INTRODUCTION

The number of cancer survivors has increased rapidly and reached approximately fourfold growth with improvements in clinical diagnosis and treatment in the United States.\(^1\) An increase in overall survival was observed in cancer survivors,\(^2\) and up to two-thirds of those survivors could survive for more than 5 years.\(^1\) There will be approximately 20 million cancer survivors by 2026 due to advanced clinical resources and prolonged life expectations.\(^3\,4\) Therefore,
TABLE 1  Baseline patient characteristics of the gastric cancer

| Patient characteristics | Total number N = 71,809 | With prior cancer N = 6667 (9.3%) | No prior cancer N = 65,142 (90.7%) | p       |
|-------------------------|-------------------------|------------------------------------|-----------------------------------|---------|
| Age (median)            | 75 years                | 78 years                           |                                   | <0.001  |
| Sex                     |                         |                                    |                                   |         |
| Male                    | 4433 (66.5%)            | 39,289 (60.3%)                     |                                   |         |
| Female                  | 2234 (33.5%)            | 25,853 (39.7%)                     |                                   |         |
| Tumor Site              |                         |                                    |                                   | <0.001  |
| Cardia                  | 2095 (31.4%)            | 18,512 (28.4%)                     |                                   |         |
| Body/fundus             | 975 (14.6%)             | 9724 (14.9%)                       |                                   |         |
| Antrum/pylorus          | 1310 (19.6%)            | 13,394 (20.6%)                     |                                   |         |
| Others                  | 2287 (34.3%)            | 23,512 (36.1%)                     |                                   |         |
| Histological Type       |                         |                                    |                                   | <0.001  |
| Adeno                   | 4826 (72.4%)            | 45,419 (69.7%)                     |                                   |         |
| Mucinous                | 128 (1.9%)              | 1222 (1.9%)                        |                                   |         |
| Signet ring cell        | 1007 (15.1%)            | 11,325 (17.4%)                     |                                   |         |
| Others                  | 706 (10.6%)             | 7176 (11.0%)                       |                                   |         |
| Tumor Size              |                         |                                    |                                   | <0.001  |
| ≤1 cm                   | 381 (5.7%)              | 3575 (5.5%)                        |                                   |         |
| 1–3 cm                  | 1055 (15.8%)            | 9743 (15.0%)                       |                                   |         |
| 3–5 cm                  | 1052 (15.8%)            | 10,020 (15.4%)                     |                                   |         |
| >5 cm                   | 1320 (19.8%)            | 15,080 (23.1%)                     |                                   |         |
| Unknown                 | 2859 (42.9%)            | 26,724 (41.0%)                     |                                   |         |
| AJCC stage (6th)        |                         |                                    |                                   | <0.001  |
| I                       | 1749 (26.2%)            | 14,254 (21.9%)                     |                                   |         |
| II                      | 668 (10.0%)             | 6603 (10.1%)                       |                                   |         |
| III                     | 547 (8.2%)              | 6171 (9.5%)                        |                                   |         |
| IV                      | 2099 (31.5%)            | 23,793 (36.5%)                     |                                   |         |
| Others                  | 1604 (24.1%)            | 14,321 (22.0%)                     |                                   |         |
| Grade                   |                         |                                    |                                   | 0.002   |
| Well                    | 404 (6.1%)              | 3971 (6.1%)                        |                                   |         |
| Moderately              | 1491 (22.4%)            | 13,274 (20.4%)                     |                                   |         |
| Poorly                  | 3195 (47.9%)            | 32,267 (49.5%)                     |                                   |         |
| Undifferentiated        | 124 (1.9%)              | 1401 (2.2%)                        |                                   |         |
| Unknown                 | 1453 (21.8%)            | 14,229 (21.8%)                     |                                   |         |
| Surgery                 |                         |                                    |                                   | <0.001  |
| Yes                     | 2857 (42.9%)            | 30,800 (47.3%)                     |                                   |         |
| No                      | 3720 (55.8%)            | 33,411 (51.3%)                     |                                   |         |
| Unknown                 | 90 (1.3%)               | 931 (1.4%)                         |                                   |         |
| Radiation               |                         |                                    |                                   | <0.001  |
| Yes                     | 631 (9.5%)              | 8423 (12.9%)                       |                                   |         |
| No                      | 6032 (90.5%)            | 56,687 (87.0%)                     |                                   |         |
| Unknown                 | 4 (0.1%)                | 32 (0.0%)                          |                                   |         |
| Chemotherapy            |                         |                                    |                                   | <0.001  |
| Yes                     | 2455 (36.8%)            | 28,873 (44.3%)                     |                                   |         |
| No/Unknown              | 4212 (63.2%)            | 36,269 (55.7%)                     |                                   |         |

(Continues)
the risk of developing a second malignancy and the treatment of long-term comorbidities should be taken into consideration.

Gastric cancer is an aggressive and malignant disease with high mortality. According to Cancer Statistics 2020, there will be 27,600 estimated new gastric cancer cases and 11,010 estimated deaths in the United States. Much progress has been made in prognostic outcomes and therapies for gastric cancer as the first primary malignancy, but the prognosis of gastric cancer as a second cancer remains to be investigated. An increasing number of clinical trials have been conducted to improve the survivorship of patients with gastric cancer. However, individuals with a history of previous malignancy were commonly excluded from patient recruitment. The rationality of the exclusion criterion has hardly been validated and supported by evidence-based guidelines. The influence of this exclusion criterion has become a great concern since the number of cancer survivors has grown rapidly. Therefore, it is of great importance to evaluate the enrollment criteria of gastric cancer patients with prior malignancies.

To our knowledge, no study has addressed these issues and determined the exact influence of a previous cancer on the prognosis of patients with gastric cancer. In this study, we aimed to investigate the clinical characteristics and prognostic outcomes of prior malignancies in patients with gastric cancer using the Surveillance, Epidemiology, and End Results (SEER) database.

## METHODS

### 2.1 Study population

Patient data were extracted from the SEER database based on the SEER 18 Registries Custom Data from 1975 to 2016 (November 2018 submission) using SEER*Stat software (version 8.3.6). Approval from our institutional review board was not required due to public access and the use of de-identified data.

Eligible patients (≥18 years) with primary gastric cancer diagnosed between 2004 and 2015 were recruited from the database. The following patients were excluded from the current study: tumor in situ or benign, inactive follow-up, unknown survival months and vital status, diagnosed on death autopsy or death certificates only, with more than one prior cancer, or unknown prior cancer information. The included individuals were divided into two groups based on whether they had a previous malignancy. Individuals with prior malignancies were then divided into subgroups based on the prior cancer site, including prostate, uterine corpus, ovary, lung and bronchus, colon and rectum, pancreas, liver and intrahepatic bile duct, esophagus, urinary bladder, kidney and renal pelvis, thyroid, brain and other nervous system, oral cavity and pharynx, breast and other cancer, and melanoma of the skin and leukemia. To avoid the impact of synchronous malignancy, patients with a prior cancer diagnosed within 6 months or with prior gastric cancer were excluded.
2.2 Covariates and outcomes

Demographic characteristics included age at diagnosis (≤70 years and >70 years), sex (male and female), race (white, black, American Indian and Alaska Native, Asian/Pacific Islander, and unknown), marital status (married, unmarried, and unknown), and insurance (yes, no, and unknown). Tumor and therapy factors included tumor site (cardia, body/fundus, antrum/pylorus, and others), tumor size (≤1 cm, 1–3 cm, 3–5 cm, >5 cm, and unknown), histological type (adenocarcinoma, mucinous cell adenocarcinoma, signet ring cell carcinoma, and others), 6th American Joint Committee on Cancer (AJCC) stage (I, II, III, IV, and others), grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, and unknown), surgery (yes, no, and unknown), radiation (yes, no, and unknown), and chemotherapy (yes, no/unknown). In addition, the stage and interval time of prior cancer were obtained from the database.

Information on outcomes, including survival months, vital status (alive and dead) and cause of death (due to gastric cancer, due to other causes, and unknown) were also abstracted. Overall survival was defined as the survival time from the diagnosis of gastric cancer to any cause of death, and gastric cancer-specific survival was defined as the time from gastric cancer diagnosis to death from gastric cancer.
2.3 | Statistical analysis

The descriptive statistics of patients’ demographic, tumor, and therapy characteristics were analyzed using the Chi-square test. The site and stage distribution of the previous malignancies were calculated and presented. Additionally, the median interval time from prior cancer diagnosis to subsequent gastric cancer diagnosis was also calculated. Kaplan–Meier curves and the log-rank test were performed to compare the overall survival between patients with and without prior cancer. A competing risk model was used to compare gastric cancer-specific mortality and non-gastric cancer-specific mortality. Furthermore, we formulated nomograms based on multivariate survival analysis. The discrimination and calibration of the nomograms were evaluated by the C-index and calibration plots. Hazard ratios (HRs) of overall and gastric cancer-specific survival were estimated using the multivariable Cox model after adjusting for the covariates of interest (prior cancer, age at diagnosis, sex, race, insurance, marital status, tumor site, histological type, tumor size, 6th AJCC stage, grade, surgery, radiation, and chemotherapy). Subgroup survival analyses were performed to determine whether prognostic outcomes were differentially associated with prior malignancy types. SPSS (version 20.0), R software (version 3.6.2), and GraphPad Prism (version 7.0) were used to conduct the statistical analyses and generate images. A significant difference was defined as a two-tailed \( p \) value <0.05.

3 | RESULTS

In our study, 71,809 primary gastric cancer patients were identified on the basis of the inclusion and exclusion criteria. Among the included cohort, 6667 (9.3%) patients had a history of previous cancer, while 65,142 (90.7%) patients did not (Table 1).

3.1 | Demographics and clinical characteristics of the cohort

There were a number of differences in clinicopathological characteristics between patients with and without pre-existing malignancies. As presented in Table 1, a higher proportion of individuals with a prior malignancy were younger, white, and married. Compared to patients without prior cancer, those with a history of prior cancer had smaller tumor sizes (19.8% vs. 23.1%, \( p < 0.001 \)), fewer of the signet ring cell histological type (15.1% vs. 17.4%, \( p < 0.001 \)), and less advanced stages (26.2% vs. 21.9%, \( p < 0.001 \)) and grades (47.9% vs.
49.5%, \(p = 0.002\)). For the therapy factors, individuals with a prior cancer were less likely to undergo surgery (42.9% vs. 47.3%, \(p < 0.001\)), radiation (9.5% vs. 12.9%, \(p < 0.001\)), and chemotherapy (36.8% vs. 44.3%, \(p < 0.001\)) and had more insurance protection (75.3% vs. 69.9%, \(p < 0.001\)).

Among the different prior cancer types, prostate (31.86%), breast (14.34%), and colon and rectum (10.32%) were the most common sites (Figure 1). Regarding the prior cancer stage distribution, the majority of patients with a previous malignancy were at a localized or regional stage (81.12%), while only 5.97% patients were at a distant stage (Figure 1). The median period of time from prior malignancy diagnosis to the subsequent gastric cancer diagnosis was 68 months. For most cancer survivors, the median time interval was more than 60 months, while the median time of survivors with esophagus (24.5 months), liver and intrahepatic bile duct (30 months), pancreatic (38 months), and lung and bronchus (38 months) cancer was less than 40 months (Figure 2).

### 3.2 Comparison of survival rates and mortality

A significant difference was observed in the overall survival rates between patients with and without prior cancer (log-rank=139.73, \(p < 0.001\), Figure 3A). As far as we know, 60-month exclusion is commonly used in clinical trials.\(^{12}\) Similarly, we found a marked difference in survival

![Graphs showing overall survival analysis](image-url)
rates between patients without prior cancer and those with prior cancer within 60 months (log-rank=44.65, \( p < 0.001 \), Figure 3B). Cancer-specific mortality was considered a competing event compared to non-cancer-specific mortality. Therefore, we adopted the competing risk model to compare the gastric and non-gastric cancer-specific mortalities between patients with and without a pre-existing cancer. As shown in Figure 3C, patients with a previous malignancy significantly differed from those without previous malignancy in both gastric and non-gastric cancer-specific mortality (both \( p < 0.001 \)). Similar results were also found in the cohort with interval times less than 60 months (both \( p < 0.001 \), Figure 3D).

As Table 2 shows, the 3-year and 5-year overall survival rates of patients with prior cancer were 45.8% and 25.9%, respectively, while those without a previous cancer were 51.6% and 31.9%. Among the cancer survivors, those with thyroid cancer (55.6%), kidney and renal pelvis (54.1%), and ovarian (53.2%) had better 3-year survival rates, and those with lung and bronchus cancer had the worst 3-year and 5-year survival rates (32.8% and 16.0%, respectively, Table 2 and Figure 4).

### TABLE 2  3-year and 5-year overall survival rate of gastric cancer patients stratified by prior cancer site

| Previous cancer site | Overall survival rate (%) |
|----------------------|---------------------------|
|                      | 3-year (95% CI)           | 5-year (95% CI) |
| No prior cancer      | 51.6 (51.4, 51.8)         | 31.9 (31.7, 32.1) |
| With prior cancer    | 45.8 (45.2, 46.4)         | 25.9 (25.3, 26.5) |
| Prostate             | 46.6 (45.5, 47.7)         | 26.5 (25.5, 27.5) |
| Uterine corpus       | 46.4 (42.3, 50.5)         | 29.6 (25.7, 33.5) |
| Ovary                | 53.2 (45.9, 60.5)         | 25.1 (18.7, 31.5) |
| Lung and bronchus    | 32.8 (30.2, 35.4)         | 16.0 (13.8, 18.2) |
| Colon and rectum     | 46.5 (44.6, 48.4)         | 25.0 (23.3, 26.7) |
| Pancreas             | 47.6 (39.9, 55.3)         | 19.0 (11.8, 26.2) |
| Liver and intrahepatic bile duct | 48.6 (40.2, 57.0) | 20.4 (17.4, 23.4) |
| Esophagus            | 44.0 (39.0, 49.0)         | 18.6 (14.6, 22.6) |
| Urinary bladder      | 41.2 (38.8, 43.6)         | 23.5 (21.4, 25.6) |
| Kidney and renal pelvis | 54.1 (50.5, 57.7)     | 29.6 (26.1, 33.1) |
| Melanoma of the skin | 47.1 (43.6, 50.6)         | 30.9 (27.6, 34.2) |
| Thyroid              | 55.6 (51.0, 60.2)         | 34.4 (29.8, 39.0) |
| Leukemia             | 36.7 (31.6, 41.8)         | 24.7 (19.9, 29.5) |
| Brain and other nervous system | 49.4 (46.6, 52.2) | 28.7 (26.1, 31.3) |
| Oral cavity and pharynx | 43.5 (40.2, 46.8)     | 20.4 (17.6, 23.2) |
| Breast               | 47.2 (45.6, 48.8)         | 29.0 (27.5, 30.5) |

#### 3.3 | Multivariable analyses of overall and cancer-specific survival

Next, we constructed the nomogram to explore the multivariable prognostic factors of patients with gastric cancer (Figures 5 and 6). The discriminative abilities of the overall and gastric cancer-specific predictions were evaluated by calculating the C-indexes, which were 0.624 and 0.720, respectively. Additionally, the 3-year and 5-year calibration curves are presented in Figures S1 and S2.

We further adopted a multivariate Cox regression model to evaluate all independent factors for overall and gastric cancer-specific prognostic outcomes (Table 3). A history of cancer was associated with worse overall and better gastric cancer-specific survival after adjusting for other covariates (HR=0.79, 95% CI=0.76–0.82, \( p < 0.001 \); and HR=1.24, 95% CI=1.18–1.30, \( p < 0.001 \), respectively). In the subgroup analysis, patients with prostate, lung and bronchus, colon and rectum, esophagus, urinary bladder, brain and other nervous system, oral cavity and pharynx, and breast cancer faced inferior overall survival and better cancer-specific survival than those without prior cancer (Table 4). Interestingly, patients with uterine corpus cancer and leukemia had worse overall survival but similar gastric cancer-specific survival, while patients with ovarian, liver and intrahepatic bile duct, kidney and renal pelvis, and melanoma of the skin cancer had better gastric cancer-specific survival but similar overall survival. In addition, patients with thyroid cancer were not associated with worse survival (Table 4).

In addition, we did a subgroup analysis and there is no difference in the overall and gastric cancer-specific survival in patients with gastric cancer between patients with a prior malignancy diagnosed 5 years ago and within 5 years (Table 3, S1 and S3). When stratified by prior cancer site, we found that the overall survival in patients with prior cancer diagnosed 5 years ago was different from patients diagnosed within 5 years including uterine corpus, melanoma of the skin, kidney and renal pelvis, brain and other nervous system (Table S2 and S4). As for the gastric cancer-specific survival, prior cancer including ovarian, lung and bronchus, colon and rectum, liver and intrahepatic bile duct, esophagus, and urinary bladder were different.

#### 4 | DISCUSSION

The burgeoning number of cancer survivors has led to an increasing trend of developing a second cancer, which has posed challenges for clinical decisions and oncological practices.\(^13\) Few studies have focused on survivors since they were commonly excluded from cohort enrollment in clinical trials.\(^14\) Similar trends were also found in gastric cancer trials,\(^6,8\) in which individuals with a history of malignancy were
excluded from the eligible population. However, there were limited guidelines regarding this exclusion criterion, and it has not been assessed or confirmed based on any sufficient data. Thus, the rationality of the criterion needs to be evaluated on the basis of a large and authoritative population.

Our study sought to investigate the clinical characteristics and prognostic effects of a previous malignancy in patients with gastric cancer. Gastric cancer is increasingly emerging as a second malignancy, similar to other cancer types. In the current study, 9.3% of patients with gastric cancer had a prior cancer among more than 70,000 patients, suggesting that prior malignancy-associated exclusion criteria might restrict a substantial proportion of patients from trial recruitment. Importantly, patients with a prior cancer had smaller tumor sizes, fewer malignant histological types, and less advanced stages and grades, which were attributed to active surveillance in cancer survivors. In addition, most of the previous cancers were at localized or regional stages. These results might be explained by the fact that those survivors tended to do well and live long enough to develop a second gastric cancer.

It was hypothesized that exposure to prior therapies might reduce treatment tolerance in clinical trials. The existence of a previous malignancy might interfere with the experimental conduct or the results of the trials. Another potential reason for excluding patients with prior cancer from clinical trials was that prior malignancies might affect the survival outcomes. In the overall population, we found that pre-existing cancer was associated with worse overall survival and better cancer-specific survival. One possible explanation was that

![Figure 4](image-url)
those patients underwent fewer therapies, such as surgery, radiation, and chemotherapy, which were negatively associated with patient prognosis. In addition, the current treatment tolerance of patients is poor because of various reasons such as poor organ function or any decreased reserve capacity after previous treatment for the prior malignancy. Notably, a 5-year previous malignancy-related exclusion window has been commonly adopted in clinical trials. Therefore, we conducted a subgroup survival analysis between patients with a prior cancer diagnosed within 5 years and those without a prior cancer. Similarly, a pre-existing malignancy increased the overall and decreased the cancer-specific mortality rates. In addition, there is no difference in the overall and gastric cancer-specific survival in patients with gastric cancer between patients with a prior malignancy diagnosed 5 years ago and within 5 years. Consistent with our results, researchers have observed an inferior prognosis in patients who had pre-existing malignancies including lung cancer, prostate cancer, lymphoma, and colon and rectum cancer. In contrast, favorable prognostic effects of previous malignancy were found in patients with gastrointestinal malignancies. These conflicting findings regarding the effects of a prior malignancy brought difficulties in determining eligible enrollment in clinical trials.

Among patients who had prior malignancies, prostate, breast, and colon and rectum cancer were the most common types in our study. Similar results were also found in individuals with pancreatic adenocarcinoma, hepatocellular cancer, and lung cancer. This might be partly explained by the fact that prostate cancer and breast cancer have a high incidence in male and female populations, respectively. Additionally, the favorable prognoses of prostate cancer and breast cancer are attributed to their inert characteristics as well as advanced clinical strategies. It seemed unlikely that these cancers had adverse effects on patient prognosis due to their indolent process. Interestingly, patients with prostate cancer and breast cancer had worse overall survival in the current study. Similar to gastric cancer, other tumor types, such as urinary bladder, and colon and rectum cancer, are associated with genetic factors and environmental factors, such as diet and smoking. Therefore, prior urinary bladder, colon and rectum, and gastric cancer may synergistically increase the mortality risk of patients. In addition, pre-existing lung and bronchus cancer was also associated with inferior
The nomogram for predicting gastric cancer-specific survival in gastric cancer patients with and without a prior cancer. Abbreviations: Histologic type, 1, Adenocarcinoma; 2, Mucinous cell adenocarcinoma; 3, Signet ring cell. Tumor site, 1, cardia; 2, body/fundus; 3, antrum/pylorus; 4, others. Tumor size, 1, ≤1 cm; 2, 1–3 cm; 3, 3–5 cm; 4, >5 cm; 5, unknown. Race, 1, white; 2, black; 3, American Indian/Alaska Native; 4, Asian or Pacific Islander; 5, unknown. AJCC, American Joint Committee on Cancer

**TABLE 3** Multivariable Cox regression analysis of overall and gastric cancer-specific survival in patients with gastric cancer

| Characteristics       | Overall adjusted HR | p     | Gastric cancer-specific adjusted HR | p     |
|-----------------------|---------------------|-------|------------------------------------|-------|
| Prior cancer          |                     |       |                                    |       |
| Yes                   | Reference           |       | Reference                          |       |
| No                    | 0.79 (0.76, 0.82)   | <0.001| 1.24 (1.18, 1.30)                  | <0.001|
| Age at diagnoses      |                     |       |                                    |       |
| ≤ 70 years            | Reference           |       | Reference                          |       |
| > 70 years            | 1.33 (1.25, 1.41)   | <0.001| 1.42 (1.31, 1.54)                  | <0.001|
| Sex                   |                     |       |                                    |       |
| Male                  | Reference           |       | Reference                          |       |
| Female                | 0.89 (0.87, 0.90)   | <0.001| 0.91 (0.89, 0.93)                  | <0.001|
| Tumor Site            |                     |       |                                    |       |
| Cardia                | Reference           |       | Reference                          |       |
| Body/fundus           | 0.90 (0.88, 0.93)   | <0.001| 0.94 (0.91, 0.98)                  | <0.001|
| Antrum/pylorus        | 1.00 (0.97, 1.03)   | 0.880 | 1.04 (1.01, 1.07)                  | 0.009 |
| Others                | 1.01 (0.99, 1.04)   | 0.315 | 1.07 (1.04, 1.09)                  | <0.001|
| Histological Type     |                     |       |                                    |       |
| Adeno                 | Reference           |       | Reference                          |       |
| Mucinous              | 1.10 (1.04, 1.17)   | 0.002 | 1.13 (1.06, 1.21)                  | <0.001|
| Signet ring cell      | 1.11 (1.09, 1.14)   | <0.001| 1.14 (1.12, 1.17)                  | <0.001|

(Continues)
| Characteristics        | Overall adjusted HR | p     | Gastric cancer-specific adjusted HR | p     |
|------------------------|---------------------|-------|------------------------------------|-------|
| Others                 | 0.83 (0.80, 0.86)   | <0.001| 0.82 (0.79, 0.86)                  | <0.001|
| Tumor Size             |                     |       |                                    |       |
| ≤ 1 cm                 | Reference           | <0.001| Reference                          | <0.001|
| 1–3 cm                 | 1.55 (1.46, 1.64)   | <0.001| 1.95 (1.80, 2.11)                  | <0.001|
| 3–5 cm                 | 1.95 (1.84, 2.07)   | <0.001| 2.52 (2.33, 2.73)                  | <0.001|
| >5 cm                  | 2.08 (1.96, 2.20)   | <0.001| 2.77 (2.56, 2.99)                  | <0.001|
| Unknown                | 2.07 (1.95, 2.18)   | <0.001| 2.70 (2.50, 2.92)                  | <0.001|
| AJCC stage (6th)       |                     |       |                                    |       |
| I                      | Reference           | <0.001| Reference                          | <0.001|
| II                     | 1.60 (1.54, 1.66)   | <0.001| 1.93 (1.85, 2.01)                  | <0.001|
| III                    | 2.14 (2.07, 2.22)   | <0.001| 2.72 (2.61, 2.84)                  | <0.001|
| IV                     | 2.80 (2.72, 2.88)   | <0.001| 3.61 (3.50, 3.74)                  | <0.001|
| Others                 | 1.00 (0.97, 1.03)   | 0.846 | 1.09 (1.04, 1.13)                  | <0.001|
| Grade                  |                     |       |                                    |       |
| Well                   | Reference           | <0.001| Reference                          | <0.001|
| Moderately             | 1.78 (1.69, 1.88)   | <0.001| 2.09 (1.95, 2.34)                  | <0.001|
| Poorly                 | 2.20 (2.09, 2.31)   | <0.001| 2.73 (2.55, 2.91)                  | <0.001|
| Undifferentiated       | 2.21 (2.05, 2.39)   | <0.001| 2.80 (2.55, 3.07)                  | <0.001|
| Unknown                | 1.51 (1.43, 1.59)   | <0.001| 1.80 (1.69, 1.93)                  | <0.001|
| Surgery                |                     |       |                                    |       |
| Yes                    | Reference           | <0.001| Reference                          | <0.001|
| No                     | 3.23 (3.15, 3.31)   | <0.001| 3.44 (3.34, 3.54)                  | <0.001|
| Unknown                | 2.23 (2.06, 2.41)   | <0.001| 2.49 (2.29, 2.71)                  | <0.001|
| Radiation              |                     |       |                                    |       |
| Yes                    | Reference           | <0.001| Reference                          | <0.001|
| No                     | 0.92 (0.89, 0.95)   | <0.001| 0.89 (0.86, 0.93)                  | <0.001|
| Unknown                | 1.02 (0.69, 1.49)   | 0.940 | 1.13 (0.75, 1.69)                  | 0.563 |
| Chemotherapy           |                     |       |                                    |       |
| Yes                    | Reference           | <0.001| Reference                          | <0.001|
| No/Unknown             | 2.06 (2.02, 2.10)   | <0.001| 2.02 (1.98, 2.07)                  | <0.001|
| Race                   |                     |       |                                    |       |
| White                  | Reference           | <0.001| Reference                          | <0.001|
| Black                  | 1.02 (0.99, 1.04)   | 0.221 | 1.02 (0.99, 1.05)                  | 0.303 |
| AI/AN                  | 1.12 (1.02, 1.22)   | 0.014 | 1.19 (1.09, 1.31)                  | <0.001|
| AP                     | 0.85 (0.83, 0.87)   | <0.001| 0.86 (0.83, 0.89)                  | <0.001|
| Unknown                | 0.25 (0.20, 0.32)   | <0.001| 0.24 (0.18, 0.31)                  | <0.001|
| Insurance              |                     |       |                                    |       |
| Yes                    | Reference           | <0.001| Reference                          | <0.001|
| No                     | 0.89 (0.84, 0.94)   | <0.001| 0.91 (0.86, 0.96)                  | <0.001|
| Unknown                | 1.08 (1.06, 1.10)   | <0.001| 1.09 (1.07, 1.11)                  | <0.001|
| Marital status         |                     |       |                                    |       |
| Married                | Reference           | <0.001| Reference                          | <0.001|
| Unmarried              | 1.20 (1.17, 1.22)   | <0.001| 1.15 (1.13, 1.18)                  | <0.001|
| Unknown                | 0.89 (0.85, 0.92)   | <0.001| 0.87 (0.83, 0.91)                  | <0.001|

Abbreviations: Adeno, Adenocarcinoma; AI/AN, American Indian/Alaska Native; AP, Asian or Pacific Islander; Mucinous, Mucinous cell adenocarcinoma; Signet ring cell, signet ring cell carcinoma.
survival. This trend might reflect a selection effect that lung cancer itself had a poor survival and prognosis.\textsuperscript{28}

Notably, some prior cancer types exerted an opposite effect on the prognostic outcomes of gastric patients. Pre-existing thyroid cancer did not contribute to worse survival in our study. This result might be attributed to its indolent progression, more intensive medical support, and reduced exposure to risk factors.\textsuperscript{17,19} Similar favorable prognostic effects were observed in ovarian cancer, pancreatic cancer, kidney and renal pelvis cancer, and melanoma of the skin. Multiple gastric cancer trials excluded patients with a history of cancer from the eligible cohort. In contrast, some trials did not exclude or mention this group of patients.\textsuperscript{7,9,10,29,30} We found that prior cancer exerted completely different impacts on the survival prognosis depending on the different prior cancer types. Therefore, excluding patients who had a pre-existing malignancy in trials should be reconsidered and should be based on the types of previous cancer. Furthermore, the eligibility criteria should be more specific and precise according to the treatment intolerance, patients’ organ function, and health status.\textsuperscript{17} For instance, the certain treatment of a prior cancer, such as radiation, chemotherapy or biological therapy, or the recurrences, might be considered for exclusion rather than the prior cancer diagnosis.

In addition, there were several potential limitations in the present study. First, detailed information on treatments and recurrence was not available in the SEER database. Second, factors of lifestyles, such as alcohol consumption, smoking, and diet, were also inaccessible, which may exert an impact on the prognostic outcomes. Third, specific information regarding the characteristics of the previous malignancy cannot be obtained in this dataset, so we focused on stage and timing only. Prior malignancies were grouped into 16 types based on commonly used categories; therefore, less common cancer types were not evaluated in our study due to the limited number of patients. Last, there might be selective and surveillance biases due to the retrospective nature of the study.

In conclusion, the clinical characteristics were significantly different between patients with and without previous malignancies. Prior malignancies had an adverse impact on the overall survival of patients with gastric cancer, and this adverse effect was more obvious in patients with initial cancer types including prostate, uterine corpus, lung and bronchus, colon and rectum, esophagus, urinary bladder, leukemia, brain and other nervous system, oral cavity and

### Table 4 Multivariable Cox regression analysis of overall and gastric cancer-specific survival in patients stratified by prior cancer site

| Characteristics                              | Overall adjusted HR | p     | Gastric cancer-specific adjusted HR | p     |
|----------------------------------------------|---------------------|-------|-------------------------------------|-------|
| None                                         | Reference           | Reference |                                    | 0.061 |
| Prostate                                    | 1.23 (1.16, 1.29)   | <0.001 | 0.80 (0.75, 0.86)                   | <0.001 |
| Uterine corpus                               | 1.52 (1.26, 1.83)   | <0.001 | 1.15 (0.91, 1.46)                   | 0.237 |
| Ovary                                        | 1.03 (0.75, 1.43)   | 0.857  | 0.61 (0.39, 0.96)                   | 0.034 |
| Lung and bronchus                            | 1.61 (1.42, 1.81)   | <0.001 | 0.81 (0.67, 0.97)                   | 0.025 |
| Colon and rectum                             | 1.33 (1.22, 1.45)   | <0.001 | 0.84 (0.38, 1.17)                   | 0.004 |
| Pancreas                                     | 1.36 (0.95, 1.94)   | 0.090  | 0.67 (0.61, 1.90)                   | 0.159 |
| Liver and intrahepatic bile duct             | 0.88 (0.60, 1.31)   | 0.530  | 0.41 (0.22, 0.77)                   | 0.005 |
| Esophagus                                    | 1.48 (1.20, 1.82)   | <0.001 | 0.36 (0.23, 0.59)                   | <0.001 |
| Urinary bladder                              | 1.32 (1.20, 1.47)   | <0.001 | 0.78 (0.67, 0.91)                   | 0.001 |
| Kidney and renal pelvis                      | 1.11 (0.94, 1.31)   | 0.234  | 0.61 (0.47, 0.78)                   | <0.001 |
| Melanoma of the skin                         | 1.13 (0.96, 1.32)   | 0.151  | 0.80 (0.64, 0.99)                   | 0.037 |
| Thyroid                                      | 1.06 (0.85, 1.33)   | 0.613  | 0.88 (0.67, 1.16)                   | 0.377 |
| Leukemia                                     | 1.55 (1.23, 1.96)   | <0.001 | 0.91 (0.65, 1.28)                   | 0.585 |
| Brain and other nervous system               | 1.20 (1.06, 1.36)   | 0.005  | 0.74 (0.62, 0.89)                   | 0.001 |
| Oral cavity and pharynx                     | 1.33 (1.15, 1.53)   | <0.001 | 0.73 (0.59, 0.91)                   | 0.004 |
| Breast                                       | 1.23 (1.14, 1.33)   | <0.001 | 0.86 (0.78, 0.96)                   | 0.005 |
| Others                                       | 1.31 (1.19, 1.44)   | <0.001 | 0.91 (0.80, 1.03)                   | 0.130 |
pharynx and breast cancer. Additionally, prior cancers, such as ovarian cancer, pancreatic cancer, kidney and renal pelvis cancer, melanoma of the skin, and thyroid cancer, were not associated with worse outcomes. Therefore, the exclusion and inclusion of patients who had previous malignancies should be reconsidered according to the specific malignancy types.

CONFLICTS OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
All data were obtained from SEER database. https://seer.cancer.gov/data/

ORCID
Lanjuan Li https://orcid.org/0000-0001-6945-0593

REFERENCES
1. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev. 2013;22:561-570.
2. Swaiwa A, Frank RD, Yang D, et al. Second primary acute lymphoblastic leukemia in adults: a SEER analysis of incidence and outcomes. Cancer Med. 2018;7:499-507.
3. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin. 2014;64:252-271.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
5. Yu J, Huang CM, Sun YH, et al. Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer the CLASS-01 randomized clinical trial. JAMA J Am Med Assoc. 2019;321:1983-1992.
6. Fujitani K, Yang H-K, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncology. 2016;17:309-318.
7. Lee H-J, Hyung WJ, Yang H-K, et al. Short-term outcomes of a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy with D2 lymphadenectomy to open distal gastrectomy for locally advanced gastric cancer (KLAST-02-RCT). Ann Surg. 2019;270:983-991.
8. Slagter AE, Jansen EPM, van Laarhoven HWM, et al. CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer. BMC Cancer. 2018;18:12.
9. Kim H-H, Han S-U, Kim M-C, et al. Effect of laparoscopic distal gastrectomy vs open distal gastrectomy on long-term survival among patients with stage I gastric cancer the KLAST-01 randomized clinical trial. Jama Oncology. 2019;5:506-513.
10. Zhou H, Zhang Y, Liu J, et al. Impact of prior cancer on outcomes in nasopharyngeal carcinoma. Annals of Translational Medicine. 2019;7:299.
11. Huang X, Zhang B, Zhao J, et al. Increased risk of second primary cancers following diagnosis of malignant intraductal papillary mucinous neoplasms of the pancreas: a population-based study. Frontiers in oncology. 2019;9:610.
12. Debano D. Coping with the oncology workforce shortage: transitioning oncology follow-up care to primary care providers. Journal of oncology practice. 2010;6:203-205.
13. He C, Zhang YU, Cai Z, et al. Effect of prior cancer on survival outcomes for patients with pancreatic adenocarcinoma: a propensity score analysis. BMC Cancer. 2019;19:11.
14. Zhou H, Huang Y, Qiu Z, et al. Impact of prior cancer history on the overall survival of patients newly diagnosed with cancer: a pan-cancer analysis of the SEER database. Int J Cancer. 2018;143:1569-1577.
15. Gerber DE, Laccetti AL, Xuan L, et al. Impact of prior cancer on eligibility for lung cancer clinical trials. J Natl Cancer Inst. 2014;106(11):djv002.
16. Laccetti AL, Pruitt SL, Xuan L, et al. Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual. J Natl Cancer Inst. 2015;107:djv002.
17. He X, Li Y, Su T, et al. The impact of a history of cancer on pancreatic ductal adenocarcinoma survival. United European Gastroenterology Journal. 2018;6:888-894.
18. Bian XY, He XK, Yang LY, et al. Prognosis of hepatocellular carcinoma among cancer survivors with other types of primary tumors. Dig Dis Sci. 2020;65(7):2140-2147.
19. Dinh KT, Mahal BA, Ziehr DR, et al. Risk of prostate cancer mortality in men with a history of prior cancer. BJU Int. 2016;117:E20-E28.
20. Pulte D, Gondos A, Brenner H. Long-term survival of patients diagnosed with non-Hodgkin lymphoma after a previous malignancy. Leuk Lymphoma. 2009;50:179-186.
21. Lopez-Encuentra A, Gomez de la Camara A, Rami-Porta R, et al. Previous tumour as a prognostic factor in stage I non-small cell lung cancer. Thorax. 2007;62:386-390.
22. Al-Husseini MJ, Saad AM, Mohamed HH, et al. Impact of prior malignancies on outcome of colorectal cancer; revisiting clinical trial eligibility criteria. BMC Cancer. 2019;19:9.
23. Pruitt SL, Laccetti AL, Xuan L, et al. Revisiting a longstanding clinical trial exclusion criterion: impact of prior cancer in early-stage lung cancer. Br J Cancer. 2017;116:717-725.
24. Pandurengan RK, Dumont AG, Araujo DM, et al. Survival of patients with multiple primary malignancies: a study of 783 patients with gastrointestinal stromal tumor. Ann Oncol. 2010;21:2107-2111.
25. Varty PP, Delrio P, Boulou PB. Survival in colorectal-carcinoma associated with previous extralocominal cancer. Ann R Coll Surg Engl. 1994;76:180-184.
26. Kulkarni J. Chapter-45 Bladder, Cancer. 2014.
27. Zhang B, Zhao J, et al. The impact of pre-existing cancer on survival of prostate cancer patients. A population-based study. Medicine. 2018;97:6:e13479.
28. Na HK, Lee JH, Park SJ, et al. Effect of Helicobacter pylori eradication on reflux esophagitis and GERD symptoms after endoscopic resection of gastric neoplasm: a single-center prospective study. BMC Gastroenterol. 2020;20:123.
30. Hampel H, Williams C, Etcheto A, et al. A precision medicine framework using artificial intelligence for the identification and confirmation of genomic biomarkers of response to an Alzheimer’s disease therapy: analysis of the blarcamesine (ANAVEX2-73) Phase 2a clinical study. Alzheimers Dement (N Y). 2020;6(1):2-73.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.