Establishment and validation of a novel nomogram incorporating clinicopathological parameters into the TNM staging system to predict prognosis for stage II colorectal cancer

Shaobo Mo1,2†, Zheng Zhou1,2†, Yaqi Li1,2, Xiang Hu1,2, Xiaoji Ma1,2, Long Zhang1,3†, Sanjun Cai1,2† and Junjie Peng1,2†

Abstract

Background: Survival outcomes are significantly different in stage II colorectal cancer (CRC) patients with diverse clinicopathological features. The objective of this study is to establish a credible prognostic nomogram incorporating easily obtained parameters for stage II CRC patients.

Methods: A total of 1708 stage II CRC patients seen at Fudan University Shanghai Cancer Center (FUSCC) from 2008 to 2013 were retrospectively analyzed in this study. Cases were randomly separated into a training set (n = 1084) and a validation set (n = 624). Univariate and multivariate Cox regression analyses were used to identify independent prognostic factors that were subsequently incorporated into a nomogram. The performance of the nomogram was evaluated by the predicted concordance index (C-index) and ROC curve to calculate the area under the curve (AUC). The clinical utility of the nomogram was evaluated using decision curve analysis (DCA).

Results: In univariate and multivariate analyses, eight parameters were correlated with disease-free survival (DFS), which were subsequently selected to generate a prognostic nomogram based on DFS. For DFS predictions, the C-index values of the nomogram were 0.842 (95% confidence interval (CI) 0.710–0.980), and 0.701 (95% CI 0.610–0.770) for the training and validation sets, respectively. The AUC values of the ROC curves for the nomogram to predicted 1, 3 and 5-year survival were 0.869, 0.858, and 0.777 (training group) and 0.673, 0.714, and 0.706 (validation group), respectively. The recurrence probability calibration curve showed good consistency between actual observations and nomogram-based predictions. DCA showed better clinical application value for the nomogram than the TNM staging system.

© The Author(s) 2020. This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Background
Colorectal cancer (CRC) is the most common malignant tumor of the digestive system and was the fourth leading cause of cancer death in China 2017 [1]. The prognosis of CRC is associated with the American Joint Commission on Cancer/International Union against Cancer (AJCC/UICC) tumor-node-metastasis (TNM) staging system. According to the TNM staging system, approximately one-quarter of CRC patients are diagnosed with stage II disease, approximately 25% of whom suffer from disease relapse after surgery [2]. However, prognosis is obviously divergent in CRC patients even with the same TNM stage due to substantial disease heterogeneity, especially for stage II CRC. Previous research showed that the outcomes in AJCC/UICC stage II CRC patients varied from close to those of stage I patients in terms of relapse and survival to being worse than those of patients with node-positive tumors [3, 4]. Therefore, the TNM staging system is not always able to accurately predict the prognosis of stage II CRC patients. Accurate postoperative personalized prognostic evaluation for patients with stage II CRC is an important step for physicians to better determine therapeutic strategies.

Clinically, whether to undergo or forego adjuvant chemotherapy has been controversial for decades, which has resulted in overtreatment and undertreatment for stage II CRC patients. Traditionally, clinicopathological features related to recurrence in stage II tumors, such as T4 lesions [5], poor histological differentiation [6], perineural invasion [7] and so on, have been identified and recommended as evidence for adjuvant chemotherapy [8, 9]. However, the results were still unsatisfactory [10, 11]. Currently, microsatellite instability (MSI) and mismatch repair deficiency (dMMR) are the most important biomarkers and are widely used to help physicians choose adjuvant chemotherapy and predict patient outcomes in stage II CRC patients [12]. Unfortunately, most stage II CRCs are classified as being microsatellite stable (MSS) or having proficient MMR (pMMR), and biomarkers are lacking for these patients. Moreover, these clinicopathological features do not clearly distinguish between patients who have a high or low risk of disease recurrence. Thus, there is a dire need to add prognostic and predictive values to the current TNM staging system with the purpose of determining those patients more likely to suffer from tumor relapse.

Several studies have tried to improve postoperative risk stratification and prediction of chemotherapy benefit for stage II CRC. Zhang et al. [13] identified a six-miRNA-based classifier that is a reliable tool for predicting prognosis and disease recurrence in patients with stage II colon cancer. Gao et al. [14] identified eight cancer hallmark-based gene signatures (30 genes each) used them to determine prognosis in stage II CRC. Despite effective risk stratification in stage II CRC, application of the identified signatures exacerbated the financial burden on patients, and the signatures remain far from application in clinical practice.

Therefore, we aimed to establish a simple-to-use and personalized scoring system meeting clinicians’ needs to predict the prognosis of stage II CRC. In the current study, information on stage II CRC diagnosed at Fudan University Shanghai Cancer Center (FUSCC) was extracted to construct and validate a nomogram to predict patient prognosis, which was subsequently proven to have strong clinical application value by decision curve analysis (DCA).

Methods
Ethics statement
The Ethical Committee and Institutional Review Board of the Fudan University Shanghai Cancer Center reviewed and approved this study protocol. All patients signed written informed consent.

Patients
A total of 1708 patients with stage II CRC diagnosed and undergoing radical surgery at FUSCC from January 1, 2008, to December 31, 2013, were retrospectively reviewed. We recruited patients meeting the following criteria: (1) patients with a pathological diagnosis of stage II CRC; (2) stage II CRC patients with primary tumor resection performed at our center; and (3) patients with complete clinicopathological information and follow-up data. Patients who met the following exclusion criteria were excluded: (1) patients who accepted neoadjuvant therapy and (2) patients who had multiple primary tumors. All eligible patients were regrouped according to the 8th AJCC/UICC TNM staging system. The detailed workflow for patient selection is shown in Fig. 1.

Fifteen variables were extracted from FUSCC in this study, including pretreatment carcinoembryonic

Conclusion: A novel nomogram was established and validated in a large population, and the nomogram is a simple-to-use tool for physicians to facilitate postoperative personalized prognostic evaluation and determine therapeutic strategies for stage II CRC patients.

Keywords: Nomogram, Colorectal cancer, Stage II, Prognosis, Clinical utility
Antigen (Pre-CEA) level, age, sex, adjuvant chemotherapy, lymphovascular invasion, perineural invasion, circumferential resection margin (CRM) status, tumor size, number of lymph nodes harvested (LNH), histological type, family history, tumor site, mismatch repair (MMR) status, histological differentiation, and T stage. Patients were separated into a training group (n = 1084, from January 1, 2008, to December 31, 2011) and a validation group (n = 624, from January 1, 2012, to December 31, 2013).

Construction and validation of the nomogram
Univariate and multivariate analyses were conducted via the Cox regression method to identify independent risk factors in the training cohort. Based on multivariate Cox regression analyses, a simple-to-use nomogram incorporating seven clinicopathological parameters into the TNM staging system was formulated. The total points for each patient in the validation group were calculated using the established nomogram, after which a Cox regression analysis of the whole cohort was performed using the total points as a parameter. The 1-, 3-, and 5-year calibration plots graphically show the relationship between the predicted and observed risk for each outcome to assess the predictive ability of the nomogram.

Concordance index (C-index), receiver operating characteristic (ROC) curve and DCA
The C-index and ROC curve methods were used to appraise the discriminating ability of the nomogram. The C-index was defined as the ratio of all patient pairs whose predictions were consistent with the results. The 1-, 3-, and 5-year ROC curves were used to evaluate the nomogram's predictive ability for different time periods. DCA was recently proposed as a novel method for evaluating predictive models and visualizing the clinical consequences of a treatment strategy [15], and it was carried out to determine the potential benefit of the predictive nomogram in this study.

Risk stratification based on the novel nomogram
To reveal the independent discrimination ability of the simple-to-use prognostic nomogram, we regrouped all patients into high-, moderate-, and low-risk groups according to the total risk scores in the study cohort. Survival curves for different risk groups were generated using the Kaplan–Meier method and were compared using the log-rank test.

Statistical analyses
The R software was used for the randomization of patients. The Chi-square test was used to compare the
Results

Demographic and clinical characteristics
A total of 1708 patients with stage II CRC were retrospectively collected from the institutional database. The clinicopathological characteristics and demographics of the entire (N = 1708), training (N = 1084), and validation (N = 624) cohorts are listed in Table 1.

In the entire group, 62.2% of patients were male, and 47.2% of patients were < 60 years at diagnosis. Most patients had an adenocarcinoma histological type, moderately differentiated tumors, and LNH ≥ 12. T3, T4a, and T4b tumors accounted for 65.8%, 32.2%, and 2.0% of all cases, respectively. Across the entire study population, a total of 72.1% of patients underwent adjuvant chemotherapy with 5-Fu-based monotherapy or combined therapy. The 5-year disease-free survival (DFS) rate was 75.9% for all patients, with a median follow-up time of 68.1 months. There was no significant difference between the training and validation cohorts in demographic and clinical characteristics.

Independent prognostic factors in stage II CRC patients
According to the results of the univariate Cox regression analysis, nine variables, age at diagnosis, pre-CEA level, T stage, histological differentiation, tumor size, LNH, perineural invasion, CRM status, and MMR status, were associated with DFS (Table 2). The Kaplan–Meier curves showed that the nine factors were related to DFS (p < 0.05, Fig. 2). In the multivariate Cox regression analysis, eight parameters, pre-CEA, age, T stage, histological differentiation, LNH, perineural invasion, CRM status, and MMR status, were defined as independent prognostic factors of stage II CRC (Table 2).

Construction and validation of the prognostic prediction nomogram
Based on the multivariate Cox regression analysis results, pre-CEA, age, T stage, histological differentiation, LNH, perineural invasion, CRM status, and MMR status were defined as independent prognostic factors, and these were integrated to develop the nomogram (Fig. 3). According to the nomogram, T stage had the greatest influence on the prognosis of stage II CRC, followed by CRM status. Clinicians could determine the total score according to the individual scores of those eight parameters and obtain a particular probability of 1-, 3-, and 5-year DFS. Detailed scores of sub-classification of each variable are listed in Additional file 1: Table S1.

The distributions of risk scores and relapse status are shown in Fig. 4a, e, and the results showed that patients with low risk scores generally had better DFS than those with high risk scores. The C-index values and ROC curves were used to evaluate the discrimination power of the nomogram. The C-indexes for the prediction of DFS in the training and validation groups were 0.842 (95% CI 0.710–0.980) and 0.701 (95% CI 0.610–0.770), respectively. To confirm that the nomogram prediction model had higher efficacy in predicting the prognosis of stage II CRC patients than T stage, time-dependent ROC analyses at 1-, 3-, and 5-year were conducted. The 1-, 3-, and 5-year AUCs of the nomogram in the training and validation groups were 0.869, 0.858, and 0.777 and 0.673, 0.714, and 0.706, respectively, compared with AUCs of 0.515, 0.593, and 0.619 and 0.553, 0.545, and 0.561, respectively, for T stage (Fig. 4b–d, f–h), which showed that the simple-to-use nomogram incorporating clinicopathological parameters into the TNM staging system was expected to be more accurate than TNM stage. In addition, calibration curves for the nomogram showed no deviations from the reference line, which meant a high degree of credibility (Fig. 5).

Independent prognostic performance of the nomogram in predicting prognosis in stage II CRC
Whether to use adjuvant chemotherapy for stage II CRC has been controversial for decades. Subgroup analyses based on adjuvant chemotherapy suggested that the high-risk patients in each subgroup were inclined to have significantly unfavorable DFS (Fig. 6). The distributions of risk score and relapse status among each subgroup are shown in Fig. 6a, d, g, j. Time-dependent ROC analyses at 1, 3 and 5 years were conducted to assess the prognostic accuracy of the nomogram in different subgroups based on adjuvant chemotherapy (Fig. 6b, e, h, k). Patients from the training and validation cohorts were separated into a low-risk group and a high-risk group. Patients in the high-risk group tended to have poorer outcomes than those in the low-risk group, regardless of the status of adjuvant chemotherapy (Fig. 6c, f, i, l). In addition, subgroup analyses were performed based on different risk factors (LNH, perineural invasion, T stage and MMR status) and demonstrated excellent independence and
### Table 1 Demographics and clinical characteristics of eligible patients with stage II CRC

| Characteristics                  | All patients N = 1708 | Training group N = 1084 | Validation group N = 624 | p value |
|----------------------------------|-----------------------|-------------------------|--------------------------|---------|
| Gender, n (%)                    |                       |                         |                          |         |
| Female                           | 645 (37.8)            | 423 (39.0)              | 222 (35.6)               | 0.157   |
| Male                             | 1063 (62.2)           | 661 (61.0)              | 402 (64.4)               |         |
| Age, n (%)                       |                       |                         |                          | 0.883   |
| < 60                             | 806 (47.2)            | 513 (47.3)              | 293 (47.0)               |         |
| ≥ 60                             | 902 (52.8)            | 571 (52.7)              | 331 (53.0)               |         |
| Pre-CEA, n (%)                   |                       |                         |                          | 0.226   |
| Negative                         | 1121 (65.6)           | 700 (64.6)              | 421 (67.5)               |         |
| Positive                         | 587 (34.4)            | 384 (35.4)              | 203 (32.5)               |         |
| Family history, n (%)            |                       |                         |                          | 0.480   |
| No                               | 1171 (68.6)           | 732 (67.5)              | 439 (70.4)               |         |
| Yes                              | 429 (25.1)            | 281 (26.0)              | 148 (23.7)               |         |
| Unknown                          | 108 (6.3)             | 71 (6.5)                | 37 (5.9)                 |         |
| Adjuvant CT, n (%)               |                       |                         |                          | 0.318   |
| No                               | 476 (27.9)            | 311 (28.7)              | 165 (26.4)               |         |
| Yes                              | 1232 (72.1)           | 773 (71.3)              | 459 (73.6)               |         |
| Tumor site, n (%)                |                       |                         |                          | 0.414   |
| Left                             | 1206 (70.6)           | 758 (69.9)              | 448 (71.8)               |         |
| Right                            | 502 (29.4)            | 326 (30.1)              | 176 (28.2)               |         |
| T stage, n (%)                   |                       |                         |                          | 0.219   |
| T3                               | 1124 (65.8)           | 697 (64.3)              | 427 (68.4)               |         |
| T4a                              | 550 (32.2)            | 365 (33.7)              | 185 (29.7)               |         |
| T4b                              | 34 (2.0)              | 22 (2.0)                | 12 (1.9)                 |         |
| Histological type, n (%)         |                       |                         |                          | 0.585   |
| Adenocarcinoma                   | 1386 (81.1)           | 877 (80.9)              | 509 (81.6)               |         |
| Mucinous adenocarcinoma          | 316 (18.5)            | 202 (18.6)              | 114 (18.3)               |         |
| Signet-ring cell carcinoma       | 6 (0.4)               | 5 (0.5)                 | 1 (0.1)                  |         |
| Histological differentiation, n (%)|                      |                         |                          | 0.840   |
| Well                             | 143 (8.4)             | 94 (8.7)                | 49 (7.8)                 |         |
| Moderate                         | 1349 (79.0)           | 853 (78.7)              | 496 (79.5)               |         |
| Poor                             | 216 (12.6)            | 137 (12.6)              | 79 (12.7)                |         |
| Tumor size, n (%)                |                       |                         |                          | 0.421   |
| < 4                              | 614 (35.9)            | 382 (35.2)              | 232 (37.2)               |         |
| ≥ 4                              | 1094 (64.1)           | 702 (64.8)              | 392 (62.8)               |         |
| LNH, n (%)                       |                       |                         |                          | 0.495   |
| < 12                             | 296 (17.3)            | 193 (17.8)              | 103 (16.5)               |         |
| ≥ 12                             | 1412 (82.7)           | 891 (82.2)              | 521 (83.5)               |         |
| Lymphovascular invasion, n (%)   |                       |                         |                          | 0.943   |
| Negative                         | 1534 (89.8)           | 974 (89.9)              | 560 (89.7)               |         |
| Positive                         | 174 (10.2)            | 110 (10.1)              | 64 (10.3)                |         |
| Perineural invasion, n (%)       |                       |                         |                          | 0.351   |
| Negative                         | 1463 (85.7)           | 922 (85.1)              | 541 (86.7)               |         |
| Positive                         | 245 (14.3)            | 162 (14.9)              | 83 (13.3)                |         |
| CRM, n (%)                       |                       |                         |                          | 0.429   |
| Negative                         | 1688 (98.8)           | 1073 (99.0)             | 615 (98.6)               |         |
| Positive                         | 20 (1.2)              | 11 (1.0)                | 9 (1.4)                  |         |
| MMR status, n (%)                |                       |                         |                          | 0.602   |
| dMMR                             | 456 (26.7)            | 294 (27.1)              | 162 (26.0)               |         |
prognostic value of the nomogram (Additional file 2: Figure S1).

Clinical value of the nomogram

DCA is a novel method for evaluating alternative prognostic strategies, which has advantages over AUC. DCA curves for the novel nomogram and T stage in the training, validation and entire groups are presented in Fig. 7. Compared with that of T stage, DCA of the nomogram had higher net benefits, which indicated that the nomogram had better clinical utility than T stage.

Prognostic nomogram for risk stratification

We determined the cut-off values by regrouping all patients in the training, validation and entire cohorts into three subgroups based on the total scores, and each group represented a distinct prognosis. The Kaplan–Meier survival curves were subsequently delineated and are shown in Fig. 8. In the training, validation and entire cohorts, group 1 (low-risk group) had the highest 5-year DFS at 90.9%, 95.2% and 94.1%, respectively, followed by group 2 (Moderate-risk group) at 75.9%, 86.3% and 83.3%, respectively; Group 3 (High-risk group) showed the lowest 5-year DFS for the training, validation, and entire cohorts: 66.1%, 71.4% and 67.3%, respectively. Significant statistical differences in survival outcomes were observed between the three groups.

Discussion

In this study, a nomogram incorporating clinicopathological parameters into the TNM staging system was established to evaluate the definite 1-, 3-, and 5-year DFS in the training and validation cohorts, the novel nomogram had a stronger ability to accurately reflect the exact survival probability in stage II CRC. Moreover, the nomogram was capable of dividing patients with stage II CRC into low-, moderate-, and high-risk groups, which indicated that the nomogram could be applied as a conventional tool in predicting the prognosis of stage II CRC.

In the present study, the prognosis of patients with stage II CRC was better in younger patients. Previous research has revealed that age is an independent prognostic factor of stage II CRC patients, with younger age being related to a better outcome [16]. In addition, CEA level was a potential prognostic factor in this study [17]. CEA is a well-established biomarker for CRC recommended by both the American Society of Clinical Oncology (ASCO) [18] and the European Group on Tumor Markers (EGTM) [19, 20]. Preoperative CEA levels were used to predict prognosis, and routine CEA monitoring during the postresection follow-up period was used to monitor local recurrence and distant metastases after surgery in CRC patients. As this nomogram showed, stage II CRC patients with high CEA levels tend to have significantly worse DFS rates than those with low CEA levels.

Whether adjuvant chemotherapy should be used for stage II CRC is still controversial. According to NCCN guidelines, patients with stage II CRCs and risk factors are recommended to receive adjuvant chemotherapy [8]. In this study, we performed subgroup analyses in stage II patients treated with or without adjuvant chemotherapy, and the results demonstrated the excellent independence and prognostic value of the nomogram. In the current study, histological differentiation, perineural invasion, CRM status, LNH less than 12, and T4 stage were identified as independent risk factors for stage II CRC. Histological differentiation was identified as an important feature for evaluating the benefit of adjuvant chemotherapy [21]. Our study showed that
Table 2  Univariable and multivariable Cox regression analyses of prognostic factors in stage II CRC patients

| Variables                  | Univariable analyses | Multivariable analyses |
|----------------------------|----------------------|------------------------|
|                            | HR (95% CI)          | p value                | HR (95% CI)          | p value                |
| Gender                     | 0.291                |                        |                       |                        |
| Female                     | Reference            |                        |                       |                        |
| Male                       |                      | 1.278 (0.811–2.014)    |                        |                        |
| Age                        | 0.001                | 0.007                  | 1.615 (1.138–2.292)   | 0.002                  |
| < 60                       | Reference            |                        | Reference             |                        |
| ≥ 60                       | 2.254 (1.402–3.623)  |                        | 1.678 (1.210–2.325)   |                        |
| Pre-CEA                    | 0.008                |                        | 0.002                 |                        |
| Negative                   | Reference            |                        | Reference             |                        |
| Positive                   | 1.795 (1.165–2.764)  | 1.678 (1.210–2.325)    | 0.002                 |                        |
| Family history             | 0.739                |                        |                       |                        |
| No                         | Reference            |                        |                       |                        |
| Yes                        | 1.278 (0.463–3.523)  | 0.500                  | 0.002                 |                        |
| Unknown                    | 1.076 (0.369–3.140)  | 0.636                  | 0.002                 |                        |
| Adjuvant CT                | 0.793                |                        |                       |                        |
| No                         | Reference            |                        |                       |                        |
| Yes                        | 1.064 (0.669–1.694)  |                        |                       |                        |
| Tumor site                 | 0.367                |                        |                       |                        |
| Left                       | Reference            |                        |                       |                        |
| Right                      | 0.901 (0.719–1.130)  |                        |                       |                        |
| T stage                    | 0.002                | 0.003                  | 0.002                 |                        |
| T3                         | Reference            |                        | Reference             |                        |
| T4a                        | 1.358 (0.975–1.891)  | 0.070                  | 1.419 (1.005–2.002)   | 0.047                  |
| T4b                        | 3.350 (1.619–6.932)  | 0.001                  | 3.221 (1.532–6.776)   | 0.002                  |
| Histological type          | 0.244                |                        |                       |                        |
| Adenocarcinoma             | Reference            |                        |                       |                        |
| Mucinous adenocarcinoma    | 1.019 (0.675–1.537)  | 0.929                  |                       |                        |
| Signet-ring cell carcinoma | 3.320 (0.819–13.454) | 0.093                 |                       |                        |
| Histological differentiation| 0.002                | 0.009                  | 0.002                 |                        |
| Well                       | Reference            |                        | Reference             |                        |
| Moderate                   | 3.428 (1.570–7.483)  | 0.002                  | 2.814 (1.274–6.218)   | 0.009                  |
| Poor                       | 1.965 (0.956–4.037)  | 0.066                  | 1.619 (0.785–3.342)   | 0.192                  |
| Tumor size                 | 0.016                | 0.061                  |                       |                        |
| < 4                        | Reference            |                        | Reference             |                        |
| ≥ 4                        | 0.675 (0.490–0.931)  | 0.721 (0.512–1.015)    | 0.012                 |                        |
| LNH                         | < 0.001              |                        |                       |                        |
| < 12                       | Reference            |                        | Reference             |                        |
| ≥ 12                       | 0.499 (0.353–0.705)  | 0.624 (0.432–0.902)    |                       |                        |
| Lymphovascular invasion    | 0.053                |                        |                       |                        |
| Negative                   | Reference            |                        |                       |                        |
| Positive                   | 1.539 (0.995–2.380)  |                        |                       |                        |
| Perineural invasion        | 0.001                | 0.029                  |                       |                        |
| Negative                   | Reference            |                        | Reference             |                        |
| Positive                   | 1.868 (1.284–2.717)  | 1.557 (1.048–2.315)    | 0.027                 |                        |
| CRM                        | 0.001                |                        |                       |                        |
| Negative                   | Reference            |                        | Reference             |                        |
| Positive                   | 3.968 (1.752–8.990)  | 2.734 (1.119–6.677)    | 0.005                 |                        |
| MMR status                 | 0.006                |                        |                       |                        |
| dMMR                       | Reference            |                        |                       |                        |
Table 2 (continued)

| Variables       | Univariable analyses | Multivariable analyses |
|-----------------|----------------------|------------------------|
|                 | HR (95% CI)          | p value                | HR (95% CI)          | p value                |
| pMMR            | 1.705 (1.165–2.494)  | 0.002                  | 1.739 (1.184–2.554)  | 0.003                  |
| Tumor stage     |                      |                        |                       |                        |
| Stage IIA       | Reference            |                        | Reference             |                        |
| Stage IIB       | 1.358 (0.975–1.891)  | 0.070                  | 1.419 (1.005–2.002)  | 0.047                  |
| Stage IIC       | 3.350 (1.619–6.932)  | 0.001                  | 3.221 (1.532–6.776)  | 0.002                  |

CRC colorectal cancer, HR hazard ratio, CI confidence interval, Pre-CEA pretreatment carcinoembryonic antigen, CT chemotherapy, LNH number of lymph nodes harvested, CRM circumferential resection margin, MMR mismatch repair, dMMR deficient mismatch repair, pMMR proficient mismatch repair

Fig. 2 Kaplan–Meier DFS curves stratified by patients’ characteristics in the training cohort: a Age at diagnosis; b Pre-CEA; c T stage; d histological differentiation; e TUMOR size; f LNH; g perineural invasion; h CRM status; i MMR status
### Points

| Characteristic | 0 | 20 | 40 | 60 | 80 | 100 |
|---------------|---|----|----|----|----|-----|
| CEA           |   |    |    |    |    |     |
| Age at diagnosis | <60 |   |    |    |    |     |
| Perineural invasion | Negative |   |    |    |    |     |
| CRM status    | Negative |   |    |    |    |     |
| LNH           | <12 |   |    |    |    |     |
| Differentiation | Well |   |    |    |    |     |
| MMR status    | dMMR |   |    |    |    |     |
| T stage       | T3  |   |    |    |    |     |
| Total Points  | 0   | 100 | 200 | 300 | 400 |     |

### Survival Rates

- **1-year Survival**
  - 0.9
  - 0.8
  - 0.7
  - 0.6
  - 0.5
  - 0.4

- **3-year Survival**
  - 0.9
  - 0.8
  - 0.7
  - 0.6
  - 0.5
  - 0.4

- **5-year Survival**
  - 0.9
  - 0.8
  - 0.7
  - 0.6
  - 0.5
  - 0.4

---

**Fig. 3** Nomograms convey the results of prognostic models using eight clinicopathological characteristics to predict DFS of patients with stage II CRC.

---

**Fig. 4**

- **a** Distribution of risk score and relapse status in the training cohort.
- **b** AUC values of ROC predicted 1-year DFS rates of Nomogram and T stage in the training cohort.
- **c** AUC values of ROC predicted 3-year DFS rates of Nomogram and T stage in the training cohort.
- **d** AUC values of ROC predicted 5-year DFS rates of Nomogram and T stage in the training cohort.
- **e** Distribution of risk score and relapse status in the validation cohort.
- **f** AUC values of ROC predicted 1-year DFS rates of Nomogram and T stage in the validation cohort.
- **g** AUC values of ROC predicted 3-year DFS rates of Nomogram and T stage in the validation cohort.
- **h** AUC values of ROC predicted 5-year DFS rates of Nomogram and T stage in the validation cohort.
poor histological differentiation was associated with a worse prognosis. Additionally, in most studies reporting perineural invasion, similar to this research, positive perineural invasion in stage II CRC patients has been shown to be associated with poor outcomes, and such patients might thus have a greater benefit from adjuvant chemotherapy than patients without perineural invasion. Moreover, perineural invasion was defined as a major prognostic and predictive factor for response to adjuvant chemotherapy in stage II CRC [22]. CRM status is considered a significant factor for surgery quality. In our study, only 1.2% of stage II CRCs were defined as CRM positive. Despite the low percentage of patients with a positive CRM status, a positive CRM status was strongly associated with an inferior prognosis. According to the results from a population-based study, Huang et al. found that a positive CRM status decreased overall survival and cause-specific survival. The farther the CRM was from the tumor lesion, the better the long-term survival [23]. Furthermore, the appropriate staging of CRC requires at least 12 lymph nodes to be sampled, as recommended by NCCN guidelines. Relevant research indicated that stage II CRC patients with LNH less than 12 tended to have shorter DFS than those with LNH more than 12, which proved the results of this nomogram [24].

Patients with stage II CRC have differences in T stage, including patients with T3, T4a, and T4b disease. Stage T3 indicates that the cancer has grown into the outermost layers of the colon or rectum but has not gone through them. Stage T4a means that the cancer has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs while T4b means that the tumor is attached to or has grown into other nearby tissues or organs [25]. It is widely accepted that a higher T stage leads to a worse prognosis, which was duplicated in our nomogram. It is worth noting that the T stage was shown to have a strong influence on the nomogram that we established and added to its ability to predict patient risk, and the ROC analysis and DCA indicate that our nomogram has better clinical value than the TNM staging system.

Clinically, MSI or dMMR status are the most important biomarkers in stage II CRC and are widely used to help clinicians choose adjuvant chemotherapy and predict patient outcomes. Stage II CRC patients with dMMR status were more likely to have low recurrence rates and a better prognosis than those with pMMR status [25]. Clinical trials demonstrated a lack of benefit of adjuvant 5-fluorouracil (FU)-based chemotherapy in stage II CRC patients with dMMR status [26]. Therefore, patients with stage II CRC with dMMR status and high-risk factors are more likely to benefit from combination chemotherapy.
However, this study still has some limitations. First, this is a retrospective study comprising a limited number of patients at a single center. A future multicenter study with a larger patient population is needed to evaluate the external utility of this nomogram. Second, due to the characteristics of retrospective studies, some useful information was missing in this study. For instance, it is not clear which kind of adjuvant chemotherapy the stage II CRC patients in the current study received and how of the types of chemotherapies were distributed among groups. Third, the 1-year AUC value of the nomogram based on the validation set was 0.673, which suggests that external cohorts are required to validate the reliability of our nomogram. Additional prospective data collection and the incorporation of other factors are encouraged to improve this model.
Conclusion

In conclusion, we established and validated a nomogram for predicting the personalized survival probability of stage II CRC patients. This convenient nomogram had a sufficient ability to discriminate patients, in addition to excellent clinical utility, suggesting that it could be a potential simple-to-use tool for physicians to facilitate postoperative personalized prognostic evaluation and determine therapeutic strategies for stage II CRC patients.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12935-020-01382-w.

Additional file 1: Table S1. Point assignments and predictive scores for each variable in the nomogram model.

Additional file 2: Figure S1. Subgroup analyses based on LNH status, perineural invasion status, T stage and MMR status.

Abbreviations

CRC: Colorectal cancer; AJCC/UICC: American Joint Commission on Cancer/International Union against Cancer; TNM: Tumor-node-metastasis; MSI: Microsatellite instability; dMMR: Mismatch repair deficiency; MSS: Microsatellite stable; pMMR: Proficient MMR; FUSCC: Fudan University Shanghai Cancer Center; DCA: Decision curve analysis; Pre-CEA: Pretreatment carcinoembryonic antigen; CRM: Circumferential resection margin; LNH: Lymph nodes harvested; C-index: The concordance index; ROC: Receiver operating characteristic; DFS: Disease-free survival; ASCO: The American Society of Clinical Oncology; EGTM: The European Group on Tumor Markers.

Acknowledgements

Not applicable.

Authors’ contributions

SBM and ZZ had the idea for this study. YQL and XH supervised the acquisition of the data. SBM and ZZ undertook the statistical analysis. SJC, LZ, and XJM provided statistical advice. All authors contributed to interpretation of the results. SBM, ZZ and JJP wrote the article and other authors contributed to the content. All authors read and approved the final manuscript.

Funding

National Natural Science Foundation of China (31470826, 31670858, 81672374); Science and Technology Commission of Shanghai Municipality (16411966300); Wu Jieping Medical Foundation of China (3206750.18136)
Availability of data and materials
The dataset used during the study are available from the corresponding author on a reasonable request.

Ethics approval and consent to participate
The Ethical Committee and Institutional Review Board of the Fudan University Shanghai Cancer Center reviewed and approved this study protocol. All patients signed written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, 270 Dong’an Road, Shanghai 200032, China. 2 Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China. 3 Department of Cancer Institute, Fudan University Shanghai Cancer Center, Fudan University, Shanghai 200032, China.

Received: 19 November 2019  Accepted: 26 June 2020
Published online: 06 July 2020

References
1. Chen W, Zheng R, Baade PD, Zeng S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32.
2. Siegel RL, Miller KD. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
3. Mo S, Dai W, Xiang W, Huang B, Li Y, Feng Y, Li Q, Cai G. Survival contradiction between stage IIA and stage IIIA rectal cancer: a retrospective study. J Cancer. 2018;9(8):1466–75.
4. Gunderson LL, Jessup JM, Greene FL, Sargent DJ, Stewart AK. Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol. 2010;28(2):264–71.
5. Teufel A, Gerken M, Hartl J, Iselt T, Fichtner-Feigl S, Stroszczynski C, Schlitt HJ, Hofstadder F; Klinikhammer-Schäke M. Benefit of adjuvant chemotherapy in patients with T4 UICC II colon cancer. BMC Cancer. 2015;15:419.
6. Kanda M, Oba K, Aoyama T, Kashiwabara K, Mayanagi S, Maeda H, Honda M, Hamada C, Sadahiro S, Sakamoto J, et al. Clinical signatures of mucinous and poorly differentiated subtypes of colorectal adenocarcinomas by a propensity score analysis of an independent patient database from three phase III trials. Dis Colon Rectum. 2018;61(4):461–71.
7. Cienfuegos JA, Martinez P, Baixauli J, Beorlegui C, Rosenstone S, Sola JJ, Rodriguez J, Hernandez-Lloreda JL. Perineural invasion is a major prognostic and predictive factor of response to adjuvant chemotherapy in stage I–II colon cancer. Ann Surg Oncol. 2017;24(4):1077–84.
8. Benson AB 3rd, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, Deming D, Engstrom PF, Enzinger PC, Fichera A, et al. Colon cancer, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;15(3):370–98.
9. Benson AB 3rd, Venook AP, Al-Hawary MM, Cederquist L, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Engstrom PF, et al. Rectal cancer, version 2.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2018;16(7):874–901.
10. Benson AB 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AF, Flynn PJ, Kryzanowska MK, Marouj J, McAlister P, Van Cutsem E, et al. American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22(16):3408–19.
11. O’Connor ES, Greenblatt DY, Lo Conte NK, Gangnon RE, Liu JJ, Heise CP, Smith MA. Adjuvant chemotherapy for stage II colon cancer with poor prognostic features. J Clin Oncol. 2011;29(25):3381–8.
12. Dotan E, Cohen SJ. Challenges in the management of stage II colon cancer. Semin Oncol. 2011;38(4):511–20.
13. Zhang J-X, Song W, Chen Z-H, Wei J-H, Liao Y-L, Lei J, Hu M, Chen G-Z, Liao B, Lu J, et al. Prognostic and predictive value of a microRNA signature in stage II colon cancer: a microRNA expression analysis. Lancet Oncol. 2013;14(13):1295–306.
14. Gao S, Tibiche C, Zou J, Zaman N, Triforo M, O’Connor-McCourt M, Wang E. Identification and construction of combinatorial cancer hallmark-based gene signature sets to predict recurrence and chemotherapy benefit in stage II colorectal cancer. JAMA Oncol. 2016;2(1):37–45.
15. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Mak. 2006;26(6):565–74.
16. Abasse Kassim S, Tang W, Abbas M, Wu S, Meng Q, Zhang C, Li X, Chen R. Clinicopathologic and epidemiologic characteristics of prognostic factors in post-surgical survival of colorectal cancer patients in Jiangsu Province, China. Cancer Epidemiol. 2019;62:101.565.
17. Shibutani M, Maeda K, Nagahara H, Ohtani H, Sakurai K, Toyokawa T, Kubo N, Tanaka H, Muguruma K, Ohira M, et al. Significance of CEA and CA19-9 combination as a prognostic indicator and for recurrence monitoring in patients with stage II colorectal cancer. Anticancer Res. 2014;34(7):3753–8.
18. Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, Somerfield MR, Hayes DF, Bast RC Jr. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24(33):5313–27.
19. Duffy MJ, van Dalen A, Haglund C, Hansson L, Klapdor R, Lamerz R, Nils-son Q, Sturgeon C, Topolcan O. Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines. Eur J Cancer. 2003;39(6):718–27.
20. Duf flu MI, van Dalen A, Haglund C, Hansson L, Holinski-Feder E, Klapdor R, Lamerz R, Peitlorni P, Sturgeon C, Topolcan O. Tumour markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines for clinical use. Eur J Cancer. 2007;43(9):1348–60.
21. Chen SH, Wan QS, Zhou D, Wang T, Hu J, He YT, Yuan HL, Wang YQ, Zhang KH. A simple-to-use nomogram for predicting the survival of early hepato-cellular carcinoma patients. Front Oncol. 2019;9:584.
22. Nikberg M, Chabok A, Letocha H, Kindler G, Gilmeinlus B, Smedh K. Lymphovascular and perineural invasion in stage II rectal cancer: a report from the Swedish colorectal cancer registry. Acta Oncol. 2016;55(12):1418–24.
23. Huang Y, Zhao M, Yin J, Lu T, Yang X, Yuan G, Li M, Liu Y, Zhan C, Wang Q. Pulmonary metastasis in newly diagnosed colorectal cancer: a population-based nomogram study. Int J Colorectal Dis. 2019;34(5):867–78.
24. Li Destri G, Barchitta M, Pesce A, Latteri S, Bosco D, Di Cataldo A, Agodi A, Puleo S. Predictive value of the number of harvested lymph nodes and cut-off for lymph node ratio in the prognosis of stage II and III colorectal cancer patients. J Invest Surg. 2019;32(1):1–7.
25. Puccini A, Berger MD, Zhang W, Lenz HJ. What we know about stage II and III colon cancer: it’s still not enough. Target Oncol. 2017;12(3):265–75.
26. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and molecular markers for colorectal cancer. Curr Treat Options Oncol. 2015;16(7):30.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.