# World Journal of Gastrointestinal Surgery

World J Gastrointest Surg 2024 June 27; 16(6): 1485-1955





Published by Baishideng Publishing Group Inc

WJGS

# World Journal of Gastrointestinal Surgery

# Contents

# Monthly Volume 16 Number 6 June 27, 2024

# **EDITORIAL**

1485	Has the open surgical approach in colorectal cancer really become uncommon?		
	Cariati M, Brisinda G, Chiarello MM		
1493	Intestinal Behçet's disease: A review of clinical diagnosis and treatment Liu Y, Gao F, Yang DQ, Jiao Y		
1501	Non-operative management of rectal cancer: Highlighting the controversies <i>Emile SH, Wignakumar A</i>		
1507	Current considerations for the surgical management of gallbladder adenomas <i>Pavlidis ET, Galanis IN, Pavlidis TE</i>		
1513	Immunotherapy in gastric cancer with liver metastasis: Challenges and opportunities <i>Bardakçi M, Ergun Y</i>		
1517	From the mathematical model to the patient: The scientific and human aspects of artificial intelligence in gastrointestinal surgery		

Arredondo Montero J

# **MINIREVIEWS**

1521 Laparoscopic right radical hemicolectomy: Central vascular ligation and complete mesocolon excision vs D3 lymphadenectomy - How I do it?

Yadav K

#### **ORIGINAL ARTICLE**

#### **Case Control Study**

1527 Perioperative outcomes of transvaginal specimen extraction laparoscopic total gastrectomy and conventional laparoscopic-assisted total gastrectomy

Zhang ZC, Wang WS, Chen JH, Ma YH, Luo QF, Li YB, Yang Y, Ma D

#### **Retrospective Cohort Study**

Optimal extent of lymphadenectomy improves prognosis and guides adjuvant chemotherapy in 1537 esophageal cancer: A propensity score-matched analysis

Tang JM, Huang SJ, Chen QB, Wu HS, Qiao GB

1548 Efficacy of laparoscopic low anterior resection for colorectal cancer patients with 3D-vascular reconstruction for left coronary artery preservation

Wang Y, Liu ZS, Wang ZB, Liu S, Sun FB



Conton	World Journal of Gastrointestinal Surgery
Conten	Monthly Volume 16 Number 6 June 27, 2024
1558	Robotic-assisted low anterior resection for rectal cancer shows similar clinical efficacy to laparoscopic surgery: A propensity score matched study
	Long SX, Wang XN, Tian SB, Bi YF, Gao SS, Wang Y, Guo XB
1571	Machine learning prediction model for gray-level co-occurrence matrix features of synchronous liver metastasis in colorectal cancer
	Yang KF, Li SJ, Xu J, Zheng YB
1582	Risk factors associated with intraoperative persistent hypotension in pancreaticoduodenectomy
	Wang XJ, Xuan XC, Sun ZC, Shen S, Yu F, Li NN, Chu XC, Yin H, Hu YL
	Retrospective Study
1592	Endoscopic ultrasound-guided biliary drainage $vs$ percutaneous transhepatic bile duct drainage in the management of malignant obstructive jaundice
	Zhu QQ, Chen BF, Yang Y, Zuo XY, Liu WH, Wang TT, Zhang Y
1601	Clinical efficacy of Gamma Knife® combined with transarterial chemoembolization and immunotherapy in
	the treatment of primary liver cancer
	Wang GF, Shu CX, Cai XD, Wang HB, Xu JH, Jia YQ
1609	Identifying the risk factors for pancreatic fistula after laparoscopic pancreaticoduodenectomy in patients with pancreatic cancer
	Xu H, Meng QC, Hua J, Wang W
1618	Correlation between postoperative chemotherapy regimen and survival in patients with resectable gastric adenocarcinoma accompanied with vascular cancer thrombus
	Yang ZF, Dong ZX, Dai CJ, Fu LZ, Yu HM, Wang YS
1629	Gastroesophageal signet ring cell carcinoma morbidity and mortality: A retrospective review
	Grinlinton M, Furkert C, Maurice A, Angelo N, Booth M
1637	Analysis of lymph node metastasis and survival prognosis in early gastric cancer patients: A retrospective study
	Liu DY, Hu JJ, Zhou YQ, Tan AR
1647	Clinical study of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in hypertriglyceridemia- induced acute pancreatitis and acute biliary pancreatitis with persistent organ failure
	Xu MS, Xu JL, Gao X, Mo SJ, Xing JY, Liu JH, Tian YZ, Fu XF
1660	Tumor recurrence and survival prognosis in patients with advanced gastric cancer after radical resection with radiotherapy and chemotherapy
	Nie SF, Wang CY, Li L, Yang C, Zhu ZM, Fei JD
1670	Prediction and analysis of albumin-bilirubin score combined with liver function index and carcinoem- bryonic antigen on liver metastasis of colorectal cancer
	Wang ZM, Pan SP, Zhang JJ, Zhou J



Conton	World Journal of Gastrointestinal Surgery				
Conten	Monthly Volume 16 Number 6 June 27, 2024				
1681	Comparative analysis of the short and medium-term efficacy of the Da Vinci robot <i>versus</i> laparoscopic total mesangectomy for rectal cancer				
	Gao WG, Shi W, Gong XC, Li ZW, Tuoheti Y				
1691	How to apply ex-vivo split liver transplantation safely and feasibly: A three-step approach				
	Zhao D, Xie QH, Fang TS, Zhang KJ, Tang JX, Yan X, Jin X, Xie LJ, Xie WG				
1700	Clinical efficacy of laparoscopic cholecystectomy combined with endoscopic papillary balloon dilation in treatment of gallbladder stones with common bile duct stones: A retrospective study				
	Liu HD, Zhang Q, Xu WS, Jin S				
1709	Evaluation of oxaliplatin and tigio combination therapy in locally advanced gastric cancer				
	Wang T, Zhang LY				
1717	Lung ultrasound score evaluation of the effect of pressure-controlled ventilation volume-guaranteed on patients undergoing laparoscopic-assisted radical gastrectomy				
	Tan J, Bao CM, Chen XY				
1726	Effect of endoscopic sphincterotomy and endoscopic papillary balloon dilation endoscopic retrograde cholangiopancreatographies on the sphincter of Oddi				
	Fu K, Yang YY, Chen H, Zhang GX, Wang Y, Yin Z				
1734	Influence of reduced-port laparoscopic surgery on perioperative indicators, postoperative recovery, and serum inflammation in patients with colorectal carcinoma				
	Wu HB, Liu DF, Liu YL, Wang XF, Cao YP				
	Clinical Trials Study				
1742	Clinical effect of spleen aminopeptide on improving liver function damage and immune function in children with infant hepatitis syndrome				
	Fang XQ, Gan T, Wang LM				
	Observational Study				
1749	Observation of therapeutic effect of lamp irradiation combined with purple gromwell oil gauze on alleviating intestinal colic in patients				
	Cen BZ, Chen YS, Li LP, Wu JW, Xie YF				
	Randomized Controlled Trial				
1756	Radiofrequency ablation combined with transcatheter arterial chemoembolization for recurrent liver cancer				
	Guo JY, Zhao LL, Cai HJ, Zeng H, Mei WD				
	Randomized Clinical Trial				
1765	Effect of high-protein peptide-based formula compared with isocaloric isonitrogenous polymeric formula in critically ill surgical patient				
	Sumritpradit P, Shantavasinkul PC, Ungpinitpong W, Noorit P, Gajaseni C				



# Contents

World Journal of Gastrointestinal Surgery

### Monthly Volume 16 Number 6 June 27, 2024

#### **Clinical and Translational Research**

- 1775 Metabolic disorders and hepatitis: Insights from a Mendelian randomization study Liang LB, Liu XP, Mao TR, Su QL
- 1791 Analysis of cancer-specific survival in patients with metastatic colorectal cancer: A evidence-based medicine study

Zhou YJ, Tan ZE, Zhuang WD, Xu XH

1803 FDX1 as a novel biomarker and treatment target for stomach adenocarcinoma

Xie XZ, Zuo L, Huang W, Fan QM, Weng YY, Yao WD, Jiang JL, Jin JQ

#### **Basic Study**

1825 Peritoneal fluid indocyanine green test for diagnosis of gut leakage in anastomotic leakage rats and colorectal surgery patients

Huang Y, Li TY, Weng JF, Liu H, Xu YJ, Zhang S, Gu WL

# SYSTEMATIC REVIEWS

Global geoepidemiology of gastrointestinal surgery rates in Crohn's disease 1835

> Weissman S, Aziz M, Bangolo A, Nagesh VK, Aung H, Mathew M, Garcia L, Chandar SA, Karamthoti P, Bawa H, Alshimari A, Kejela Y, Mehdi N, Joseph CA, Kodali A, Kumar R, Goyal P, Satheesha S, Nivedita F, Tesoro N, Sethi T, Singh G, Belal A, Intisar A, Khalid H, Cornwell S, Suresh SB, Ahmed K, Marole KK, Anand OP, Reshi RB, Mehta TI, Elias S, Feuerstein JD

# **META-ANALYSIS**

1845 Compare clinical efficacy and safety of neoadjuvant therapy and neoadjuvant chemoradiotherapy for locally advanced rectal cancer: Meta-analysis

Wang Y, Yang Y, Liu QQ, Wang SZ

1857 Sarcopenia adversely impacts clinical outcomes in patients undergoing pancreaticoduodenectomy: A systematic review and meta-analysis

Zhang QH, Ma JD, Lu YM, Zhang RN, Zhao ZH, Li YT, Chen QP

1871 Comparison efficacy and safety of total laparoscopic gastrectomy and laparoscopically assisted total gastrectomy in treatment of gastric cancer

Li L, Liu DY, Leng J, Tao XM, Wu HQ, Zhu YP

1883 Application value of indocyanine green fluorescence imaging in guiding sentinel lymph node biopsy diagnosis of gastric cancer: Meta-analysis

Zhang QJ, Cao ZC, Zhu Q, Sun Y, Li RD, Tong JL, Zheng Q

#### SCIENTOMETRICS

1894 Visualizing the landscape of appendiceal tumor research after 2010: A bibliometric study Ji JN, Yin ZB



Contents

World Journal of Gastrointestinal Surgery

# Monthly Volume 16 Number 6 June 27, 2024

#### **CASE REPORT**

1910	No-touch isolation technique in emergency pancreaticoduodenectomy for neoplastic hemorrhage: Two case reports and review of literature			
	Cho A, Katagiri S, Ota M, Onizawa S, Higuchi R, Sugishita T, Niwa Y, Ishita T, Mouri T, Kato A, Iwata M			
1918	Malignant myopericytoma originating from the colon: A case report			
	Zhang HL, Zhang M, Guo JQ, Wu FN, Zhu JD, Tu CY, Lv XL, Zhang K			
1926	Novel magnetic compression technique for the treatment of postoperative anastomotic stenosis in rectal cancer: A case report			
	Zhang MM, Sha HC, Xue HR, Qin YF, Song XG, Li Y, Li Y, Deng ZW, Gao YL, Dong FF, Lyu Y, Yan XP			
1933	Magnetic compression anastomosis to restore biliary tract continuity after obstruction following major abdominal trauma: A case report			
	Zhang MM, Tao J, Sha HC, Li Y, Song XG, Muensterer OJ, Dong FF, Zhang L, Lyu Y, Yan XP			
1939	Colo-colonic intussusception as a rare complication of colonoscopy with polypectomy: Two case reports			
	Xiang SH, Xu GQ			
1948	Resection of polyps involving the appendiceal orifice by combined endo-laparoscopic surgery: Two case reports			
	Zhang YY, Lu JY, Wang Q, Yang AM			

# **LETTER TO THE EDITOR**

Evaluating bacterial contamination and surgical site infection risks in intracorporeal anastomosis: Role of 1953 bowel preparation

Lee J

# Contents

Monthly Volume 16 Number 6 June 27, 2024

# **ABOUT COVER**

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# **AIMS AND SCOPE**

The primary aim of World Journal of Gastrointestinal Surgery (WJGS, World J Gastrointest Surg) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

# **INDEXING/ABSTRACTING**

The WJGS is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports<sup>®</sup> cites the 2023 journal impact factor (JIF) for WJGS as 1.8; JIF without journal self cites: 1.7; 5-year JIF: 1.9; JIF Rank: 123/290 in surgery; JIF Quartile: Q2; and 5-year JIF Quartile: Q3.

# **RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Zi-Hang Xu; Production Department Director: Xiang Li; Cover Editor: Jia-Ru Fan.

NAME OF JOURNAL	INSTRUCTIONS TO AUTHORS
World Journal of Gastrointestinal Surgery	https://www.wignet.com/bpg/gcrinfo/204
<b>ISSN</b>	GUIDELINES FOR ETHICS DOCUMENTS
ISSN 1948-9366 (online)	https://www.wjgnet.com/bpg/GerInfo/287
LAUNCH DATE	GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
November 30, 2009	https://www.wjgnet.com/bpg/gerinfo/240
FREQUENCY	PUBLICATION ETHICS
Monthly	https://www.wjgnet.com/bpg/GerInfo/288
EDITORS-IN-CHIEF	PUBLICATION MISCONDUCT
Peter Schemmer	https://www.wjgnet.com/bpg/gerinfo/208
EDITORIAL BOARD MEMBERS	ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/1948-9366/editorialboard.htm	https://www.wjgnet.com/bpg/gerinfo/242
PUBLICATION DATE	STEPS FOR SUBMITTING MANUSCRIPTS
June 27, 2024	https://www.wjgnet.com/bpg/GerInfo/239
COPYRIGHT	ONLINE SUBMISSION
© 2024 Baishideng Publishing Group Inc	https://www.f6publishing.com

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# World Journal of Gastrointestinal Surgery

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World J Gastrointest Surg 2024 June 27; 16(6): 1791-1802

DOI: 10.4240/wjgs.v16.i6.1791

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

#### **Clinical and Translational Research**

# Analysis of cancer-specific survival in patients with metastatic colorectal cancer: A evidence-based medicine study

#### Yin-Jie Zhou, Zhi-E Tan, Wei-Da Zhuang, Xin-Hua Xu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single-blind

Peer-review report's classification Scientific Quality: Grade C Novelty: Grade C Creativity or Innovation: Grade C Scientific Significance: Grade C

P-Reviewer: Yadav BS, India

Received: March 8, 2024 Revised: April 29, 2024 Accepted: May 16, 2024 Published online: June 27, 2024 Processing time: 113 Days and 23.1 Hours



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# Abstract

#### BACKGROUND

Metastatic colorectal cancer (mCRC) is a common malignancy whose treatment has been a clinical challenge. Cancer-specific survival (CSS) plays a crucial role in assessing patient prognosis and treatment outcomes. However, there is still limited research on the factors affecting CSS in mCRC patients and their correlation.

#### AIM

To predict CSS, we developed a new nomogram model and risk grading system to classify risk levels in patients with mCRC.

#### **METHODS**

Data were extracted from the United States Surveillance, Epidemiology, and End Results database from 2018 to 2023. All eligible patients were randomly divided into a training cohort and a validation cohort. The Cox proportional hazards model was used to investigate the independent risk factors for CSS. A new nomogram model was developed to predict CSS and was evaluated through internal and external validation.

#### RESULTS

A multivariate Cox proportional risk model was used to identify independent risk



factors for CSS. Then, new CSS columns were developed based on these factors. The consistency index (C-index) of the histogram was 0.718 (95%CI: 0.712-0.725), and that of the validation cohort was 0.722 (95%CI: 0.711-0.732), indicating good discrimination ability and better performance than tumor-node-metastasis staging (C-index: 0.712-0.732). For the training set, 0.533, 95%CI: 0.525-0.540; for the verification set, 0.524, 95%CI: 0.513-0.535. The calibration map and clinical decision curve showed good agreement and good potential clinical validity. The risk grading system divided all patients into three groups, and the Kaplan-Meier curve showed good stratification and differentiation of CSS between different groups. The median CSS times in the low-risk, medium-risk, and high-risk groups were 36 months (95%CI: 34.987-37.013), 18 months (95%CI: 17.273-18.727), and 5 months (95%CI: 4.503-5.497), respectively.

#### CONCLUSION

Our study developed a new nomogram model to predict CSS in patients with synchronous mCRC. In addition, the risk-grading system helps to accurately assess patient prognosis and guide treatment.

**Key Words:** Colorectal tumor; Surveillance epidemiology and end results database; Nomogram analysis; Survival prognosis; Retrospective study

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**Core Tip:** This study utilized an evidence-based approach to analyze cancer-specific survival (CSS) in patients with metastatic colorectal cancer (mCRC). By systematically collecting, integrating, and analyzing relevant data, we explored CSS in mCRC patients and its influencing factors to provide clinicians with more accurate prognostic assessments and treatment decision support. The importance of this study is that it can provide a basis for individualized treatment of mCRC patients and promote the maximization of treatment effects, thereby improving the quality of life and survival rate of patients.

Citation: Zhou YJ, Tan ZE, Zhuang WD, Xu XH. Analysis of cancer-specific survival in patients with metastatic colorectal cancer: A evidence-based medicine study. *World J Gastrointest Surg* 2024; 16(6): 1791-1802 URL: https://www.wjgnet.com/1948-9366/full/v16/i6/1791.htm DOI: https://dx.doi.org/10.4240/wjgs.v16.i6.1791

# INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant neoplasms, ranking third in incidence (10.2%) and second in mortality (9.2%)[1-3]. In countries in Eastern Europe, Latin America, and Asia, the incidence and mortality of CRC are increasing annually[4]. There are no obvious signs or symptoms of CRC in the early stages, and more than one-fifth of patients have developed distant metastases at the time of diagnosis[5]. Among patients with CRC, patients with simultaneous metastases have lower survival rates than patients with heterochronous metastases[6]. The most common metastatic organs for CRC are the liver and lung, while bone metastases are rare, and brain metastases occur in only 1% of CRC patients[7]. Although metastatic CRC (mCRC) has the worst prognosis, there are large differences in survival outcomes between patients with different metastatic organs. The 1-year survival rate for patients with liver and lung metastases is greater than 80%, while the 1-year survival rates for patients with bone and brain metastases are 30% and 11%, respectively[8]. Therefore, accurate screening for different risk factors is critical for physicians to predict mCRC outcomes.

Currently, the American Joint Committee on Cancer (AJCC) staging system is the primary method for predicting survival outcomes in patients with mCRC[9]. However, the T stage, N stage, and M stage are the only factors for distinguishing different prognoses, and this scheme is far from satisfactory in terms of prediction accuracy[10]. A nomogram is a visual tool used to predict the probability of an endpoint occurring and to quantify survival risk. According to the different regression coefficients, the columniogram can include significant factors to improve the prediction accuracy. To date, nomograms have been successfully used to predict the prognosis of patients with CRC but have rarely been used for patients with mCRC[11].

Therefore, our goal was to develop a new nomographic model to predict tumor-specific survival for patients with simultaneous mCRC and to divide this model into different risk levels to accurately assess patient prognosis.

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Figure 1 Nomogram for predicting the tumor-specific survival of patients with metastatic colorectal cancer. CEA: Carcinoembryonic antigen; CSS: Cancer-specific survival.

# MATERIALS AND METHODS

#### Research subjects

This study obtained all the data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute using SEER Stat software (version 8.3.6). The data were collected and reported using data items and codes recorded by the North American Association of Central Cancer Registries. The inclusion criteria for patients were as follows: (1) Were diagnosed with CRC between 2018 and 2023; (2) were diagnosed with simultaneous metastasis; and (3) had a histological diagnosis. The exclusion criteria were as follows: (1) No patients with distant metastasis; and (2) unknown missing data, such as race, primary tumor site, T stage, N stage, carcinoembryonic antigen (CEA) status, surgical status, and survival time.

The following variables were collected: Race, sex, age at diagnosis, primary site, grade, T stage, N stage, CEA status, distant metastatic status (liver, lung, bone, brain), surgery (primary tumor resection), chemotherapy, cancer-specific survival (CSS), and survival time. CSS was assessed by 1-, 2-, and 3-year survival rates, defined as the time from the date of diagnosis to the date of death or study due to CRC, according to the eighth edition of the AJCC tumor-node-metastasis staging system.

#### Research method

All eligible patients were randomly divided into training and validation groups (at a ratio of 7:3). The Pearson chi-square test was used to examine demographic differences between all coqueues, training coqueues, and validation coqueues. A multivariate Cox proportional risk model was used to explore independent risk factors for CSS, and a predictive nomogram model was built using a training cohort. The C-index, calibration curve, and decision curve analysis (DCA) were used for internal and external verification.

#### Nomogram analysis

X-tile software was used to determine the optimal critical value according to the total score of the column graph to establish a risk grading system, and all patients were divided into low-, medium-, and high-risk groups. Kaplan-Meier (K-M) curves of CSS were constructed and compared with a logarithmic rank test. Statistical analysis was performed



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<table-container>&lt; 30103(57)104(57)305(58)</table-container>	Age at diagnosis (yr)				1.73	0.188
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InV471(2%)192(2%)14(614(614(7%)00.7714407(3.1)16(13.1)61(3.0)12(2 </td <td>I-II</td> <td>11127 (70.3)</td> <td>7793 (70.3)</td> <td>3334 (70.2)</td> <td></td> <td></td>	I-II	11127 (70.3)	7793 (70.3)	3334 (70.2)		
Harding164 (A2)164 (A3)	III-IV	4711 (29.7)	3295 (29.7)	1416 (29.8)		
12209(1)146 (13.2)619 (3.9)147 (3.9)341379 (6.9)929 (6.9)143 (2.9)143 (2.9)N=V=V=V1629 (3.4)266 (2.7)1243 (2.9)143 (2.9)121629 (3.4)122 (3.3)307 (7.3)147Maculine1238 (7.8)605 (7.8)673 (7.3)143 (7.9)Iminice1238 (7.8)605 (7.8)673 (7.3)143 (7.9)Iminice1238 (7.8)605 (7.8)673 (7.3)143 (7.9)Iminice1378 (7.9)636 (7.9)143 (7.9)6.93Iminice1371 (7.9)296 (7.9)1433 (7.9)143 (7.9)Iminice1473 (7.9)636 (7.9)1433 (7.9)1433 (7.9)Iminice1473 (7.9)636 (7.9)1433 (7.9)1433 (7.9)Iminice1473 (7.9)636 (7.9)1433 (7.9)1433 (7.9)Iminice1473 (7.9)636 (7.9)1433 (7.9)1433 (7.9)Iminice1473 (7.9)636 (7.9)1433 (7.9)1433 (7.9)Iminice1473 (7.9)636 (7.9)1433 (7.9)1433 (7.9)Iminice1473 (7.9)636 (7.9)1433 (7.9)1433 (7.9)Iminice1493 (7.9)1363 (7.9)1433 (7.9)1433 (7.9)Iminice1493 (7.9)1493 (7.9)1493 (7.9)1493 (7.9)Iminice140 (7.9)144 (7.9)1512 (7.9)1493 (7.9)Iminice1434 (7.9)144 (7.9)1512 (7.9)1493 (7.9)Iminice1434 (7.9)144 (7.9)1512 (7.9)1	T staging				0.08	0.777
341379 (86)927 (86.)142 (20.)162 (0.4)N=1240 (26.)266 (26.)143 (26.)143 (26.)12162 (73.)367 (73.)100 (73.)100 (73.)CE = trainine238 (26.)367 (73.)100 (73.)100 (73.)Immine137 (26.)238 (21.3)167 (72.)100 (73.)Immine137 (29.)238 (21.3)137 (73.)100 (73.)Immine131 (29.)238 (27.)133 (20.)100 (73.)Immine131 (20.)239 (27.)133 (20.)100 (73.)Immine152 (20.)239 (27.)133 (20.)133 (20.)Immine163 (20.)250 (20.)135 (20.)135 (20.)Immine152 (20.)166 (26.)155 (26.)135 (27.)Immine152 (20.)166 (26.)157 (26.)135 (27.)Immine152 (20.)166 (26.)157 (26.)157 (27.)Immine152 (20.)166 (26.)157 (26.)157 (26.)Immine152 (20.)166 (26.)167 (20.)150 (20.)Immine152 (20.)167 (20.)150 (20.)150 (20.)Immine152 (20.)167 (20.)160 (20.)160 (20.)Immine152 (20.)167 (20.)160 (20.)160 (20.)Immine152 (20.)167 (20.)160 (20.)160 (20.)Immine152 (20.)167 (20.)160 (20.)160 (20.)Immine152 (20.)167 (20.)160 (20.)160 (20.)Immine1	1-2	2079 (13.1)	1461 (13.2)	618 (13.0)		
N star160409 (26)266 (27)124 (26,20)203 (26,20)1/2160 (26,02)362 (26,30)367 (7,3)300CE stars1278 (78,20)670 (75,5)670 (77,3)370 (72,7)Immine360 (21,8)238 (27,5)107 (22,7)340Immine471 (29,9)239 (27,1)433 (02,1)317 (68,1)Immine471 (29,0)250 (20,3)317 (68,1)318Immine1267 (80,0)838 (97,1)313 (60,1)318Immine1267 (80,0)250 (20,3)913 (13,0)318Immine1262 (61,0)160 (62,2)151 (30,0)317 (68,1)Immine1262 (61,0)160 (62,2)151 (30,0)317 (68,1)Immine1262 (61,0)160 (62,2)151 (30,0)317 (68,1)Immine1262 (61,0)160 (62,0)151 (30,0)317 (30,0)Immine1262 (61,0)160 (62,0)151 (50,0)317 (50,0)Immine1262 (61,0)160 (92,0)151 (30,0)317 (30,0)Immine1262 (61,0)160 (92,0)161 (30,0)161 (30,0)Immine1262 (61,0)160 (92,0)161 (92,0)161 (92,0)Immine1262 (61,0)161 (70,0)160 (70,0)161 (70,0)Immine1562 (93,0)161 (93,0)161 (93,0)161 (93,0)Immine1562 (93,0)161 (93,0)160 (93,0)161 (93,0)Immine1562 (93,0)161 (93,0)160 (93,0)161 (93,0)Immine1562 (93,0)161	3-4	13759 (86.9)	9627 (86.8)	4132 (87.0)		
0420 (26.)296 (27.)124 (26.)124 (26.)127 (26.)1-2162 (27.)162 (27.)167 (27.)177 (27.)Maxuline1237 (78.2)238 (27.)177 (27.)178 (27.)Kur metatase107 (27.)178 (27.)178 (27.)178 (27.)No473 (29.0)238 (27.)143 (02.)178 (27.)Kur metatase1107 (01.)790 (03.)317 (69.)188 (27.)No1267 (80.0)838 (97.)313 (69.)188 (27.)No1267 (80.0)250 (20.3)91 (13.)179 (27.)No1262 (61.)1069 (62.)151 (27.)137 (27.)No152 (64.)1069 (62.)150 (27.)137 (27.)No152 (61.)1069 (27.)109 (13.)14.1No152 (61.)1069 (27.)109 (27.)137 (27.)No152 (61.)1073 (29.0)107 (27.)137 (27.)No152 (26.1)1069 (27.)150 (27.)137 (27.)No152 (26.1)107 (27.)107 (27.)137 (27.)No152 (26.1)107 (27.)107 (27.)137 (27.)No156 (29.0)107 (27.)107 (27.)107 (27.)No156 (29.0)107 (27.)107 (27.)107 (27.)No156 (27.)157 (27.)107 (27.)107 (27.)No156 (27.)157 (27.)107 (27.)107 (27.)No156 (27.)157 (27.)107 (27.)107 (27.)No156 (27.)157 (27.)	N stage				0.576	0.448
1.2169(74)182(73)307(73)CE-stars278609Maculine1237 (72,0)6705 (75,0)6707 (72,0)Fininice360 (13,0)238 (25,0)107 (22,0)Lutretastase107 (21,0)609609No473 (29,0)239 (29,7)1433 (02,0)Yes1107 (70,1)770 (73,0)337 (68,0)143No107 (21,0)770 (73,0)337 (68,0)143Verturetastase220 (23,0)615 (13,0)143No163 (20,0)250 (23,0)615 (13,0)143No1526 (61,0)106 (62,0)615 (75,9)143No1526 (61,0)106 (62,0)1537 (65,0)143No1526 (90,0)1067 (90,0)150 (13,0)141No1562 (90,0)107 (20,0)160 (14,0)150 (12,0)No1562 (90,0)107 (90,0)160 (12,0)160 (12,0)No1562 (90,0)161 (20,0)161 (21,0)160 (12,0)No1562 (90,0)164 (20,0)150 (12,0)150 (12,0)No1562 (90,0)164 (20,0)150 (12,0)160 (12,0)No1562 (90,0)164 (20,0)150 (12,0)150 (12,0)No1562 (90,0)164 (20,0)150 (12,0)150 (12,0)No150 (12,0)150 (12,0)150 (12,0)150 (12,0)No150 (12,0)150 (12,0)150 (12,0)150 (12,0)No150 (12,0)150 (12,0)150 (12,0)No150 (12,0	0	4209 (26.6)	2966 (26.7)	1243 (26.2)		
CE k and the set of the set	1-2	11629 (73.4)	8122 (73.3)	3507 (73.8)		
Maculine1238 (78.2)8705 (78.5)6473 (77.3)Image: Partial p	CEA status				2.721	0.099
Image: Image:	Masculine	12378 (78.2)	8705 (78.5)	3673 (77.3)		
Live metatases0.26<	Feminine	3460 (21.8)	2383 (21.5)	1077 (22.7)		
No4731 (29,9)3298 (29,7)433 (30,2)Yes107 (70,1)709 (70,3)317 (69,8)UT2020.138V1267 (30,0)8388 (79,7)3835 (80,7)Yes365 (20,0)250 (20,3)915 (19,3)Yes1262 (60,1)1069 (62,0)105 (79,5)Yes1226 (64,1)1069 (62,0)4557 (95,9)Yes1236 (20,0)1069 (92,0)103 (10,0)Yes1236 (20,0)1069 (92,0)457 (95,9)YesYes1236 (20,0)1069 (92,0)Yes1236 (20,0)1093 (90,0)470 (90,1)YesYes1236 (20,0)107 (30,0)Yes1236 (20,0)107 (30,0)470 (90,1)YesYes1236 (20,0)107 (20,0)YesYes1236 (20,0)109 (20,0)YesYes1236 (20,0)109 (20,0)YesYes1236 (20,0)124 (20,0)YesYesYes1236 (20,0)YesYesYes1236 (20,0)YesYesYes1236 (20,0)YesYesYes1236 (20,0)YesYesYes1236 (20,0)YesYesYes1236 (20,0)YesYesYes1236 (20,0)Yes	Liver metastases				0.286	0.593
Yes1107 (70.1)770 (70.3)3317 (69.3)Lutratases2.02 (70.3)3137 (69.3)1.02 (70.2)No1267 (80.0)888 (77.7)385 (80.7)Yes316 (20.0)2.02 (0.3.0)915 (19.3)Borratestases1.02 (90.2)915 (19.3)Yes1.226 (96.1)1066 (96.2)4557 (95.9)No1.526 (96.1)1066 (96.2)4557 (95.9)Yes1.62 (90.1)1066 (96.2)109 (10.1)Na1.526 (96.1)1066 (96.2)109 (10.1)Yes1.526 (96.1)1066 (96.2)109 (10.1)Yes1.526 (96.1)1069 (96.2)109 (10.1)Yes1.526 (96.1)1067 (97.9)No1.562 (99.0)1097 (99.0)109 (99.1)Yes1.561 (10.1)1097 (99.1)Yes1.562 (99.0)1097 (99.0)109 (99.1)Yes1.562 (99.0)1097 (99.0)109 (99.1)Yes1.562 (99.0)1097 (99.1)Yes1.562 (99.0)1097 (99.0)109 (99.1)Yes1.562 (99.0)1.512 (99.0)109 (99.1)Yes1.562 (99.0)1.512 (99.0)109 (99.1)Yes1.523 (99.0)1.512 (99.0)109 (99.1)Yes1.523 (99.0)1.512 (99.0)1.512 (99.0)Yes1.523 (99.	No	4731 (29.9)	3298 (29.7)	1433 (30.2)		
Lurpertain2.020.138No1267 (80,0)883 (97,0)883 (80,7)883 (80,7)Yes136 (20,0)250 (20,3)95 (93,0)95 (93,0)No1526 (96,1)1669 (96,2)4557 (59,0)97 (93,0)Yes162 (90,1)169 (96,2)193 (10,0)193 (10,0)No152 (90,0)190 (90,0)193 (90,0)193 (90,0)No156 (90,0)107 (90,0)409 (90,0)194 (90,0)Yes164 (20,0)105 (20,0)105 (20,0)106 (20,0)No136 (20,0)144 (20,0)105 (20,0)105 (20,0)No136 (20,0)164 (78,0)690 (79,0)105 (79,0)	Yes	11107 (70.1)	7790 (70.3)	3317 (69.8)		
No       12673 (80.0)       8838 (79.7)       8835 (80.7)         Yes       3165 (20.0)       250 (20.3)       915 (19.3)         Botter       1262 (96.1)       10669 (96.2)       4557 (95.9)         Yes       612 (3.9)       10669 (96.2)       4557 (95.9)         Yes       612 (3.9)       10669 (96.2)       4557 (95.9)         Yes       612 (3.9)       10969 (96.2)       4557 (95.9)         Yes       612 (3.9)       1093 (90.2)       193 (41.2)         No       1568 (99.0)       10973 (99.0)       4709 (99.1)       1.31         Yes       156 (1.0)       1073 (99.0)       4709 (99.1)       4.04         Yes       156 (1.0)       105 (1.0)       101 (1.0)       1.01         Swetcal       Yes       1364 (2.0)       105 (12.1)       0.01         Yes       1233 (7.9)       244 (28.0)       105 (22.1)       Yes       1.01	Lung metastases				2.202	0.138
Yes3165 (20.0)2250 (20.3)915 (19.3)Bon	No	12673 (80.0)	8838 (79.7)	3835 (80.7)		
Borr0.720.	Yes	3165 (20.0)	2250 (20.3)	915 (19.3)		
No       1526 (96.1)       1666 (96.2)       457 (95.9)         Yes       612 (3.9)       19 (3.8)       193 (4.1)         No       162 (90.0)       1973 (90.0)       470 (90.1)         Yes       1561 (0.1)       15 (1.0)       410.9)         Yes       1561 (0.1)       15 (1.0)       1001         No       1561 (0.1)       15 (1.0)       1001       0.014         Yes       150 (0.1)       15 (1.0)       1011 (0.1)       1011 (0.1)         Yes       149 (20.1)       1051 (20.1)       1011 (0.1)       1011 (0.1)         Yes       1233 (77.9)       644 (78.0)       699 (77.9)       1011 (0.1)	Bone metastases				0.724	0.395
Yes       612 (3.9)       419 (3.8)       193 (4.1)         Brain metastases       1.032       0.31         No       15682 (99.0)       10973 (99.0)       4709 (99.1)       4709         Yes       156 (1.0)       115 (1.0)       41 (0.9)       410         Surgical       Yes       164 (2.0)       1051 (22.1)       0.014         Yes       1233 (77.9)       644 (78.0)       6699 (77.9)       6699 (77.9)	No	15226 (96.1)	10669 (96.2)	4557 (95.9)		
Brain metastases       1.032       0.31         No       15682 (99.0)       10973 (99.0)       4709 (99.1)         Yes       156 (1.0)       115 (1.0)       41 (0.9)         Surgical       0.014       0.906         No       3495 (22.1)       2444 (22.0)       1051 (22.1)         Yes       1233 (77.9)       8644 (78.0)       3699 (77.9)	Yes	612 (3.9)	419 (3.8)	193 (4.1)		
No       15682 (99.0)       10973 (99.0)       4709 (99.1)         Yes       156 (1.0)       15 (1.0)       41 (0.9)         Surgical	Brain metastases	· · /			1.032	0.31
Yes     156 (1.0)     115 (1.0)     41 (0.9)       Surgical     0.014     0.906       No     3495 (22.1)     2444 (22.0)     1051 (22.1)       Yes     12343 (77.9)     8644 (78.0)     3699 (77.9)	No	15682 (99.0)	10973 (99.0)	4709 (99.1)		
Surgical     0.014     0.906       No     3495 (22.1)     2444 (22.0)     1051 (22.1)       Yes     12343 (77.9)     8644 (78.0)     3699 (77.9)	Yes	156 (1.0)	115 (1.0)	41 (0.9)		
No         3495 (22.1)         2444 (22.0)         1051 (22.1)           Yes         12343 (77.9)         8644 (78.0)         3699 (77.9)	Surgical				0.014	0.906
Yes 12343 (77.9) 8644 (78.0) 3699 (77.9)	No	3495 (22.1)	2444 (22.0)	1051 (22.1)		
	Yes	12343 (77.9)	8644 (78.0)	3699 (77.9)		
Chemotherapy 0.026 0.872	Chemotherapy				0.026	0.872



None/unknown	4235 (26.7)	2969 (26.8)	1266 (26.7)
Yes	11603 (73.3)	8119 (73.2)	3484 (73.3)

CEA: Carcinoembryonic antigen.



Figure 2 Calibration curves based on cancer-specific survival for metastatic colorectal cancer patients. A-C: Calibration curves based on 1-, 2-, and 3-year cancer-specific survival (CSS) of the training cohort; D-F: Calibration curves based on 1-, 2-, and 3-year CSS of the validation cohort.

using SPSS 21.0 statistical software (IBM SPSS Statistics for Windows; Armonk, NY, United States), GraphPad Prism 6 (GraphPad Software), X-Tile software (Yale University), and R Statistical Software 3.6.2 (www.r-project.org/).

#### Statistical analysis

SPSS 23.0 statistical software was used for analysis. The  $\chi^2$  test was used for comparison of counting data, and the *t* test was used for comparison of measurement data. The survival rate was calculated by the life table method, the survival curve was plotted by the K-M method, and comparisons were performed by the log-rank method. Multiple factor analysis was performed by the Cox proportional risk regression model, and *P* < 0.050 was considered to indicate statistical significance.

#### RESULTS

#### Baseline population information

According to the inclusion criteria, a total of 15838 patients eligible for inclusion were included in this study, among whom 11088 (70.0%) patients were randomly assigned to the training cohort and 4750 (30.0%) patients were randomly assigned to the verification cohort. The demographic characteristics of this study population are shown in Table 1.

In this study, there were 8560 males (54.0%) and 7278 females (46.0%), of which the majority were white (76.2%), 13759 (86.9%) were T3-4, 11629 (73.4%) were N1-2, and CEA was positive (78.2%). The incidence of distant metastasis in the liver, lung, bone, and brain was 11107 (70.1%), 3165 (20.0%), 612 (3.9%), and 156 (1.0%), respectively. A total of 12343 patients (77.9%) received surgery, and 11603 patients (73.3%) received chemotherapy. There was no significant difference between the training cohort and the verification cohort (P > 0.05).

#### Prediction factor determination

The Cox proportional hazards model was used to identify independent risk factors for CSS. Multivariate analysis revealed that the independent risk factors in the training cohort were race, age at diagnosis, primary site, tumor grade, N stage, CEA status, liver metastasis, lung metastasis, bone metastasis, brain metastasis, surgery, and chemotherapy



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#### Zhou YJ et al. Analysis of CSS in patients with mCRC

#### (Table 2).

Based on the significant risk factors for CSS, a predictive nomogram model of CSS was established (Figure 1). The regression coefficients and estimates of the training queue are shown in Table 3. The nomogram was evaluated with internal and external validation. The C-index of the column chart was 0.718 (95%CI: 0.712-0.725), and the C-finger number of the verification set was 0.722 (95%CI: 0.711-0.732), indicating good identification ability and better performance than TNM staging (C-index: Training set, 0.533, 95%CI: 0.525-0.540; verification set, 0.524, 95%CI: 0.513-0.535). A calibration diagram of the CSS showed good agreement between the predicted and actual values of the training and validation samples, with 1000 bootstrap samples (Figure 2). The DCA curve showed a large net gain between most threshold probabilities at different time points, indicating good potential clinical validity for predicting CSS (Figure 3).

#### Establishment of the risk classification system

In addition, X-Tile software was used to determine the optimal cutoff value and establish a risk classification system (Figure 4). All patients were classified as low risk (5852/11088, 52.78%, score: 0-164), medium risk (3487/11088, 31.45%, score: 165-247) or high risk (1749/11088, 15.77%, score: 248-524). In theory, the total score ranges from 0 to 524. K-M curves showed that the risk grading system had good layering and differentiation ability for different CSS groups (Table 4, Figure 5).

#### DISCUSSION

The prognosis of mCRC patients is significantly worse than that of non-mCRC patients. mCRC mortality varies widely from patient to patient, suggesting the importance and necessity of reclassifying the exact risk level based on the AJCC staging system[12-14]. However, due to the limitations of the included factors, the existing prediction models lack individualization and comprehensive evaluation, and the sample sizes of most studies[15-17] are small, which also limits their universal applicability. In this study, we developed a new CSS predictive nomogram based on simultaneous mCRC data from large population cohorts.

We identified predictors of CSS that were consistent with previous studies, including race, age at diagnosis, primary site, grade, N stage, CEA status, liver metastasis, lung metastasis, bone metastasis, brain metastasis, surgery, and chemotherapy[18]. For patients with mCRC, both surgery and chemotherapy are important for improving outcomes, as recommended by the United States National Comprehensive Cancer Network (NCCN) guidelines and the European Society of Medical Oncology guidelines[19]. Modest suggested that the effective rate of first-line systemic treatment is 38% to 65%, and the disease control rate is 81% to 90% [20]. Compared to earlier studies, this column chart is the first to include chemotherapy status as a risk predictor for predicting CSS. The highest score of mCRC patients who did not receive chemotherapy was 100, which was greater than that of mCRC patients who did not receive surgery, indicating that the regression coefficient of the effect of chemotherapy on CSS was greater than that of surgery[21-23]. In addition, patients who did not receive chemotherapy or who did not receive chemotherapy were not separately recorded in the SEER database as confounding risk factors in this study, which may reduce the actual regression coefficient of not receiving chemotherapy is positively associated with survival benefits in patients with mCRC, and our study further highlights the unique advantages of simultaneous mCRC chemotherapy.

In addition to chemotherapy, our study revealed that primary tumor resection is also important for prognosis. Several studies[30-32] support this idea in mCRC, especially in patients with liver or lung metastases. The NCCN guidelines recommend that patients with mCRC should be evaluated by a multidisciplinary team and, if possible, that the metastatic disease and primary tumor should be removed. Therefore, primary tumor resection remains controversial for mCRC patients whose metastases cannot be resected. Studies[33-35] have shown that primary tumor resection significantly extends overall survival (OS) in mCRC patients with unresectable metastases (median OS: 13.8 months vs 6.3 months, P =0.0001). Another study[36] also supported the idea that primary tumor removal resulted in better survival for mCRC patients with unresectable metastases (2-year CSS: 50.2% vs 28.1%, P < 0.001). In conclusion, primary tumor resection has a positive impact on patient survival. As mentioned above, the liver and lungs are the most common sites of CRC metastasis, and bone and brain metastases are very rare. In addition, the prognostic significance of different metastatic organs was inconsistent. The occurrence of brain metastases is often associated with the worst survival, and studies[37-39] have reported that the median survival of CRC patients with brain metastases is 3 to 6 months, that of CRC patients with bone metastases is 5 to 7 months, that of CRC patients with liver metastases is 22.8 months, and that of CRC patients with lung metastases is 36.2 to 49 months. Another study confirmed this idea, with brain metastases having the largest coefficient of impact among the four metastatic organs of CRC. Our study showed that the regression coefficients of CSS in descending order were brain metastasis, bone metastasis, liver metastasis, and lung metastasis. Due to the presence of the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (CSF), brain metastases are often the ultimate organs of metastasis for CRC, while other extracranial metastases occur in areas such as the liver and lungs. The BBB and CSF also hinder chemotherapy efficacy, which may be another reason for the poor prognosis.

On the basis of multiple regression analysis, we developed a new nomograph to integrate multiple predictors and help accurately predict the survival of patients with synchronous mCRC. One study constructed a nomogram for predicting the survival of CRC patients. Another study also developed an OS nomogram model for predicting mCRC with strong consistency. Compared to existing predictive models, our column charts integrate more predictive variables, such as chemotherapy and surgery, to provide comprehensive predictions for CSS. In addition, through X-Tile software, we established a risk classification system with an optimal cutoff value that is more accurate and reliable. This approach

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Table 2 Multivariate analysis of COX based on training cohorts					
	Multivariate analysis				
Variable	HR (95%CI)	P value			
Race					
Black people	1				
White race	0.894 (0.834-0.959)	0.002			
Other	0.835 (0.752-0.928)	0.001			
Sex					
Male	1				
Female	0.965 (0.918-1.015)	0.17			
Age at diagnosis (yr)					
< 70	1				
≥70	1.162 (1.099-1.228)	< 0.001			
Primary tumor location					
Colon	1				
Rectum	0.715 (0.678-0.754)	< 0.001			
Tumor differentiation					
I-II	1				
III-IV	1.721 (1.630-1.817)	< 0.001			
T staging					
1-2	1				
3-4	1.085 (0.999-1.179)	0.053			
N stage					
0	1				
1-2	1.304 (1.226-1.386)	< 0.001			
CEA status					
Masculine	1				
Feminine	0.699 (0.655-0.746)	< 0.001			
Liver metastases					
No	1				
Yes	1.406 (1.326-1.490)	< 0.001			
Lung metastases					
No	1				
Yes	1.341 (1.260-1.426)	< 0.001			
Bone metastases					
No	1				
Yes	1.621 (1.438-1.827)	< 0.001			
Brain metastases					
No	1				
Yes	1.718 (1.370-2.155)	< 0.001			
Surgical	Surgical				
No	1				
Yes	0.459 (0.429-0.492)	< 0.001			

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#### Zhou YJ et al. Analysis of CSS in patients with mCRC



CEA: Carcinoembryonic antigen; HR: Hazard ratio.



Figure 3 The nomogram model predicts the clinical decision curve of cancer-specific survival in metastatic colorectal cancer patients. A-C: Clinical decision curves based on 1-, 2-, and 3-year cancer-specific survival (CSS) in the training cohort; D-F: Clinical decision curves based on 1-, 2-, and 3-year CSS in the validation cohort.



Figure 4 X-tile software was used to calculate the optimal truncation value and establish a risk classification system. A and B: The optimal cutoff values of the predicted total scores, including the low-risk group (score: 0-164), medium-risk group (score: 165-247) and high-risk group (score: 248-480); C: Kaplan-Meier curves for different risk levels according to the cancer-specific survival of the training cohort.

helps to assess the level of risk in patients with mCRC, allowing for individualized treatment and an accurate prognosis. In addition, we provide estimated points for each important prognostic factor to improve clinical application[40].

There are several limitations to our study. First, this study is a retrospective analysis of existing selection bias. Furthermore, the SEER database does not contain detailed information on chemotherapy regimens or targeted therapies, which hinders further subgroup analysis. Then, the SEER data are used to verify the validity of the column graph prediction, which lacks the verification of real data.

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# Table 3 Regression coefficients and estimated scores for building a Nomogram prediction model based on a training cohort

	Nomogram			
Variable	Regression coefficients	Estimated score		
Race				
Black people	17.846261	18		
White race	6.960746	7		
Other	0	0		
Age at diagnosis (yr)				
< 70	0	0		
≥70	14.55836	15		
Primary tumor location				
Colon	32.76881	33		
Rectum	0	0		
Tumor differentiation				
I-II	0	0		
III-IV	54.39289	54		
N stage				
0	0	0		
1-2	27.38794	27		
CEA status				
Masculine	35.56051	36		
Feminine	0	0		
Liver metastases				
No	0	0		
Yes	34.12213	34		
Lung metastases				
No	0	0		
Yes	29.0965	29		
Bone metastases				
No	0	0		
Yes	49.30787	49		
Brain metastases				
No	0	0		
Yes	54.35879	54		
Surgical				
No	75.074	75		
Yes	0	0		
Chemotherapy				
None/unknown	100	100		
Yes	0	0		
Range	0-524.474061	0-524		
Score	531.434807	531		

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CEA: Carcinoembryonic antigen.

Table 4 Analyzes tumor-specific survival rates in patients with different risk classes, %				
Variable	Low-risk group	Medium-risk group	High-risk group	
variable	( <i>n</i> = 8140)	( <i>n</i> = 4737)	( <i>n</i> = 2013)	
1 yr CSS	86.10	63.00	31.50	
2 yr CSS	67.30	38.00	16.10	
3 yr CSS	49.70	24.60	8.90	
5 yr CSS	31.30	14.20	4.30	
Median CSS	36 months	18 months	5 months	
95%CI	34.987-37.013	17.273-18.727	4.503-5.497	

CSS: Cancer-specific survival.



Figure 5 Kaplan-Meier survival curves for patients with different risk levels were drawn according to their cancer-specific survival. A: Platoon line; B: Training queue; C: Authentication queue.

# CONCLUSION

In summary, we developed a new nomogram model to predict CSS in patients with synchronous mCRC. The verification of the model showed that the model has good discriminability and consistency. The risk grading system can grade the risk level of mCRC patients, accurately evaluate patient prognosis, and guide treatment.

# FOOTNOTES

Author contributions: Zhou YJ wrote the manuscript; Tan ZE and Zhuang WD collected the data; and Xu XH guided the study; All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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S-Editor: Li L L-Editor: A



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