Original Article

Construction and assessment of a joint prediction model and nomogram for colorectal cancer

Liming Chen[1], Xi Ma[1], Huajiang Dong[2], Bo Qu[3], Tao Yang[4], Min Xu[4], Guannan Sheng[4], Jun Hu[5], Aidong Liu[6]

[1]Department of Anorectal Surgery, Tianjin Hospital, Tianjin, China; [2]Logistics University of the Chinese People's Armed Police Force, Tianjin, China; [3]Institute of Disaster and Emergency Medicine, Tianjin University, Tianjin, China; [4]Department of General Surgery, Tianjin First Central Hospital, Tianjin, China; [5]Department of Colorectal Cancer Surgery, Tianjin Medical University Cancer Institute and Hospital, the National Clinical Research Center of Cancer and Key Laboratory of Cancer Prevention and Therapy, Tianjin, China; [6]Department of Pathology, Tianjin Hospital, Tianjin, China

Contributions: (I) Conception and design: L Chen, J Hu, A Liu; (II) Administrative support: X Ma, H Dong; (III) Provision of study materials or patients: L Chen, X Ma, B Qu, T Yang; (IV) Collection and assembly of data: M Xu, G Sheng, J Hu; (V) Data analysis and interpretation: M Xu, G Sheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jun Hu. Department of Colorectal Cancer Surgery, Tianjin Medical University Cancer Institute and Hospital, the National Clinical Research Center of Cancer and Key Laboratory of Cancer Prevention and Therapy, Tianjin, China. Email: junhu@tmu.edu.cn; Aidong Liu. Department of Pathology, Tianjin Hospital, No. 406, Jiefang South Road, Hexi District, Tianjin, China. Email: liuaidong303@163.com.

Background: Colorectal cancer (CRC) is one of the most common tumors in the digestive system, and all its risk factors are not yet known. It is important to identify valuable clinical indicators to predict the risk of CRC.

Methods: A total of 227 participants, comprising 162 healthy adults and 65 patients diagnosed with CRC at Tianjin Hospital from January 2017 to March 2022, were included in this study. Electrochemiluminescence was adopted to test the expression levels of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA199). Univariate and multivariate logistic regression analyses were performed to identify independent risk factors for CRC, and a joint prediction model was then constructed. A nomogram was prepared, and the model was later assessed using the receiver operating characteristic curve and calibration curve.

Results: The univariate analysis showed that there were statistically significant differences between the two groups in terms of smoking (χ^2=8.67), fecal occult blood (χ^2=119.41), *Helicobacter pylori* (*H. pylori*) infection (χ^2=30.87), a history of appendectomy (χ^2=5.47), serum total bile acid levels (t=19.80), serum CEA levels (t=37.82), serum CA199 levels (t=6.82), and serum ferritin levels (t=54.31) (all P<0.05). The multiple logistic regression analysis showed that smoking, fecal occult blood, *H. pylori* infection, a history of appendectomy, serum CEA levels, and serum CA199 levels were independent risk factors for CRC (all P<0.05). Based on the above findings, a joint prediction model was constructed, and the area under the receiver operator characteristic (ROC) curve of the model was 0.842. A nomogram and calibration curve was drawn, and the internal validation results indicated that the model had good diagnostic value.

Conclusions: Smoking, fecal occult blood, *H. pylori* infection, a history of appendectomy, serum CEA levels, and serum CA199 levels are independent risk factors for CRC, and the prediction model based on these factors had good predictive ability.

Keywords: Colorectal cancer (CRC); risk factor; joint prediction model

Submitted Aug 25, 2022. Accepted for publication Oct 18, 2022.
doi: 10.21037/jgo-22-917
View this article at: https://dx.doi.org/10.21037/jgo-22-917

Introduction

Colorectal cancer (CRC) is the 3rd and 2nd most common cancer in men and women worldwide, respectively, and accounts for about 10% of deaths from all cancers (1). In China, CRC is also a prevalent malignant tumor detrimental to the digestive system. According to recently released data from GLOBOCAN, an estimated 555,477 newly diagnosed CRC cases and 286,162 CRC-related deaths occurred in China in 2020 (2). With its high morbidity and mortality rates, CRC places a heavy burden on both society and individuals (3).

At present, CRC is primarily treated with integrated therapies focused on surgery. However, the rates of survival among CRC patients vary significantly depending on the cancer staging at the time of diagnosis. For example, the 5-year survival rate of patients reaches 90% if the tumors are locally controlled, but plummets to only 13% in cases of remote metastasis (4). This is because the early symptoms of CRC remain hidden, and CRC only tends to be detected at later stages. Consequently, the optimal timing for surgery is often missed.

Generally speaking, unlike a sudden pathological change, CRC progresses in the order of normal mucous glandular epithelium, low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia, and adenocarcinoma (5,6). Thus, early CRC detection and treatment are crucial if patient prognosis is to be improved. Currently, early CRC screening is mainly performed through a fecal occult blood test (FOBT) and enteroscopy. However, enteroscopy is an invasive procedure that patients often are reluctant to undergo. Additionally, due to the limited availability related to the complexity, costliness, and time-consuming process of the procedure, it would be unrealistic to conduct mass enteroscopies in China (7). Conversely, FOBT can be easily performed, but has poor reliability as a single indicator, and thus tends to produce unsatisfactory results (8).

Considerable research has been conducted using tumor markers for examination as an non-invasive diagnostic method (9). However, issues arise in the use of tumor markers for CRC diagnosis, as the levels of tumor markers may be increased in patients with both benign and malignant tumors and inflammatory diseases in other systems. As CRC is highly heterogeneous, a single tumor marker is not usually as sensitive or specific as an independent diagnostic indicator (10). Thus, this study intends to construct an easy-to-implement method for predicting CRC by combining several clinical indicators to provide a basis for early clinical detection and diagnosis of CRC. We present the following article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-917/rc).

Methods

General information

The CRC group comprised 65 patients who had undergone a radical operation after receiving a diagnosis of colon adenocarcinoma at Tianjin Hospital in Tianjin, China from January 2017 to March 2022. To be eligible for inclusion in this study, patients had to meet the following inclusion criteria: (I) have received a pathological diagnosis as per the guidelines of the World Health Organization (WHO) and have undergone a properly performed post-operative pathological examination and review by two pathologists; and (II) have complete clinical and follow-up data. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had dual or multiple primary malignancies; (II) were prone to genetic malignant transformations, such as inflammatory enteropathy and familial polyposis; (III) had undergone radiochemotherapy; and/or (IV) had contracted any serious infectious disease in the past 3 months. The control (CON) group comprised the serum specimens of 162 randomly selected healthy adult patients who had received a checkup in the above period. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tianjin Hospital (No. 2022-150) and informed consent was taken from all the patients.

Indicators for clinical observation

Data on gender, age, body mass index (BMI), FOBT, smoking, appendectomy, and cholecystectomy were collected from patients' past medical histories. The testing data collected included hemoglobin, albumin, bile acid, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA199), serum ferritin, and *Helicobacter pylori* (*H. pylori*) infection data.

Testing methods

The FOBT was conducted using the gold-standard method; reagent was purchased from Siemens. Hemoglobin and NLR were tested with a Sysmex hematology analyzer;

reagent was purchased from Sysmex. The levels of albumin and bile acid were tested with a fully automated Siemens chemistry analyzer; reagent was purchased from Siemens. CRP was tested with a Siemens POCT immunometer; reagent was purchased from Siemens. CEA and CA199 were tested by electrochemiluminescence; reagent was purchased from Roche. The carbon-14 breath test was performed for *H. pylori*; reagent was purchased from Shanghai Biohub International. Quality control was ensured across all the tests.

Statistical analysis

SPSS 26.0 software was employed for the statistical analysis of the data. The quantitative data are expressed as the $\bar{x}\pm s$. A normality test or homogeneity of variance test was performed first, and the normally distributed data were compared between the groups by means of an independent samples *t*-test. The non-normally distributed data are expressed as the median (interquartile range), and the rank-sum test was used for the intergroup comparisons. The enumeration data are expressed as the frequency, and the χ^2 test was used for the intergroup comparisons.

A joint model was built for CRC prediction by including the statistically significant indicators from the univariate analysis in the multivariate logistic regression analysis and screening the independent risk factors for CRC. Next, the model's prediction performance was assessed using the receiver operating characteristic (ROC) curve. R software (V4.1.2) and the rms package were used to create the nomogram model. Bootstrap re-sampling was performed for internal verification, and a calibration curve was drawn. A P value <0.05 was considered statistically significant.

Results

Baseline information

The CRC group comprised 65 patients (35 men and 30 women) with a median age of 68 years. Among the 65 patients, 23 were well differentiated, 34 were moderately differentiated, and 8 were poorly differentiated. Further, 15 had lymph node metastasis, and 50 did not. In relation to the TNM (Tumor Node Metastasis) staging, 11 were at stage I, 38 were at stage II, 14 were at stage III, and 2 were at stage IV (with liver metastasis). The CON group comprised 162 patients (95 men and 67 women) with a median age of 69 years. An intergroup comparison of gender and age revealed no statistically significant differences between the two groups (P>0.05).

Univariate analysis

The univariate analysis of the available data revealed statistically significant differences between the two groups in terms of smoking, fecal occult blood, *H. pylori* infection, a history of appendectomy, serum total bile acid levels, serum CEA levels, serum CA199 levels, and serum ferritin levels (P<0.05; see *Table 1*).

Multivariate logistic regression analysis

The statistically significant indicators in the univariate analysis were then included in the multivariate logistic regression analysis. The results revealed that smoking, fecal occult blood, *H. pylori* infection, a history of appendectomy, serum CEA levels, and serum CA199 levels were independent risk factors for CRC (see *Table 2*).

Joint prediction model construction and assessment

On the basis of the results of the multivariate logistic regression analysis, a joint prediction model was built. The following formula was used:

$$Y = -4.388 + 1.101X_1 + 1.487X_2 + 1.519X_3 + 1.126X_4 + 1.234X_5 + 2.236X_6 \quad [1]$$

where X_1 refers to smoking, X_2 refers to *H. pylori* infection, X_3 refers to a history of appendectomy, X_4 refers to fecal occult blood, X_5 refers to serum CEA levels, and X_6 refers to serum CA199 levels. Next the equation $P=1/(1 + exp(-Y))$ was used to calculate the predictive value of the model for each patient. Afterwards, the model was assessed based on the ROC curve. The results showed that the model's area the under curve (AUC) of ROC was 0.842, indicating that its diagnostic performance was superior to that of each of the other single indicators (see *Table 3* and *Figure 1*).

Nomogram and calibration curve preparation

According to the results of the multivariate logistic regression analysis, the nomogram function in the rms package in R was used to draw a nomogram, and the calibration function for a calibration curve. The analysis of the calibration curve indicated that the nomogram was

Table 1 Results of the univariate analysis of the clinical indicators related to CRC

Clinical indicators	CON group	CRC group	Statistic	P value
Age (years)	71.80±3.87	70.77±10.44	1.09	0.277
Gender (male/female)	95/67	35/30	0.44	0.509
Smoking (Y/N)	30/132	24/41	8.67	0.003
FOBT (P/N)	10/152	50/15	119.41	<0.001
H. pylori infection (P/N)	20/142	30/35	30.87	<0.001
Appendectomy (Y/N)	5/157	7/58	5.47	0.019
Cholecystectomy (Y/N)	6/156	5/60	2.34	0.126
Serum CEA (ng/mL)	1.13±0.20	8.58±2.49	37.82	<0.001
BMI (kg/m^2)	21.49±2.62	21.67±3.44	0.43	0.668
SF (μg/L)	60.45±7.81	412.77±81.91	54.31	<0.001
Albumin (g/L)	39.33±8.62	37.73±9.97	1.21	0.226
Total bile acid (μmol/L)	2.87±0.33	3.96±0.46	19.80	<0.001
NLR	1.51±0.23	1.56±0.20	1.71	0.089
CRP (mg/L)	6.87±1.08	7.17±1.61	1.64	0.101
Hemoglobin (g/L)	125.40±14.22	124.12±14.00	0.72	0.472
Serum CA199 (U/mL)	22.52±19.47	56.94±56.59	6.82	0.001

Data are presented as No. and mean ± standard deviation. CRC, colorectal cancer; CON, control; Y/N, yes/no; P/N, positive/negative; FOBT, fecal occult blood test; BMI, body mass index; SF, serum ferritin; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

Table 2 Results of the multivariate logistic regression analysis of the CRC-related clinical indicators

Clinical indicators	Regression coefficient b	Wald-statistic	OR (95% CI)	P value
Constant	–4.388	5.74	–	0.0001
Smoking	1.101	2.95	4.13 (1.76–10.32)	0.0034
H. pylori infection	1.487	3.62	6.26 (2.41–17.75)	0.0011
Appendectomy	1.519	2.42	9.10 (1.83–50.02)	0.0055
FOBT	1.126	2.91	3.07 (1.27–7.69)	0.0082
Serum CEA	1.234	3.21	23.57 (8.45–80.37)	0.0001
Serum CA199	2.236	4.45	14.65 (4.68–53.99)	0.0001

CRC, colorectal cancer; FOBT, fecal occult blood test; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; OR, odds ratio.

suitable for predicting the onset of CRC (see *Figures 2*,*3*).

Discussion

Following improvements in surgical techniques, the 5-year survival rate of CRC patients after surgery has been rising steadily and has now reached 50–60%; however, the overall survival rate of CRC patients remains <60% (11). In addition to the biological features of CRC, surgical therapy plus early detection and diagnosis are crucial to increasing patients' survival rates. In this study, we examined multiple factors related to the onset and progression of CRC, including smoking, fecal occult blood, *H. pylori* infection, a history of appendectomy, serum CEA levels, and serum

Table 3 Results of the ROC curve for the independent risk factors for CRC *vs.* the prediction model

Clinical indicators	AUC	95% CI	P value
Smoking	0.647	0.568–0.727	0.0005
H. pylori infection	0.632	0.549–0.716	0.0173
Appendectomy	0.545	0.459–0.630	0.2944
Fecal occult blood	0.597	0.513–0.680	0.0231
Serum CEA levels	0.680	0.599–0.761	0.0001
CA199	0.667	0.585–0.750	0.0001
Prediction model	0.842	0.784–0.899	0.0001

ROC, receiver operating characteristic; CRC, colorectal cancer; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; AUC, area the under curve.

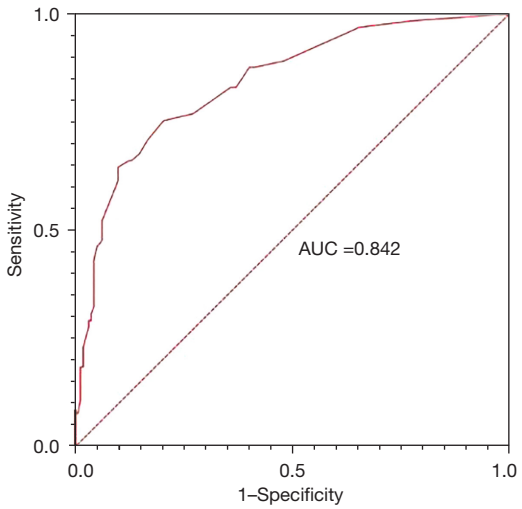

Figure 1 ROC curve of the joint prediction model. AUC, area the under curve; ROC, receiver operating characteristic.

CA199 levels and then developed a joint prediction model to offer an optimal plan for the screening of CRC.

It has long been thought that smoking significantly increases the risk of malignant tumors in many systems, including the lung, oral cavity, throat, esophagus, bladder, kidney, and pancreas, but its role in the morbidity of CRC patients was only recently established (12). The results of our multivariate analysis showed that smoking is an independent risk factor for the onset of CRC. Similarly, Botteri *et al.* (13) analyzed the effects of smoking on the risk of CRC, and found that the risk of CRC increases in a dose-dependent manner with rises in the duration and intensity of smoking. In relation to the mechanism of the carcinogenicity of smoking, the 69 different carcinogenic compounds in tobacco smoke affect the onset and progression of tumors through various channels, such as tumor-related genes (14). Thus, quitting smoking does reduce the risk of CRC.

The FOBT, a regular checkup item in CRC screening, is primarily conducted in chemical and immunological ways. The chemical testing method is prone to interference from dietary and living factors, and thus can produce false positive results. The immunological testing method causes the bloody feces, which stay too long in the intestine, to loose antigenicity, and thus can produce false negative results (15). Thus, the simultaneous application of both methods may help to enhance the accuracy of testing. Notwithstanding the above, as a single diagnostic indicator, the FOBT has poor sensitivity (16).

Based on the finding that fecal occult blood remains an independent factor for CRC prediction, this study included it in the joint prediction model and attained a higher diagnostic value. This study showed that serum CEA level, like fecal occult blood, is an independent factor for CRC prediction, but it cannot be used as a single prediction indicator due to its low positive rate (of approximately 25%) in early CRC (17). However, it plays a significant role in predicting post-operative relapses of CRC.

Studies (18,19) recently reported that *H. pylori* infection, which is mostly considered a risk factor for gastric cancer (20), is associated with the onset of CRC. In relation to its mechanism, Holmes *et al.* (21) observed a significant increase in the serum gastrin levels of CRC patients compared to normal patients. The hypergastrinemia may be attributed to the colonization of *H. pylori* in the stomach. Assuming that *H. pylori* enlarges the risk of CRC by increasing serum gastrin levels, we hypothesized that

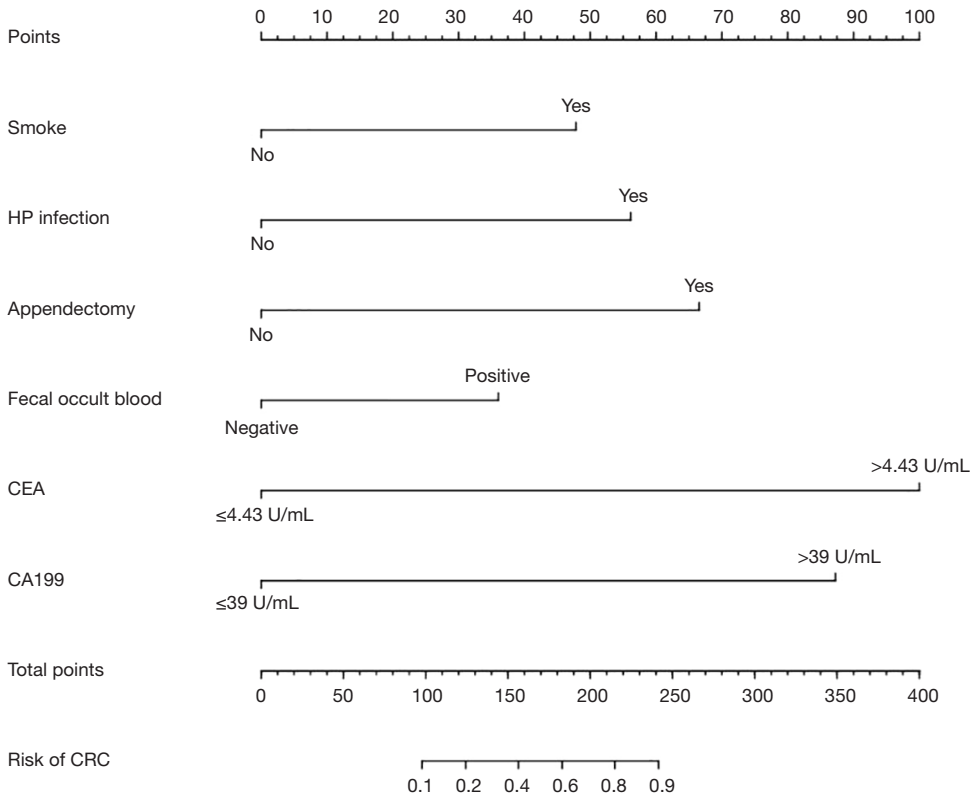

Figure 2 A CRC prediction nomogram. HP, *H. pylori*; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 19-9; CRC, colorectal cancer.

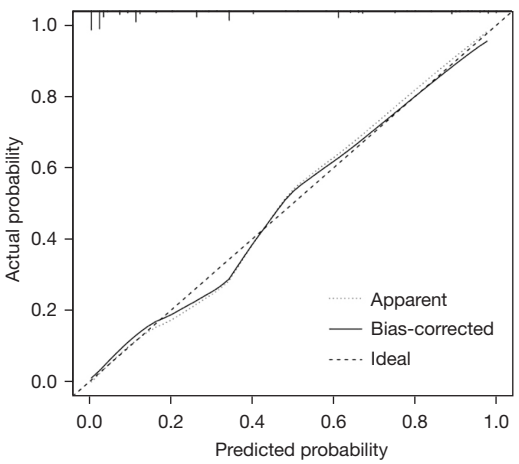

Figure 3 A calibration curve for the CRC prediction model. CRC, colorectal cancer.

eradicating *H. pylori* infection could be a major approach for CRC prevention. To clarify the connection between *H. pylori* infection and CRC, we included it in this study and proved that it is an independent risk factor for CRC. However, the mechanism behind the increased risk of CRC as a result of *H. pylori* infection requires further research and our conclusion needs to be proven in large multi-center studies.

There has been reported that appendectomy increases the risk of CRC (22). One theory of its possible mechanism is that the appendix is essential to the development of lymphatic tissues in the intestinal tract and a lack of such tissues hinders inflammation and reduces disruptive self-reactions in the large intestine. Another theory suggests that appendectomy alters the structure and function of the intestinal florae (23). The appendix hosts a multitude of intestinal florae, which differ from those in the large intestine in terms of structure and may re-enter the large intestine in the event of appendicitis. The microscopic florae in the appendix exist as biological membrane, contact the epithelial cells in the large intestine, and may promote the onset and progression of CRC through the process of an adenoma (24). However, further evidence is required to

ascertain the details of the mechanism. According to the present study in which appendectomy was included as an indicator, more cases a history of appendectomy were found among the CRC patients than the normal patients (P<0.05), and appendectomy was later proven to be an independent risk factor for the onset of CRC.

Following the continuous development in molecular biology and immunological technology, serum tumor markers have gradually been identified based on the knowledge that malignant tumors in different systems have relatively specific markers. As our understandings deepen, research has shown that a single marker tends to be extremely insensitive and unspecific in the diagnosis of malignant tumors of certain systems due to the polymorphism of tumors and the interference by some non-tumor diseases (25).

Tumor markers, such as CEA and CA199, have been shown to be highly expressed in the malignant tumors of multiple systems, including CRC tissues. The rate of CEA positive expression is only 40% or so among CRC patients, which indicates that it has low sensitivity and specificity (26). CA199 is mainly secreted by tumors in the digestive system, especially pancreatic cancer and CRC. Each of these markers, when used as a single indicator, has been shown to have low sensitivity and specificity (27). However, a previous study (28) suggested that the combined use of CA199 with other factors greatly enhances the accuracy of CRC diagnosis. However, it is not yet known whether the diagnostic accuracy can be improved by the simultaneous usage of multiple tumor markers. Our multivariate logistic analysis suggested that the levels of serum CEA and CA199 are independent risk factors for CRC. We included them in a prediction model, and found that the diagnostic performance of the model was superior to that of each single indicator alone, which also shows that the combination of multiple indicators increased the diagnostic accuracy of the model. The specificity and accuracy were significantly improved compared to the related study by Ding *et al.* (29).

In this study, we built a joint model for CRC prediction based on a multivariate logistic regression analysis, and achieved satisfactory values through internal verification. Further, a basic assessment showed that the CRC risk nomogram based on the model had good predictive value. Thus, we established a feasible and simple approach for clinical CRC screening. However, as the study involved a small number of cases from a single center, the model needs to be optimized by increasing the sample count and including data from multiple centers.

Acknowledgments

Funding: This research was supported by grants from the National Nature Science Foundation of China (Grant No. 81101870), the Natural Science Foundation of China (No. 81801240), the Project of Science and Technology Department of Chinese Anti-Cancer Association (Grant No. CORP-258:2021001045), the CAMS Innovative Fund for Medical Science (Grant No. 2018-I2M-AI-012), and the Science and Technology Research Development Plan of Tangshan City in 2019 (Grant No. 19150207E).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-917/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-917/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-917/coif). All authors report that this research was supported by grants from the National Nature Science Foundation of China (Grant No. 81101870), the Natural Science Foundation of China (No. 81801240), the Project of Science and Technology Department of Chinese Anti-Cancer Association (Grant No. CORP-258:2021001045), the CAMS Innovative Fund for Medical Science (Grant No. 2018-I2M-AI-012), and the Science and Technology Research Development Plan of Tangshan City in 2019 (Grant No. 19150207E). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tianjin Hospital (No. 2022-150). Each patient provided written informed consent.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Zhang Y, Chen Z, Li J. The current status of treatment for colorectal cancer in China: A systematic review. Medicine (Baltimore) 2017;96:e8242.
3. Li J, Ma X, Chakravarti D, et al. Genetic and biological hallmarks of colorectal cancer. Genes Dev 2021;35:787-820.
4. Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33.
5. Gao Y, Wang J, Zhou Y, et al. Evaluation of Serum CEA, CA19-9, CA72-4, CA125 and Ferritin as Diagnostic Markers and Factors of Clinical Parameters for Colorectal Cancer. Sci Rep 2018;8:2732.
6. Contasta I, Berghella AM, Pellegrini P, et al. Passage from normal mucosa to adenoma and colon cancer: alteration of normal sCD30 mechanisms regulating TH1/TH2 cell functions. Cancer Biother Radiopharm 2003;18:549-57.
7. Wilkins T, McMechan D, Talukder A. Colorectal Cancer Screening and Prevention. Am Fam Physician 2018;97:658-65.
8. Ladabaum U, Dominitz JA, Kahi C, et al. Strategies for Colorectal Cancer Screening. Gastroenterology 2020;158:418-32.
9. Shah R, Jones E, Vidart V, et al. Biomarkers for early detection of colorectal cancer and polyps: systematic review. Cancer Epidemiol Biomarkers Prev 2014;23:1712-28.
10. Zheng X, Amos CI, Frost HR. Pan-cancer evaluation of gene expression and somatic alteration data for cancer prognosis prediction. BMC Cancer 2021;21:1053.
11. Wrobel P, Ahmed S. Current status of immunotherapy in metastatic colorectal cancer. Int J Colorectal Dis 2019;34:13-25.
12. Botteri E, Iodice S, Bagnardi V, et al. Smoking and colorectal cancer: a meta-analysis. JAMA 2008;300:2765-78.
13. Botteri E, Borroni E, Sloan EK, et al. Smoking and Colorectal Cancer Risk, Overall and by Molecular Subtypes: A Meta-Analysis. Am J Gastroenterol 2020;115:1940-9.
14. Grando SA. Connections of nicotine to cancer. Nat Rev Cancer 2014;14:419-29.
15. Randel KR, Schult AL, Botteri E, et al. Colorectal Cancer Screening With Repeated Fecal Immunochemical Test Versus Sigmoidoscopy: Baseline Results From a Randomized Trial. Gastroenterology 2021;160:1085-1096.e5.
16. Sokoro A, Singh H. Fecal Occult Blood Test for Evaluation of Symptoms or for Diagnostic Testin. Am J Gastroenterol 2020;115:679-80.
17. Das V, Kalita J, Pal M. Predictive and prognostic biomarkers in colorectal cancer: A systematic review of recent advances and challenges. Biomed Pharmacother 2017;87:8-19.
18. Liou JM, Malfertheiner P, Lee YC, et al. Screening and eradication of Helicobacter pylori for gastric cancer prevention: the Taipei global consensus. Gut 2020;69:2093-112.
19. Liu IL, Tsai CH, Hsu CH, et al. Helicobacter pylori infection and the risk of colorectal cancer: a nationwide population-based cohort study. QJM 2019;112:787-92.
20. Burnett-Hartman AN, Newcomb PA, Potter JD. Infectious agents and colorectal cancer: a review of Helicobacter pylori, Streptococcus bovis, JC virus, and human papillomavirus. Cancer Epidemiol Biomarkers Prev 2008;17:2970-9.
21. Holmes L Jr, Rios J, Berice B, et al. Predictive Effect of Helicobacter pylori in Gastric Carcinoma Development: Systematic Review and Quantitative Evidence Synthesis. Medicines (Basel) 2021;8:1.
22. Lee S, Jang EJ, Jo J, et al. Long-term impacts of appendectomy associated with increased incidence of inflammatory bowel disease, infection, and colorectal cancer. Int J Colorectal Dis 2021;36:1643-52.
23. Rothwell JA, Mori N, Artaud F, et al. Colorectal cancer risk following appendectomy: a pooled analysis of three large prospective cohort studies. Cancer Commun (Lond) 2022;42:486-9.
24. Chen J, Sali A, Vitetta L. The gallbladder and vermiform appendix influence the assemblage of intestinal microorganisms. Future Microbiol 2020;15:541-55.
25. Duffy MJ, Lamerz R, Haglund C, et al. Tumor markers in colorectal cancer, gastric cancer and gastrointestinal stromal cancers: European group on tumor markers 2014

guidelines update. Int J Cancer 2014;134:2513-22.
26. Sefrioui D, Beaussire L, Gillibert A, et al. CEA, CA19-9, circulating DNA and circulating tumour cell kinetics in patients treated for metastatic colorectal cancer (mCRC). Br J Cancer 2021;125:725-33.
27. Yang T, Lin X, Zhang L, et al. Integration of IgG and IgA autoantibodies for early diagnosis of hepatocellular carcinoma. Clin Chim Acta 2021;523:423-9.
28. Wang J, Wang X, Yu F, et al. Combined detection of preoperative serum CEA, CA19-9 and CA242 improve prognostic prediction of surgically treated colorectal cancer patients. Int J Clin Exp Pathol 2015;8:14853-63.
29. Ding D, Han S, Zhang H, et al. Predictive biomarkers of colorectal cancer. Comput Biol Chem 2019;83:107106.

(English Language Editor: L. Huleatt)

Cite this article as: Chen L, Ma X, Dong H, Qu B, Yang T, Xu M, Sheng G, Hu J, Liu A. Construction and assessment of a joint prediction model and nomogram for colorectal cancer. J Gastrointest Oncol 2022;13(5):2406-2414. doi: 10.21037/jgo-22-917

