**Name of journal:** ***World Journal of*** ***Gastroenterology***

**ESPS Manuscript NO: 38295**

**Manuscript Type: ORIGINAL ARTICLE**

***Basic Study***

**Multi-cytokines profiling in serum for early detection of gastric cancer**

Li J *et al*. Early detection of gastric cancer

Jian Li, Liang Xu, Zeng-Ci Run, Wen Feng, Wen Liu, Peng-Jun Zhang, Zhi Li

**Jian Li, Zeng-Ci Run, Zhi Li,** Department of general surgery, Affiliated Tumor Hospital of Zhengzhou University, Zhengzhou 450000, Henan Province, China

**Liang Xu,** Department of Oncology, General Hospital of Liaohe Oil Field, Panjin 124010, Liaoning Province, China

**Wen Feng,** Department of pathology, Affiliated Tumor Hospital of Zhengzhou University, Zhengzhou 450000, Henan Province, China

**Wen Liu,** Department of Central Laboratory, Affiliated Tumor Hospital of Zhengzhou University, Zhengzhou 450000, Henan Province, China

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

**ORCID number:** Jian Li (0000-0002-2168-4240); Liang Xu (0000-0002-5238-5905); Zeng-Ci Run (0000-0002-9979-6082); Wen Feng (0000-0001-8658-5465); Wen Liu (0000-0001-5455-623X); Peng-Jun Zhang (0000-0002-7391-2495); Zhi Li (0000-0003-0388-4537).

**Author contributions:** Li J, Zhang PJ and Li Z designed the study; Li J, Xu L, Feng W and Liu W performed the research; Li J, Xu L, Run ZC, Feng W and Liu W analyzed the date; Li J wrote the paper; Li J and Li Z revised the manuscript for final submission; Li J and Xu L contributed equally to this study; Li Z and Zhang PJ are the co-corresponding authors.

**Supported by** Henan province science and technology research projects, No. 162102310041; National Key R&D Program of China, No. 2016YFC0106604; and National Natural Science Foundation of China, No. 81502591.

**Institutional review board statement:** The study was reviewed and approved by the Affiliated Tumor Hospital of Zhengzhou University Institutional review board.

**Informed consent statement:** All study participants or their legal guardian provided written informed consent prior to study enrollment.

**Conflict-of-interest statement:** We declare that we have no financial or personal relationships with other individuals or organizations that can inappropriately influence our work and that there is no professional or other personal interest of any nature in any product, service and/or company that could be construed as influencing the position presented in or the review of the manuscript.

**Open Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Correspondence to:** **Zhi Li, MD, Chief Doctor,** Department of general surgery, Affiliated Tumor Hospital of Zhengzhou University, 127 Dong Ming Road, Jin Shui District, Zhengzhou 450000, Henan Province, China. lizhihn2009@163.com

**Telephone:** +86-371-65588142

**Fax:** +86-371-65588142

**Received:** February 12, 2018

**Peer-review started:** February 12, 2018

**First decision:** February 23, 2018

**Revised:** February 27, 2018

**Accepted:** March 18, 2018

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To investigate the value of the multi-parameter joint analysis in the early diagnosis of gastric cancer (GC) in clinical practice.

***METHODS***

Concentrations of CEA, CA724 and three kinds of cytokines (TNF-α, IL-6 and IL-8) in 176 GC patients, 117 atypical hyperplasia patients, and 204 healthy control individuals were used for building the diagnostic model, then 58 GC patients, 41 atypical hyperplasia patients, and 66 healthy control individuals were enrolled independently. The joint of the indicators were analyzed by binary logistic regression analysis method.

***RESULTS***

For discriminating the healthy control group and the GC group, IL-6 had the best diagnostic value, and the area under curve (AUC) of joint analysis was 0.95 (0.93-0.97). For the early stage and advanced stage GC, the AUC were 0.95 (0.92-0.98) and 0.95 (0.92-0.97). For discriminating the atypical hyperplasia group and GC group, CA724 had the best diagnostic value, and the AUC of joint analysis was 0.97 (0.95-0.99). For the early stage and advanced stage GC, the AUC were 0.98 (0.96-0.99) and 0.96 (0.94-0.98). After evaluation, for discriminating the GC, early stage GC and advanced cancer with the healthy control group, the diagnostic sensitivity was 89.66%, 84.21%, 92.31%, repectively. And the specificity was 92.42%, 90.91% and 90.91%. For discriminating the GC, early stage GC and advanced cancer with the atypical hyperplasia group, the diagnostic sensitivity was 87.93%, 78.95%, 92.31%, repectively. And the specificity was 87.80%, 85.37% and 90.24%.

***CONCLUSION***

We have built a diagnostic model included the CEA, CA724, IL-6, IL-8, and TNF-α. It may provide a potential assistant screening method for the early detection of GC.

**Key words:** Gastric cancer; Atypical hyperplasia; Serum; Cytokine; Early detection

**©The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** We aimed to use the multi-parameter joint analysis for improving the sensitivity and specificity. By combined the CEA, CA724, IL-6, IL-8, and TNF-α, we have built a diagnostic model, and it may provide a potential assistant screening method for the early detection of gastric cancer.

Li J, Xu L, Run ZC, Feng W, Liu W, Zhang PJ, Li Z. Multi-cytokines profiling in serum for early detection of gastric cancer. *World J Gastroenterol* 2018; In press

**INTRODUCTION**

Gastric cancer (GC) is a kind of malignant tumor derived from gastric mucosal epithelial cells[[1-3](#_ENREF_1)]. It ranks the fourth in the worldwide incidence of all types of malignancies, and ranks second the number of deaths[[4](#_ENREF_4)]. In china, the GC is one of the malignant tumors with high morbidity and mortality[[5](#_ENREF_5)]. The death rate accounts for about 25% to 30% of all kinds of cancer[[6](#_ENREF_6)]. Its pathogenesis involved in aging of the body, eating habits and psychological factors[[7-9](#_ENREF_7)]. In recent years, the incidence of GC shows a larger life pressures, poor diet and overload work. The occurrence and development of GC is a multistep process[[10](#_ENREF_10)]. Now, in clinical practice, the main treatment of GC is surgery, and the five years survival rate is very low[[11](#_ENREF_11)], however, if the GC is detected at early stage, the five years survival rate is up to 90%[[12](#_ENREF_12)]. Early diagnosis and treatment of GC is extremely important for GC.

At present, there are many ways for diagnosis of GC in scientific research and clinical practice[[13](#_ENREF_13)]. Serologic bio-markers are important detection methods. In the early GC, the tumor markers in blood have increased to some extent (such as, CEA and CA724). They have been used as important methods for GC screening, early diagnosis and prognosis evaluation[[14](#_ENREF_14)]. But no specific tumor marks has been found at present. The diagnosis of a single tumor marker has some limitation[[15](#_ENREF_15)]. The detection rate of GC is still very low. Cytokines is a small molecule secreted by cells for various stimuli, involved in biological effect by binding to specific receptors on target cells[[16](#_ENREF_16)]. Many studies had demonstrated that its production and cellular immune function are important regulatory factors in the development of tumors[[17-19](#_ENREF_17)]. As a multifunctional cytokine, these inflammatory factors not only directly damage tumor cells, but also are important mediators that mononuclear cells killing tumor cells. The relationship of cytokines and GC provides a new direction for exploring the pathological mechanism of GC and may also provide a potential diagnostic and treatment of GC in clinical development. Studies have confirmed that patients with cancer usually accompanied by defects in immune function, especially cellular immune dysfunction. TNF-α, IL-6 and IL-8 are important mediators of inflammatory reaction and a series of pathophysiological processes *in vivo*[[20-22](#_ENREF_20)]. Their diagnostic values of GC have also been evaluated, however, their joint diagnostic value with the conventional biomarker, such as, CEA and CA724, have little study on the diagnostic value.

In this study, we first excavated the diagnostic value of CEA, CA724 and three kinds of cytokines (TNF-α, IL-6 and IL-8) for GC group. Then the joint analysis of those biomarkers was analyzed by using binary logistic regression method. We aimed to use the multi-parameter joint analysis for improving the sensitivity and specificity, and to provide a novel potential method for the early diagnosis of GC in clinical practice.

**MATERIALS AND METHODS**

***Samples enrolled***

Written consent was obtained. The study was reviewed and approved by the Affiliated Tumor Hospital of Zhengzhou University Institutional review board. This study ranged from January 2015 to December 2016. 176 GC patients were enrolled in our study (63 early stage and 113 advanced stage). The results were confirmed by pathological examination. All the GC patients were enrolled before the surgery, chemotherapy, radiotherapy and immunotherapy. 117 atypical hyperplasia patients were also enrolled. The examination results were confirmed by gastroscopy and pathological examination. 204 healthy control individuals were also enrolled. Those people were without obvious disease, the tests are checked by B-mode Ultrasound and CT examination, excluding heart, brain, kidney and other important organ diseases. After building the diagnostic model, 58 GC patients (19 early stage and 39 advanced stage), 41 atypical hyperplasia patients, and 66 healthy control individuals were enrolled independently.

***Serum collection and detection equipment***

After collection of whole blood samples, the tube was centrifuged for 7 minutes at 3500 r/min and immediately stored at -80°C. The CEA and CA724 are detected by Roche Modular E170 automatic electrochemiluminescence immunoassay analyzer. The reagents, standards and control are purchased from Roche. IL-6, IL-8, and TNF-α in serum are detected by Luminex 200, and the detection kits were purchased by Millpore.

***Concentrations of IL-6, IL-8, and TNF-α in serum***

Serum samples of diseases group and control group were stored in a refrigerator at -80°C. When performed the experiment, the serum were thawed. 100 μL serum was transferred to centrifuge tubes. Put all reagents to equilibrate to room temperature at 25°C, and use deionized water with Wash Buffer for 10 times dilution. The protocol was list as below. First, 200 μL of Assay Buffer was added to each reaction well. After sealing, mix thoroughly on a horizontal shaker, vacuum the Assay Buffer, and blot the Assay Buffer on the bottom of the plate. Second, 25 μL of each standard or control were added to the appropriate wells, and 25 μL of assay buffer were also added to each well, then 25 μL of serum matrix diluent were added to the standard and control wells. Third, after mixing the microspheres well, 25 μL of hybrid microspheres were added to each well, cover with the sealing film and foil, and incubate overnight at 4°C on a horizontal shaker. Forth, after washing, 25 μL of the detection antibody was added to each well, incubate for 1 hour at room temperature. Then 25 μL of Streptavidin-PE was added to each well, incubate for 30 min at room temperature. Fifth, after washing, the 96 well plate was located in the Luminex reading instrument, and according to the standard curve, the levels were calculated.

***Statistical analysis***

SPSS21.0 statistical software was used to analyze the data of our study. Serum levels of CEA, CA724, IL-6, IL-8, and TNF-α in the different groups were compared by One-way ANOVA analysis method. The diagnostic value was evaluated by area under curve (AUC) of receiver operator characteristic (ROC), the cutoff value was determined by the Youden index. The joint of the indicators were analyzed by binary logistic regression analysis method[[23](#_ENREF_23)]. *P* < 0.05 meant the statistically significant.

**RESULTS**

***Comparison of CEA, CA724, IL-6, IL-8, and TNF-α in the three groups***

As shown in Figure 1, the concentration of CEA, CA724, IL-6, IL-8, and TNF-α in the healthy control group, atypical hyperplasia group and GC group were compared. As shown in Figure 1A, the concentration of IL-6 in the healthy control group, atypical hyperplasia group and GC group were 10.05 (6.47, 18.26), 50.17 (23.93, 110.40), and 63.96 (38.93, 139.10), respectively. IL-8 were 0.48 (0.07, 1.17), 0.85 (0.33, 2.44), and 1.80 (0.11, 6.28), respectively (Figure 1B). TNF-α were 5.49 (4.16, 7.21), 6.73 (5.31, 8.27), and 10.20 (5.88, 16.41), respectively (Figure 1C). CEA were 1.53 (0.91, 2.26), 1.51 (1.15, 2.05), and 2.35 (1.12, 5.22), respectively (Figure 1D). CA724 were 2.02 (1.15, 4.30), 2.21 (1.02, 3.41), and 4.03 (1.52, 11.62), respectively (Figure 1E). Compared to the healthy control group, the IL-6, IL-8, TNF-α, CEA, and CA724 in the atypical hyperplasia group and GC group showed significant difference. Compared to the atypical hyperplasia group, IL-6, IL-8, TNF-α, and CA724 in the GC group showed significant difference.

***Diagnostic value of CEA, CA724, IL-6, IL-8, and TNF-α for the detection of GC***

As shown in Table 1, when the CEA, CA724, IL-6, IL-8, and TNF-α were used alone for discriminating the healthy control group and the GC group. The AUC of the five indicators ranged from 0.64 to 0.93. The IL-6 had the best diagnostic value for discriminating the healthy control group and GC group. When the cutoff value was 20.31 pg/mL, the sensitivity and specificity were 92.05% and 78.92%, respectively. The two conventional biomarker CEA and CA724, the AUC were 0.65 (0.60-0.71) and 0.64 (0.58-0.70), respectively. For discriminating the atypical hyperplasia group and GC group, as shown in Figure 2A, the conventional biomarker CA724 had the best diagnostic value, the AUC was 0.68 (0.62-0.74). When the cutoff value was 9.13 U/mL, the sensitivity and specificity were 31.25% and 97.44%, respectively. The three kinds of cytokines, IL-6, IL-8, and TNF-α, showed poorer diagnostic value, their AUC were 0.59 (0.52-0.66), 0.55 (0.49-0.63) and 0.68 (0.62-0.74) (Figure 2B, 2C, and 2D).

***Joint analysis of CEA, CA724, IL-6, IL-8, and TNF-α for the detection of GC***

After evaluating the diagnostic value of the CEA, CA724, IL-6, IL-8, and TNF-α alone, then the binary logistic regression was used to analyze the joint analysis of those indicators. As shown in Figure 3A, for discriminating the healthy control group and GC group, the AUC was 0.95 (0.93- 0.97). For the early stage GC, the AUC was 0.95 (0.92- 0.98), and the advanced stage was 0.95 (0.92- 0.97), which were shown in Figure 3B and 3C. For discriminating the healthy control group and GC group, our joint analysis method showed the similar diagnostic value for the early stage and advanced stage GC. For discriminating the atypical hyperplasia group and GC group, the four indicators CA724, IL-6, IL-8, and TNF-α were used for the joint analysis. As shown in Figure 4A, for discriminating the atypical hyperplasia group and GC group, the AUC was 0.97 (0.95- 0.99). For the early stage GC, the AUC was 0.98 (0.96- 0.99), and the advanced stage was 0.96 (0.94- 0.98), which were shown in Figure 4B and 4C. For discriminating the atypical hyperplasia group and GC group, our joint analysis method also showed the similar diagnostic value for the early stage and advanced stage GC.

***Validation of the joint analysis for the detection of GC***

After building the diagnostic model, 58 GC patients (19 early stage and 39 advanced stage), 41 atypical hyperplasia patients, and 66 healthy control individuals were enrolled independently. Then the diagnostic model included CEA, CA724, IL-6, IL-8, and TNF-α for discriminating the healthy control group and GC group, and the diagnostic model included CA724, IL-6, IL-8, and TNF-α for discriminating the atypical hyperplasia group and GC group were evaluated. After evaluation, for discriminating the GC, early stage GC and advanced cancer with the healthy control group, the diagnostic sensitivity was 89.66%, 84.21%, 92.31%, repectively. And the specificity was 92.42%, 90.91% and 90.91%. For discriminating the GC, early stage GC and advanced cancer with the atypical hyperplasia group, the diagnostic sensitivity was 87.93%, 78.95%, 92.31%, repectively. And the specificity was 87.80%, 85.37% and 90.24%.

**DISCUSSION**

According to the estimates of the World Health Organization, nearly 7 million people die from tumors each year in the world and have an increasing trend year by year. GC is one of the common malignant tumors that endanger human health. It ranks second in the number of all-cause cancer deaths. The occurrence and development of GC is a multi-stage process involving multiple gene and multi-molecular level changes. In the pre-GC there will be a precancerous lesion, most of the precancerous lesion will remain unchanged, and a small part of develop to cancer. Correa cascade is the most commonly recognized pattern of gastric carcinogenesis[[24](#_ENREF_24)]. Because most of the gastrointestinal cancer in the early stage have no obvious symptoms and cannot be detected in time, but when clinical symptoms are often found to be late, resulting in the survival rate of postoperative malignant tumors is very low. Early detection is the key to improve the survival rate of patients and the cure rate[[12](#_ENREF_12)]. Therefore, early detection of GC is crucial to the improvement of treatment of GC.

CEA is a cell surface structure antigen. It is a tumor-associated antigen extracted from embryonic tissue and can be 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[[25](#_ENREF_25)]. CA72-4 is a kind of high molecular weight glycoprotein, which is one of the best tumor markers in the diagnosis of GC. It has high specificity for GC and has good application value in digestive system malignant tumors[[26](#_ENREF_26)]. The results of our study showed that the serum levels of CEA and CA72-4 in GC group were significantly higher than those in atypical hyperplasia group and healthy control group. The results were consistent with the previous studies[[27](#_ENREF_27),[28](#_ENREF_28)], and indicated that they have certain diagnostic value for the diagnosis of GC.

Because of the inflammation in cancer is a multi-factorial process, and phagocytes are effector cells that initiate inflammation. It can use a variety of surface receptors to identify invading foreign microorganisms, and finally kill microorganisms. In this process, activated phagocytes secrete a large number of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α. There expression showed significant increase in inflammatory diseases. As a very important immunosuppressive regulator, IL-8 is a cytokine secreted by fibroblasts, epithelial cells and mononuclear macrophages, and plays an important role in the growth, differentiation or gene expression of many kinds of cells[[29](#_ENREF_29)]. The expression was more in the tumor tissue, serum, and malignant effusion of the thoracic and abdominal cavity of GC, but less in normal tissues and serum. In addition, it also plays an important role in the angiogenesis of gastric tumors. It can act on vascular endothelial cells and induce large-scale proliferation of endothelial cells to promote angiogenesis[[30](#_ENREF_30)]. In our experiment, the level of IL-8 in gastric diseases (GC group and atypical hyperplasia group) was significantly higher than that healthy control group. The results showed that IL-8 was highly expressed in GC and gastric inflammatory diseases, which was consistent with the previous studies. IL-6 has been demonstrated that it plays a role in tumor metastasis and tumor angiogenesis[[31](#_ENREF_31)]. The IL-6 gene is active in many tumor tissues or peripheral blood vessels and the secretion of various cytokines is increased. Numerous studies had demonstrated that it not only directly stimulated monocyte-derived macrophages and fibroblasts to secrete IL-6, but also cancer cells can secrete a large amount of IL-1α to promote the proliferation of malignant cells in their own growth process[[32](#_ENREF_32)]. The imbalance of IL-6 and its receptor will affect the stability of the whole environment and lead to the disorder of immune function, which may induce the tumor[[33](#_ENREF_33)]. In our study, the level of IL-6 in GC was significantly higher than that in atypical hyperplasia. Previous studies also found that tumors were associated with IL-6 abnormal expression. TNF-α is a multifunctional cytokine produced by macrophages and activated T cells. It involved in inducing acute albumin reaction, activating neutrophils and lymphocytes, regulating the metabolic activity of tissues and promoting the release of other cytokines[[11](#_ENREF_11)]. Studies have shown that TNF-α can kill a variety of tumor cells, enhance the body's anti-tumor effect, but also promote the growth and metastasis of some tumors. It can cause tumor tissue hypoxia, vascular damage around the tumor and promote the cytotoxic effect of NK cells and macrophages, thereby enhancing the body's immunity and inhibiting tumor growth[[34](#_ENREF_34)]. When TNF-α is abnormal, the patient's immune system was disorder, and then trigger the systemic cytotoxicity, resulted in the tumor cells escape the host immune surveillance and continue to grow[[35](#_ENREF_35)]. In our study, the level of TNF-α in GC group and atypical hyperplasia group was significantly higher than the healthy control group, suggesting that TNF-α may be closely related to the occurrence and development of GC. As an important regulator of inflammation, TNF-α may play a role in tumor-associated inflammatory processes, increasing the risk of inflammation-induced tumors. Our results were consistent with the previous studies.

Although we have built a potential diagnostic model for the early detection of GC, however, there are still some limitations in our study. First, the cytokines in our study were only three, and the other kinds of cytokines were not included in our study. Second, the Luminex 200 detection system may be too sensitive to have high variance which may affect the results of our study. Third, the sample size of our study was relatively small, and the diagnostic model validation is only performed in a small cohort.

In conclusion, we have built a diagnostic model included the CEA, CA724, IL-6, IL-8, and TNF-α. It may provide a potential assistant screening method for the early detection of GC.

**ARTICLES HIGHLIGHTS**

***Research background***

Early diagnosis and treatment of gastric cancer (GC) is extremely important for GC, however, now there are still no effective detection method for the early detection of GC.

***Research motivation***

Many studies had demonstrated that the joint analysis of a panel of indicators may improve the diagnostic value for kinds of cancers. And the cytokines had also been demonstrated that play important role in the development of cancer.

***Research methods***

Concentrations of CEA, CA724, TNF-α, IL-6 and IL-8 in 176 GC, 117 atypical hyperplasia, and 204 healthy control individuals were used for building the model, then 58 GC, 41 atypical hyperplasia, and 66 healthy control individuals were used for validation. The joint of the indicators were analyzed by binary logistic regression analysis method.

***Research results***

For discriminating the GC, early stage GC and advanced cancer with the healthy control group, the diagnostic sensitivity was 89.66%, 84.21%, 92.31%, repectively. And the specificity was 92.42%, 90.91% and 90.91%. For discriminating the GC, early stage GC and advanced cancer with the atypical hyperplasia group, the diagnostic sensitivity was 87.93%, 78.95%, 92.31%, repectively. And the specificity was 87.80%, 85.37% and 90.24%.

***Research conclusions***

We have built a diagnostic model included the CEA, CA724, IL-6, IL-8, and TNF-α, and it may provide a potential assistant screening method for the early detection of GC.

***Research perspectives***

Our study provides a simple, effective and non-invasive detection method for the assistant detection of gc. In the future study, the multicenter and larger sample size should be performed to validate the diagnostic value.

**REFERENCES**

1 **Karimi P**, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev* 2014; **23**: 700-713 [PMID: 24618998 DOI: 10.1158/1055-9965.EPI-13-1057]

2 **Pasechnikov V**, Chukov S, Fedorov E, Kikuste I, Leja M. Gastric cancer: prevention, screening and early diagnosis. *World J Gastroenterol* 2014; **20**: 13842-13862 [PMID: 25320521 DOI: 10.3748/wjg.v20.i38.13842]

3 **Spence AD**, Cardwell CR, McMenamin ÚC, Hicks BM, Johnston BT, Murray LJ, Coleman HG. Adenocarcinoma risk in gastric atrophy and intestinal metaplasia: a systematic review. *BMC Gastroenterol* 2017; **17**: 157 [PMID: 29228909 DOI: 10.1186/s12876-017-0708-4]

4 **Yoon H**, Kim N. Diagnosis and management of high risk group for gastric cancer. *Gut Liver* 2015; **9**: 5-17 [PMID: 25547086 DOI: 10.5009/gnl14118]

5 **Ning FL**, Zhang CD, Wang P, Shao S, Dai DQ. Endoscopic resection versus radical gastrectomy for early gastric cancer in Asia: A meta-analysis. *Int J Surg* 2017; **48**: 45-52 [PMID: 28987558 DOI: 10.1016/j.ijsu.2017.09.068]

6 **Zheng Q**, Chen C, Guan H, Kang W, Yu C. Prognostic role of microRNAs in human gastrointestinal cancer: A systematic review and meta-analysis. *Oncotarget* 2017; **8**: 46611-46623 [PMID: 28402940 DOI: 10.18632/oncotarget.16679]

7 **Maleki SS**, Röcken C. Chromosomal Instability in Gastric Cancer Biology. *Neoplasia* 2017; **19**: 412-420 [PMID: 28431273 DOI: 10.1016/j.neo.2017.02.012]

8 **Kalisperati P**, Spanou E, Pateras IS, Korkolopoulou P, Varvarigou A, Karavokyros I, Gorgoulis VG, Vlachoyiannopoulos PG, Sougioultzis S. Inflammation, DNA Damage, <i>Helicobacter pylori</i> and Gastric Tumorigenesis. *Front Genet* 2017; **8**: 20 [PMID: 28289428 DOI: 10.3389/fgene.2017.00020]

9 **Sunakawa Y**, Lenz HJ. Molecular classification of gastric adenocarcinoma: translating new insights from the cancer genome atlas research network. *Curr Treat Options Oncol* 2015; **16**: 17 [PMID: 25813036 DOI: 10.1007/s11864-015-0331-y]

10 **Akhavan-Niaki H**, Samadani AA. Molecular insight in gastric cancer induction: an overview of cancer stemness genes. *Cell Biochem Biophys* 2014; **68**: 463-473 [PMID: 24078401 DOI: 10.1007/s12013-013-9749-7]

11 **Ahn S**, Park DY. Practical Points in Gastric Pathology. *Arch Pathol Lab Med* 2016; **140**: 397-405 [PMID: 27128297 DOI: 10.5858/arpa.2015-0300-RA]

12 **Beeharry MK**, Liu WT, Yan M, Zhu ZG. New blood markers detection technology: A leap in the diagnosis of gastric cancer. *World J Gastroenterol* 2016; **22**: 1202-1212 [PMID: 26811658 DOI: 10.3748/wjg.v22.i3.1202]

13 **Uedo N**, Yao K. Endoluminal Diagnosis of Early Gastric Cancer and Its Precursors: Bridging the Gap Between Endoscopy and Pathology. *Adv Exp Med Biol* 2016; **908**: 293-316 [PMID: 27573777 DOI: 10.1007/978-3-319-41388-4\_14]

14 **Feng F**, Tian Y, Xu G, Liu Z, Liu S, Zheng G, Guo M, Lian X, Fan D, Zhang H. Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. *BMC Cancer* 2017; **17**: 737 [PMID: 29121872 DOI: 10.1186/s12885-017-3738-y]

15 **Zhang Q**, Qu H, Sun G, Li Z, Ma S, Shi Z, Zhao E, Zhang H, He Q. Early postoperative tumor marker responses provide a robust prognostic indicator for N3 stage gastric cancer. *Medicine (Baltimore)* 2017; **96**: e7560 [PMID: 28796039 DOI: 10.1097/MD.0000000000007560]

16 **Bagheri V**, Memar B, Momtazi AA, Sahebkar A, Gholamin M, Abbaszadegan MR. Cytokine networks and their association with Helicobacter pylori infection in gastric carcinoma. *J Cell Physiol* 2018; **233**: 2791-2803 [PMID: 28121015 DOI: 10.1002/jcp.25822]

17 **Bockerstett KA**, DiPaolo RJ. Regulation of Gastric Carcinogenesis by Inflammatory Cytokines. *Cell Mol Gastroenterol Hepatol* 2017; **4**: 47-53 [PMID: 28560288 DOI: 10.1016/j.jcmgh.2017.03.005]

18 **Jäkel CE**, Vogt A, Gonzalez-Carmona MA, Schmidt-Wolf IG. Clinical studies applying cytokine-induced killer cells for the treatment of gastrointestinal tumors. *J Immunol Res* 2014; **2014**: 897214 [PMID: 24741629 DOI: 10.1155/2014/897214]

19 **Tye H**, Jenkins BJ. Tying the knot between cytokine and toll-like receptor signaling in gastrointestinal tract cancers. *Cancer Sci* 2013; **104**: 1139-1145 [PMID: 23710764 DOI: 10.1111/cas.12205]

20 **Zhang JZ**, Liu CM, Peng HP, Zhang Y. Association of genetic variations in IL-6/IL-6R pathway genes with gastric cancer risk in a Chinese population. *Gene* 2017; **623**: 1-4 [PMID: 28442395 DOI: 10.1016/j.gene.2017.04.038]

21 **Zhou F**, Cheng L, Qiu LX, Wang MY, Li J, Sun MH, Yang YJ, Wang JC, Jin L, Wang YN, Wei QY. Associations of potentially functional variants in IL-6, JAKs and STAT3 with gastric cancer risk in an eastern Chinese population. *Oncotarget* 2016; **7**: 28112-28123 [PMID: 27049718 DOI: 10.18632/oncotarget.8492]

22 **Shi J**, Li YJ, Yan B, Wei PK. Interleukin-8: A potent promoter of human lymphatic endothelial cell growth in gastric cancer. *Oncol Rep* 2015; **33**: 2703-2710 [PMID: 25891418 DOI: 10.3892/or.2015.3916]

23 **Zhang P**, Zou M, Wen X, Gu F, Li J, Liu G, Dong J, Deng X, Gao J, Li X, Jia X, Dong Z, Chen L, Wang Y, Tian Y. Development of serum parameters panels for the early detection of pancreatic cancer. *Int J Cancer* 2014; **134**: 2646-2655 [PMID: 24615168 DOI: 10.1002/ijc.28584]

24 **Futawatari N**, Fukuyama T, Yamamura R, Shida A, Takahashi Y, Nishi Y, Ichiki Y, Kobayashi N, Yamazaki H, Watanabe M. Early gastric cancer frequently has high expression of KK-LC-1, a cancer-testis antigen. *World J Gastroenterol* 2017; **23**: 8200-8206 [PMID: 29290656 DOI: 10.3748/wjg.v23.i46.8200]

25 **Shafaghi A**, Mansour- Ghanaei F, Joukar F, Nabavi F, Mansour- Ghanaei A, Esrafilian Soltani A. Stage Association of Preoperative Serum Carcinoembryonic Antigen with Gastric Adenocarcinoma in Iranian Patients *Asian Pac J Cancer Prev* 2017; **18**: 2669-2672 [PMID: 29072067 DOI: 10.22034/APJCP.2017.18.10.2669]

26 **Zou L**, Qian J. Decline of serum CA724 as a probable predictive factor for tumor response during chemotherapy of advanced gastric carcinoma. *Chin J Cancer Res* 2014; **26**: 404-409 [PMID: 25232212 DOI: 10.3978/j.issn.1000-9604.2014.07.02]

27 **Chen XZ**, Zhang WK, Yang K, Wang LL, Liu J, Wang L, Hu JK, Zhang B, Chen ZX, Chen JP, Zhou ZG, Mo XM. Correlation between serum CA724 and gastric cancer: multiple analyses based on Chinese population. *Mol Biol Rep* 2012; **39**: 9031-9039 [PMID: 22752725 DOI: 10.1007/s11033-012-1774-x]

28 **Chen XZ**, Zhang WH, Yang K, Zhang B, Chen ZX, Chen JP, Zhou ZG, Hu JK. Quantitative comparisons of summary receiver operating characteristics (sROC) curves among conventional serological tumor biomarkers for predicting gastric cancer in Chinese population. *Tumour Biol* 2014; **35**: 9015-9022 [PMID: 24906604 DOI: 10.1007/s13277-014-1986-x]

29 **van Harten-Gerritsen AS**, Balvers MG, Witkamp RF, Kampman E, van Duijnhoven FJ. Vitamin D, Inflammation, and Colorectal Cancer Progression: A Review of Mechanistic Studies and Future Directions for Epidemiological Studies. *Cancer Epidemiol Biomarkers Prev* 2015; **24**: 1820-1828 [PMID: 26396142 DOI: 10.1158/1055-9965.EPI-15-0601]

30 **Lee KE**, Khoi PN, Xia Y, Park JS, Joo YE, Kim KK, Choi SY, Jung YD. Helicobacter pylori and interleukin-8 in gastric cancer. *World J Gastroenterol* 2013; **19**: 8192-8202 [PMID: 24363509 DOI: 10.3748/wjg.v19.i45.8192]

31 **Wu CW**, Wang SR, Chao MF, Wu TC, Lui WY, P'eng FK, Chi CW. Serum interleukin-6 levels reflect disease status of gastric cancer. *Am J Gastroenterol* 1996; **91**: 1417-1422 [PMID: 8678006]

32 **Judd LM**, Alderman BM, Howlett M, Shulkes A, Dow C, Moverley J, Grail D, Jenkins BJ, Ernst M, Giraud AS. Gastric cancer development in mice lacking the SHP2 binding site on the IL-6 family co-receptor gp130. *Gastroenterology* 2004; **126**: 196-207 [PMID: 14699500]

33 **Lippitz BE**, Harris RA. Cytokine patterns in cancer patients: A review of the correlation between interleukin 6 and prognosis. *Oncoimmunology* 2016; **5**: e1093722 [PMID: 27467926 DOI: 10.1080/2162402X.2015.1093722]

34 **Buell JF**, Reed E, Lee KB, Parker RJ, Venzon DJ, Amikura K, Arnold S, Fraker DL, Alexander HR. Synergistic effect and possible mechanisms of tumor necrosis factor and cisplatin cytotoxicity under moderate hyperthermia against gastric cancer cells. *Ann Surg Oncol* 1997; **4**: 141-148 [PMID: 9084851]

35 **Jiménez FP**, Estévez MP. [Role of cytokines in chronic gastritis by Helicobacter pylori]. *Acta Gastroenterol Latinoam* 2001; **31**: 137-141 [PMID: 11577565]

**P-Reviewer:** Goldaracena N, Snowdon vk, Takamatsu S **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): B, b

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 Diagnostic value of the five indicators for discriminating the healthy control group and gastric cancer group**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Indicator | AUC | 95%CI of AUC | Cutoff Value | Sensitivity (%) | Specificity (%) |
| IL-6 | 0.92 | 0.91-0.94 | 20.31 | 92.05 | 78.92 |
| IL-8 | 0.65 | 0.60-0.71 | 1.45 | 55.68 | 79.41 |
| TNF-α | 0.76 | 0.71-0.81 | 7.82 | 65.91 | 82.84 |
| CEA | 0.65 | 0.60-0.71 | 3.45 | 36.36 | 92.65 |
| CA724 | 0.64 | 0.58-0.70 | 5.80 | 40.91 | 84.34 |

AUC: area under curve; IL: Interleukin; TNF: tumor necrosis factor.

 

A B

 

D

C



E

**Figure 1 Comparison of CEA, CA724, IL-6, IL-8, and TNF-α in three groups.** A: IL-6; B: IL-8; C: TNF-α; D: CEA; E: CA724. IL: Interleukin; TNF: tumor necrosis factor.

 

A B

 

C d

**Figure 2 Diagnostic value of IL-6, IL-8, TNF-α, and CA724 for discriminating the atypical hyperplasia group and gastric cancer group.** A: IL-6; B: IL-8; C: TNF-α; D: CA724. IL: Interleukin; TNF: tumor necrosis factor.



A b



C

**Figure 3** **Joint analysis of CEA, CA724, IL-6, IL-8, and TNF-α for discriminating the healthy control group and gastric cancer group.** A: Healthy control group *vs* gastric cancer group; B: Healthy control group *vs* early stage gastric cancer group; C: Healthy control group *vs* advanced stage gastric cancer group. IL: Interleukin; TNF: tumor necrosis factor.

 

A b



C

**Figure 4 Joint analysis of IL-6, IL-8, TNF-α, and CA724 for discriminating the atypical hyperplasia group and gastric cancer group.** A: atypical hyperplasia group *vs* gastric cancer group; B: atypical hyperplasia group *vs* early stage gastric cancer group; C: atypical hyperplasia group *vs* advanced stage gastric cancer group. IL: Interleukin; TNF: tumor necrosis factor.