A nomogram for prediction of stage III/IV gastric cancer outcome after surgery: A multicenter population-based study

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Abstract
Most patients with gastric cancer (GC) are first diagnosed at stage III-IV and surgery resection remains the primary therapeutic modality for these patients. However, clinical staging used for prediction of those patients provides limited information. We collected clinicopathological data and disease-progression information from 508 patients with stage III-IV GC at three Chinese hospitals and 1298 patients from the Surveillance, Epidemiology, and End Results database. Based on the stepwise multivariate regression model, we constructed a novel nomogram to predict overall survival (OS). The performance of discrimination for this model was measured using Harrell’s concordance index (C-index) and receiver-operating characteristic curve (ROC), and was validated using calibration plots. Multivariate Cox regression analyses showed that tumor size, age at diagnosis, N stage, tumor grade, and distant metastases were outstanding independent prognostic factors of stage III-IV GC. We developed a nomogram based on these five prognostic predictors. In the training set, the C-index of the nomogram was 0.645 (95% CI: 0.611-0.679), which was higher than that of the American Joint Committee on Cancer TNM system alone (sixth TNM: 0.544; seventh TNM: 0.575; eighth TNM: 0.568). Similar results were observed in validation cohort. Moreover, calibration plots demonstrated good consistency between the actual and predicted OS probabilities. According to the nomogram, GC individuals could be classified into three groups (low-, middle-, and high-risk) (P < .001). Our nomogram complements the current staging system for prediction of individual prognosis with stage III-IV GC, and may be helpful for making individualized treatment decisions.

KEYWORDS
nomogram, prognosis, SEER database, stomach neoplasm
INTRODUCTION

Gastric cancer (GC) is one of the deadliest tumors around the world. Most patients with GC are first diagnosed at stage III-IV and the outcomes in these patients are poor. Surgery appears to be a good treatment strategy for such patients. Nevertheless, there are few studies with a focus on the prediction of overall survival (OS) of stage III-IV GC patients who underwent radical surgical treatment.

The tumor-node-metastases (TNM) staging system is the key determinant for the prediction of survival and decisions regarding clinical treatment. However, there are significantly different prognoses among patients at the same stage, especially advanced GC. Age, gender, tumor grade, and tumor size may account for this phenomenon. The gastric cancer staging system based on American Joint Committee on Cancer staging systems (AJCC) has constantly altered over the years reaching its recent eighth edition. The major change from seventh system is the separation of N3a (7-15 positive regional lymph nodes) and N3b (>15 positive regional lymph nodes) in the eighth TNM classification. A retrospective control study showed that the eighth AJCC-TNM system can better determine the outcomes of GC patients. Therefore, developing a tool that integrates multiple confirmed prognostic factors into a single numerical estimate of survival may be helpful for individualized treatment decisions and postoperative counseling.

Nomograms have been described as alternatives and even as new standards for the management of several cancers, including liver, colon, and breast cancer. A large number of clinical studies have confirmed that a nomogram integrated with multiple variables achieved better prognostic predictions than with TNM systems alone. For stage II-III GC patients, a nomogram showed more accurate predictive ability than the TNM stage alone based on systemic prognostic score, TNM stage, and tumor location. Nevertheless, few studies focused on predicting OS after surgery for III-IV GC patients, particularly in the Chinese population.

Therefore, we investigated the independent prognostic factors and constructed a nomogram with multiple variables to predict outcomes of stage III-IV GC patients after surgery, which complements the current staging system for prediction of individual prognosis with stage III-IV GC.

MATERIALS AND METHODS

2.1 Patients

We collected information for 1843 patients with GC who underwent complete gastric resection between April 1, 2004 and July 1, 2017, as routine surveillance population at three hospitals in China: The First Affiliated Hospital of Nanjing Medical University, The Northern Jiangsu People’s Hospital and The Cancer Hospital of Nanjing medical University. Our study was approved by the Institutional Review Board of Nanjing Medical University (FWA00001501). After signing informed consent, we selected patients (older than 18 years) who met the following inclusion criteria: (1) stomach adenocarcinoma confirmed by at least two pathologists; (2) no combined malignancy; (3) definite pathological information for T stage, number of positive lymph nodes and distant metastasis; and (4) clinical stage III or IV after local or distant curative surgery. A total of 508 patients with available clinicopathological characteristics and follow-up information were included in the training cohort (Figure 1).

Then, we selected GC patients (older than 18 years) who underwent radical resection between January 1, 2004 and December 1, 2013 from the Surveillance, Epidemiology, and End Results (SEER) database as the external validation set. The inclusion criteria were as follows: (1) patients at stage III-IV received radical surgery; (2) gastrectomy with >16 nodes examined; (3) adequate follow-up; and (4) confirmed single primary GC (ICD-O-3 codes: 8010 – 8231 and 8255-8576). A total of 1298 patients with newly diagnosed stage III-IV were finally enrolled in the external validation cohort.

All the patients in our study were reclassified according to the eighth, seventh, and sixth editions of the AJCC staging system.

2.2 Data collection

First, clinical data including gender, age, and years at diagnosis of patients were recorded. Second, according to their pathological reports, we recorded tumor differentiation (G1, G2, G3), the maximum diameter of the primary tumor, number of positive lymph nodes (N stage), tumor location (upper (U), middle (M), or lower (L) portion of the stomach), depth of tumor invasion (T stage), and distant metastasis (M). Third,
all patients in the training cohort underwent a standard following up process after surgery to obtain accurate survival information.

We followed up each patient every 6 months through telephone contacts until death or loss to follow-up (until July 15, 2019). Information on adjuvant treatment (radiotherapy and chemotherapy) and survival information (cause of death, time of death, and alive, dead,) were collected. Definition of the OS was the period between the last resection surgery and date of death or loss to follow-up (until July 2019).

2.3 | Construction of the nomogram

We classified continuous variables (age, lymph nodes) as classification variables. To stratify patients at different risks, cutoff points for age and tumor size were selected using the X-tile program. Age was divided into two parts using the cutoff of 63 years (Figure S1A). Tumor size was also classified into three groups using cutoffs 5.0 and 7.0 cm (Figure S1B). The Kaplan-Meier (KM) method was used to draw survival curves and estimate the median survival time (MST) and OS for each variable. Univariate analysis by log-rank test was used to assess the significance of each variable in the training cohort. The stepwise multivariate regression model was applied using variables with P-values < 0.05 to identify independent predictors. We selected the final model by a backward step-down process with the Akaike information criterion (AIC). The nomogram is based on proportionally converting each regression coefficient in multivariate analysis to a 0- to 10- point scale. The effect of the variable with the highest β coefficient is assigned 10 points and the points are added to obtain total points, which are converted to predicted probabilities (Total points = 3.33 × LNM +4.74 × Age +6.59 × Metastasis +2.32 × Tumor grade + 4.00 × Tumor size).

2.4 | Model performance

C-index was used to evaluate discrimination of novel model performance. We compared the discriminative abilities of the nomogram using the sixth, seventh, and eighth TNM staging systems. Calibration plots for 1-, 3-, and 5-year OS probability were drawn to compare the predicted event and actual event. Receiver operating characteristic curves (ROC) and area under curve (AUC) were used to assess the model’s ability to distinguish events and nonevents. The “Rcorrp.cens” package in R was used to compare the nomogram and other models. Bootstrapping (1000 resamples) was used for bias correction. Additionally, a risk classification system for advanced GC was generated by X-tile program according to the calculated total points of each patient by using the nomogram for clinical use.

2.5 | Statistical analysis

All the data were imported by EpiData (version 3.0.2) software. All tests were significant at P < .05. All statistical analyses were performed by R software (version 3.6.3) (https://www.r-project.org/).
## TABLE 1 Baseline characteristics of study patients

| Characteristics | Training cohort | Validation cohort |
|-----------------|-----------------|-------------------|
|                 | Patients N = 508 (%) | Deaths N = 295 (%) | MST (months) | Patients N = 1298 (%) | Deaths N = 1017 (%) | MST (months) |
| Age (year)      |                 |                   |             |                   |                   |             |
| <63             | 232 (45.67)     | 116 (39.32)       | 58.6        | 542 (41.76)       | 375 (36.87)       | 28.0        |
| ≥63             | 276 (54.33)     | 179 (60.68)       | 37.5        | 756 (58.24)       | 642 (63.13)       | 18.0        |
| Gender          |                 |                   |             |                   |                   |             |
| Male            | 385 (75.79)     | 228 (77.29)       | 42.1        | 831 (64.02)       | 642 (63.13)       | 22.0        |
| Female          | 123 (24.21)     | 67 (22.71)        | 54.3        | 467 (35.98)       | 375 (36.87)       | 20.0        |
| Location        |                 |                   |             |                   |                   |             |
| Upper third (C) | 257 (50.59)     | 150 (50.85)       | 45.3        | 326 (25.12)       | 230 (22.62)       | 25.0        |
| Middle third (M)| 152 (29.92)     | 81 (27.46)        | 58.6        | 452 (34.82)       | 356 (35.00)       | 20.0        |
| Lower third (A) | 94 (18.50)      | 60 (20.34)        | 34.0        | 520 (40.06)       | 431 (42.38)       | 20.0        |
| Missing         | 5 (0.98)        | 4 (1.36)          | –           | –                  | –                  | –           |
| Tumor size (cm) |                 |                   |             |                   |                   |             |
| <5              | 178 (35.04)     | 94 (31.86)        | 65.5        | 396 (30.51)       | 307 (30.19)       | 23.0        |
| 5-7             | 261 (51.38)     | 148 (50.17)       | 39.6        | 551 (42.45)       | 424 (41.69)       | 21.0        |
| >7              | 69 (13.58)      | 53 (17.97)        | 19.8        | 351 (27.04)       | 286 (28.12)       | 19.0        |
| Tumor grade     |                 |                   |             |                   |                   |             |
| G1/G2           | 298 (58.66)     | 167 (56.61)       | 49.5        | 376 (28.97)       | 278 (27.34)       | 25.0        |
| G3              | 210 (41.34)     | 128 (43.39)       | 42.1        | 922 (71.03)       | 739 (72.66)       | 20.0        |
| T stage         |                 |                   |             |                   |                   |             |
| T1              | –               | –                 | –           | 7 (0.54)          | 6 (0.59)          | 10.0        |
| T2              | –               | –                 | –           | 49 (3.78)         | 33 (3.24)         | 27.0        |
| T3              | –               | –                 | –           | 571 (43.99)       | 439 (43.17)       | 23.0        |
| T4a             | 359 (70.67)     | 210 (71.19)       | 42.1        | 509 (39.21)       | 407 (40.02)       | 20.0        |
| T4b             | 149 (29.33)     | 85 (28.81)        | 45.6        | 162 (12.48)       | 132 (12.98)       | 18.0        |
| Lymph node metastasis (LNM) |       |                   |             |                   |                   |             |
| N0              | –               | –                 | –           | 31 (2.39)         | 18 (1.77)         | 31.0        |
| N1              | 137 (26.97)     | 67 (22.71)        | 74.6        | 114 (8.78)        | 71 (6.98)         | 44.0        |
| N2              | 172 (33.86)     | 100 (33.90)       | 40.8        | 341 (26.27)       | 232 (22.81)       | 31.0        |
| N3a             | 161 (31.69)     | 96 (32.54)        | 44.4        | 518 (39.91)       | 424 (41.69)       | 18.0        |
| N3b             | 38 (7.48)       | 32 (10.85)        | 14.1        | 294 (22.65)       | 272 (26.75)       | 16.0        |
| Distant metastasis |             |                   |             |                   |                   |             |
| M0              | 481 (94.69)     | 271 (91.86)       | 46.3        | 1078 (83.05)      | 814 (80.04)       | 23.0        |
| M1              | 27 (5.31)       | 24 (8.14)         | 20.8        | 220 (16.95)       | 203 (19.96)       | 15.0        |
| Adjuvant treatment* |           |                   |             |                   |                   |             |
| None            | 195 (38.39)     | 115 (38.98)       | 42.9        | –                 | –                 | –           |
| Chemo           | 239 (47.05)     | 130 (44.07)       | 47.5        | –                 | –                 | –           |
| Chemo + Radio   | 72 (14.17)      | 48 (16.27)        | 41.9        | –                 | –                 | –           |
| Missing         | 2 (0.39)        | 2 (0.68)          | –           | –                 | –                 | –           |
| Staging system  |                 |                   |             |                   |                   |             |
| Sixth           |                 |                   |             |                   |                   |             |

(Continues)
3 | RESULTS

3.1 | Patient features

In total, 1806 GC patients at stage III-IV who received surgical resection were analyzed (508 for the training cohort and 1298 for the validation cohort). The median follow-up time was 83.9 months (range: 13.1-172.3 months) for the training cohort and 21.0 months (range: 4.0-154.0 months) for the validation cohort. The median survival time of the training and validation cohort were 44.4 months and 21.0 months, respectively. The characteristics of two cohorts were listed in Table 1.

3.2 | Construction and validation of the nomogram

Nine variables with prognostic capacity were evaluated using univariate analysis. Five variables, including age, tumor grade, tumor size, lymph nodes, and distant metastases were associated with OS significantly in the training set (Table 2). Multivariate Cox regression analysis confirmed that age (HR: 1.52, 95% CI: 1.19-1.93), tumor size (for 5-7 cm, HR: 1.35, 95% CI: 1.03-1.75; for > 7 cm, HR :2.09, 95% CI: 1.48-2.94), lymph nodes (for N2, HR: 1.37, 95% CI: 1.00-1.87; for N3a, HR: 1.46, 95% CI: 1.06-2.02; for N3b, HR: 3.43, 95% CI: 2.22-5.29), and distant metastasis (HR: 1.69, 95% CI: 1.10-2.59) remained independent prognostic predictors for OS (Table 2). The survival curves of nine risk variables are drawn in Figure S2A–i.

Based on the minimum AIC, we constructed a nomogram to predict 5-year OS for stage III-IV GC patients following complete resection by incorporating five independent prognostic factors (Figure 2A). The resulting model was internally validated by the bootstrap method. The C-index of the nomogram (0.645, 95% CI: 0.611-0.679) was higher than that of the sixth TNM system (0.544, 95% CI: 0.512-0.576, P < .05), the seventh TNM system (0.575, 95% CI: 0.543-0.607, P < .05), and the eighth TNM system (0.568, 95% CI: 0.535-0.601, P < .05) in the training cohort (Table 3). The calibration plot was depicted in Figure 2B, which appeared to show good consistency between the actual event and predicted event. The 1-, 3-, and 5-year AUC values of ROC were 0.697, 0.652, and 0.642, respectively, which were superior to the current TNM systems. (Figure S3A–C).
In the external validation set, the nomogram showed a C-index of 0.626 (95% CI: 0.612-0.640) for the evaluations of death risk, which was higher than that of the eighth (0.611, 95% CI: 0.593-0.629, \( P < .05 \)), seventh (0.609, 95% CI: 0.591-0.627, \( P < .05 \)), and sixth (0.592, 95% CI: 0.574-0.610, \( P < .05 \)) AJCC TNM systems (Table 3). The calibration plots displayed an excellent agreement in the external validation cohort for 1-, 3-, and 5- year OS (Figure 2C). The AUC for nomogram were higher than for the AJCC staging systems which indicated the good discriminative ability of the nomogram (Figure S3D–F).

We further divided the validation cohort into three subgroups according to ethnicity (Asian, African, and Caucasian). The C-index of this nomogram was the highest in Asian population (C-index: 0.644, 95% CI: 0.609-0.679) among all ethnic subgroups (African, 0.604, 95% CI, 0.561-0.647; Caucasians, 0.628, 95% CI: 0.604-0.652) (Table 3). Similarly, the AUC values at 5 years OS for nomogram was higher in

### TABLE 2  Univariate and multivariate analysis of the training cohort

| Characteristics                      | Univariate analysis | Multivariate analysis |
|--------------------------------------|---------------------|-----------------------|
|                                      | HR (95% CI)         | \( P \)-value          | HR (95% CI) | \( P \)-value |
| Age (year)                           |                     |                       |            |              |
| <63                                  | 1.00                | –                     | 1.00        | –             |
| \( \geq 63 \)                         | 1.43 (1.13-1.81)    | 0.003                 | 1.52 (1.19-1.93) | <0.001        |
| Gender                               |                     |                       |            |              |
| Male                                 | 1.00                | –                     | –           | –             |
| Female                               | 0.90 (0.69-1.19)    | 0.46                  | –           | –             |
| Location                             |                     |                       |            |              |
| Upper third (C)                      | 1.00                | –                     | –           | –             |
| Middle third (M)                     | 0.92 (0.70-1.21)    | 0.55                  | –           | –             |
| Lower third (A)                      | 1.13 (0.84-1.53)    | 0.41                  | –           | –             |
| Missing                              | –                   | –                     | –           | –             |
| Tumor size (cm)                      |                     |                       |            |              |
| <5                                   | 1.00                | –                     | 1.00        | –             |
| 5-7                                  | 1.48 (1.14-1.92)    | 0.003                 | 1.35 (1.03-1.75) | 0.03          |
| >7                                   | 2.41 (1.72-3.38)    | <0.001                | 2.09 (1.48-2.94) | <0.001        |
| Tumor grade                          |                     |                       |            |              |
| G1/G2                                | 1.00                | –                     | 1.00        | –             |
| G3                                   | 1.35 (1.07-1.70)    | 0.01                  | 1.25 (0.99-1.59) | 0.06          |
| T stage                              |                     |                       |            |              |
| T4a                                  | 1.00                | –                     | –           | –             |
| T4b                                  | 0.94 (0.73-1.22)    | 0.66                  | –           | –             |
| Lymph node metastasis (LNM)          |                     |                       |            |              |
| N0                                   |                     |                       |            |              |
| N1                                   | 1.00                | –                     | 1.00        | –             |
| N2                                   | 1.43 (1.05-1.95)    | 0.02                  | 1.37 (1.00-1.87) | 0.05          |
| N3a                                  | 1.54 (1.13-2.11)    | 0.01                  | 1.46 (1.06-2.02) | 0.02          |
| N3b                                  | 3.74 (2.45-5.73)    | <0.001                | 3.43 (2.22-5.29) | <0.001        |
| Distant metastasis                   |                     |                       |            |              |
| M0                                   | 1.00                | –                     | 1.00        | –             |
| M1                                   | 2.04 (1.35-3.11)    | <0.001                | 1.69 (1.10-2.59) | 0.02          |
| Adjuvant treatment*                  |                     |                       |            |              |
| None                                 | 1.00                | –                     | –           | –             |
| Chemo                                | 0.89 (0.69-1.14)    | 0.36                  | –           | –             |
| Chemo + Radio                        | 1.11 (0.79-1.55)    | 0.56                  | –           | –             |

Note: Chemo, chemotherapy; Radio, radiation therapy; HR, hazard ratio; CI, confidence interval.
Asians than in Africans and Caucasians (Figure S3H–i). The calibration plots for the nomogram in three subgroups showed accurate predictive ability (Figure S4A–C). These findings suggested that our nomogram might be more useful in the Asian population.

3.3 | Performance of the nomogram in stratifying risk of patients

We calculated the total points associated with OS based on the nomogram in the internal validation set and external validation set. Total points as a continuous variable with normal distribution were shown in Figure S5. The optimal cutoff value of total points was selected to be 16.07 and 19.40 by the X-tile analysis. Patients were divided into three subgroups (high-risk, >19.40; middle-risk, 16.07-19.40; low-risk, <16.07). The MST of the high-, middle-, and low-risk groups was 14.7, 41.3, and 61.5 months in internal validation set, respectively. Also, that in external validation cohort was 15.0, 17.0, and 30.0 months, respectively. The OS probability for the three subgroups in the training set were 50.7%, 37.4%, and 17.6% ($P < .001$, Figure 3A), respectively. Similarly, we observed significant differences in the external validation set (OS: low-risk, 31.8%, middle-risk, 14.3%, and high-risk, 6.0%; $P < .001$, Figure 3B). This stratification could effectively discriminate the survival outcomes for the three proposed subgroups in both training and validation sets.

4 | DISCUSSION

In this study, we analyzed 1806 GC patients at stage III-IV who underwent racial resection. According to five independent prognostic factors (age, tumor size, tumor grade, N stage, and distant metastasis), we constructed a novel nomogram to
predict the outcomes of III-IV GC after surgical treatment. This nomogram showed higher prognostic efficacy and good performance in internal and external cohorts than the AJCC staging systems. It will be helpful to identify the independent factors of survival in GC patients at stage III-IV and to guide the choice of individualized treatment.

Fewer than 28% of patients with advanced or metastases disease survive 5 years after surgical treatment because of multicentric tumors, vascular invasion, and distant metastases. Combining surgery and radiotherapy could improve OS. However, treatment (chemotherapy and radiotherapy) was not an independent risk factor for advanced GC in this study. The finding was similar to results of another study. The Japanese treatment guidelines recommend adjuvant therapy combined with surgery for advanced GC. The MST of GC patients with stage IV is 13-16 months. In our study, the MST of GC patients at stage IV who underwent surgical resection was 20.8 months. Considering chemotherapy resistance and cumulative adverse events, surgery was recommended as a part of a comprehensive treatment strategy at some time point during the entire treatment course. Combined resection of the metastatic site (which is performed at the surgeon’s discretion based on the laparotomy findings) is mainly responsible for the high risk of death. However, current TNM staging systems in predicting OS of cancer have limitations. Thus, it is necessary to identify patients at the high-risk level after resection.

Five independent prognostic factors were integrated to construct the novel nomogram. Multiple studies have revealed that patients diagnosed at the age of <50 and >80 years had higher risks of death. Tumor differentiation grade is an independent prognostic factors of survival in GC patients. Tumor size ≥4.8 cm in diameter represents poor prognosis for GC pathologic grade. We also found that the differences in hazard risk (HR) among the three subgroups (<5.0 cm, 5.0-7.0 cm, and >7.0 cm) were significant (P < .05).

The 5-year survival probability of patients with GC in the Asian cohort was higher than that of the African and Caucasian cohorts (5-year OS 26.21%, 23.74%, and 24.16%, respectively, P < .001) in our external cohorts, and the results was supported by a previous study. Meanwhile, our nomogram exhibits a better performance in the Asian population. These differences may due to genetic inheritance, culture, and dietary habits of the various ethnicities.

There are some limitations to this study. First, a large multicenter survey is needed in the future to verify the conclusions of this investigation, because the study only collected 508 patients to construct a nomogram. Second, the C-index of the nomogram was 0.626 in external cohort, which was smaller than that of the internal cohort (C-index: 0.645). The explanation may be that the ethnic composition ratio was different between internal and external sets. Third, in the training set, we found that the predictive ability of the seventh TNM classification was higher than that of the eighth AJCC. We did not observe the same regularity in the validation cohort. The explanation may be that patients were captured in the training cohorts without examining more than 16 lymph nodes. Finally, there was reporting bias as to gastroesophageal junction tumors because the study was

### TABLE 3 Predictive validation for nomogram and AJCC staging systems

| System          | C-index | 95% CI   | Z-score |
|-----------------|---------|----------|---------|
| **Training cohort** |         |          |         |
| AJCC sixth TNM  | 0.544   | 0.512-0.576 | 2.64 |
| AJCC seventh TNM| 0.575   | 0.543-0.607 | 4.50 |
| AJCC eighth TNM | 0.568   | 0.535-0.601 | 4.01 |
| Nomogram        | 0.645   | 0.611-0.679 | 8.32 |
| **Validation cohort** |       |          |         |
| AJCC sixth TNM  | 0.592   | 0.574-0.610 | 10.52 |
| AJCC seventh TNM| 0.609   | 0.591-0.627 | 12.01 |
| AJCC eighth TNM | 0.611   | 0.593-0.629 | 12.40 |
| Nomogram        | 0.626   | 0.612-0.640 | 13.90 |
| **Race**        |         |          |         |
| Asian           | 0.644   | 0.609-0.679 | 8.01 |
| African         | 0.604   | 0.561-0.647 | 4.69 |
| Caucasian       | 0.628   | 0.604-0.652 | 10.67 |

*Note: AJCC, American Joint Committee on Cancer; C-index, Harrell’s concordance-index; CI, confidence interval.*

### FIGURE 3 Survival curves stratified by the risk score calculated by the total points of the nomogram (low-risk, <16.07; middle-risk, 16.07-19.40). A, Survival curves for different risk groups in the internal validation cohort. B, Survival curves for different risk groups in the external validation cohort.
based on a multi-institutional “gastric” database and clinical statistics of patients were collected by report ten years prior when esophagogastric junction cancer was not clearly defined.

5 CONCLUSION

In summary, we constructed and validated an accurate prognostic nomogram model for GC patients at stage III–IV based on age, tumor grade, tumor size, lymph nodes, and distant metastases clinical variables. The nomogram showed powerful predictive ability by internal and external validation, which is more accurate and useful than the current AJCC staging systems. This tool might help clinicians conduct personalized prognostic evaluations and could be applied as a widely applied tool for future clinical evaluation.

DATA SHARING STATEMENT

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTEREST

All authors had declared that they have no interest conflicts.

ETHICAL DISCLOSURE

The authors declared that they have followed the principles in the Declaration of Helsinki for all human or animal experimental investigations. Informed consent has been obtained from the participants involved for studies involving human subjects.

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AUTHOR CONTRIBUTIONS

Conceptualization: Zhiying Gao and Jing Ni; investigation: Zhiying Gao, Hui Ding, Caiwang Yan, Gang Li, and Chuanli Ren; writing—manuscript: Zhiying Gao and Jing Ni; writing—review and editing: Feng Pan and Guangfu Jin; funding acquisition: Guangfu Jin;

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Songun I, Putter H, Kranenburg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol. 2010;11:439-449.
3. Ajani JA, D’Amico TA, Almanna H, et al. Version 3.2016, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2016;14:1286-1312.
4. Dong D, Tang L, Li ZY, et al. Development and validation of an individualized nomogram to identify occult peritoneal metastasis in patients with advanced gastric cancer. Ann Oncol. 2019;30(3):431-438.
5. Kim SG, Seo HS, Lee HH, Song KY, Park CH. Comparison of the differences in survival rates between the 7th and 8th editions of the AJCC TNM staging system for gastric adenocarcinoma: a single-institution study of 5,507 patients in Korea. Journal of gastric cancer. 2017;17:212-219.
6. Deng J, Zhang R, Pan Y, et al. Tumor size as a recommendable variable for accuracy of the prognostic prediction of gastric cancer: A retrospective analysis of 1,521 patients. Ann Surg Oncol. 2015;22:565-572.
7. Feng F, Liu J, Wang F, et al. Prognostic value of differentiation status in gastric cancer. BMC Cancer. 2018;18:865.
8. Schlesinger-Raab A, Mihaljevic AL, Egert S, et al. Outcome of gastric cancer in the elderly: a population-based evaluation of the Munich Cancer Registry. Gastro Can. 2016;19:713-722.
9. Zhao LY, Zhang WH, Chen XZ, et al. Prognostic significance of tumor size in 2405 patients with gastric cancer: A retrospective cohort study. Medicine. 2015;94:e2288.
10. Sano T, Coit DG, Kim HH, et al. Proposal of a new stage grouping of gastric cancer for TNM classification: International gastric cancer association staging project. Gastro Can. 2017;20:217-225.
11. Son T, Sun J, Choi S, et al. Multi-institutional validation of the 8th AJCC TNM staging system for gastric cancer: Analysis of survival data from high-volume Eastern centers and the SEER database. J Surg Oncol. 2019;120:676-684.
12. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16:e173–e180.
13. Rudloff U, Jacks LM, Goldberg JJ, et al. Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. J Clin Oncol. 2010;28:3762-3769.
14. Thompson AM, Turner RM, Hayen A, et al. A preoperative nomogram for the prediction of ipsilateral central compartment lymph node metastases in papillary thyroid cancer. Thyroid. 2014;24:675-682.
15. Wang Y, Li J, Xia Y, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol. 2013;31:1188-1195.
16. Liu X, Wu Z, Lin E, et al. Systemic prognostic score and nomogram based on inflammatory, nutritional and tumor markers predict cancer-specific survival in stage II-III gastric cancer patients with adjuvant chemotherapy. Clin Nut. 2019;38:1853-1860.
17. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. CA. 2017; 67: 93-99.
18. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010; 17: 1471-474.
19. Greene F, Page D, Fleming I, Fritz J, Balch C, Haller D. AJCC cancer staging manual. 6th ed. 2002.
20. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: A new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. Clin Can Res. 2004;10:7252-7259.
21. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol. 2008;26:1364-1370.
22. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Statistics Med. 1996;15:361-387.
23. Strong VE, Wu AW, Selby LV, et al. Differences in gastric cancer survival between the U.S. and China. J Surg Oncol. 2015;112:31-37.
24. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24(18):2903-2909.
25. Fujitani K, Yang HK, 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 Oncol. 2016;17(3):309-318.
26. Association Japanese Gastric Cancer. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Can. 2017;20(1):1-19.
27. Yoshida K, Ninomiya M, Takakura N, et al. Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. Clin. Cancer Res. 2006;12(11 Pt 1):3402-3407.
28. Koizumi W, Kim YH, Fujii M, et al. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). J. Cancer Res. Clin. Oncol. 2014;140(2):319-328.
29. Yoshida K, Yamaguchi K, Okumura N, Tanahashi T, Kodera Y. Is conversion therapy possible in stage IV gastric cancer: the proposal of new biological categories of classification. Gastric Cancer. 2016;19(2):329-338.
30. Han DS, Suh YS, Kong SH, et al. Outcomes of surgery aiming at curative resection in good responder to induction chemotherapy for gastric cancer with distant metastases. J Surg Oncol. 2013;107(5):511-516.
31. Fukuchi M, Ishiguro T, Ogata K, et al. Prognostic role of conversion surgery for unresectable Gastric Cancer. Ann. Surg. Oncol. 2015;22(11):3618-3624.
32. Coupland VH, Allum W, Blazeby JM, et al. Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. BMC Cancer. 2012;12:11.
33. Dickson GH, Singh KK, Escofet X, Kelley K. Validation of a modified GTNM classification in peri-junctional oesophago-gastric carcinoma and its use as a prognostic indicator. Europ J Surg Oncol (EJSO). 2001;27:641-644.
34. Kattan MW, Karpeh MS, Mazumdar M, Brennan MF. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. J Clin Oncol. 2003;21:3647-3650.
35. Wang HM, Huang CM, Zheng CH, et al. Tumor size as a prognostic factor in patients with advanced gastric cancer in the lower third of the stomach. World J Gastroenterol.. 2012;18:5470-5475.
36. Kim J, Sun CL, Mailey B, et al. Race and ethnicity correlate with survival in patients with gastric adenocarcinoma. Ann Oncol. 2010;21:152-160.

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

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