this view; Carbohydrate antigen (CA199) is an oligosaccharide tumor-associated antigen, expressed in the esophageal glandular epithelium of the digestive system, gastrointestinal Tract epithelium, pancreatic duct

epithelium, etc.(28). CA199 is reported to have the highest sensitivity in the diagnosis of gastrointestinal tumors(29). However, this study found that the sensitivity of CA199 was only 23.88%, which was not much different from that of Pang Fangning et al.(22) with a sensitivity of 19.0%; Carbohydrate antigen (CA242) is a mucin-like glycoprotein, a new type of tumor-associated antigen, Zhao LY(30), and other reports found that the sensitivity of serum CA242 to detect gastric cancer was as high as 25%~ 60%. The results of this study showed that the sensitivity of serum CA242 in patients with gastric cancer was only 24.25%. Due to the different tumor stages, regions, genders, study subjects, etc., the diagnostic sensitivity of the research results is slightly different. At the same time, the results of this study showed that it could provide a quantitative reference for clinical diagnosis of gastric cancer. In addition, the results of the CMH test in this study showed that although CA199 and CA242 were risk factors for gastric cancer, the risk factors were different due to the influence of gender. For the male, the risk value was greater. Results of age stratification showed that for people older than 54 years old, CA125 positive was a risk factor, but for people less than or equal to 54 years old, it was not a risk factor.

So far, no ideal tumor markers with 100% sensitivity and 100% specificity have been found in gastric cancer detection. The optimal serum biomarker for the detection of early gastric cancer is still under investigation(31). The existing tumor markers and tumors do not possess a complete one-to-one correspondence, but only a correlation. Therefore, medical experts believe that to improve the detection rate of early tumors, it is necessary to conduct multiple tumor markers combined detection. It can be observed from this article and kinds of literature that the sensitivity of single detection of tumor markers was low, ranging from 16.04% to 25.00%, and the combined detection of multiple indicators could be used to make up for shortcomings to a certain extent. The results of Yang Xueqin et al.(32) showed that the overall sensitivity of multi-tumor markers was only 35.9%. In this study, comprehensive sensitivity for detecting gastric cancer was 41.79%. The sensitivity of single detection of tumor markers in the M0 stage was lower, ranging from 5.47% to 16.92%, while the sensitivity in the M1 stage was higher, ranging from 34.33% to 62.69% and comprehensive sensitivity for detecting gastric cancer was up to 79.10% (Table 5). Our results showed that as gastric cancer changes from the M0 stage to the M1 stage, the positive rate of tumor markers increased significantly. The positive of CA125 and AFP should be considered whether there was distant metastasis of cancer cells.

It could be known from this article and many documents(14) that gastric cancer is related to age, gender, and individual tumor markers, and the combined detection of multi-index tumor markers can be used for early screening of gastric cancer to a certain extent. However, their documents also have some limitations. According to the clinical test results of tumor markers, the data are seriously skewed and cannot be quantitatively analyzed through data transformation or processing. This is one point that distinguishes this study from other studies. And there were a few limitations to our study. Firstly, This is an analysis that comes from a single center in western China, the results of this study may not represent the overall Chinese population well. Secondly, Since some patients were diagnosed as advanced, the gastric cancer group did not subdivide the tumor stage, nor did it study the relationship between tumor location and tumor markers. Thirdly, multi-tumor markers testing is not included in the scope of physical examination for healthy people, so the sample size of the control group is small. In conclusion, gastric cancer is associated with age, gender, and the positive of AFP, CEA, CA125, CA199, and CA242. The positive of AFP and CA125 is related to the distant metastasis of gastric cancer; The combined detection of multiple tumor markers can be used for initial screening of gastric cancer to a certain extent.

To improve the sensitivity of early screening and early diagnosis of gastric cancer, and to reduce the missed diagnosis rate to a certain extent, the higher-risk population is firstly identified through tumor marker detection, and then imaging, gastroscopy, and colonoscopy are performed on them, which will be more conducive to digestion

systematic malignant tumor detection, easy to obtain materials for tumor marker detection, convenient operation, low cost, so it is feasible in large-scale gastric cancer screening, and multi-tumor markers detection can screen a variety of common cancers, early intervention and treatment are conducive to reducing the medical burden of the country and individuals, and joint testing of multiple tumor markers should be advocated.

Declarations

Acknowledgements

Not applicable.

Abbreviations

AFP, alpha fetoprotein; NSE, neuron-specific enolase; FER, Ferritin; CEA, carcinoembryonic antigen; CA1125, carbohydrate antigen 125; CA153, carbohydrate antigen 153; CA199, carbohydrate antigen 199; CA242, carbohydrate antigen 242

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Figures

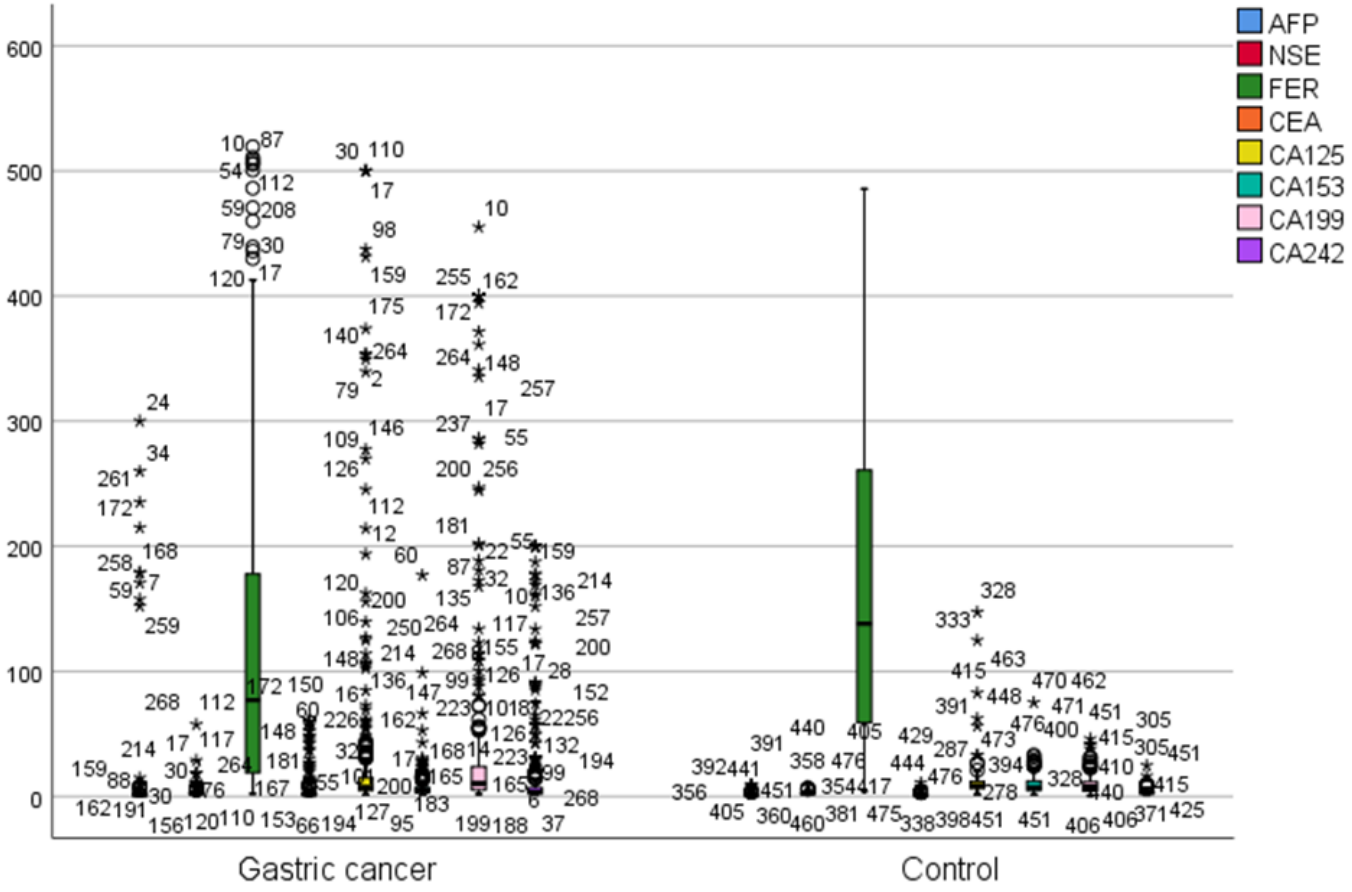

Figure 1

Distribution of Tumor Markers levels with Gastric Cancer and Control (Box and Whisker Plot).

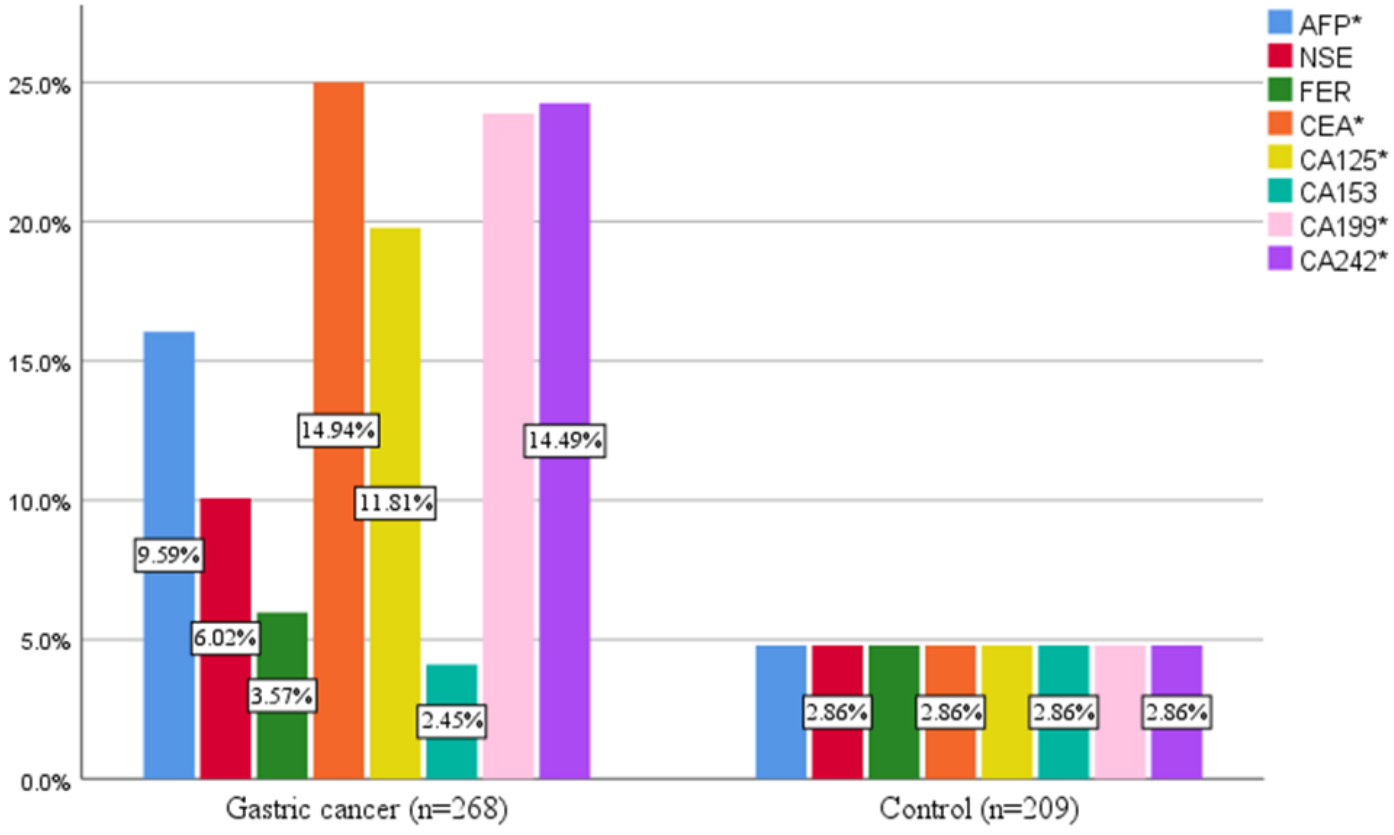

Figure 2

Comparison of tumor markers between two groups. *The chi-square test revealed a significant correlation between AFP, CEA, CA125, CA199, CA242 levels and these features of gastric cancer

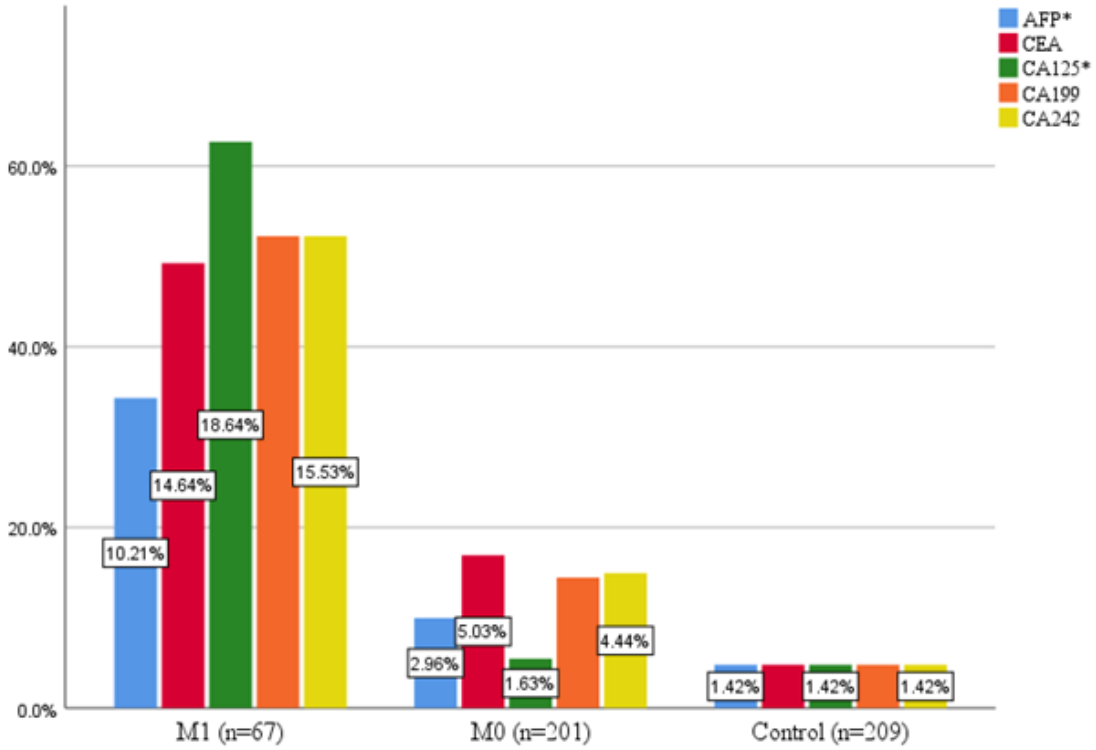

Figure 3

Comparison of tumor markers among three groups *AFP, CA125 in the M1 stage were statistically significant compared with the M0 stage and the control group (P<0.001), but AFP (P=0.045) and CA125 (P=0.752) were not statistically significant compared with the M0 stage and control group.