Cancer-Specific Survival Analysis in Patients with Gastric Cancer: Based on Competing Risk Model

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Abstract

Background

Competing risk events are prone to cause bias in the estimation of all-cause mortality. In order to eliminate the impact of competing events on survival analysis, we constructed a competing risk model. Besides, we attempted to build nomograms to predict gastric cancer-specific mortality (GCSM) and other-cause mortality (OCM).

Methods

The competing risk model was constructed to evaluate all-cause mortality, GCSM and OCM, by using the gastric cancer data from 2004 to 2013 in the Surveillance, Epidemiology, and End Results Program (SEER) dataset. Nomograms were used to predict the risk of individual dying from gastric cancer and other causes based on competing risk model.

Results

A total of 15299 cases were screened out. The 1-year, 5-year, and 8-year survival probabilities were 48.9 %, 22.1 %, and 16.4 % for all-cause mortality, respectively. Univariate and multivariate analyses showed that sex, race, marital status, age at diagnosis, malignant, tumor diameter and TNM staging were all significant prognostic factors of gastric cancer. The GCSM and OCM models showed the risk of death treated by radiotherapy decreased from 0.689 to 0.494 after considering competing risk events. Furthermore, the nomograms showed good accuracy for GCSM prediction of the 1-, 5-, 8-year, the AUC values of the nomograms were 0.801 [95% CI, 0.793–0.808], 0.820 [95% CI, 0.810–0.829] and 0.823 [95% CI, 0.808–0.844]. The AUC values of the nomograms for predicting 1-, 5-, and 8-year OCM were 0.784 [95% CI, 0.778–0.792], 0.755 [95% CI, 0.748–0.765] and 0.747 [95% CI, 0.739–0.759].

Conclusions

Overall, the prognosis of patients with Gastric cancer is poor. The competing risk model could accurately evaluate the probability of dying from gastric cancer and other causes. Nomograms showed relatively good performance and could be considered as convenient individualized predictive tools for predicting GCSM and OCM.

Background

Cancer is a major global public health problem. As the World Health Organization (WHO) points out, cancer is one of the four major non-communicable diseases (NCDs) affecting human health and development [1]. In 2015, cancer became the second leading cause of death globally, second only to cardiovascular diseases [2]. According to the latest global cancer statistics, in 2018 alone, there were about 18.1 million new cancer patients and 9.6 million cancer deaths worldwide [3]. Worst still, more than 60% of the world's cancer cases occur in Africa, Asia, and Central and South America, and these regions
account for about 70% of the cancer deaths [4]. Most of these countries belong to low and middle-income countries. Thus, the particularly heavy burden projected to fall on these countries, which makes it implausible to cope with. Moreover, it should be noted that in addition to NCDs such as cancer, these countries also face the threat of infectious disease [5]. Coupled with the aging populations and the spread of industrialized lifestyles (such as increasing use of tobacco, consumption of alcohol and highly processed foods, and lack of physical activity) in these countries [6]. As a result, cancer poses a significant challenge to the already fragile health systems of these countries, compared to developed countries. Besides, from a broader perspective, cancer is not only a public health problem, but also an economic one. Furthermore, cancer is expensive, it not only increases the cost of human survival, such as the trauma of morbidity, reduced life opportunities, early death and difficulties, problems and adverse effects on family members [7], but also causes loss of social function of patients, financial stress, inequality problem and social stability [8]. Therefore, the metaphor of cancer as the killer of human civilization in the 21st century is not sensational.

Stomach cancer, also called gastric cancer, includes tumors that develop in tissues lining of the stomach, which begin at the gastroesophageal junction and end at the pylorus [9]. Although its incidence has decreased over the past few decades [10], it is still the fifth most frequently diagnosed cancer and the third leading cause of cancer death [3]. According to the estimate of GLOBOCAN 2018, there were over 1,000,000 newly diagnosed cases, which accounts for 782,700 cancer-related deaths (equating to 1 in every 12 deaths globally) globally in 2018 [3, 11]. Almost three-quarters of the new cases occurred in Asia, and more than two-fifths occurred in China. Further, a study from China showed that patients spent $5,694 a year on stomach cancer [12]. Therefore, more attention should be paid to this disease.

At present, epidemiological studies on gastric cancer mainly include morbidity, mortality, risk, prognosis and tumor biomarkers in different regions, countries, race, gender, et al [13–17]. Robust evidence suggests that TNM and treatment methods affect the prognosis of patients with gastric cancer [18]. Therefore, international practice often guides clinical diagnosis and treatment according to the TNM stage, and improve the prognosis of patients [19]. However, most of the above studies are based on all-cause death, but this rough index will undoubtedly bring high deviation [20]. Specifically, these studies ignored the impact of competing risk events on the mortality risk of gastric cancer patients, which may exaggerate the percentage of patients actually dying from diseases or even overestimating the mortality probability, and thus unable to relatively accurately assess the actual impact of treatment methods and stages on the mortality risk of patients [21]. At present, the primary way to deal with competing risk events of gastric cancer is to make it ignored or censored. For example, some studies try to use the cause-specific hazard regression model, but even so, estimates remain biased [20, 22, 23]. In this model, competing risk events are removed or treated as censored data [20, 24]. This approach is debatable, because as the incidence of competing risk events increases, research bias will inevitably increase [25]. Therefore, it is necessary to get a clear picture of the actual survival of gastric cancer.

As we all know, robust scientific evidence is the foundation for clinical diagnosis treatment and management of diseases. Therefore, it is necessary to make it clearly the impact of competing risk events
on the actual survival of gastric cancer. In response to the above call, the purpose of the current study is to conduct a methodological discussion based on the data of gastric cancer provided by SEER program between 2004 and 2013 in the US. Specifically, a sub-distribution hazards regression model (competing risk model) was constructed to analyze and evaluate the true death risk of gastric cancer, to directly explain the effect of covariates on the cumulative incidence curve. Furthermore, the nomogram chart was produced as a visual and intuitive evidence to predict and compare the survival probability of patients. It can be predicted that the research results may be useful to guide clinicians and researchers in the diagnosis, treatment, risk management and prognostic care of patients with different gastric cancer characteristics.

**Methods**

**Data Source**

In this study, we utilized SEER database, which is supported by the Surveillance Research Program in NCI’s Division of Cancer Control and Population Sciences. As one of the most representative large cancer registration databases in North America, it records the biological information about a million patients who have been diagnosed in some states and counties in the United States for 40 years (since 1973). In addition to the necessary demographic data, this information includes tumor information such as the location of the primary tumor, tumor size, tumor code, etc., as well as disease indexes, such as morbidity, mortality, and treatment options, etc. Initially, there were only seven SEER cancer registries that included racial and ethnic subgroups of epidemiological significance, and the number has now gradually expanded to the current eighteen. What is more, the database covers approximately 26% of the U.S. population and 97% of cancer. Therefore, it represents both geographical and social diversity to some extent.

For this study, data were obtained through approved guidelines. Each registry of the SEER project receives the approval of its institutional review committee every year, obtaining consent or giving up information in order to connect registered participants with data for research purposes [26]. All registries received federal confidential certificates protecting the identity of research participants. Moreover, the Office for Human Research Protection considered this research to be on nonhuman subjects because the subjects were patients who had been researched by the United States Department of Health and Human Services and were publicly accessible and de-identified [27]. Thus, no institutional review board approval was required. Patients diagnosed with gastric cancer between 2004 and 2013 were screened from the SEER program. The national cohort provided complete information on demographic data.

**Analytic Cohort**

The cohort consisted of patients diagnosed with gastric cancer from January 1, 2004 to December 31, 2013. Patient data were obtained using the case-listing function in the SEER*Stat Version 8.3.4
It is worth noting that as the goal of this study is a methodological exploration based on big data on gastric cancer, we have adopted a comprehensive strategy. Specifically, we identified Gastric Cancer cases based on the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems for Gastric Cancer [ICD–GC–C16]. Thus, this study includes all nine subcategories of cancer cases labeled on histology codes (C16.0 – C16.9): (1) C16.0 – Cardia; (2) C16.1 – Fundus of stomach; C16.2 – Body of stomach; (4) C16.3 – Pyloric antrum; (5) C16.4 – Pylorus; C16.5 – Lesser curvature of stomach, unspecified; (7) C16.6 – Greater curvature of stomach, unspecified; (8) C16.8 – Overlapping lesion of the stomach and C16.9 – Stomach, unspecified. Besides, to ensure transparency and replicability, our study took a systematic and standardized procedure to screen potential eligible patients. Inclusion and exclusion criteria were shown by Fig. 1:

- First, we excluded 258 patients with gastric cancer who had lost survival time information;
- Second, we excluded 1777 patients without TNM staging information;
- Third, we also excluded 4319 patients with unknown causes of death and non-first primary gastric cancer.
- Finally, we included 15299 patients with gastric cancer in this study.

**Main Outcomes**

Competing risk events are defined as non-cancer deaths or other cancer deaths that hinder the occurrence of gastric cancer deaths [28]. All-cause mortality of gastric cancer is defined as the total mortality of gastric cancer patients caused by any cause. Gastric cancer-specific mortality (GCSM) is defined as a mortality rate caused by gastric cancer [ICD–GC–C16], and patients who die from all other causes are classified as other-cause mortality (OCM). Survival is defined as the interval between the date of diagnosis and the date of death of the subject.

**Statistical Analysis**

In this study, the Kaplan-Meier method was used to estimate all-cause survival curves, and the log-rank test was used to test the all-cause curves among all follow-up patients. We used the cumulative incidence function and the competing risk curve to describe the death and survival of a specific cause, and used the Gray test to compare the survival curves between competing risk events [29]. We defined the target outcome event as death from gastric cancer and the competing risk event as death from other causes.

The proportional hazards regression model was used to adjust the effect of covariates on all-cause mortality [30]. Because gastric cancer patients may die from other diseases due to their comorbidity, their death of other diseases may hinder the death event of the gastric cancer [31]. In order to solve this problem, we used a sub-distribution hazards regression model to analyze GCSM, OCM and cumulative
incidence. The model is a survival analysis model considering covariates with assuming an individual could experience number of competing risk events. With the help of this methods, the cumulative incidence function could be estimated and the information of non-outcome events could be mined from patient data [32].

In the competitive risk model, the sub-distribution hazard is a key concept, and it is defined as the hazard of failing from a given cause of competing events. We can write competing risk model for cause \( r \) as

\[
\lambda_r(t) = \lim_{\Delta t \to 0} \frac{\text{Pr} \left( t < T < t + \Delta t, \ R = r \mid T \geq t \cap (T \neq r) \right)}{\Delta t} = -\frac{d}{dt} \log(1 - i_r(t))
\]

Where \( i_r(t) = \text{Pr} \left( T \leq t, \ R = r \right) \) is the cumulative incidence function for cause \( r \) \((r=1, \ldots, k)\). Semiparametric proportional hazards model for the competing risk model of cause \( r \) with covariate vector \( X \) as

\[
\lambda_r(t \mid X) = \lambda_{0r}(t) \exp(\beta_r^T X)
\]

where \( \lambda_{0r}(t) \) is the baseline hazard of cause \( r \), and \( \beta_r \) is the coefficient vector of the covariates. In this study, we can estimate the cumulative incidence function of gastric cancer and other causes.

Nomograms map the predicted probabilities into points on a scale from 0 to 100 in a user graphical interface. The total points accumulated by the various covariates correspond to the predicted probability for a patient, dying from GCSM and OCM, by competing risk model [33]. We recode each object to make it easier to draw a nomogram of individual competing risk. The area under ROC curve (AUC) also known as concordance index (C-index) usually used to assessing the discrimination of a model, which was used to evaluate nomograms combined with Brier score [34].

The tests were two-sided, and statistical significance level was set to \( p < 0.05 \). All statistical analysis and graphic plotting were performed using R version 3.5.3 R software (The R Foundation for Statistical Computing, Vienna, Austria). And the software packages “cmprsk” and “riskRegression” were used to build the competing risk model. The “mstate” package was used to draw the nomogram.

**Results**

**Patient characteristics and survival rate**

From January 2004 to December 2013, the SEER database included 21653 patients with gastric cancer, and 15299 patients with gastric cancer were included in the study. At the end of the follow-up, 10932 cancer patients died. The median survival time was about 12 months. Table 1 showed the survival rate of 1-, 5- and 8-year estimated by the Kaplan-Meier method, which were 48.9%, 22.1% and 16.4%, respectively. The log-rank test showed that there were differences in all-cause survival rates among sex, race,
treatment, cancer grade, cancer behavior, tumor size and TNM stage. The survival rate of married people is higher than that of unmarried people. As shown in Table 1, the survival rate of gastric cancer patients in the same survival period showed a gradient decline with the increase of age, that is, the higher of diagnostic age, the lower of survival rate. Compared with patients without any treatment, surgery, radiation therapy and combination therapy can increase the survival rate of patients, and combination therapy has the highest survival rate. The survival time of benign cancer was about 2–3 times as long as that of malignant cancer. The 5-year survival rate of gastric cancer was very low with higher a TNM stage (e.g. T4, N3, M1 survival rates were 0.058, 0.078, 0.028, respectively).
Table 1  
Patient Characteristics and Results of Univariate Analysis of All-cause

| Characteristic               | No. of Patients (%) | No. of Events | Proportion Surviving | p     |
|-----------------------------|---------------------|---------------|----------------------|-------|
|                             |                     |               | 1-year | 5-year | 8-year |       |
| All patients                | 15299 (100)         | 10932         | 0.489  | 0.211  | 0.164  |       |
| Sex                         |                     |               |        |        |        |       |
| Male                        | 9669 (63.2)         | 6913          | 0.498  | 0.210  | 0.163  | 0.002 |
| Female                      | 5630 (36.8)         | 4019          | 0.475  | 0.212  | 0.164  |       |
| Race                        |                     |               |        |        |        |       |
| White                       | 10369 (67.8)        | 7556          | 0.479  | 0.198  | 0.149  | < 0.001 |
| Black                       | 1968 (12.9)         | 1466          | 0.451  | 0.193  | 0.147  |       |
| Other                       | 2962 (19.3)         | 1910          | 0.553  | 0.269  | 0.229  |       |
| Marital status              |                     |               |        |        |        |       |
| Married                     | 8469 (55.4)         | 5814          | 0.535  | 0.239  | 0.186  | < 0.001 |
| Unmarried                   | 6107 (39.9)         | 4645          | 0.427  | 0.165  | 0.128  |       |
| Unknown                     | 725 (4.7)           | 473           | 0.479  | 0.267  | 0.201  |       |
| Age at diagnosis(years)     |                     |               |        |        |        |       |
| ≤ 50                        | 1964 (12.8)         | 1270          | 0.548  | 0.256  | 0.223  | < 0.001 |
| ≤ 60                        | 2793 (18.3)         | 1832          | 0.564  | 0.259  | 0.219  |       |
| ≤ 70                        | 2639 (23.8)         | 2440          | 0.540  | 0.245  | 0.205  |       |
| ≤ 80                        | 3723 (24.3)         | 2709          | 0.473  | 0.213  | 0.157  |       |
| >80                         | 3180 (20.8)         | 2681          | 0.350  | 0.103  | 0.050  |       |
| Treat                       |                     |               |        |        |        |       |
| No                          | 6655 (43.5)         | 5781          | 0.238  | 0.042  | 0.029  | < 0.001 |
| Surgery                     | 4380 (28.6)         | 2387          | 0.707  | 0.402  | 0.314  |       |
| Radiation                   | 1740 (11.4)         | 1425          | 0.389  | 0.074  | 0.037  |       |
| Both                        | 2524 (16.5)         | 1339          | 0.823  | 0.386  | 0.313  |       |
| Grade                       |                     |               |        |        |        |       |
| Ž                            | 566 (3.7)           | 265           | 0.744  | 0.467  | 0.367  | < 0.001 |
| Characteristic | No. of Patients (%) | No. of Events | Proportion Surviving | $p$       |
|---------------|---------------------|---------------|----------------------|-----------|
|               |                     |               | 1-year | 5-year | 8-year |             |
| No. of Patients | 3248 (21.2) | 2143 | 0.591 | 0.268 | 0.203 | <0.001 |
| No. of Events | 8047 (52.6) | 5921 | 0.473 | 0.186 | 0.144 | <0.001 |
| Unknown | 331 (2.2) | 233 | 0.518 | 0.235 | 0.198 | <0.001 |
| No. of Events | 3107 (20.3) | 2370 | 0.377 | 0.165 | 0.135 | <0.001 |
| Behavior |               |               |         |         |         |   |
| Benign | 139 (0.9) | 56 | 0.806 | 0.617 | 0.485 | <0.001 |
| Malignant | 15160 (99.1) | 10876 | 0.486 | 0.207 | 0.160 | <0.001 |
| Tumor size |               |               |         |         |         |   |
| < 2 cm | 1158 (7.6) | 468 | 0.781 | 0.535 | 0.440 | <0.001 |
| < 5 cm | 3451 (22.6) | 2139 | 0.645 | 0.307 | 0.233 | <0.001 |
| ≥ 5 cm | 4216 (27.6) | 3055 | 0.524 | 0.197 | 0.156 | <0.001 |
| Unknown | 6474 (42.2) | 5270 | 0.331 | 0.111 | 0.083 | <0.001 |
| T stage |               |               |         |         |         |   |
| ≤ T1c | 7400 (48.4) | 5335 | 0.426 | 0.215 | 0.169 | <0.001 |
| T2 | 4052 (26.5) | 2512 | 0.652 | 0.292 | 0.230 | <0.001 |
| T3 | 1949 (12.7) | 1414 | 0.581 | 0.182 | 0.126 | <0.001 |
| T4 | 1898 (12.4) | 1671 | 0.297 | 0.058 | 0.045 | <0.001 |
| N stage |               |               |         |         |         |   |
| N0/Nx | 8669 (56.7) | 6085 | 0.463 | 0.236 | 0.183 | <0.001 |
| N1 | 4933 (32.2) | 3567 | 0.517 | 0.193 | 0.149 | <0.001 |
| N2 | 1203 (7.9) | 885 | 0.563 | 0.157 | 0.121 | <0.001 |
| N3 | 494 (3.2) | 395 | 0.496 | 0.078 | 0.073 | <0.001 |
| M stage |               |               |         |         |         |   |
| M0/Mx | 9773 (63.9) | 6013 | 0.632 | 0.311 | 0.243 | <0.001 |
| M1 | 5526 (36.1) | 4919 | 0.236 | 0.028 | 0.019 | <0.001 |
| Year at diagnosis |               |               |         |         |         |   |
| 2004–2006 | 4571 (29.9) | 3850 | 0.467 | 0.198 | 0.154 | <0.001 |
| Characteristic | No. of Patients (%) | No. of Events | Proportion Surviving | p |
|---------------|---------------------|---------------|----------------------|---|
|               |                     |               | 1-year   | 5-year | 8-year |
| 2007–2010     | 6067 (39.6)         | 4701          | 0.484    | 0.209  | 0.174  |
| 2011–2013     | 4661 (30.5)         | 2381          | 0.524    | 0.296  | 0.296  |

Note: Radiation radiation therapy; Both surgery combined with radiation therapy; T stage Tumor (Topography); N stage Involvement of lymph nodes; M stage Metastasis; All-cause all-cause mortality; No. Number.

p of difference in median survival time among all follow-up patients of gastric cancer using a log-rank test.

All-cause Survival Model Results

As shown in Table 2, all-cause mortality risk, adjusted for demographic, clinical characteristics, including sex, race, tumor size, et al., was presented in the all-cause survival model section. The mortality risk of female patients with gastric cancer was significantly lower than that of male patients (HR = 0.980, [95% CI, 0.871–0.946], p < 0.001). There was no difference in mortality risk (all causes) between black and white patients with gastric cancer (HR = 1.049, [95% CI, 0.991–1.110], p = 0.103). The higher the TNM stage of gastric cancer, the higher the HR of death. Also, Table 1,2 showed that the risk of all-cause mortality was significantly lower in patients with gastric cancer near the end of follow-up.
Table 2
Risk of dying from All-cause, Gastric Cancer and Other Causes

| Characteristic       | All-cause | GCSM          | OCM          |
|----------------------|-----------|---------------|--------------|
|                      | HR (95% CI) | p            | Sub-HR (95% CI) | p       | Sub-HR (95% CI) | p       |
| **Sex**              |           |               |              |           |               |           |
| Male                 | Reference | Reference     | Reference    |           |               |           |
| Female               | 0.908 (0.871–0.946) | < 0.001 | 1.187 (1.129–1.248) | < 0.001 | 0.652 (0.606–0.701) | < 0.001 |
| **Race**             |           |               |              |           |               |           |
| White                | Reference | Reference     | Reference    |           |               |           |
| Black                | 1.049 (0.991–1.110) | 0.103 | 1.331 (1.240–1.428) | < 0.001 | 0.672 (0.603–0.748) | < 0.001 |
| Other                | 0.878 (0.835–0.924) | < 0.001 | 1.241 (1.169–1.316) | < 0.001 | 0.550 (0.498–0.606) | < 0.001 |
| **Marital status**   |           |               |              |           |               |           |
| Married              | Reference | Reference     | Reference    |           |               |           |
| Unmarried            | 1.175 (1.127–1.224) | < 0.001 | 1.011 (0.960–1.065) | 0.672 | 1.206 (1.127–1.290) | < 0.001 |
| Unknown              | 0.932 (0.847–1.025) | 0.148 | 0.952 (0.845–1.073) | 0.420 | 0.963 (0.814–1.138) | 0.662 |
| **Age at diagnosis** |           |               |              |           |               |           |
| ≤ 50                 | Reference | Reference     | Reference    |           |               |           |
| ≤ 60                 | 1.121 (1.043–1.204) | 0.002 | 0.953 (0.879–1.034) | 0.251 | 1.350 (1.189–1.534) | < 0.001 |
| ≤ 70                 | 1.240 (1.159–1.328) | < 0.001 | 1.044 (0.966–1.129) | 0.283 | 1.385 (1.226–1.565) | < 0.001 |
| ≤ 80                 | 1.570 (1.467–1.679) | < 0.001 | 1.239 (1.145–1.340) | < 0.001 | 1.471 (1.302–1.662) | < 0.001 |
| > 80                 | 2.246 (2.093–2.411) | < 0.001 | 1.648 (1.515–1.792) | < 0.001 | 1.584 (1.395–1.798) | < 0.001 |
| **Treat**            |           |               |              |           |               |           |
| No                   | Reference | Reference     | Reference    |           |               |           |
| Surgery              | 0.332 (0.312–0.353) | < 0.001 | 0.448 (0.415–0.482) | < 0.001 | 0.698 (0.631–0.772) | < 0.001 |
| Characteristic | All-cause | GCSM | OCM |
|---------------|----------|------|-----|
|               | HR (95% CI) | p   | Sub-HR (95% CI) | p   | Sub-HR (95% CI) | p   |
| Radiation     | 0.689 (0.648–0.732) | < 0.001 | 0.494 (0.454–0.539) | < 0.001 | 1.738 (1.588–1.902) | < 0.001 |
| Both          | 0.290 (0.268–0.313) | < 0.001 | 0.353 (0.321–0.388) | < 0.001 | 0.775 (0.685–0.878) | < 0.001 |
| Grade         |           |      |                 |      |                 |      |
| Reference     |           |      |                 |      |                 |      |
| Reference     | 1.323 (1.164–1.505) | < 0.001 | 1.350 (1.128–1.617) | 0.001 | 1.077 (0.914–1.268) | 0.380 |
| Reference     | 1.666 (1.470–1.888) | < 0.001 | 1.947 (1.634–2.320) | < 0.001 | 0.846 (0.721–0.994) | 0.042 |
| Reference     | 1.515 (1.268–1.810) | < 0.001 | 1.749 (1.389–2.203) | < 0.001 | 0.865 (0.667–1.122) | 0.273 |
| Unknown       | 1.531 (1.346–1.742) | < 0.001 | 1.607 (1.342–1.925) | < 0.001 | 0.993 (0.838–1.176) | 0.930 |
| Behavior      |           |      |                 |      |                 |      |
| Benign        |           |      |                 |      |                 |      |
| Malignant     | 2.386 (1.829–3.113) | < 0.001 | 5.072 (2.879–8.937) | < 0.001 | 0.765 (0.579–1.010) | 0.058 |
| Tumor size    |           |      |                 |      |                 |      |
| < 2 cm        |           |      |                 |      |                 |      |
| < 5 cm        | 1.408 (1.272–1.560) | < 0.001 | 1.453 (1.260–1.675) | < 0.001 | 1.200 (1.048–1.375) | 0.008 |
| ≥ 5 cm        | 1.592 (1.438–1.762) | < 0.001 | 1.902 (1.652–2.190) | < 0.001 | 0.994 (0.864–1.144) | 0.940 |
| Unknown       | 1.682 (1.523–1.857) | < 0.001 | 1.940 (1.687–2.230) | < 0.001 | 1.045 (0.912–1.197) | 0.531 |
| T stage       |           |      |                 |      |                 |      |
| ≤T1c          |           |      |                 |      |                 |      |
| T2            | 1.004 (0.951–1.061) | 0.879 | 1.093 (1.021–1.170) | 0.011 | 0.956 (0.878–1.041) | 0.303 |
| T3            | 1.279 (1.195–1.369) | < 0.001 | 1.347 (1.239–1.463) | < 0.001 | 1.015 (0.912–1.129) | 0.780 |
| T4            | 1.332 (1.257–1.413) | < 0.001 | 1.448 (1.345–1.558) | < 0.001 | 0.782 (0.697–0.877) | < 0.001 |
| Characteristic | All-cause | GCSM | OCM |
|---------------|-----------|------|-----|
|               | HR (95% CI) | p     | Sub-HR (95% CI) | p     | Sub-HR (95% CI) | p |
| N stage       |           |       |                 |       |                 |   |
| N0/Nx         | Reference |       | Reference       |       | Reference       |   |
| N1            | 1.086 (1.037–1.138) | < 0.001 | 1.007 (0.950–1.068) | 0.801 | 1.189 (1.104–1.281) | < 0.001 |
| N2            | 1.596 (1.470–1.720) | < 0.001 | 1.651 (1.507–1.809) | < 0.001 | 0.986 (0.851–1.141) | 0.855 |
| N3            | 1.937 (1.736–2.160) | < 0.001 | 1.839 (1.631–2.074) | < 0.001 | 0.991 (0.789–1.245) | 0.940 |
| M stage       |           |       |                 |       |                 |   |
| M0/Mx         | Reference |       | Reference       |       | Reference       |   |
| M1            | 1.891 (1.805–1.981) | < 0.001 | 1.742 (1.643–1.846) | < 0.001 | 0.917 (0.848–0.991) | 0.029 |
| Year at diagnosis |       |       |                 |       |                 |   |
| 2004–2006     | Reference |       | Reference       |       | Reference       |   |
| 2007–2010     | 0.906 (0.867–0.946) | < 0.001 | 0.884 (0.837–0.933) | < 0.001 | 0.923 (0.862–0.989) | 0.023 |
| 2011–2013     | 0.788 (0.747–0.831) | < 0.001 | 0.717 (0.672–0.765) | < 0.001 | 0.698 (0.639–0.761) | < 0.001 |

Note: HR Hazard Rate; Sub-HR Sub-distribution Hazards Rate; CI Confidence Interval; Radiation radiation therapy; Both surgery combined with radiation therapy; T stage Tumor (Topography); N stage Involvement of lymph nodes; M stage Metastasis; All-cause all-cause mortality; GCSM gastric cancer-specific mortality; OCM other-cause mortality.

**Competing Risk Model Results**

In Table 2 and Fig. 2, the mortality risk of women was significantly higher than that of men in gastric cancer patients who died of gastric cancer, while the mortality risk of women in gastric cancer patients who died of other causes was significantly lower than that of men. The all-cause risk model shows that there is no difference in mortality risk between black and white patients with gastric cancer, but the competing risk model shows that the mortality risk of black patients with gastric cancer is significantly higher than that of white patients. This fact is concealed by competing risk events. There was no difference in mortality risk between unmarried and married patients with gastric cancer (Sub-HR = 1.011, [95% CI, 0.960–1.065], p = 0.672). The all-cause mortality risk of unmarried patients was exaggerated due to the impact of competing risk events. Furthermore, GCSM and OCM regression model showed that the
risk of death in patients with gastric cancer treated by radiotherapy decreased from 0.689 to 0.494 after considering competing risk events. Therefore, the higher mortality of all other causes in patients treated by radiotherapy masked the efficacy of radiotherapy for gastric cancer. Also, the results of the competing risk regression model suggest that patients with gastric cancer who have not been treated and died of other causes have a higher mortality rate from radiation therapy (see Fig. 2B). In addition, after eliminating the impact of competing risk events (dying from other causes), the hazards risk of death between benign tumors and malignant cancers increased from 2.386 [95% CI, 1.829–3.113] to 5.072 [95% CI, 2.879–8.937].

**Nomogram Of Individual Prognosis Of Gastric Cancer**

We constructed nomograms to predict the probability of GCSM and OCM at 1-, 5-, and 8-year (Fig. 3 and Fig. 4). All the independent predictors of GCSM and OCM were integrated into the nomogram so as to help identify gastric cancer patients who may have higher GCSM and/or OCM. In this study, we obtained the points for each predictor listed in the nomogram and the total points is equal to the sum of the points of predictor, which can show the mortality of 1-, 5-, and 8-year. Within the nomogram, treat and grade represent the two most influential variables for GCSM (Fig. 3). In predicting OCM, treat and race were the most influential.

**Comparison Of Auc Values Of The Nomogram**

A cross-validation method was used to evaluate the prediction performance of the nomograms of the competing risk model, and the prediction accuracy index AUC or Brier score were used to evaluate the model. Figure 5 showed the calibration plots for the Fine-Gray model of GCSM and OCM at year 1, 5, and 8. It is worth noting that the whole dataset was used in fitting the model. The nomogram showed good accuracy for GCSM prediction of the 1-, 5-, 8-year, the AUC values of the nomogram were 0.801 [95% CI, 0.793–0.808], 0.820 [95% CI, 0.810–0.829] and 0.823 [95% CI, 0.808–0.844]. Furthermore, a smaller value of the Brier score indicates a better model. In the current study, the Brier score of the GCSM at 1-, 5- and 8-year were 0.183 [95% CI, 0.180–0.187], 0.136 [95% CI, 0.133–0.140] and 0.125 [95% CI, 0.120–0.132]. The nomogram for OCM prediction which was based competing risk model, also showed good accuracy, the AUC values of the nomogram for predicting 1-, 5- and 8-year OCM were 0.784 [95% CI, 0.778–0.792], 0.755 [95% CI, 0.748–0.765] and 0.747 [95% CI, 0.739–0.759]. The Brier score of the OCM at 1-, 5- and 8-year were 0.182 [95% CI, 0.180–0.185], 0.203 [95% CI, 0.200–0.206] and 0.205 [95% CI, 0.201–0.210]. It was shown that the nomograms had good accuracy for GCSM and OCM prediction.

**Discussion**

Previous studies have generally shown that gastric cancer had one of the lowest survival rates and poor prognosis among solid tumors [35, 36]. In order to provide evidence for clinical treatment and prognosis prediction, it is necessary to establish an efficient risk prediction system that can be used to estimate the
survival rate and probability of death for these patients. However, gastric cancer is heterogeneous in the true cause of death in individual patients. It may not be rigorous to solely use all-cause survival data to evaluate prognosis [37]. Furthermore, several previously reported nomograms of gastric cancer patients only focused on the overall survival of patients, ignoring the non-gastric cancer-specific mortality, which is biased in the estimation of the survival of patients [38, 39]. Thus, we established a competing risk model to control the impact of competing risk events, which could accurately evaluate the probability of death of gastric cancer patients. Besides, we attempted to develop and validate nomograms to predict the probability of death in providing individual GCCM and OCM risk estimates.

Our all-cause mortality model found that female gastric cancer patients have a significantly lower mortality rate than men, which is consistent with some previous studies [40, 41]. Some previous studies tried to explain this gender difference from a physiological dimension. Specifically, estrogen may play a large role in preventing gastric cancer [42–44]. Therefore, this evidence may explain to a certain extent that men (estrogen-deficient) patients with gastric cancer have a higher risk of death than women. However, in this study, we also used a competing risk model to fit the data. Surprisingly, using the same set of data, the competing risk model turned out to be the opposite, with women at a higher risk of dying from stomach cancer than men. Thus, this inconsistent result forced us to focus on the distinction of statistical models (competing risk model vs. all-cause mortality model). Sure enough, there is already much robust evidence that the all-cause risk model or the cause-specific risk model ignores the effects of competing risk events and may result in biased estimates of death risk [21, 25, 37]. In contrast, the competing risk model considers competing risk events, so it handles this kind of survival data with multiple potential outcomes, and the conclusions drawn are more reliable and in line with the actual situation [21, 45]. Therefore, in this study, we use the competing risk model to conclude gender differences (female gastric cancer has a higher risk of death than men), which we believe is reliable.

The race is an essential factor in cancer research. In our study, there was no difference in all-cause mortality between African American and white gastric cancer, which was consistent with some previous studies [46, 47]. It is worth noting that our competing risk model shows that African Americans have higher gastric cancer-specific mortality (GCSM) than whites. As we know above, this result is relatively stable and reliable. Besides, we have evidence that some studies have shown that the death risk of gastric cancer was highest among Asians/Pacific Islanders, followed by Blacks and was least common in Whites [48, 49]. This difference may be due to the higher survival rate of white gastric cancer patients dying from other causes than gastric cancer [10, 50], and the difference between white and African Americans can be generalized to the difference between other races and whites. Migrant epidemiology studies have shown that the relationship between race and gastric cancer incidence seems to be mainly regulated by environmental effects rather than genetic variation [50], which may provide a theoretical basis for explaining the differences between race.

Previous studies have shown that marital status affects the survival time and quality of life of gastric cancer patients [51, 52]. Besides, several recent studies have shown that ignoring the effects of dying from other causes, unmarried gastric cancer, especially widowed patients, have a higher risk of all-cause
mortality and GCSM [52, 53]. Furthermore, in another study, the authors reported that marriage had a protective effect on the undertreatment and other causes of mortality [54]. However, the results of the competing risk model show that there was no difference in GCSM of the married and unmarried patients, and the risk of the later dying from other causes is significantly higher than the former. Therefore, the contradiction between GCSM and all-cause mortality mainly aroused from the higher risk of competing events in unmarried gastric cancer. Furthermore, married patients who benefited from their spouse's support and care may reduce side effect on the survival from other diseases and improve the survival rate of gastric cancer [54].

At present, age at diagnosis has been proved to be an independent factor in the prognosis of gastric cancer, and the survival rate of gastric cancer decreases with age at diagnosis increase [55]. Similarly, our all-cause mortality analysis showed that after adjusting for other variables, the gastric cancer mortality increased with age at diagnosis increase. Previous studies told us the long-term prognosis of elderly gastric cancer patients was usually worse than younger [56]. However, the impact of age at diagnosis on GCSM continued to be controversial [57]. Also, our competing risk model found that the GCSM of people over the age of 70 was higher than that of the younger population, and there was no difference in the GCSM of people under the age of 70. In contrast, the OCM of those under 70 is significantly different. Moreover, age-related comorbidities or complications may explain the increase in non-cancer-specific mortality in elderly patients [58]. Consistent with the previous study, OCM is the main form of competing risk events in the elderly population [59]. Therefore, it is feasible and necessary to consider the effects of OCM when analyzing the prognosis, especially for elderly patients.

Cancer research should ultimately focus on how to provide better advice to clinicians, such as treatment, prognostic assessment, and management of patients, so as to improve patients’ survival rate and quality of life [60–62]. Surgery, radiotherapy, and combination therapy can reduce the risk of death and mortality of gastric cancer, so it is necessary for the gastric cancer patients to get appropriate therapy [63, 64]. The all-cause analysis showed that the 1-year survival rate of gastric cancer patients after surgery was about twice that of those after radiotherapy, while 5- and 8-year survival rate was about 6 and 10 times. So, surgery is still one of the most effective methods for patients with gastric cancer [65]. The results of the all-cause risk model and the competing risk model showed that surgery and surgery combined with radiotherapy reduced the risk of death in gastric cancer patients, but competing risk events exaggerated or masked the effect [37]. It was worth noting that when the impact of competing risk events was considered, the mortality of radiotherapy in the short term was reduced and closed to that of surgery. The risk of dying from other causes after radiotherapy was about 1.738 times that of the untreated, which was an essential source of the difference between all-cause and GCSM. It might be that radiotherapy is not necessarily effective for other causes (other cancers and diseases), and the risk of death from other causes sequentially increases after radiotherapy. Currently, selection bias of cancer treatment schemes is prevalent in clinical practice [66]. Therefore, competing risk events and their impacts should be fully considered in the treatment and management of cancer. OCM is one of the primary forms of competing risk events in survival analysis [25]. It should be paid much attention when evaluating prognosis. Otherwise, biased estimates may exist, which may lead to contrary conclusions [58].
Previous studies have indicated that the TNM stage of tumors directly determines the strategies and methods of clinical treatment, prognosis evaluation, and treatment [67, 68]. This study found that with the increase of the T stage, all-cause mortality and GCSM increases. Recent studies have obtained similar results, and the results may be closely related to lymph node metastasis [69]. Besides, in T4, the risk of specific death is significantly higher than in T1c, and the risk of death from other causes is considerably lower than in T1c. This may be related to the higher risk of death of gastric cancer in stage T4, and the prognosis is worse than other diseases. Furthermore, the most robust prognostic indicator of gastric cancer is the involvement of lymph nodes (N stage) [70]. Although a study showed that there was still no consensus on the relationship between lymph node metastasis and prognosis in patients with gastric cancer [71], the predictive value of lymph node metastasis for prognosis was confirmed [72]. In this study, the higher the degree of involvement of lymph nodes (N stage), the higher the risk of dying from all-cause and GCSM. The current study also found the difference of increasing death risk between increasing the low and high-N stage. Patients in the low-N stage suffered more death risk from other causes, while those in the high-N stage suffered more from gastric cancer.

Several limitations were identified in this study. First, there are no gastric cancer markers in SEER datasets, such as CEA, ZEB1, ZEB2, CA19-9 and pepsinogen, and some prognostic variables, such as surgical resection status, chemotherapy, and other treatment modalities and infiltration depth, which may be an effective complement to existing studies. Second, because of the prolonged research span, surgical methods and radiotherapy technology were developing continuously. It was assumed that these factors were unchanged, and so the survival time and risk may be biased. Besides, compared with other years of diagnosis, the follow-up time of patients diagnosed in 2011−2013 were relatively limited, and the information would be lost by survival analysis. Finally, some indicators related to patients’ basic information, such as complications, are not used as predictors of competing risk profile. Although generally accepted methods of contour map construction and evaluation are used, the accuracy of the model needs to be assessed based on external validation of other populations.

The competing risk model was constructed in this study to assess all-cause mortality, GCSM and OCM, and adjusted cancer-related factors such as treatment, age at diagnosis, tumor grade, TNM stage, and so on. Through this model, we dug the impact of competing events on the risk of death of gastric cancer and obtain unbiased estimates of the cumulative incidence of outcome events associated with covariates.

**Conclusion**

In conclusion, based on the competing risk model and proportional hazard model, this study established cumulative risk models for all-cause, GCSM, and OCM of gastric cancer patients in 1-, 5- and 8-years, avoiding biased estimates to some extent. Besides, our study provides an individual nomogram for predicting cumulative fatality rates for gastric cancer specificity and other causes, which can provide precise treatment and better disease management to facilitate doctors to make accurate personal prognosis estimates and decisions. This study explores the impact of competing risk events on survival
event analysis. The numerical method and results could also be used for other similar studies though the conclusions still need further external verification.

**Abbreviations**

GCSM: Gastric cancer-specific mortality; OCM: Other-cause mortality; All-cause: All-cause mortality; AUC: The area under ROC curve; C-index: Concordance index; NCDs: Non-communicable diseases; SEER: The National Cancer Institute’s Surveillance, Epidemiology, and End Results; No.: Number; HR: Hazard Rate; Sub-HR: Sub-distribution Hazards Rate; CI: Confidence Interval.

**Declarations**

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**Availability of data and materials**

The data that support the findings of this study are available in the Surveillance, Epidemiology, and End Results (SEER) database at https://seer.cancer.gov/.

**Authors’ contributions**

G. Z., contributed to conceptualization, methodology, data curation, software, and original manuscript writing; Y. Z., contributed to data curation, methodology, review and editing of writing; J. L., contributed to the review and editing of writing; W. M., contributed to data curation and the review and editing of writing; X. W., contributed to supervision, software, and validation; J. F. and E. T., contributed to supervision and formal analysis; S. W. and F. S., contributed to methodology and the review and editing of writing. All authors gave final approval and agreed to be accountable for all aspects of the work.

**Ethics approval and consent to participate**
This was an observational study using national registry data from public platforms. The medical ethics were exempted during the epidemic.

**Consent for publication**

Not applicable.

**Competing interests**

The author declares that he has no competing interests.

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