**ORIGINAL ARTICLE**

# The incidence, associated factors, and predictive nomogram for early death in stage IV colorectal cancer

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## Abstract

**Purpose** The purpose of the present study was to investigate the incidence and associated factors for early death in stage IV colorectal cancer (CRC) and to construct the predictive nomogram.

**Methods** Patients with stage IV CRC, who had been diagnosed between 2010 and 2014 in the Surveillance, Epidemiology, and End Results datasets, were eligible for this retrospective cohort study. The univariable and multivariable logistic regression models were conducted to determine the associated factors for early death (survival time ≤ 3 months). The predictive nomogram was constructed and the internal validation was performed.

**Results** Ten thousand two hundred sixty-three out of 36,461 (28.1%) eligible patients resulted in all causes of early death (25.8% for cancer-specific early death and 2.3% for non-cancer early death). Advanced age, marital status, right colon, poor differentiation, higher N stage, and bone metastasis were positively associated with all causes of early death, cancer-specific early death, and non-cancer early death, while higher T stage, positive carcinoembryonic antigen, and distant metastases (bone, lung, liver, and brain) were only positively associated with all causes of early death and cancer-specific early death. The calibration curve for all causes of early death, cancer-specific early death, and non-cancer early death showed the prediction curve closely approximated at the 45° line and the areas under the curve were 75.7% (95% CI, 74.9–76.4%), 75.9% (95% CI, 75.1–76.6%), and 76.9% (95% CI, 76.3–77.6%), respectively.

**Conclusions** The nomogram was calibrated to predict all causes of early death development, cancer-specific early death development, and non-cancer early death development. These findings can be utilized in early screening and to tailor targeted treatment regimens for stage IV CRC patients.

**Keywords** Colorectal cancer · Stage IV · SEER · Early death · Nomogram

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## Introduction

Colorectal cancer (CRC) is one of the major causes of cancer morbidity and mortality both in men and women worldwide. Over 1.36 million newly diagnosed CRC cases and approximately 694,000 deaths were estimated in 2012 [1]. Approximately, a quarter of the CRC patients were reported to present with distant metastatic disease at initial diagnosis. Distant metastatic disease is accepted to be the leading cause of poor survival [2, 3]. In a study in Japan, the 5-year survival rate of CRC in patients with distant metastasis was about 10.0% and the median survival time was approximately 5.0 months [4].

In the past few decades with the development of advanced treatment and surveillance, the metastatic CRC showed significant improvement in relative survival [5]. However, a number of stage IV CRC patients still suffer early death after diagnosis according to American Joint Committee on Cancer Staging Manual. The variability in these outcomes has not been well documented [4, 6]. Thus, it is important to investigate the incidence and the factors potentially contributing to early death. A further exploration of the associated factors may help to identify patients with an increased early death risk and to guide the creation of targeted treatment regimens [7, 8]. Studies with large sample sizes were seldom conducted before.

This study used a population-based cohort of stage IV CRC patients to evaluate the incidence of early death and to examine the associated factors contributing to early death (survival time ≤ 3 months) after initial diagnosis. Furthermore, the work resulted in a predictive nomogram incorporating the associated factors for predicting the early death in stage IV CRC patients.

## Methods

### Population

The design of this investigation was a population-based cohort study. The US National Cancer Institute's open public database, Surveillance, Epidemiology, and End Results (SEER), provides the cancer incidence and survival data from 18 established cancer registries across the USA. SEER is a particularly useful tool for assessing epidemiological characteristics of cancer. The present study included the International Federation of Genecology and Obstetrics–identified stage M1 de novo metastatic CRC patients in the SEER database. The data for metastatic sites of the bone, liver, lung, and brain were not collected until 2010. Thus, CRC patients diagnosed between 2010 and 2014 (with at least 1-year follow-up) were included in the present study. Cases with benign tumor, diagnosed at autopsy, via death certificate, with

unspecified follow-up, or with unknown metastatic information were excluded (Fig. 1). SEER*Stat Software version 8.3. 5 (https://seer.cancer.gov/seerstat/) (Information Management Service, Inc., Calverton, MD, USA) was used to generate the case listing. Based on the previous studies, early death in cancer patients was defined as death ≤ 3 months following initial diagnosis [9, 10].

### Ethics approval

Cancer is a reportable disease in every state of the USA. The data in the SEER database does not require informed patient consent. The present study was complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study used previously collected deidentified data, which was deemed exempt from a review by the Ethics Board of the Tianjin Medical University Cancer Institute and Hospital.

### Statistical analysis

Quantitative data were described as mean ± standard deviation (SD) and the difference between groups were analyzed by Student's $t$ tests. Categorical data were presented as the number and the percentage ($N$, %). The Pearson chi-squared test was used to evaluate the difference in the early death incidence between categorical variables. The primary outcome was all causes of death, cancer-specific early death, and non-cancer early death, which was defined as death that occurred within the 3 months after diagnosis. The Cochran-Armitage trend test was used to test for changes in the early death incidence. The right colon includes the appendix, cecum, ascending colon, hepatic flexure of the colon, and transverse colon. The left colon encompasses the splenic flexure, descending colon, sigmoid colon, sigmoid colon, and rectum. The univariable logistic regression model determined the associated factors potentially contributing to early death. Factors with a $p < 0.05$ were incorporated into the multivariable regression model. The final model selection was performed by a backward stepdown selection process using the Akaike information criterion. The subjects with unknown information were not included in the multivariable analysis.

The predictive nomogram for all causes of death, cancer-specific early death, and non-cancer early death was formulated based on the results of multivariable logistic analysis using the rms package in R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). To evaluate the calibration of the nomogram, a regression smoothing method was used to produce the calibration plots by bootstrapping with 1000 resamples. These were applied where the relationship between the observed and predicted probabilities of early death was described graphically. The discrimination of the nomogram was evaluated by the

**Fig. 1** Flowchart for selection procedure of the stage IV colorectal cancer patients
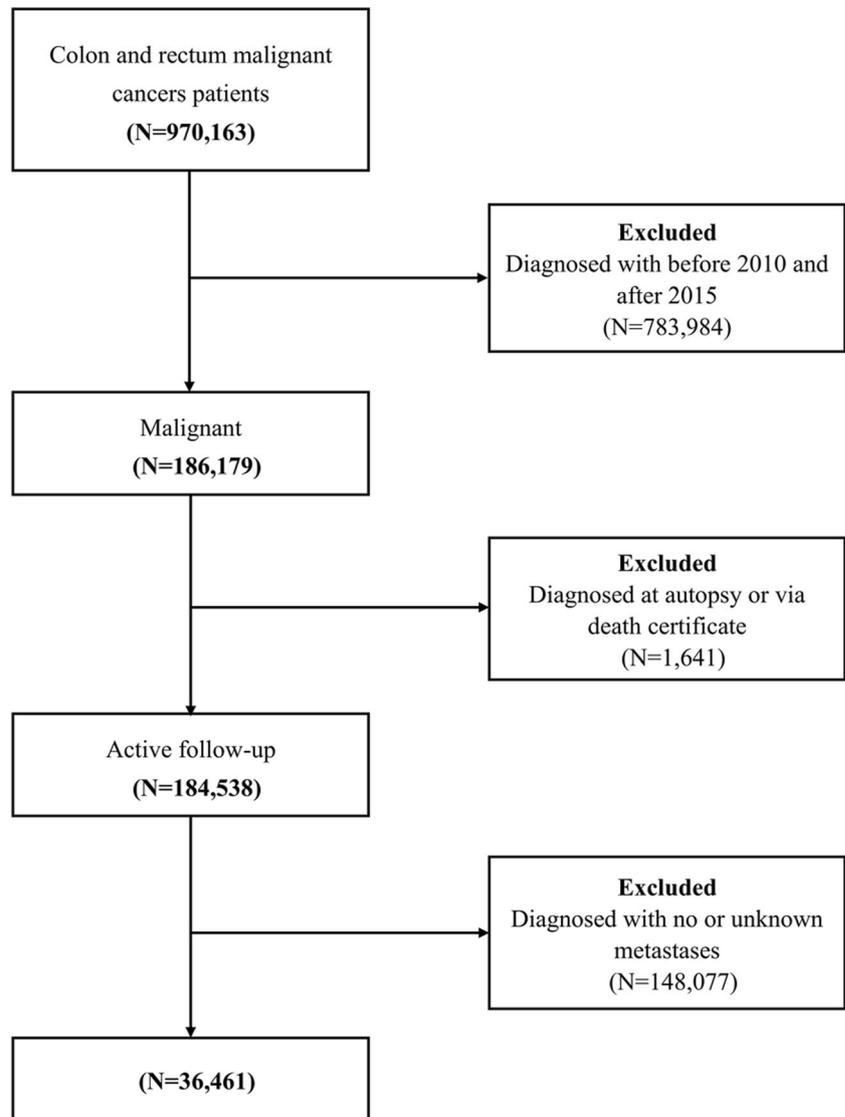
receiver operating characteristic (ROC) curve. The area under the curve (AUC) of 0.5 indicated no discrimination between the patients with/without early death, and an AUC of 1.0 indicated perfect discrimination.

Statistically significant levels were two-tailed and set at $p < 0.05$. Statistical analyses were conducted by the IBM Statistical Package for the Social Sciences (SPSS) version 23.0 software package for Windows (SPSS, Inc., Chicago, IL, USA).

## Results

### Demographic and clinical characteristics

A total of 36,461 eligible stage IV colorectal cancer patients were included in the present study. The mean age of patients was $65.37 \pm 14.39$ years, 53.8% of patients ($N = 19,625$) were male, and 46.2% of patients ($N = 16,836$) were female. Females presented at a significantly older age at diagnosis than males ($66.39 \pm 15.05$ years vs. $64.48 \pm 13.74$ years, $p < 0.001$). Most of the patients were Caucasian (76.6%, $N = 27,927$) and about half of them were married (48.7%, $N = 17,745$). The percentages of bone, lung, liver and brain metastases were 5.7%, 23.1%, 70.5%, and 1.3%, respectively. Patients' characteristics are showed in Table 1.

### Incidence of early death

A total of 10,263 (28.1%) CRC patients succumbed to all causes of early death, while the incidences of early death of cancer-specific and non-cancer early deaths were 25.8% ($N = 9405$) and 2.3% ($N = 858$), respectively.

**Table 1** Univariable logistic regression for analyzing the risk factors for early death

| Factors | Patients no. (%) | | | | Total early death | | Cancer-specific early death[c] | | Non-cancer-specific early death[d] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No early death | Total early death | Cancer-specific early death | Non-cancer-specific early death | OR (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value |
| **Age (years)** | | | | | | | | | | |
| ≤ 50 | 5063 (19.3) | 647 (6.3) | 618 (6.6) | 29 (3.4) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| 51–60 | 6511 (24.9) | 1466 (14.3) | 1376 (14.6) | 90 (10.5) | 1.76 (1.60–1.95) | < 0.001 | 1.73 (1.56–1.92) | < 0.001 | 2.41 (1.59–3.67) | < 0.001 |
| 61–70 | 6897 (26.3) | 2230 (21.7) | 2076 (22.1) | 154 (17.9) | 2.53 (2.30–2.78) | < 0.001 | 2.47 (2.24–2.72) | < 0.001 | 3.90 (2.62–5.81) | < 0.001 |
| 71–80 | 4791 (18.3) | 2594 (25.3) | 2330 (24.8) | 264 (30.8) | 4.24 (3.85–4.66) | < 0.001 | 3.98 (3.62–4.39) | < 0.001 | 9.62 (6.54–14.15) | < 0.001 |
| 81–90 | 2616 (10.0) | 2694 (26.2) | 2438 (25.9) | 256 (29.8) | 8.06 (7.31–8.89) | < 0.001 | 7.64 (6.91–8.44) | < 0.001 | 17.08 (11.60–25.16) | < 0.001 |
| ≥ 90 | 320 (1.2) | 632 (6.2) | 567 (6.0) | 65 (7.6) | 15.46 (13.20–18.09) | < 0.001 | 14.52 (12.36–17.04) | < 0.001 | 35.46 (22.57–55.73) | < 0.001 |
| **Sex** | | | | | | | | | | |
| Female | 11,869 (45.3) | 4967 (48.4) | 4561 (48.5) | 406 (47.3) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Male | 14,329 (54.7) | 5296 (51.6) | 4844 (51.5) | 452 (52.7) | 0.88 (0.84–0.93) | < 0.001 | 0.88 (0.84–0.92) | < 0.001 | 0.92 (0.81–1.06) | 0.24 |
| **Marital status** | | | | | | | | | | |
| Unmarried[a] | 11,169 (42.6) | 5614 (54.7) | 5111 (54.3) | 503 (58.6) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Married | 13,661 (52.1) | 4084 (39.8) | 3776 (40.1) | 308 (35.9) | 0.60 (0.57–0.62) | < 0.001 | 0.60 (0.58–0.63) | < 0.001 | 0.50 (0.43–0.58) | < 0.001 |
| Unknown | 1368 (5.2) | 565 (5.5) | 518 (5.4) | 47 (5.5) | NA | NA | NA | NA | NA | NA |
| **Race** | | | | | | | | | | |
| White | 19,956 (76.2) | 7971 (77.7) | 7297 (77.6) | 674 (78.6) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Black | 3818 (14.6) | 1536 (15.0) | 1404 (14.9) | 132 (15.4) | 1.01 (0.94–1.07) | 0.83 | 1.01 (0.94–1.08) | 0.87 | 1.02 (0.85–1.24) | 0.81 |
| Others[b] | 2374 (9.1) | 735 (7.2) | 684 (7.3) | 51 (5.9) | 0.78 (0.71–0.85) | < 0.001 | 0.79 (0.72–0.86) | < 0.001 | 0.64 (0.48–0.85) | 0.002 |
| Unknown | 50 (0.2) | 21 (0.2) | 20 (0.2) | 1 (0.1) | NA | NA | NA | NA | NA | NA |
| **Insurance status** | | | | | | | | | | |
| Uninsured | 1257 (4.8) | 534 (5.2) | 503 (5.3) | 31 (3.6) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Medical aid | 4036 (15.4) | 1669 (16.3) | 1502 (16.0) | 167 (19.5) | 0.97 (0.87–1.09) | 0.65 | 0.93 (0.83–1.05) | 0.23 | 1.68 (1.14–2.47) | 0.009 |
| Insured | 20,372 (77.8) | 7644 (74.5) | 7004 (74.5) | 640 (74.6) | 0.88 (0.80–0.98) | 0.02 | 0.86 (0.77–0.96) | 0.005 | 1.27 (0.88–1.84) | 0.19 |
| Unknown | 533 (2.0) | 416 (4.1) | 396 (4.2) | 20 (2.3) | NA | NA | NA | NA | NA | NA |
| **Histological grade** | | | | | | | | | | |
| Grade I | 1343 (5.1) | 254 (2.5) | 231 (2.5) | 23 (2.7) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Grade II | 13,598 (51.9) | 2940 (28.6) | 2667 (28.4) | 273 (31.8) | 1.14 (0.99–1.32) | 0.06 | 1.14 (0.99–1.32) | 0.077 | 1.17 (0.76–1.80) | 0.47 |
| Grade III | 4700 (17.9) | 2030 (19.8) | 1869 (19.9) | 161 (18.8) | 2.28 (1.98–2.64) | < 0.001 | 2.31 (1.99–2.69) | < 0.001 | 2.00 (1.29–3.11) | 0.002 |
| Grade IV | 909 (3.5) | 402 (3.9) | 371 (3.9) | 31 (3.6) | 2.34 (1.96–2.80) | < 0.001 | 2.37 (1.97–2.85) | < 0.001 | 1.99 (1.15–3.44) | 0.013 |
| Unknown | 5648 (21.6) | 4637 (45.2) | 4267 (45.4) | 370 (43.1) | NA | NA | NA | NA | NA | NA |
| **Lymphatic metastasis** | | | | | | | | | | |
| N0 | 8249 (31.5) | 3645 (35.5) | 3310 (35.2) | 335 (39.0) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| N1 | 8597 (32.8) | 2473 (24.1) | 2271 (24.1) | 202 (23.5) | 0.65 (0.61–0.69) | < 0.001 | 0.66 (0.62–0.70) | < 0.001 | 0.58 (0.49–0.69) | < 0.001 |

**Table 1** (continued)

| Factors | Patients no. (%) | | | | Total early death | | Cancer-specific early death[c] | | Non-cancer-specific early death[d] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No early death | Total early death | Cancer-specific early death | Non-cancer-specific early death | OR (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value |
| N2 | 6389 (24.4) | 1579 (15.4) | 1459 (15.5) | 120 (14.0) | 0.56 (0.52–0.60) | <0.001 | 0.57 (0.53–0.61) | <0.001 | 0.46 (0.37–0.57) | <0.001 |
| Unknown | 2963 (11.3) | 2566 (25.0) | 2365 (25.1) | 201 (23.4) | NA | NA | NA | NA | NA | NA |
| T stage | | | | | | | | | | |
| T1 | 2281 (8.7) | 1150 (11.2) | 1074 (11.4) | 76 (8.9) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| T2 | 688 (2.6) | 104 (1.0) | 92 (1.0) | 12 (1.4) | 0.30 (0.24–0.37) | <0.001 | 0.28 (0.23–0.36) | <0.001 | 0.52 (0.28–0.97) | 0.039 |
| T3 | 9331 (35.6) | 1695 (16.5) | 1516 (16.1) | 179 (20.9) | 0.36 (0.33–0.39) | <0.001 | 0.35 (0.32–0.38) | <0.001 | 0.58 (0.44–0.76) | <0.001 |
| T4 | 7711 (29.4) | 2428 (23.7) | 2234 (23.8) | 194 (22.6) | 0.63 (0.57–0.68) | <0.001 | 0.62 (0.56–0.67) | <0.001 | 0.76 (0.58–0.99) | 0.041 |
| Unknown | 6187 (23.6) | 4886 (47.6) | 4489 (47.7) | 397 (46.3) | NA | NA | NA | NA | NA | NA |
| Primary site | | | | | | | | | | |
| Left colon | 14,647 (55.9) | 4181 (40.7) | 3845 (40.9) | 336 (39.2) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Right colon | 10,023 (38.3) | 4340 (42.3) | 3962 (42.1) | 378 (44.1) | 1.52 (1.44–1.59) | <0.001 | 1.51 (1.43–1.59) | <0.001 | 1.64 (1.42–1.91) | <0.001 |
| Unknown | 1528 (5.8) | 1742 (17.0) | 1598 (17.0) | 144 (16.8) | NA | NA | NA | NA | NA | NA |
| CEA | | | | | | | | | | |
| Negative | 3556 (13.6) | 749 (7.3) | 682 (7.3) | 67 (7.8) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Positive | 14,217 (54.3) | 5188 (50.6) | 4799 (51.0) | 389 (45.3) | 1.73 (1.59–1.89) | <0.001 | 1.76 (1.61–1.92) | <0.001 | 1.45 (1.12–1.89) | 0.005 |
| Unknown | 8425 (32.2) | 4326 (42.2) | 3924 (41.7) | 402 (46.9) | NA | NA | NA | NA | NA | NA |
| Brain metastases | | | | | | | | | | |
| No | 24,927 (95.1) | 9271 (90.3) | 8490 (90.3) | 781 (91.0) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 238 (0.9) | 238 (2.3) | 222 (2.4) | 16 (1.9) | 2.69 (2.24–3.22) | <0.001 | 2.74 (2.28–3.29) | <0.001 | 2.15 (1.29–3.58) | 0.003 |
| Unknown | 1033 (3.9) | 754 (7.3) | 693 (7.4) | 61 (7.1) | NA | NA | NA | NA | NA | NA |
| Bone metastases | | | | | | | | | | |
| No | 24,069 (91.9) | 8641 (84.2) | 7892 (83.9) | 749 (87.3) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 1170 (4.5) | 914 (8.9) | 862 (9.2) | 52 (6.1) | 2.18 (1.99–2.38) | <0.001 | 2.25 (2.05–2.46) | <0.001 | 1.43 (1.07–1.90) | 0.015 |
| Unknown | 959 (3.7) | 708 (6.9) | 651 (6.9) | 57 (6.6) | NA | NA | NA | NA | NA | NA |
| Lung metastases | | | | | | | | | | |
| No | 19,579 (74.7) | 6778 (66.0) | 6149 (65.4) | 629 (73.3) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 5662 (21.6) | 2769 (27.0) | 2591 (27.5) | 178 (20.7) | 1.41 (1.34–1.49) | <0.001 | 1.46 (1.38–1.54) | <0.001 | 0.98 (0.83–1.16) | 0.80 |
| Unknown | 957 (3.7) | 716 (7.0) | 665 (7.1) | 51 (5.9) | NA | NA | NA | NA | NA | NA |
| Liver metastases | | | | | | | | | | |
| No | 7630 (29.1) | 2229 (21.7) | 1993 (21.2) | 236 (27.5) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 18,003 (68.7) | 7701 (75.0) | 7106 (75.6) | 595 (69.3) | 1.46 (1.39–1.55) | <0.001 | 1.51 (1.43–1.60) | <0.001 | 1.07 (0.92–1.25) | 0.40 |
| Unknown | | 333 (3.2) | 306 (3.3) | 27 (3.1) | NA | NA | NA | NA | NA | NA |

**Table 1** (continued)

| Factors | Patients no. (%) | | | | Total early death | | Cancer-specific early death[c] | | Non-cancer-specific early death[d] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No early death | Total early death | Cancer-specific early death | Non-cancer-specific early death | OR (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value |
| Surgery | | | | | | | | | | |
| No | 10,746(41.0) | 7234(70.5) | 6675(71.0) | 559(65.2) | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 15,372(58.7) | 2969(28.9) | 2671(28.4) | 298(34.7) | 0.29(0.27–0.30) | <0.001 | 0.28(0.27–0.29) | <0.001 | 0.37(0.32–0.43) | <0.001 |
| Unknown | 80(0.3) | 60(0.6) | 59(0.6) | 1(0.1) | NA | NA | NA | NA | NA | NA |

*Ref* reference, *OR* odds ratio, *CEA* carcinoembryonic antigen, *NA* not available

[a] Includes single, separated, widowed, and divorced

[b] Includes American Indian/Alaska Native and Asian or Pacific Islander

[c] Cancer-specific death: death attributed to cancer

[d] Non-cancer death: including accidents and adverse effects, Alzheimer's, atherosclerosis, cerebrovascular diseases, chronic liver disease and cirrhosis, chronic obstructive pulmonary disease and allied conditions, complications of pregnancy, childbirth, puerperium, diabetes mellitus, diseases of the heart, homicide and legal intervention, hypertension without heart disease, nephritis, nephrotic syndrome and nephrosis, in situ, benign or unknown behavior neoplasm, other causes of death, other diseases of arteries, arterioles, capillaries, other infectious and parasitic diseases including HIV, septicemia, suicide and self-inflicted injury, symptoms, signs and ill-defined conditions, and state DC available but no COD

Females had a significantly higher incidence of all causes of early death than males (29.5% vs. 27.0%; $\chi^2 = 28.37$, $p < 0.001$). All causes of early death incidence presented with marked fluctuations in age, and the total incidence of early death decreased at 1–30 years, plateaued at 31–50 years, and significantly increased with age > 51 years ($\chi^2 = 3272.06$, $p$ for trend $< 0.001$). From 1 to 30 years of age, all causes of early death incidence decreased in males and increased in females. For the other listed age groups, males and females showed similar results (Fig. 2A).

The incidence of all causes of early death in different colorectal cancer sites was not the same. The lowest incidence of early death was the appendix (8.4%), followed by the cecum (30.2%) and ascending colon (33.6%), and the greatest incidence of early death was with lesions of the hepatic flexure of colon (35.3%). The early death incidence decreased with lesions from the transverse colon (33.7%) to the splenic flexure (28.5%), descending colon (26.1%), sigmoid colon (23.3%), sigmoid colon (23.3%), and rectum (19.0%). The left colon sites (22.2%) presented significantly lower incidences than the right colon sites (30.2%) ($\chi^2 = 273.97$, $p < 0.001$). Male and female subgroups showed similar results (Fig. 2B).

The incidence of all causes of early death was highest for brain metastases (50.0%), followed by bone (43.9%), lung (32.8%), and liver metastases (30.0%) (Fig. 2C). The early death incidence significantly increased with the number of metastatic organ sites ($\chi^2 = 473.43$, $p$ for trend $< 0.001$) (Fig. 2D). Male and female stage IV CRC patients presented with similar results.

## Risk factors for developing early death

Univariate logistic regression showed advanced age, marital status, American Indian/Alaska Native and Asian or Pacific Islander race, insured status, poor differentiation, higher N and T stages, right colon, higher carcinoembryonic antigen (CEA), bone and brain metastases, and surgery were all significantly associated with all causes of death, cancer-specific early death, and non-cancer early death, while liver and brain metastases were only positively associated with all causes of early death and cancer-specific early death (Table 1).

After incorporating these factors into the multivariable logistic regression, results showed advanced age, poor differentiated grade, higher N stage, higher T stage, right colon, positive CEA, and bone, lung, liver, and brain metastases were all positively associated with all causes of early death and cancer-specific early death, while marital status, insured status, and history of surgery on primary sites were all negatively associated with all causes of early death and cancer-specific early death (Table 2). In addition, advanced age, marital status, poor differentiated
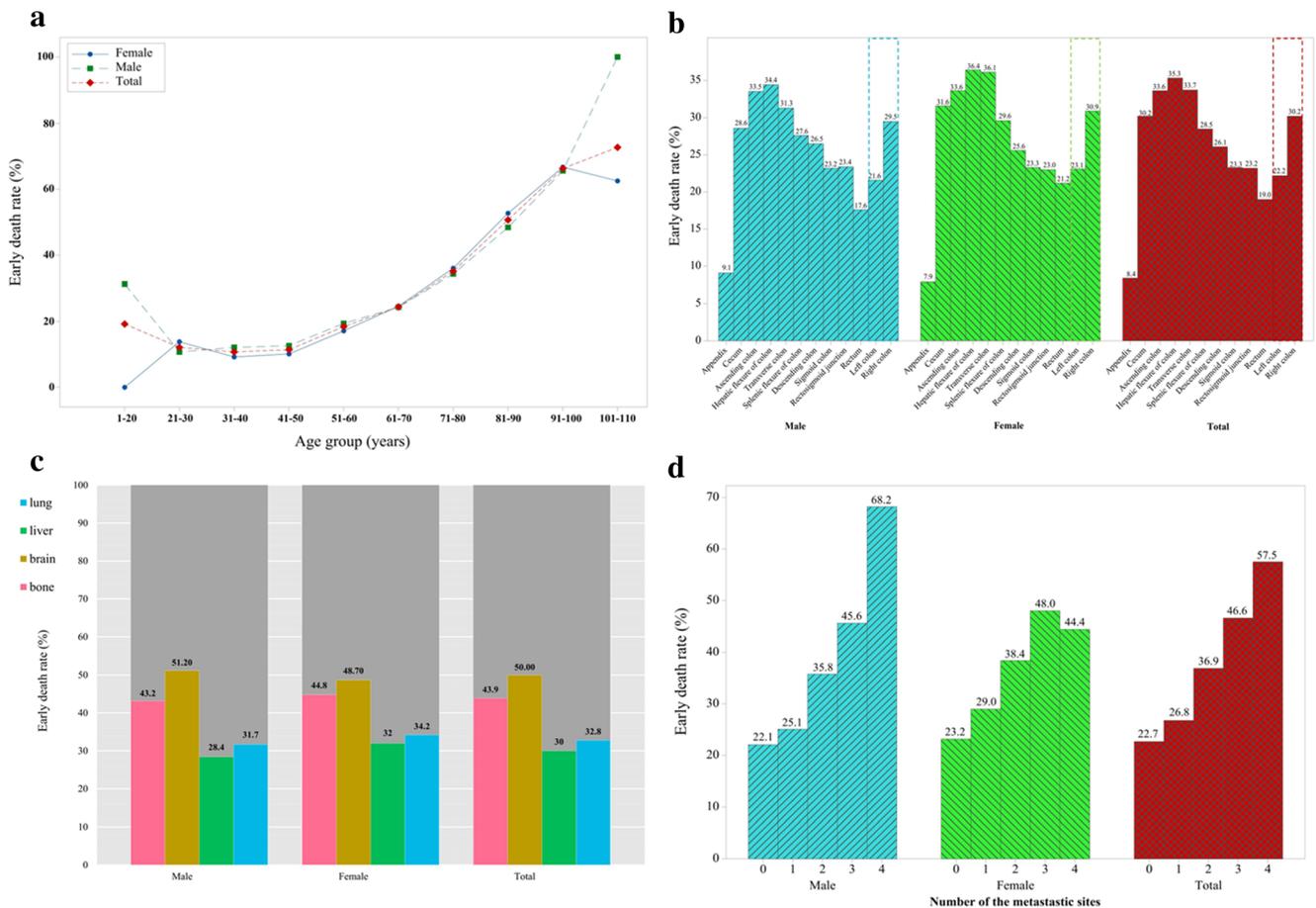
Fig. 2 The trend and distribution of early death incidence of stage IV colorectal cancer patients. Stratified by age (A), different colorectal cancer sites (B), different distant metastases by organs/systems (C), and number of the metastatic organs (D)

grade, and higher N stage were significantly associated with non-cancer early death; however, the association between non-cancer early death and right colon and bone metastasis nearly reaches the significant level.

## Performance of the nomogram for predicting early death

Based on the aforementioned factors in the multivariable model, three nomograms were constructed to predict the probability of developing all causes of early death, cancer-specific early death, and non-cancer early death among stage IV CRC patients, respectively (Fig. 3A–C). Internal validation suggested prediction curves (solid line) of the calibration curve were all closely approximated at the 45° line, indicating a precise prediction of these three predictive models (Fig. 4A–C). In addition, the AUC for these three nomograms in predicting all causes of early death, cancer-specific early death, and non-cancer early death were 75.7% (95% CI, 74.9–76.4%), 75.9% (95% CI, 75.1–76.6%), and 76.9% (95% CI 76.3–77.6%), respectively, which exhibited good discrimination (Fig. 4D–F).

## Discussion

Globally, CRC is one of the main causes of cancer death. The prognosis of CRC mainly depends on its clinical stage. Patients with stage IV CRC were reported to have the worst prognosis [11, 12]. In the present cohort with 36,461 stage IV CRC patients, more than a quarter of stage IV CRC patients succumbed to their disease soon after diagnosis (≤ 3 months). Previous studies have determined the prognosis for stage IV CRC patients but focused on median survival and prognostic factors without specifying early death or associated factors [13–15]. To our knowledge, the present study is the first to describe the incidence and the associated factors of early death for stage IV CRC patients.

In the present study, a number of factors were found to be positively associated with early death development in stage IV CRC, including advanced age, poor differentiated grade, higher N stage, higher T stage, right colon, positive CEA, and distant metastases (bone, lung, liver, and brain). The marital status, insured status, and surgery on primary sites were found to be negatively associated with early death.

**Table 2** Multivariable logistic regression for analyzing the risk factors for early death

| Factors | Total early death | | Cancer-specific early death[c] | | Non-cancer-specific early death | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value |
| Age (years) | | | | | | |
| ≤ 50 | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| 51–60 | 1.52 (1.25–1.86) | < 0.001 | 1.48 (1.21–1.82) | < 0.001 | 2.73 (1.10–6.79) | 0.031 |
| 61–70 | 2.27 (1.87–2.75) | < 0.001 | 2.23 (1.83–2.72) | < 0.001 | 3.56 (1.46–8.67) | 0.005 |
| 71–80 | 4.48 (3.69–5.44) | < 0.001 | 4.10 (3.35–5.00 | < 0.001 | 13.90 (5.95–32.47) | < 0.001 |
| 81–90 | 7.29 (5.92–8.97) | < 0.001 | 6.77 (5.47–8.37) | < 0.001 | 19.36 (8.13–46.09) | < 0.001 |
| ≥ 90 | 8.11 (5.34–12.33) | < 0.001 | 7.69 (4.99–11.84) | < 0.001 | 19.96 (5.84–68.26) | < 0.001 |
| Sex | | | | | | |
| Female | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Male | 1.07 (0.97–1.19) | 0.18 | 1.05 (0.94–1.17) | 0.42 | NS | NS |
| Marital status | | | | | | |
| Unmarried[a] | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Married | 0.72 (0.64–0.80) | < 0.001 | 0.72 (0.65–0.81) | < 0.001 | 0.67 (0.49–0.92) | 0.013 |
| Unknown | NA | NA | NA | NA | NA | NA |
| Race | | | | | | |
| White | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Black | NS | NS | NS | NS | NS | NS |
| Others[b] | NS | NS | NS | NS | NS | NS |
| Unknown | NA | NA | NA | NA | NA | NA |
| Insurance status | | | | | | |
| Uninsured | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Medical aid | 0.73 (0.58–0.93) | 0.012 | 0.73 (0.57–0.93) | 0.012 | 0.79 (0.34–1.86) | 0.59 |
| Insured | 0.51 (0.41–0.63) | < 0.001 | 0.51 (0.40–0.64) | < 0.001 | 0.55 (0.24–1.22) | 0.14 |
| Unknown | NA | NA | NA | NA | NA | NA |
| Histological grade | | | | | | |
| Grade I | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Grade II | 1.07 (0.83–1.39) | 0.60 | 1.03 (0.79–1.34) | 0.83 | 1.85 (0.74–4.58) | 0.19 |
| Grade III | 2.17 (1.67–2.84) | < 0.001 | 2.18 (1.66–2.87) | < 0.001 | 2.26 (0.88–5.81) | 0.09 |
| Grade IV | 2.50 (1.81–3.44) | < 0.001 | 2.48 (1.78–3.44) | < 0.001 | 3.65 (1.28–10.42) | 0.016 |
| Unknown | NA | NA | NA | NA | NA | NA |
| Lymphatic metastasis | | | | | | |
| N0 | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| N1 | 1.04 (0.91–1.20) | 0.55 | 1.09 (0.95–1.26) | 0.22 | 0.73 (0.50–1.06) | 0.10 |
| N2 | 1.31 (1.13–1.53) | < 0.001 | 1.43 (1.22–1.67) | < 0.001 | 0.61 (0.40–0.92) | 0.019 |
| Unknown | NA | NA | NA | NA | NA | NA |
| T stage | | | | | | |
| T1 | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| T2 | 0.47 (0.32–0.70) | < 0.001 | 0.45 (0.30–0.68) | < 0.001 | 0.79 (0.26–2.45) | 0.68 |
| T3 | 0.65 (0.54–0.79) | < 0.001 | 0.62 (0.51–0.76) | < 0.001 | 1.09 (0.59–2.03) | 0.78 |
| T4 | 1.00 (0.83–1.21) | 0.98 | 0.97 (0.80–1.18) | 0.74 | 1.48 (0.79–2.76) | 0.22 |
| Unknown | NA | NA | NA | NA | NA | NA |
| Primary site | | | | | | |
| Left colon | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Right colon | 1.60 (1.44–1.79) | < 0.001 | 1.62 (1.44–1.82) | < 0.001 | 1.37 (0.99–1.90) | 0.059 |
| Unknown | NA | NA | NA | NA | NA | NA |
| CEA | | | | | | |
| Negative | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |

**Table 2** (continued)

| Factors | Total early death | | Cancer-specific early death[c] | | Non-cancer-specific early death | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | p value | OR (95% CI) | p value | OR (95% CI) | p value |
| Positive | 1.63 (1.42–1.87) | < 0.001 | 1.68 (1.45–1.94) | < 0.001 | 1.21 (0.83–1.77) | 0.32 |
| Unknown | NA | NA | NA | NA | NA | NA |
| Brain metastases | | | | | | |
| No | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 2.70 (1.80–4.04) | < 0.001 | 2.83 (1.80–4.12) | < 0.001 | 2.11 (0.64–6.98) | 0.22 |
| Unknown | NA | NA | NA | NA | NA | NA |
| Bone metastases | | | | | | |
| No | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 2.53 (2.05–3.12) | < 0.001 | 2.59 (2.09–3.21) | < 0.001 | 1.93 (0.98–3.78) | 0.056 |
| Unknown | NA | NA | NA | NA | NA | NA |
| Lung metastases | | | | | | |
| No | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 1.28 (1.13–1.45) | < 0.001 | 1.30 (1.14–1.48) | < 0.001 | NS | NS |
| Unknown | NA | NA | NA | NA | NA | NA |
| Liver metastases | | | | | | |
| No | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 1.45 (1.29–1.63) | < 0.001 | 1.51 (1.34–1.71) | < 0.001 | NS | NS |
| Unknown | NA | NA | NA | NA | NA | NA |
| Surgery | | | | | | |
| No | Ref | 1.0 | Ref | 1.0 | Ref | 1.0 |
| Yes | 0.47 (0.40–0.54) | < 0.001 | 0.44 (0.38–0.51) | < 0.001 | 0.74 (0.47–1.16) | 0.19 |
| Unknown | NA | NA | NA | NA | NA | NA |

*Ref* reference, *OR* odds ratio, *CEA* carcinoembryonic antigen, *NA* not available

[a] Includes single, separated, widowed, and divorced

[b] Includes American Indian/Alaska Native and Asian or Pacific Islander

[c] Cancer-specific death: death attributed to cancer

[d] Non-cancer death: including accidents and adverse effects, Alzheimer's, atherosclerosis, cerebrovascular diseases, chronic liver disease and cirrhosis, chronic obstructive pulmonary disease and allied conditions, complications of pregnancy, childbirth, puerperium, diabetes mellitus, diseases of the heart, homicide and legal intervention, hypertension without heart disease, nephritis, nephrotic syndrome and nephrosis, in situ, benign or unknown behavior neoplasm, other causes of death, other diseases of arteries, arterioles, capillaries, other infectious and parasitic diseases including HIV, septicemia, suicide and self-inflicted injury, symptoms, signs and ill-defined conditions, and state DC not available or state DC available but no COD

Previous studies showed that advanced age was an independent predictor for poor prognosis in CRC patients [16, 17]. This study was the first to prove that advanced age is an independent associated factor for early death in stage IV CRC patients. Old age and early death can be significantly correlated for several reasons. Life-threatening non-infectious chronic disease, including other cancer, cardiovascular, cerebrovascular, chronic obstructive pulmonary diseases, and diabetes are more prevalent in the older population. This patient population is more likely to have weak immune systems, which accelerates deterioration leading to the poor survival [18, 19]. Young patients tend to have less comorbidity and better tolerate the side effects of adjuvant therapy [20], and young CRC patients have the opportunity for more aggressive resection of the primary tumor than is done for older patients [16].

A number of studies have been carried out to describe the differences between right-sided colon cancer and left-sided colon cancer [21–25]. Left-sided colon cancer was reported to originate from the midgut and right-sided colon cancer from the hindgut [21]. Right-sided colon cancer has been widely accepted to correlate with a worse prognosis than left-sided colon cancers in all stages of the CRC cancers [21–23, 25, 26]. The present findings support the increased early mortality of patients with stage IV CRC of a right-sided origin. The detailed reason is still unclear. One potential explanation is that the sided neoplasms (left or right colon) are caused by the different biological and environmental factors and/or genetic differences [22, 23]. Right-sided colon cancer as opposed to left-sided cancer is more likely to be exophytic and present with anemia [21]. This may partly explain why the early death is more likely to be caused by right-sided colon cancer.

**Fig. 3** Nomogram for predicting (A) all causes early death, (B) cancer-specific early death, and (C) non-cancer early death in stage IV colorectal cancer patients
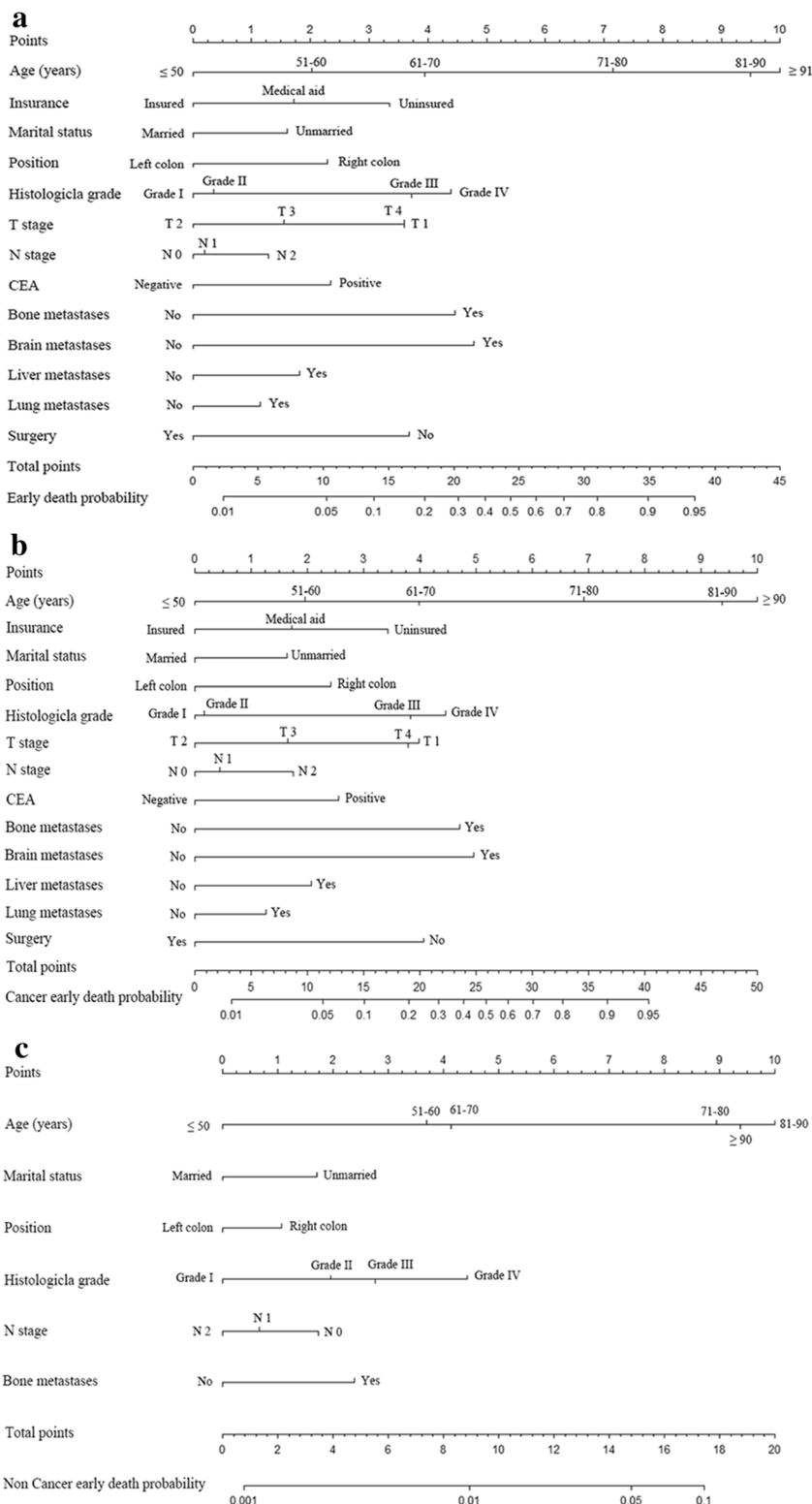


Insurance status, which reflects the patient's economic status, determines the patient's options for both diagnostic approach and treatment strategy. Additionally, unmarried patients are more likely to be depressed and stressed after diagnosis of advanced cancer, and depression and stress were reported to be significantly associated with cancer-related death [27]. This may account for the results that being unmarried and uninsured resulted in the higher early death probability.
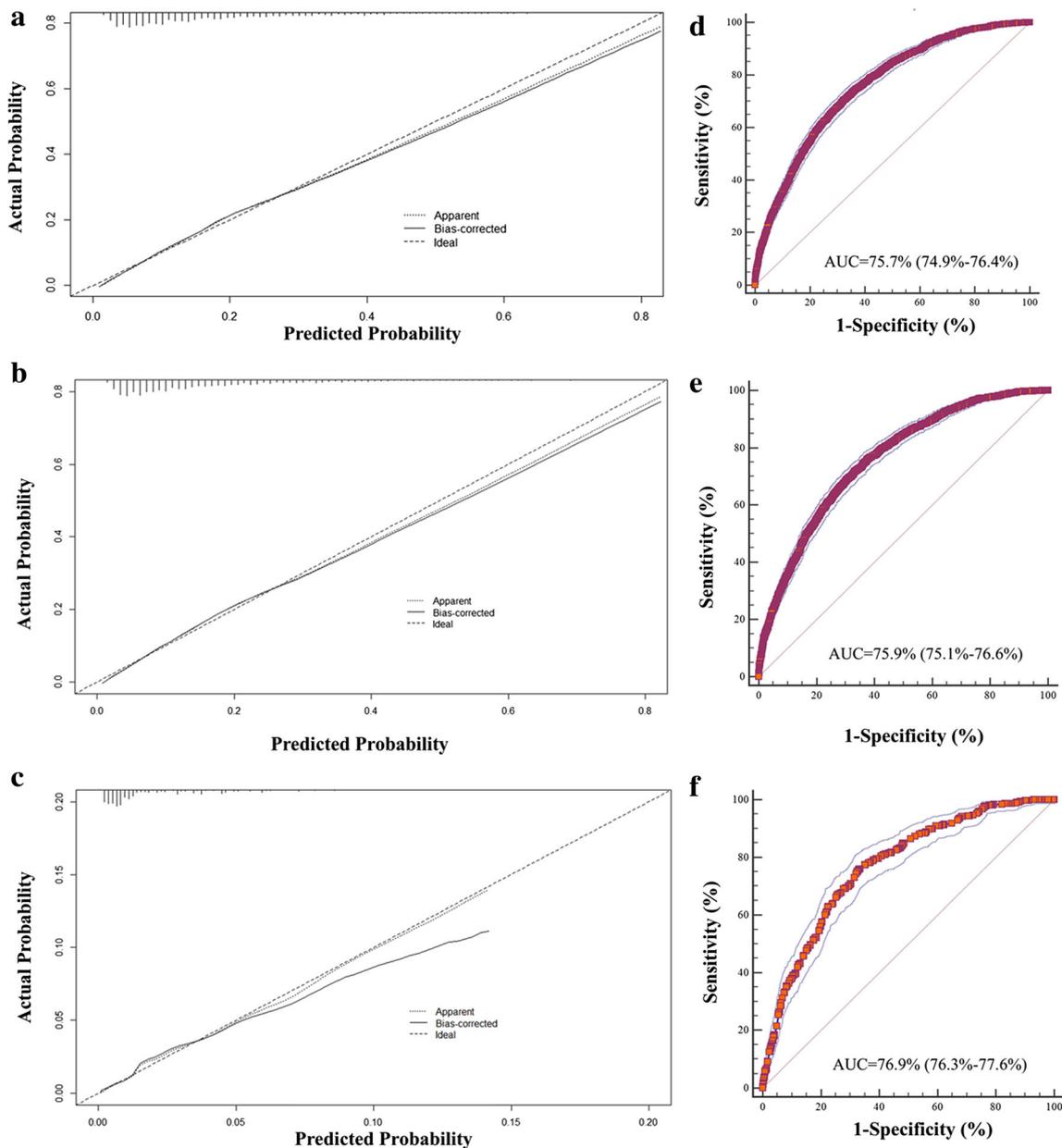
**Fig. 4** The calibration curve and ROC curve for assessing the calibration and discrimination of the nomogram in predicting all causes of early death (A, D), cancer-specific early death (B, E), and non-cancer early death (C, F)

A predictive nomogram was constructed based on the aforementioned factors associated with early death. The nomogram showed good predictive abilities for early death among stage IV CRC patients. It can provide both clinicians and patients a portable decision tool for early death screening and the clinical decision to tailor targeted treatment regimens during the patient's index admission stage.

A series of important factors were reported to affect the prognosis of patients with CRC. As the latest study reported, more years of life lost after diagnosis of CRC was noticed for patients after non-surgical treatment (1.3 years vs. 4.8 years) [28]. Elective bowel resection for incurable stage IV CRC

increased the survival compared with patients without resection [29]. Nevertheless, no significant difference was found in mortality among conventional open surgery, laparoscopic surgery, and robot-assisted surgery, even though better short-term performance was noticed after operation for patients with the current surgeries [30]. As to the comorbidities of individual patient, no significant influence on survival was found in the univariable regression analysis [29]. The neoadjuvant chemotherapy after surgery was not supported in a meta-analysis compared with surgery alone for colorectal cancer [31]. All these factors should be thoroughly investigated in the future with available information.

Our study has several limitations. Firstly, only initial diagnosed stage IV CRC patients were included in the study. The patients who developed metastasis at a later course were not recorded in public SEER datasets. Thus, the incidence of early death among stage IV CRC patients might be confounded, and more studies will be needed to further validate the results. Factors which are widely accepted to be correlated with mortality, such as performance status, type of treatment received, health care facilities, and/or comorbidities, were not available in the present study. Thirdly, only internal validation of the nomogram was performed. An external validation is warranted to extend the extrapolation of the reported results. Fourthly, the SEER program of the National Cancer Institute (NCI) only includes approximately 30% of the total US population and provides an important data source for epidemiologic analysis, which may limit the prediction ability of the nomogram.

## Conclusion

In summary, early death presents in more than a quarter of the stage IV CRC patients. A series of factors associated with early death were identified. A well-calibrated nomogram basing on these factors was constructed to predict probability of the early death development. The nomogram may help clinicians to conduct early death screening and targeted treatment regimens tailored for high-risk CRC patients.

## Compliance with ethical standards

The present study was complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Conflict of interest**   The authors declare that they have no conflict of interest.

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