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Blood index panel for gastric cancer detection

Guang-Hong Guo, Yi-Bin Xie, Peng-Jun Zhang, Tao Jiang

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Guang-Hong Guo, Department of Laboratory Medicine, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, China

Yi-Bin Xie, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Peng-Jun Zhang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Interventional Therapy Department, Peking University Cancer Hospital and Institute, Beijing 100142, China

Tao Jiang, Medicine Innovation Research Division of Chinese PLA General Hospital, Beijing 100853, China

Corresponding author: Tao Jiang, MD, Doctor, Medicine Innovation Research Division of Chinese PLA General Hospital, No. 28 Fuxing Road, Beijing 100853, China.
laoai2915@163.com

Abstract

BACKGROUND

Gastric cancer is a common malignant tumor. Early detection and diagnosis are crucial for the prevention and treatment of gastric cancer.

AIM

To develop a blood index panel that may improve the diagnostic value for discriminating gastric cancer and gastric polyps.

METHODS

Thirteen tumor-related detection indices, 38 clinical biochemical indices and 10 cytokine indices were examined in 139 gastric cancer patients and 40 gastric polyp patients to build the model. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation. After area under the curve evaluation and univariate and multivariate analyses.

RESULTS

Five tumor-related detection indices, 12 clinical biochemical indices and 1 cytokine index showed significant differences between the gastric cancer and gastric polyp groups. Carbohydrate antigen (CA) 724, phosphorus (P) and ischemia-modified albumin (IMA) were included in the blood index panel, and the area under the curve (AUC) of the index panel was 0.829 (0.754, 0.905). After validation, the AUC was 0.811 (0.700, 0.923). Compared to the conventional index

CA724, the blood index panel showed significantly increased diagnostic value.

CONCLUSION
We developed an index model that included CA724, P and IMA to discriminate the gastric cancer and gastric polyp groups, which may be a potential diagnostic method for clinical practice.

Key Words: Gastric cancer; Gastric polyp; Blood; Index; Panel

Core Tip: Early diagnosis and early treatment of gastric cancer is the key to improving the survival and cure rates of patients. Therefore, early detection and diagnosis are crucial for the prevention and treatment of gastric cancer. In this study, the we aimed to evaluate the diagnostic value of the blood index panel for gastric cancer.

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INTRODUCTION

Gastric cancer is a common malignant tumor that endangers human health, and it ranks second only to lung cancer in the number of deaths resulting from various malignant tumors[1]. The occurrence and development of gastric cancer is a multistage process involving changes at the gene and molecular levels. There is a period of precancerous lesions in the early stage of gastric cancer, and most of the precancerous lesions remain unchanged, while some develop into cancer[2]. The Correa cascade is a generally recognized model of gastric cancer, which is superficial gastritis-atrophic gastritis-intestinal metaplasia-dysplasia-gastric cancer. In recent years, the incidence of gastrointestinal malignant tumors in China has increased significantly[3]. Because most gastrointestinal malignant tumors have no obvious symptoms during the early stage, they cannot be detected quickly. The postoperative survival rate of malignant tumors is very low[4]. Early diagnosis and early treatment of gastric cancer is the key to improving the survival and cure rates of patients. Therefore, early detection and diagnosis are crucial for the prevention and treatment of gastric cancer[5].

With further research, finding a simple, fast and easy dynamic observation method that can screen high-risk groups of gastric cancer (such as patients with atypical hyperplasia) would be beneficial for early diagnosis, and serum biomarkers (tumor markers, combined screening of cytokines and biochemical indicators) may be new targets for the early diagnosis of gastric cancer. Tumor markers reflect the occurrence and development of tumors and the degree of activation or inactivation of tumor-related genes. Since these substances are secreted by tumor cells and released into the blood and body fluids during tumor proliferation, they can be used to indicate the presence of tumors[6,7]. An ideal tumor marker has the characteristics of high sensitivity and high specificity, is present in body fluids, especially blood, and is easy to detect. In recent years, due to the rapid development of molecular biology, markers related to gastric cancer have been continuously discovered. The cell surface structural antigen carcinoembryonic antigen (CEA) is a tumor-associated antigen that can be extracted from embryonic tissue and detected in a variety of body fluids. As one of the most common tumor markers, it is widely used as a diagnostic and monitoring index for various gastrointestinal tumors (especially gastric adenocarcinoma)[8-10]. Carbohydrate antigen (CA) 724 is a high molecular weight glycoprotein and one of the best tumor markers for the diagnosis of gastric cancer. CA724 is highly specific for gastric cancer and has good application value in digestive system malignant tumors[10-12]. In addition, cytokines also play important roles in the initiation and treatment of cancer. Cytokines produced by tumor cells or the tumor stroma can stimulate the survival, proliferation, and metastasis of cancer cells. These factors were demonstrated to be potential biomarkers for various cancers[13-15].

In our study, we examined 13 tumor-related indices, 38 clinical biochemical indices and 10 cytokines in gastric cancer and gastric polyp patients and aimed to develop an index panel that can improve the diagnostic value of discriminating gastric cancer and gastric polyp patients. This panel may become a detection method for clinical practice.

MATERIALS AND METHODS

Study subjects

Signed informed consent was obtained, and this study was approved by the Ethics Committee of the First Center of Chinese PLA General Hospital. A total of 269 serum samples were collected from patients with gastric cancer and gastric polyps who were admitted to the First Center of Chinese PLA General Hospital. The inclusion criteria for gastric cancer and gastric polyps were as follows: (1) Primary; (2) Confirmed by pathological diagnosis; (3) No radiotherapy or chemotherapy before surgery; (4) Preoperative diagnosis with more than two imaging results; and (5) Complete medical records and follow-up data. The exclusion criteria were as follows: (1) Received radiotherapy, chemotherapy, and immunotherapy; (2) Immune system diseases; (3) Chronic wasting diseases and infectious diseases; and (4) Other types of malignant tumors. A total of 139 gastric cancer patients and 40 gastric polyp patients were enrolled for model building. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation. The two groups were age- and sex-matched. Three milliliters of fasting venous blood was collected from the subjects, incubated for 30 min, and centrifuged at 3500 r/min for 7 min to separate the serum, and the specimens without hemolysis or chyle were qualified and stored at -80 °C.

Tumor-related and clinical biochemical index detection

The 13 tumor-related indices included CEA, alpha fetoprotein (AFP), carbohydrate antigen 125 (CA125), CA199, CA153, CA724, cytokeratin fragment 211 (Cyfra211), ferritin (Ferr), neuron-specific enolase (NSE), squamous cell carcinoma (SCC), pepsinogen (PG) I, PG II, and PGI/II. The 38 clinical biochemical indices included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), total bilirubin (TB), direct bilirubin (DB), total bile acid (TBA), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), glucose (GLu), urea nitrogen (UN), creatinine (Cr), uric acid (UA), cholesterol (CHO), triglyceride (TG), creatine kinase (CK), lactate dehydrogenase (LDH), isoenzyme of creatine kinase (CKMB), calcium (Ca), phosphorus (P), magnesium (Mg), potassium (K), sodium (Na), chlorine (Cl), carbon dioxide (CO_2), lipoprotein a (LPa), high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A1 (ApoA1), apoB, cysteine (CYS), sialic acid (SA), homocysteine (HCY), C-reactive protein (CRP), amylase (AMY), lipase (LPS), superoxide dismutase (SOD), and ischemia-modified albumin (IMA).

CEA, AFP, CA199, CA724, CA125, CA153, Cyfra211, Ferr, NSE, ALT, AST, TP, ALB, ALP, GGT, Glu, UN, CR, UA, CHO, TG, CK, Ca, P, Mg, K, Na, CL, CO2, HDL, LDL, CRP, AMY, and LPS detection kits, standards and controls were purchased from Roche Diagnostics Ltd. ApoA1, ApoB, CYS, Lp (a), and CKMB detection kits, standards and quality controls were purchased from Beijing Leadman Biochemical Co., Ltd. SCC, PG I and PG II assay kits, standards and controls were purchased from Abbott Laboratories. TBA and HCY detection kits, standards and quality controls were purchased from Beijing Jiuqiang Biotechnology Co., Ltd. TB and DB detection kits, standards and controls were purchased from Hitachi Japan. IMA test kits, standards and quality controls were purchased from Changsha Yikang Technology Development Co., Ltd. SA detection kits, standards and quality controls were purchased from Zhejiang Dongou Diagnostics Products Co., Ltd. SOD detection kits, standards and quality controls were purchased from Fujian Fuyuan Biotechnology Co., Ltd. The serum was collected from the -80 °C serum specimen bank, and after being thawed, 500-1000 μL was dispensed into a centrifuge tube and assigned a new number. The Modular 7600 automatic biochemical analyzer, Roche E170 immunoassay analyzer and Architect i2000 immunoassay system were used to complete quality control and calibrations before the assays. After analysis, the experimental data from each instrument were exported for statistical analysis.

Cytokine detection

The 10 cytokines included granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFNγ), interleukin-1β (IL-1β), IL-2, IL-4, IL-6, IL-8, IL-10, monocyte chemoattractant protein (MCP-1), and tumor necrosis factor α (TNFα) and were analyzed by a Luminex Instrument Model 200 Liquid Core Analyzer according to the instructions of the Human Cytokine/Chemokine Detection Kit. All reagents were equilibrated to room temperature (20 °C-25 °C) before the test. A schematic diagram of sample loading in a 96-well plate was drawn on paper (standards, 0, 3.2, 16, 80, 400, 2000, and 10000 ng/mL, QC I, QC II, sample), and duplicate wells were recommended. Then, 200 μL of assay buffer was added to each reaction well, which was sealed and shaken on a horizontal shaking instrument for 10 min (room temperature, 20 °C-25 °C). The excess assay buffer was blotted from the bottom with filter paper or paper towels. Then, 25 μL of analysis buffer was added to the background standard well, 25 μL of buffer was added to each sample well, 25 μL of each standard or quality control was added to the corresponding reaction well, and 25 μL of the appropriate matrix diluent was added to the background wells, standard wells, and quality control wells. When the analyte was serum or plasma, the serum matrix provided by the kit was used. When the analyte was tissue culture fluid or other supernatant, the corresponding medium was used as a diluent. A total of 25 μL of sample was added to the appropriate reaction well, the microspheres were mixed, and 25 μL of the mixed microspheres was added to each

well. The wells were covered with parafilm and aluminum foil and incubated at room temperature (20 °C-25 °C) on a horizontal shaker for 1 h (when the test substance was serum or plasma, overnight incubation at 4 °C can improve the sensitivity). Then, the liquid was gently aspirated, the wells were washed with wash solution (200 μL/well) twice, the liquid was aspirated, and the washing solution at the bottom of the reaction plate was dried with filter paper or paper towel. The detection antibody was added (25 μL/well), and the plates were covered with parafilm and aluminum foil, shaken on a horizontal shaker and incubated at room temperature for 30 min. Streptavidin-PE (25 μL/well) was added, and the plates were covered with parafilm and aluminum foil, shaken on a horizontal shaker and incubated at room temperature for 30 min. Then, the liquid was gently aspirated, the wells were washed with wash solution (200 μL/well) twice, the liquid was aspirated, and the washing solution at the bottom of the reaction plate was blotted with filter paper or paper towel. Sheath fluid (100 μL/well) was added. The plates were covered with aluminum foil and shaken on a horizontal shaker for 5 min to resuspend the microspheres. The microspheres were read on a Luminex instrument, and the results were calculated.

Statistical analysis

SPSS 22.0 was used in this study. Measurement data are expressed as the median (25%, 75%). If the data were normally distributed, they were compared by two independent samples t tests. If not, they were compared by the rank sum test. The area under the curve (AUC) was used to evaluate the diagnostic value. Univariate and multivariate analyses were used to analyze the Exp (B) of the indices. Logistic regression analysis was used to build the index model. *Z* scores were used to compare the AUCs of the two groups.

RESULTS

Comparison of the tumor-related detection indices between the gastric cancer and gastric polyp groups

As shown in Table 1, 13 tumor-related detection indices, including CEA, AFP, CA125, CA199, CA153, CA724, CY211, Ferr, NSE, SCC, PG I/II, PG II, and PG I, were compared between the gastric cancer and gastric polyp groups. Among the 13 tumor-related detection indices, CEA (P = 0.014), CA125 (P = 0.033), CA199 (P = 0.017), CA724 (P = 0.007) and PG I/II (P = 0.008) showed significant differences between the two groups, and the other 8 tumor-related detection indices (AFP, CA153, CY211, Ferr, NSE, SCC, PG II, and PG I) showed no significant differences.

Comparison of the clinical biochemical indices of the gastric cancer and gastric polyp groups

As shown in Table 2, 38 clinical biochemical indices, including ALT, AST, TP, ALB, TB, DB, TBA, ALP, GGT, GLu, UN, Cr, UA, CHO, TG, CK, LDH, CKMB, Ca, P, Mg, K, Na, Cl, CO_2, LP (a), HDL, LDL, ApoA1, ApoB, CYS, SA, HCY, CRP, AMY, LPS, SOD and IMA, were compared between the gastric cancer and gastric polyp groups. ALB (P = 0.007), CHO (P = 0.035), TG (P = 0.017), Ca (P = 0.025), P (P = 0.008), Cl (P = 0.008), HDL (P = 0.004), LDL (P = 0.010), ApoA1 (P = 0.001), ApoB (P = 0.021), SOD (P = 0.001) and IMA (P = 0.001) showed significant differences between the two groups. The other 26 tumor-related detection indices, including ALT, AST, TP, TB, DB, TBA, ALP, GGT, GLu, UN, Cr, UA, CK, LDH, CKMB, Mg, K, Na, CO_2, LP (a), CYS, SA, HCY, CRP, AMY and LPS, showed no significant differences.

Comparison of the cytokine indices in the gastric cancer and gastric polyp groups

As shown in Table 3, 10 tumor-related detection indices, including GM-CSF, IFNγ, IL-10, IL-1β, IL-2, IL-4, IL-6, IL-8, MCP-1, and TNFα, were compared between the gastric cancer and gastric polyp groups. Because IL-2 and IL-4 were lower than the detection limit in most samples, these two cytokine indices were deleted. After analysis, only TNFα (P = 0.001) showed a significant difference between the two groups, and the other 7 tumor-related detection indices, including GM-CSF, IFNγ, IL-10, IL-1β, IL-6, IL-8, and MCP-1, showed no significant differences.

Diagnostic value evaluation of a single differential index for discriminating the gastric cancer and gastric polyp groups

After comparing the tumor-related, clinical biochemical and cytokine indices between the gastric cancer and gastric polyp groups, the diagnostic value of the differential indices for discriminating between the gastric cancer and gastric polyp groups was evaluated. As shown in Table 4, the differential indices of CEA (P = 0.014), CA125 (P = 0.033), CA199 (P = 0.017), CA724 (P = 0.007), PG I/II (P = 0.008), ALB (P = 0.007), CHO (P = 0.035), TG (P = 0.017), Ca (P = 0.025), P (P = 0.008), Cl (P = 0.008), HDL (P = 0.004), LDL (P = 0.010), ApoA1 (P = 0.001), ApoB (P = 0.021), SOD (P = 0.001), IMA (P = 0.001) and TNFα (P = 0.001) were evaluated by the area under the curve. Only CA199 and CHO showed no significant differences. CEA, CA125, CA724, PG I/II, ALB, TG, Ca, P, Cl, HDL, LDL, ApoA1, ApoB, SOD, IMA and TNFα

Table 1 Comparison of tumor related detection index between gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
CEA	1.16 (1.55, 2.11)	1.11 (2.33, 5.11)	0.014
AFP	1.64 (2.63, 3.62)	1.43 (2.24, 3.23)	0.499
CA125	6.86 (9.91, 14.81)	8.56 (13.73, 24.39)	0.033
CA199	4.8 (7.74, 13.91)	5.07 (10.52, 29.36)	0.017
CA153	6.53 (9.3, 12.54)	6.42 (9.03, 13.15)	0.268
CA724	0.84 (1.34, 3.68)	1.43 (3.33, 11)	0.007
CY211	1.32 (1.67, 2.35)	1.7 (2.47, 4.46)	0.390
Ferr	63.86 (144.35, 268.48)	26.19 (79.3, 174.4)	0.176
NSE	8.39 (10.06, 11.87)	7.55 (9.27, 11.57)	0.732
SCC	0.43 (0.7, 1.08)	0.5 (0.7, 1)	0.247
PG1/2	1.3 (4.31, 6.26)	0.67 (2.98, 4.26)	0.008
PG2	7.65 (13.9, 29.68)	9.9 (19.3, 32.4)	0.199
PG1	12.83 (58.5, 115.93)	20.3 (53.8, 82)	0.255

CEA: Carcinoembryonic antigen; AFP: Alpha fetoprotein; CA125: Carbohydrate antigen 125; CY211: Cytokeratin 211; Ferr: Ferritin; NSE: Neuron-specific enolase; SCC: Squamous cell carcinoma; PG: Pepsinogen.

showed significant differences. The AUC of the best indicator, IMA, was 0.790 (0.705, 0.875). The *P* value was < 0.001. The AUC of the conventional index CA724 was 0.702 (0.614, 0.789). The *P* value was <0.001.

Univariate and multivariate analysis of the differential index between gastric cancer and gastric polyp groups

After the diagnostic value evaluation of a single differential index for discriminating the gastric cancer and gastric polyp groups was performed, 16 indices, including CEA, CA125, CA724, PG I/II, ALB, TG, Ca, P, Cl, HDL, LDL, ApoA1, ApoB, SOD, IMA and TNFα, were further analyzed by univariate and multivariate analysis. As shown in Table 5, after the univariate analysis, the 3 indices Exp (B), CA724 (*P* = 0.03), P (*P* = 0.03) and IMA (*P* = 0.03) showed significant differences. The other indices (CEA, CA125, PG I/II, ALB, TG, Ca, Cl, HDL, LDL, ApoA1, ApoB, SOD and TNFα) showed no significant differences. Then, the 3 indices that showed significant differences were further analyzed by multivariate analysis. The Exp (B) of CA724, P and IMA was 1.17 (1.02, 1.34), 0.13 (0.03, 0.58), and 0.85 (0.78, 0.92), respectively.

Diagnostic value evaluation of the index panel for differentiating the gastric cancer and gastric polyp groups

CA724, P and IMA were analyzed by logistic regression analysis to build a diagnostic index panel to differentiate the gastric cancer and gastric polyp groups. As shown in Figure 1A, for discriminating 139 gastric cancer and 40 gastric polyp patients, the AUC index panel was 0.829 (0.754, 0.905), and the conventional index CA724 was 0.704 (0.617, 0.791). The AUC of the index panel showed a significant increase compared to CA724 by z score statistics. After building the index model, as shown in Figure 1B, samples from independent individuals, including 68 gastric cancer patients and 22 gastric polyp patients, were used to validate the model. The AUC of the index panel and CA724 was 0.811 (0.700, 0.923), and that of the conventional index CA724 was 0.779 (0.668, 0.890).

DISCUSSION

The pepsinogen PG is a protein polypeptide chain composed of 375 amino acids, which can be divided into two categories according to biochemical and immunological properties: PG I and PG II. PG I is mainly synthesized by chief cells and cervical mucous cells, while PG II can be synthesized by gastric antrum mucous cells and proximal duodenal Brunner glands, in addition to chief cells and cervical mucous cells[16]. Synthesized PG I and PG II are mainly secreted into the gastric cavity, but a zymogen level of approximately 5% can be reversed and diffuse into the blood, which allows it to be detected in the blood. Studies have shown that the level of PG I can reflect the secretory function of gastric glands to a certain extent, and its level is positively correlated with the maximum secretion of gastric acid but

Table 2 Comparison of clinical biochemical index gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
ALT	11.73 (15.75, 19.35)	10.7 (13.2, 18.3)	0.322
AST	13.93 (17.85, 20.45)	13.1 (15.6, 18.6)	0.252
TP	64.73 (69.4, 72.3)	61.9 (66.2, 69.4)	0.095
ALB	38.9 (41.5, 43.8)	36.5 (38.9, 41)	0.007
TB	8.75 (11.8, 14.95)	6.8 (9.4, 13.7)	0.116
DB	2.33 (3.65, 4.7)	2.4 (3.3, 4.9)	0.248
TBA	2.65 (4.4, 5.98)	2.6 (3.9, 7.4)	0.622
ALP	44.65 (66.85, 77.48)	56.2 (65.2, 81.9)	0.076
GGT	13.13 (16.05, 27.43)	13.3 (16.5, 24)	0.773
GLu	4.74 (5.27, 5.6)	4.72 (5, 5.49)	0.627
UN	4.37 (5.22, 6.49)	4.5 (5.21, 6.23)	0.812
Cr	58.83 (65.3, 75.15)	57.5 (68.2, 77.8)	0.838
UA	261.1 (301.15, 371.9)	228.4 (278.1, 330.5)	0.117
CHO	3.99 (4.34, 5.18)	3.56 (4.16, 4.68)	0.035
TG	1.2 (1.46, 1.81)	0.98 (1.25, 1.48)	0.017
CK	37.68 (55.9, 82.83)	38.6 (56.8, 76.1)	0.740
LDH	139.65 (153.85, 174.43)	118.1 (138, 158.9)	0.792
CKMB	3.15 (6.7, 10.73)	2.4 (6.2, 9.3)	0.357
Ca	2.16 (2.26, 2.34)	2.13 (2.19, 2.26)	0.025
P	1.31 (1.53, 1.81)	1.2 (1.36, 1.51)	0.008
Mg	0.82 (0.87, 0.94)	0.79 (0.85, 0.94)	0.188
K	3.76 (4.05, 4.41)	3.79 (3.99, 4.29)	0.319
Na	141.23 (143.7, 146.35)	141.3 (143.1, 144.5)	0.579
Cl	104.6 (106.6, 108.38)	103.3 (105.3, 106.9)	0.008
CO2	19.75 (22.15, 26.55)	22.3 (24.9, 27.3)	0.281
LP (a)	6.14 (17.34, 35.2)	9.51 (14.82, 26.13)	0.582
HDL	0.95 (1.12, 1.38)	0.83 (1.03, 1.15)	0.004
LDL	2.33 (2.77, 3.34)	1.98 (2.4, 2.93)	0.010
ApoA1	1.08 (1.32, 1.59)	0.96 (1.11, 1.24)	0.001
ApoB	0.7 (0.84, 1.04)	0.66 (0.77, 0.9)	0.021
CYS	0.91 (1, 1.17)	0.84 (0.96, 1.09)	0.816
SA	53.85 (61.4, 65.38)	55.8 (64.5, 70.6)	0.179
HCY	9.85 (13.47, 16.5)	10.63 (13.62, 17.74)	0.414
CRP	0.43 (0.9, 3.78)	0.7 (1.9, 5.4)	0.702
AMY	47.2 (56.9, 77.23)	40.9 (54.8, 68.1)	0.433
LPS	28.25 (34.85, 44.13)	28.2 (35.7, 44.5)	0.291
SOD	141.33 (164.3, 189.5)	108.3 (127.4, 157.4)	0.001
IMA	62.73 (66, 69.35)	56 (60.2, 63.6)	0.001

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TP: Total protein; ALB: Albumin; TB: Total bilirubin; DB: Direct bilirubin; TBA: Total bile acid; ALP: alkaline phosphatase; GGT: γ-glutamyltransferase; Glu: Glucose; UN: Urea nitrogen; Cr: Creatinine; UA: Uric acid; CHO: Cholesterol; TG: Triglyceride; CK: Creatine kinase; LDH: Lactate dehydrogenase; CKMB: Isoenzyme of creatine kinase; Ca: Calcium; P: Phosphorus; Mg: Magnesium; K:

Potassium; Na: Sodium; Cl: Chlorine; CO_2: Carbon dioxide; LPa: Lipoprotein a; HDL: High-density lipoprotein; LDL: Low-density lipoprotein;, ApoA1: Apolipoprotein A1; CYS: Cysteine; SA: Sialic acid; HCY: Homocysteine; CRP: C-reactive protein; AMY: Amylase; LPS: Lipase; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin.

Table 3 Comparison of cytokine index gastric cancer and gastric polyp group

Indicator	Gastric polyp (*n* = 40)	Gastric cancer (*n* = 139)	*P* value
GM-CSF	1.24 (2.7, 6.27)	0.01 (0.53, 2.32)	0.640
IFNγ	0.08 (0.25, 1.08)	0.01 (0, 0.82)	0.585
IL-10	2.14 (3.39, 5.24)	1.63 (4.06, 9.34)	0.326
IL-1β	0.02 (0.31, 1.14)	0.01 (0.08, 0.94)	0.905
IL-6	0.34 (0.94, 2.58)	0.1 (1.98, 7.16)	0.483
IL-8	23.73 (51.11, 112.94)	39.4 (62.55, 138.23)	0.697
MCP-1	321.54 (429.78, 594.82)	310.31 (448.27, 612.02)	0.993
TNFα	5.53 (7.09, 8.72)	5.7 (9.87, 16.6)	0.001

GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFNγ: Interferon-γ; IL: Interleukin; MCP-1: Monocyte chemoattractant protein; TNFα: Tumor necrosis factor α.

Table 4 Diagnostic value evaluation of single differential index for discriminating the gastric cancer and gastric polyp group

Indicator	AUC	*P* value	Lower	Upper
CEA	0.627	0.014	0.543	0.712
CA125	0.637	0.008	0.546	0.729
CA199	0.592	0.078	0.500	0.683
CA724	0.702	< 0.001	0.614	0.789
PG1/2	0.628	0.014	0.517	0.738
ALB	0.687	< 0.001	0.585	0.788
CHO	0.599	0.057	0.499	0.700
TG	0.655	0.003	0.561	0.748
Ca	0.640	0.007	0.534	0.746
P	0.668	0.001	0.566	0.769
Cl	0.635	0.009	0.537	0.733
HDL	0.648	0.004	0.551	0.746
LDL	0.633	0.010	0.532	0.735
ApoA1	0.702	0.000	0.602	0.802
ApoB	0.609	0.036	0.505	0.714
SOD	0.755	< 0.001	0.676	0.834
IMA	0.790	< 0.001	0.705	0.875
TNFα	0.656	0.003	0.575	0d.736

CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; PG: Pepsinogen; ALB: Albumin; CHO: Cholesterol; TG: Triglyceride; Ca: Calcium; P: Phosphorus; Cl: Chlorine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ApoA1: Apolipoprotein A1; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin; TNFα: Tumor necrosis factor α.

Table 5 Univariate and multivariate analysis of the differential index between gastric cancer and gastric polyp groups

Indicator	Univariate analysis					Multivariate analysis				
	Wals	*P* value	Exp (B)	Lower	Upper	Wals	*P* value	Exp (B)	Lower	Upper
CEA	1.02	0.31	1.04	0.97	1.11					
CA125	1.53	0.22	0.99	0.98	1.01					
CA724	4.50	0.03	1.18	1.01	1.38	5.21	0.02	1.17	1.02	1.34
PG12	0.96	0.33	0.91	0.75	1.10					
ALB	0.01	0.93	0.99	0.85	1.16					
TG	0.79	0.37	0.64	0.23	1.72					
Ca	0.01	0.91	0.84	0.04	19.42					
P	4.45	0.03	0.15	0.03	0.88	7.05	0.01	0.13	0.03	0.58
Cl	2.73	0.10	0.85	0.71	1.03					
HDL	0.34	0.56	2.09	0.17	25.09					
LDL	0.10	0.76	0.84	0.27	2.60					
ApoA1	2.42	0.12	0.09	0.00	1.86					
ApoB	0.39	0.53	4.36	0.04	45.13					
SOD	1.22	0.27	0.99	0.98	1.00					
IMA	4.50	0.03	0.89	0.79	0.99	14.77	< 0.001	0.85	0.78	0.92
TNFα	3.07	0.08	1.08	0.99	1.19					

CEA: Carcinoembryonic antigen; CA125: Carbohydrate antigen 125; PG: Pepsinogen; ALB: Albumin; CHO: Cholesterol; TG: Triglyceride; Ca: Calcium; P: Phosphorus; Cl: Chlorine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ApoA1: Apolipoprotein A1; SOD: Superoxide dismutase; IMA: Ischemia-modified albumin; TNFα: Tumor necrosis factor α.

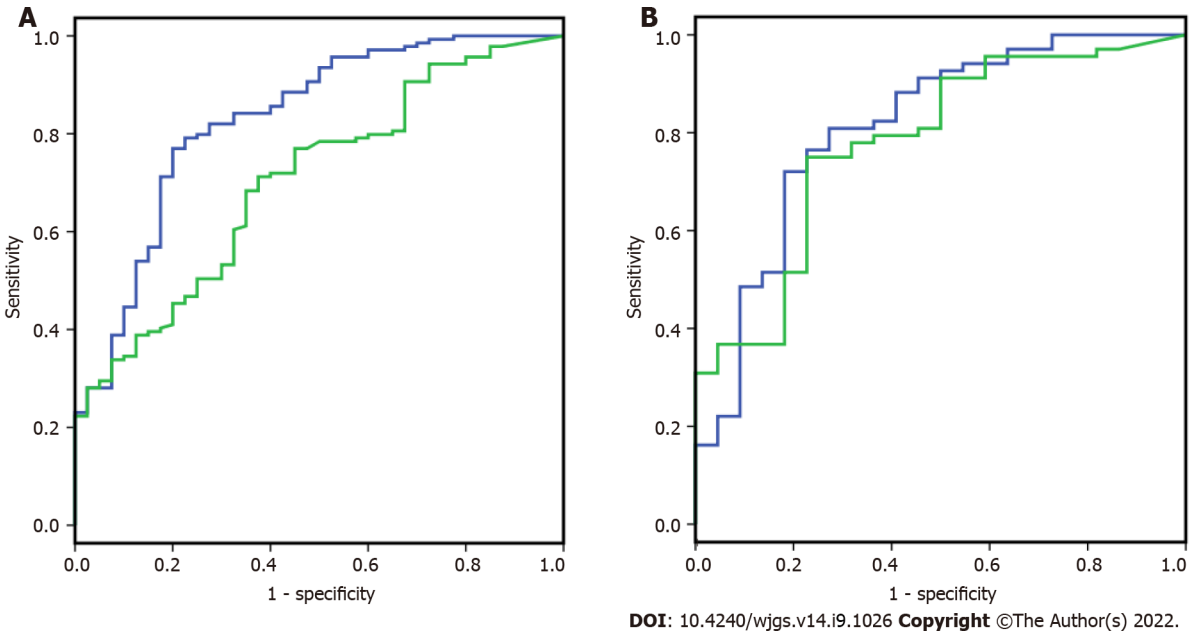

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Figure 1 Diagnostic value evaluation of index panel for discriminating the gastric cancer and gastric polyp group. A: Training model; B: Validation model. Blue line represents index model. Green line represents carbohydrate antigen 724.

negatively correlated with the degree of gastric body inflammation and atrophy[17]. An increase in the level of PG II suggests an inflammatory response in the gastric mucosa, while a decrease in the level of PG I suggests atrophy of the gastric corpus[13]. When the gastric mucosa atrophies and develops severe injury, the number of gastric glands and fundic glands will decrease or be replaced by pyloric glands,

and the pyloric glands lack gastric chief cells and cervical mucous cells, which will lead to a decreases in the level of PG I and the ratio of PG I/II[18]. In our study, the result was 1.3 (4.31, 6.26) in the gastric polyp group and 0.67 (2.98, 4.26) in the gastric cancer group. The AUC was 0.628, which has certain clinical significance in the early diagnosis of gastric cancer.

Cytokines are important in the diagnosis of gastric cancer. Cytokines are small molecular proteins secreted by cells in response to various stimuli that can exert biological effects by binding to specific receptors on target cells[19]. Cytokine production and cellular immune function are important in the occurrence and development of tumors and have certain diagnostic and prognostic value in gastric diseases[20]. The occurrence and development of gastric cancer are biological processes involving multiple stages and multiple factors. A large number of studies have shown that activated inflammatory factors are involved in the occurrence and development of gastric cancer. The immune function of cells is closely related to the occurrence and development of tumors. These inflammatory factors, as multifunctional cytokines, can not only directly damage tumor cells but are also important mediators by which monocytes kill tumor cells[20,21]. Studying the relationship between cytokines and gastric cancer provides a new direction for exploring the pathological mechanism of gastric cancer and provides a theoretical basis for the clinical development of more effective diagnosis and treatment. Studies have confirmed that tumor patients typically have immune function defects, especially cellular immune dysfunction[22]. TNFα is an important mediator of the inflammatory response and a series of pathophysiological processes in vivo. The dysregulation of cytokines and their receptors is closely related to the occurrence and development of tumors[23]. TNFα is known for its ability to significantly induce hemorrhagic necrosis of tumors in mice and is a multifunctional cytokine produced by macrophages and activated T cells. The functions of TNFα mainly include inducing an acute albumin response, activating neutrophils and lymphocytes, regulating the metabolic activity of tissues, and promoting the release of other cytokines[24]. Studies have shown that TNFα can not only kill a variety of tumor cells and enhance antitumor effects but also promote the growth and metastasis of certain tumors. When the concentration is appropriate, TNFα can cause tumor tissue hypoxia and vascular damage around the tumor and promote the cytotoxic effects of NK cells and macrophages, thereby enhancing immunity and inhibiting tumor growth. When TNFα is abnormally elevated in the body, the immune system is disturbed, causing systemic cytotoxicity, and tumor cells evade immune surveillance and continue to grow[25]. TNFα can promote the production of more TNFα in thymic cancer cells cultured in vitro. Tumor cells themselves can also promote the production of TNFα by myeloid cells by secreting versican, and TNFα can promote the accumulation of myeloid cells with a vascular endothelial phenotype to the tumor site, promote the formation of blood vessels, and then promote tumor growth and transfer[26]. In our study, compared to that in the gastric polyp group, the level of TNFα was significantly increased in the gastric cancer group. As an important inflammatory regulator, TNFα may play a role in tumor-associated inflammatory processes, increasing the risk of inflammation-induced tumors.

There are still some limitations in this study. First, the detection indices were only examined in the gastric polyp and gastric cancer groups, and a healthy control group was not evaluated. Second, the stage of gastric cancer was not evaluated and should be evaluated in future studies. Third, the sample size of the gastric polyp group was relatively small, which may cause bias in this study.

CONCLUSION

In summary, we developed an index model that included CA724, P and IMA to distinguish between gastric cancer and gastric polyps. After validation, when compared to the conventional index CA724, the panel showed improvements in detecting gastric cancer and may be a potential discriminating method for use in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Early detection and diagnosis are crucial for the prevention and treatment of gastric cancer in clinical practice.

Research motivation

Blood index panels have been shown to improve the diagnostic value in many studies compared with single indices.

Research objectives

We aimed to develop a blood index panel that can improve the diagnostic value for discriminating gastric cancer and gastric polyps.

Research methods

Tumor-related detection indices, clinical biochemical indices and cytokine indices were analyzed in samples from 139 gastric cancer patients and 40 gastric polyp patients for model building. An additional 68 gastric cancer patients and 22 gastric polyp patients were enrolled for validation.

Research results

Carbohydrate antigen (CA) 724, phosphorus (P) and ischemia-modified albumin were included in the blood index panel, and the area under the curve (AUC) index of the panel was 0.829 (0.754, 0.905). After validation, the AUC index was 0.811 (0.700, 0.923). Compared to the conventional CA724 used in the training and validation, the AUC index was 0.704 (0.617, 0.791) and 0.779 (0.668, 0.890). The blood index panel showed significantly increased diagnostic value.

Research conclusions

We have developed a potential method for differentiating gastric cancer and gastric polyps based on a blood index panel. this tool may be helpful in clinical practice.

Research perspectives

A healthy control group and stage of gastric cancer should be evaluated in future studies, and a larger sample size should be used.

FOOTNOTES

Author contributions: Guo GH and Jiang T designed the study; Guo GH and Zhang PJ performed the research; Guo GH and Xie YB analyzed the date; Guo GH wrote the paper; Jiang T and Zhang PJ revised the manuscript for final submission; Guo GH and Xie YB contributed equally to this study; Zhang PJ and Jiang T are the co-corresponding authors; and all authors have read and agreed to the published version of the manuscript.

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ORCID number: Guang-Hong Guo 0000-0002-0897-0410; Yi-Bin Xie 0000-0002-0255-3018; Peng-Jun Zhang 0000-0002-7391-2495; Tao Jiang 0000-0002-2127-9085.

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