Value of Radiotherapy in Primary Gastric Cancer and Establishment of a Prognostic Nomogram Model

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Research

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Abstract

Background: This study aimed to compare the use of radiotherapy (RT) in gastric cancer (GC) patients from the SEER database and established a nomogram to assess cancer-specific survival (CSS).

Methods: Patients from the SEER database between 2004 and 2013 were analyzed. Survival was analyzed by Kaplan-Meier curves and log-rank test. Prognostic factors in multivariate Cox analysis were screened to construct a nomogram. The performance the nomogram was validated via concordance index (C-index), calibration plots, and decision curve analyses (DCAs).

Results: 9653 GC patients were analyzed totally. In the entire cohort, patients who received pre/postoperative RT had better survival than those who did not receive RT ($P = 0.043$ and < 0.001, respectively). Similar results were observed in lymph node-positive patients. However, no significant survival benefit was seen in lymph node-negative patients between postoperative RT group and no RT group ($P = 0.057$), but patients who received postoperative RT and those who did not receive RT experienced better survival than those who received preoperative RT ($P < 0.001$ and 0.001, respectively). Prognostic factors of GC analyzed by Cox regression model included age, race, tumor grade, tumor histology type, primary tumor site, T stage, lymph node metastasis ratio, RT status, and chemotherapy information independently ($P < 0.001$). The nomogram was established and showed excellent prediction performance, and its C-index of 0.725 were significantly higher than those of nomograms based AJCC system with C-index at 0.643. In addition, the calibration plots performed good consistency between the predicted and actual survival probabilities, and the DCAs indicated better clinical net benefits than the traditional AJCC system.

Conclusions: RT can improve CSS in GC patients, especially those with positive lymph nodes. The construction and verification of a nomogram based on SEER database can effectively predict the survival outcomes of GC patients.

Background

Gastric cancer (GC) is one of the commonest causes of tumor death in the world. Nearly 1 million new patients are diagnosed with GC each year, ranking fourth in the incidence of malignant tumors and second in cancer-related death [1]. The incidence rate varies greatly globally, with the first-highest incidence in parts of Eastern Europe, East Asia, and Latin America. The clinicopathological characteristics of GC also differ according to the region, especially between Asia and the West [2].

Despite differences in the biological behavior and treatment preference of GC in different regions, complete excision of the area in primary tumor and local lymph node dissection are the only potential treatments for patients with resectable or curable GC [3]. However, the symptoms of GC patients are usually not easy to observe in the early stage, and in most countries, most patients are diagnosed at an advanced stage. In addition, patients with GC usually have a poor prognosis with simple surgical resection. Therefore, adjuvant therapy is essential.

According to perioperative adjuvant therapy trials conducted in Asia and the West, adjuvant therapy methods in Asia and the West are different. In the U.S. and Europe, the treatment standard for GC patients with T2 or above or lymph node positivity stipulated is either perioperative chemotherapy based on category 1 evidence or preoperative radiotherapy (RT) and chemotherapy based on category 2b evidence in the NCCN guidelines [4, 5]. In Asian countries, compared with Western countries, due to the widespread use of radical gastrectomy and D2 lymph node dissection, more and more studies have focused on investigating postoperative adjuvant chemotherapy without RT or neoadjuvant therapy with D2 lymph node dissection [6, 7].

Therefore, the absolute benefit of RT is often overlooked. This article retrospectively analyzed patients with locally advanced nonmetastatic GC through the Surveillance, Epidemiology, and End Results (SEER) database, discussed the value of RT in primary GC, and predicted the patients' cancer-specific survival (CSS) outcomes by establishing a nomogram prediction model.

Methods

Patient Selection

Data were obtained from the largest publicly available cancer database (the SEER database), which almost covered 28% of the U.S. population [1]. SEER*Stat is used to capture patient available information on the official network (https://seer.cancer.gov/) through an online program provided by SEER.

Data from the SEER database on GC patients, who diagnosed between 2004 and 2013, and patients who met the strict screening criteria were analyzed. The flowchart of detailed selection was shown in Fig. 1. Patients who received either postoperative RT (Postop RT group), preoperative RT (Preop RT group) or no RT (No RT group) and had AJCC stage IB to IV M0 disease were included in the analysis.

Clinicopathological Data

Patient demographics (age, sex, and race), tumor characteristics (differentiation, site of the primary tumor, clinical T and N stage, tumor histology, 6th edition AJCC stage, and lymph node involvement), treatment (radiotherapy, chemotherapy), and survival data were gained from the SEER database. A median age of 60 years was chosen as the cut-off value. Patient characteristics are demonstrated in Table 1.

Table 1
Patient demographics and tumor characteristics

Variable	No RT (%, n = 5421)	Preop RT (%, n = 1002)	Postop RT (%, n = 3230)	P-value
Age				< 0.001
< 60 years	1230 (22.7)	406 (40.5)	1367 (42.3)	
≥ 60 years	4191 (77.3)	596 (59.5)	1863 (57.7)	
Sex				< 0.001
Male	3255 (60.0)	843 (84.1)	2020 (62.5)	
Female	2166 (40.0)	159 (15.9)	1210 (37.5)	
Race				< 0.001
White	3610 (66.6)	897 (89.5)	1983 (61.4)	
Black	726 (13.4)	38 (3.8)	475 (14.7)	
Others	1085 (20.0)	67 (6.7)	772 (23.9)	
Grade				< 0.001
Well	157 (2.9)	47 (4.7)	69 (2.1)	
Moderate	1535 (28.3)	359 (35.8)	713 (22.1)	
Poor	3621 (66.8)	573 (57.2)	2357 (73.0)	
Undifferentiated	108 (2.0)	23 (2.3)	91 (2.8)	
Histology				< 0.001
Adenocarcinoma	4138 (76.3)	843 (84.1)	2194 (67.9)	
Mucinous adenocarcinoma	183 (3.4)	30 (3.0)	96 (3.0)	
Signet ring cell carcinoma	1100 (20.3)	129 (12.9)	940 (29.1)	
Primary site				< 0.001
Upper third	1373 (25.3)	930 (92.8)	788 (24.1)	

Preop, preoperative; RT, radiotherapy; Postop, postoperative; NOS, not otherwise specified

Variable	No RT (%, n = 5421)	Preop RT (%, n = 1002)	Postop RT (%, n = 3230)	P-value
Mid and low third	3139 (57.9)	56 (5.6)	1954 (60.5)	
Overlapping stomach	424 (7.8)	11 (1.1)	263 (8.1)	
Stomach (NOS)	485 (8.9)	5 (0.5)	233 (7.2)	
AJCC stage				< 0.001
I	1640 (30.3)	227 (22.7)	538 (16.7)	
II	1562 (28.8)	431 (43.0)	1066 (33.0)	
III	1477 (27.2)	288 (28.7)	1187 (36.7)	
IV	742 (13.7)	56 (5.6)	439 (13.6)	
T stage				< 0.001
T1	290 (5.3)	45 (4.5)	195 (6.0)	
T2	3335 (61.5)	585 (58.4)	1807 (55.9)	
T3	1312 (24.2)	324 (32.3)	969 (30.0)	
T4	484 (8.9)	48 (4.8)	259 (8.0)	
N stage				< 0.001
N0	1709 (31.5)	278 (27.7)	527 (16.3)	
N1	2312 (42.6)	626 (62.5)	1650 (51.1)	
N2	974 (18.0)	83 (8.3)	798 (24.7)	
N3	426 (7.9)	15 (1.5)	255 (7.9)	
Chemotherapy				< 0.001
Yes	1769 (32.6)	989 (98.7)	3002 (92.9)	
No	3652 (67.4)	13 (1.3)	228 (7.1)	
Preop, preoperative; RT, radiotherapy; Postop, postoperative; NOS, not otherwise specified				

Statistical Analysis

The primary endpoint was CSS for GC patients, which was defined from the time of period of beginning date of diagnosis to ending date of tumor-related specific death. The Kaplan-Meier method and log-rank

test were applied to survival analysis, and the chi-square test was devoted to the comparison of categorical variables. A receiver operating characteristic (ROC) curve to select cut-off values was used for the lymph node metastasis ratio (LNR) and evaluate its predictive value for CSS. Cox regression models were constructed to determine prognostic factors affecting primary nonmetastatic GC. A nomogram was constructed according to the factors that showed statistical significance determined by Cox regression analysis.

Using concordance index (C-index), calibration plots, and decision curve analyses (DCAs) to evaluate the accuracy of the nomogram model. The C-index was indicated to the discriminability of the model and constructed to compare the performance of the nomogram model and the traditional AJCC staging system. The calibration plots were created by comparing the actual survival probabilities with the nomogram-predicted probabilities of CSS. The DCAs were conducted to compare the clinical usefulness and net benefit of the predictive model. All statistical processing was accomplished with IBM SPSS Statistics software version 22.0, MedCalc software and R software version 3.6.2. A statistically significant cut-off value was set as $P < 0.05$.

Results

In this study, a total of 64,357 patients were initially enrolled. After strict screening, about 9,653 patients met the criteria. The patients were separated into three groups according to the RT status (No RT, Preop RT and Postop RT groups). The specific patient information was as follows: 5421 patients did not receive RT, 1002 patients received preoperative RT, and 3230 patients received postoperative RT, accounting for 56.2%, 10.4%, and 33.5%, respectively (see Table 1 for details).

Survival And Lnr Categories

The definition of LNR was the positive nodes number divided by the total number of lymph nodes detected. The ROC curves were generated for the comparison of the discrimination for the LNR and positive lymph nodes number (no. of positive lymph nodes). As shown in Fig. 2a-c, the AUC values of LNR used to present the 1-, 3- and 5-year survival rates of patients were 0.699 (95% CI: 0.690 ~ 0.709), 0.705 (95% CI: 0.696 ~ 0.714), and 0.702 (95% CI: 0.693 ~ 0.711), respectively; the AUC values of the number of positive lymph node metastases used to determine the 1-, 3-, and 5-year survival rates of the patients was 0.670 (95% CI: 0.661 ~ 0.680), 0.683 (95% CI: 0.674 ~ 0.692), and 0.684 (95% CI: 0.675 ~ 0.0.694), respectively; and the survival predictions of the two were statistically significant ($P < 0.001$). Using LNR to predict the GC patient prognosis was more accurate, objective and effective. Therefore, we grouped the selection of the LNR through the cut-off point of the ROC curve.

As shown in Fig. 2d, the best cut-off point of the LNR was 0.1714, with a sensitivity of 63.1% and a specificity of 67.6% for predicting the prognosis of GC patients. The AUC was 0.696 (95% CI: 0.687 ~ 0.705, $P < 0.001$). We identified the patients with negative lymph nodes as a group (LNR1: LNR = 0%), the

rest patients with positive lymph nodes were classified into two groups: LNR2: 0% < LNR ≤ 17.14%; and LNR3: LNR > 17.14%.

Kaplan-Meier survival analysis was performed according to LNR grouping (Fig. 3a). The results showed a significant group difference, in which LNR1 vs LNR2, P < 0.001; LNR2 vs LNR3, P < 0.001; and LNR3 vs LNR1, P < 0.001.

Survival analysis of the No RT, Preop RT and Postop RT groups

The survival curves of the No RT, Preop RT and Postop RT groups are presented in Fig. 3b. Significant differences were seen in the survival of all patients between the three groups: No RT vs Preop RT, P = 0.043; No RT vs Postop RT, P < 0.001; and Preop RT vs Postop RT, P < 0.001. The median survival time were 31months, 34 months, and 47 months in No RT, Preop RT and Postop RT groups, respectively. And 1-, 3-, and 5-year CSS rates were 71.9%, 46.8%, and 38.9% in No RT group, 84.3%, 48.9%, and 38.3% in Preop RT group, 84.9%, 55.0%, and 46.0% in Postop RT group, respectively.

Among the patients with negative regional lymph nodes, Postop RT group showed no significant survival benefit over No RT group (P = 0.057), but Postop RT and No RT groups showed significant survival benefits over Preop RT group, with P values of < 0.001 and 0.001, respectively (Fig. 3c).

For the patients with positive regional lymph nodes, both Preop RT (P < 0.001) and Postop RT (P < 0.001) groups showed significant survival benefits over No RT group, and Postop RT group showed obvious survival benefits over Preop RT group (P < 0.001) (Fig. 3d).

Based on AJCC stage, the subgroup analyzed Postop RT group, No RT group and Preop RT group. The results showed that Postop RT group had a significant survival benefits than No RT group (P = 0.005), and No RT group showed significant survival benefits over Preop RT group (P < 0.001) in AJCC I stage (Fig. 4a). While in AJCC II stage, Postop RT group showed significant survival benefits over both No RT and Preop RT groups (P < 0.001), and no survival difference was seen between Preop RT group and No RT group (P = 0.106) (Fig. 4b). Both Preop RT and Postop RT groups showed significant survival benefits over No RT group (P < 0.05), and no significant survival benefit was seen between Postop RT group and Preop RT group in both AJCC III stage and IV stage, with p values of 0.240 and 0.932, respectively (Fig. 4c, d).

Comparison of Pathological Features between Preop RT group and Postop RT and No RT combined groups

Table 2 shows different pathological features in lymph node and primary tumor statuses between patients in the Preop RT group and those in the Postop RT and No RT combined groups. Lymph node pathology included lymph node metastases number, detected lymph nodes number and LNR, and the Kruskal-Wallis test was used to compare whether the two groups were different. The number of positive lymph nodes (mean rank, 3344.23 vs 4998.74 [P < 0.001]), lymph nodes removed (mean rank. 4383.52 vs 4878.37 [P < 0.001]) and LNR (mean rank. 3423.52 vs 4989.56 [P < 0.001]) in the Preop RT group were

significantly less when compared with the Postop RT and No RT combined groups. For the T stage of the primary tumor status, the chi-square test was used to compare the differences between the Preop RT group and the Postop RT and No RT combined groups. The distributions according to AJCC T classification were as follows: 4.5% vs 5.6% for T1 (P = 0.142), 58.4% vs 59.4% for T2 (P = 0.520), 32.3% vs 26.4% for T3 (P < 0.001), and 4.8% vs 8.6% for T4 (P < 0.001). The distribution of T1 and T2 did not have a significant group difference. However, a significant group difference was seen in the distribution of T3 and T4. T3 was more widely distributed in the Preop RT group, and T4 was more widely distributed in the Postop RT and No RT combined group. This result indicates that preoperative RT did not affect the primary tumor, but the microscopic lymph node disease.

Table 2
Comparison of Pathological Features between Preop RT group and Postop RT and No RT combined groups

Characteristic	Preop RT	Postop RT and No RT	P-value
No. of positive LNs: mean rank	3344.23	4998.74	< 0.001 [a]
No. of LNs removed: mean rank	4383.52	4878.37	< 0.001 [a]
LNR: mean rank	3423.52	4989.56	< 0.001 [a]
Tumor classification, %			
T1	45 (4.5%)	485 (5.6%)	0.142 [b]
T2	585 (58.4%)	5142 (59.4%)	0.520 [b]
T3	324 (32.3%)	2281 (26.4%)	< 0.001 [b]
T4	48 (4.8%)	743 (8.6%)	< 0.001 [b]
Preop, preoperative; RT, radiotherapy; Postop, postoperative; LNR, lymph node metastasis			
a. Kruskal-Wallis test.			
b. Chi-square test.			

The Analyzation Of Cox Regression Model

In the primary GC cohort, the median survival time was 36 months, and the 1-, 3-, and 5-year CSS rates were 77.6%, 49.8%, and 41.3%, respectively. The hazard ratios for CSS are listed in Table 3 obtained by Cox regression model according to all variables. All variables except for sex (P = 0.280) were revealed as prognostic factors in Cox regression models (i.e., age, race, tumor differentiation, tumor histology type, primary tumor site, T stage, LNR, RT status, and chemotherapy information).

Table 3
Multivariate analyses for CSS using the Cox regression model

Variable	All patients		Lymph node-positive patients	
	HR (95% CI)	P-value	HR (95%CI)	P-value
Age				
< 60 years	1		1	
≥ 60 years	1.275 (1.200- 1.355)	< 0.001	1.254 (1.174–1.339)	< 0.001
Sex				
Male	1		1	
Female	0.969 (0.915–1.026)	0.280	0.965 (0.906–1.028)	0.268
Race				
White	1		1	
Black	1.058 (0.974–1.148)	0.182	1.091 (0.998–1.193)	0.055
Others	0.795 (0.739–0.856)	< 0.001	0.821 (0.758–0.889)	< 0.001
Grade				
Well	1		1	
Moderate	1.061 (0.876–1.285)	0.545	1.126 (0.892–1.420)	0.318
Poor	1.307 (1.083–1.577)	0.005	1.449 (1.154–1.820)	0.001
Undifferentiated	1.476 (1.149–1.897)	0.002	1.663 (1.245–2.223)	0.001
Histology				
Adenocarcinoma	1		1	
Mucinous adenocarcinoma	0.979 (0.839–1.141)	0.782	1.042 (0.882–1.231)	0.628
Signet ring cell carcinoma	1.175 (1.099–1.257)	< 0.001	1.205 (1.121–1.295)	< 0.001
Primary site				
Upper third	1		1	
Mid and low third	0.770 (0.719–0.824)	< 0.001	0.826 (0.767–0.890)	< 0.001
Overlapping stomach	0.861 (0.771–0.963)	0.009	0.963 (0.855–1.084)	0.531
Stomach, NOS	0.852 (0.762–0.952)	0.005	0.927 (0.821–1.047)	0.223
T stage				

Preop, preoperative; RT, radiotherapy; Postop, postoperative; LNR, lymph node ratio; HR, hazard ratio

Variable	All patients		Lymph node-positive patients	
	HR (95% CI)	P-value	HR (95%CI)	P-value
T1	1		1	
T2	1.885 (1.623–2.190)	< 0.001	2.255 (1.941–2.619)	< 0.001
T3	2.733 (2.344–3.185)	< 0.001	3.354 (2.877–3.909)	< 0.001
T4	3.525 (2.982–4.166)	< 0.001	4.098 (3.458–4.858)	< 0.001
Lymph node ratio				
0%	1		-	
0%<LNR ≤ 17.14%	1.687 (1.542–1.847)	< 0.001	-	-
LNR > 17.14%	3.446 (3.200- 3.712)	< 0.001	-	-
Radiation record				
No RT	1		1	
Preop RT	0.917 (0.825–1.009)	0.092	0.844 (0.751–0.948)	0.004
Postop RT	0.710 (0.662–0.763)	< 0.001	0.742 (0.689- 0.800)	< 0.001
Chemotherapy				
Yes	1		1	
No	1.378 (1.286–1.477)	< 0.001	1.487 (1.380–1.603)	< 0.001
Preop, preoperative; RT, radiotherapy; Postop, postoperative; LNR, lymph node ratio; HR, hazard ratio				

Among the subgroups, patients ≥ 60 years old, patients with poorly-differentiated and undifferentiated tumors, patients with signet ring cell carcinoma, patients with a high T stage and LNR underwent a higher risk of death than the references. Patients with sites of mid- and low-third and overlapping stomachs, patients with postoperative RT, and patients undergoing chemotherapy had a lower risk of death than the references. Preoperative RT group did not reduce the risk of death than no RT group in the multivariate analysis (HR: 0.917, 95%CI [0.825 ~ 1.009]).

Additionally, multivariate COX regression analysis based on lymph node status suggested preop RT (HR: 0.844, 95%CI [0.751 ~ 0.948]) and postop RT (HR: 0.742, 95%CI [0.689 ~ 0.800]) were associated with a lower risk of death than No RT in lymph node-positive patients, which is consistent with Kaplan-Meier survival analysis. The other factors related results are presented in Table 3.

Establishment And Validation Of The Nomograms

The selected prognostic factors were used to construct the nomogram for 1-, 3- and 5-year CSS by using multivariate Cox regression model (Fig. 5). The nomogram included parameters such as age, race, tumor differentiation, tumor histology type, primary tumor site, T stage, LNR, RT status, chemotherapy information.

The performance of the model (i.e., discrimination, calibration and clinical usefulness) was evaluated through C-index, calibration plots, and DCAs. The C-index value of the nomogram for CSS was significantly greater than those of nomogram based AJCC system (0.725 [95%CI: 0.717 ~ 0.734] vs. 0.643 [95%CI: 0.635 ~ 0.651]). Moreover, high-quality calibration plots demonstrated excellent consistency between the actual and nomogram-predicted survival probabilities (Fig. 6a-c). The DCAs curves revealed relatively good performance for the model according to clinical application. The threshold probabilities of the new model had excellent net benefits for predicting the 1-, 3- and 5-year CSS compared with the AJCC system (Fig. 6d-f). Therefore, we believe that the prediction model has highly accurate prediction ability as a whole and can be used in clinical work.

Discussion

Even adjuvant therapy has been designed to be a tool to improve GC patients' prognosis, it is still the leading cause of tumor-related death. The benefit of RT in GC patients remains controversial [8]. The earliest confirmed application of RT in GC came from the Intergroup 0116 trial. It has been shown that patients who had postoperative chemoradiation therapy had survival benefit than those who underwent surgery alone [9]. However, this conclusion was questioned for its low (10%) utilization in D2 lymphadenectomy and its inclusion of stage IB patients [9].

In our study, the Kaplan-Meier analysis of the primary cohort from the SEER database showed that both preoperative and postoperative RT increased the CSS of GC patients. Similar survival results were obtained in patients with positive lymph nodes. Additionally, Cox regression analysis of lymph node-positive patients showed preop RT and postop RT groups had lower death risk than no RT groups. It is noted that in patients with negative local lymph nodes, a correlation between preoperative RT and poor survival outcomes was listed (Fig. 3c). Previous literature showed patients who received preoperative chemoradiation with 5-fluorouracil had both overall long-term and recurrence-free survival compared to those who received perioperative chemotherapy alone in a large retrospective U.S. multi-institutional study [10]. Besides, patients with N1 disease and those who had tumors with lymphovascular invasion benefited the most from preoperative chemoradiation in the propensity-adjusted model. However, the result indicated less benefit from preoperative chemoradiation from patients with N0 disease and those with tumors that did not have lymphovascular invasion [10]. In another study, the Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial, which was aimed to make adjuvant chemotherapy comparison with chemoradiation, failed to demonstrate a difference in disease-free survival and overall survival in the whole cohort study, however, the subgroup analysis demonstrated that patients with intestinal type histology and positive lymph nodes, in particular, may benefit from

chemoradiation [11, 12]. Therefore, above researches presented in this article suggest that RT in GC patients may benefit those with positive local lymph nodes.

In the subgroup survival analysis based on AJCC stage, we found that with the increase of tumor stage, the effect of RT became more and more significant, especially preoperative RT. A rational explanation was preoperative RT could downstage the advanced tumor and increases the chance of curative resection for advanced tumors. Additionally, neoadjuvant chemoradiation has been reported to improve the R0 resection and achieve pathological complete remission (PCR) in advanced GC. A 30% PCR rate and 70% R0 resection rate using preoperative chemoradiation were observed in a multi-institutional single-arm phase I trial in the U.S, which consisted of induction chemotherapy followed by radiation plus concurrent fluorouracil [13]. In additionally, a 26% PCR rate and 77% R0 resection rate were also reported in phase II multi-institutional trial in the U.S. (RTOG9904) with two cycles of induction chemotherapy followed by concurrent chemoradiotherapy [14]. Therefore, pathological complete or partial response due to neoadjuvant therapy may be associated with improved overall survival, disease-free survival and D2 dissection [14, 15].

The clinical impacts of the LNR in GC patients had been previously reported [16–19]. In this study, the prognostic value of the LNR and the positive lymph node metastases number in GC patients was compared and analyzed based on the 1-, 3-, and 5-year survival. The results showed that the LNR had a better predictive value in GC patients than the positive lymph node metastases number. In addition, survival analysis showed a correlation between a high LNR and poor CSS. It was consistent with Kim et al. finding that a relation between a high LNR and poor disease-free survival with advanced GC in the ARTIST trial [20]. The multivariate analysis in our study also demonstrated that the LNR was a meaningful predictor of poor CSS. Therefore, using LNR to predict the prognosis of GC patients is accurate, effective and objective, so this study proposes the use of the LNR as a parameter for the establishment of a nomogram.

This study noted that compared with the Postop RT and No RT combined groups, the number of positive lymph nodes, removed lymph nodes and LNR in the Preop RT group were significantly reduced (Table 2). However, preoperative RT does not seem to have a similar effect on the primary tumor because the tumor T classification distribution was not consistent with that of the Postop RT and No RT combined groups. In addition, a small retrospective series from Spain demonstrated that there was a significantly higher probability of achieving a Becker Ia-b response, a favorable pathological response and grade D nodal regression when comparing neoadjuvant chemoradiation to neoadjuvant chemotherapy in resectable advanced GC, Nodal, rather than primary, response was associated with longer 5-year progression-free survival and overall survival. However, no significant survival differences were seen in patients with a baseline negative lymph node status regardless of neoadjuvant treatment in either 5-year progression-free survival (chemotherapy 53%; chemoradiation 80%; P = 0.45) or 5-year overall survival (chemotherapy 58%; chemoradiation 51%, P = 0.92) [21]. This result suggests that preoperative RT may benefit patients with local lymph node metastasis and has little effect on the primary tumor T classification.

In our study, the main difference in pathological features between the Preop RT group and the Postop RT and No RT combined groups was local lymph nodes, not the T stage of the tumor. One explanation for this difference is that although the published data reported complete pathological remission, due to limitations of the SEER database itself, patients treated in some trials may not be included and reflected in the SEER database. In addition, lacking information on concurrent or sequential chemotherapy in SEER database, which also affects the remission rate. Another limitation of the SEER database itself is the lack of clinical staging data for GC. Table 1 showed that 31.5%, 27.7% and 16.3% of patients were node negative in the No RT, Preop RT and Postop RT groups, respectively. If preoperative RT was used to transform a patient from a clinically lymph node-positive status to a pathologically lymph node-negative status, then in the negative lymph node preoperative RT group, the mortality rate will be overestimated because this group will include clinical lymph node-positive patients. On the side, the survival benefit of the positive lymph node preoperative RT group may be underestimated because it may have excluded patients with complete clinical remission of locally positive lymph nodes after neoadjuvant therapy.

Several studies have revealed the predictive abilities of nomograms for predicting GC. In this study, the nomogram was used to calculate the CSS outcomes of a single GC patient using Cox regression to screen 9 independent variables. According to the nomogram, the weighting of the LNR was the largest. The top three factors that affect CSS are the LNR, T stage and tumor grade. The nomogram presented herein showed excellent prediction performance, and its C-index value of 0.725 using significant prognosis factors was significantly higher than the C-index value of 0.643 using traditional AJCC system. The calibration plots were close to the ideal 45º dotted line. The DCAs curves with higher cut-off probability levels indicated that the new model had better clinical application value (net benefit) compared with the AJCC system in terms of the 1-, 3- and 5-year CSS. In addition, one of the advantages of the nomogram model is to include the LNR instead of the N stage as an effective parameter. The aforementioned LNR has been shown to be superior to the number of local positive lymph node metastases in predicting patient prognosis, so it can improve the role of prognosis prediction. The prediction model can be used as an important early warning sign for the survival of GC patients for risk estimation. If a patient's risk estimate is high, doctors and nurses can take appropriate measures to promote a clinical prognostic assessment and personalized treatment.

It has been actively prospectively investigated whether chemoradiation provides a survival benefit in addition to or instead of chemotherapy. However, it failed to show a differential survival between patients to receive perioperative chemotherapy vs preoperative chemotherapy and postoperative chemoradiation therapy by randomized CRITICS trial [22]. And the subsequent CRITICS-II trial is optimizing neoadjuvant therapy through comparing only neoadjuvant chemotherapy, only neoadjuvant chemoradiation, and neoadjuvant chemotherapy followed by chemoradiation [23]. Furthermore, another randomized prospective TOPGEAR trial aimed at determining whether preoperative chemoradiation, in addition to perioperative chemotherapy has better outcomes than perioperative chemotherapy alone [24]. the interim results have demonstrated that preoperative chemoradiation can be stabilized delivered to majority of patients with a higher safety [25].

Although the SEER database is the largest epidemiological cancer registry in the U.S., the current study does have some limitations related to the SEER database that need to be addressed. The SEER database does not cover information about the resection margin status, whether the resection is complete, and whether adjacent organs were removed. No information about patient comorbidities, performance status and the nutritional status were given. The chemotherapy regimens and the sequence of chemotherapy were not clear. Information about targeted therapy was not given. And postoperative complications were unknown. Moreover, information about the use of salvage therapy with tumor recurrence or progression was lacking. In addition, it is possible that younger patients with a better performance status had a much higher chance to receive preoperative RT than no RT [10].

Above all, the SEER database does reflect the real-world outcomes of patients, although it still has its inherent biases. After considering these limitations, we give a conclusion of this study that RT may improve the survival prognosis of GC patients, and the nomogram described herein can be used to predict a patient's prognosis.

Conclusions

Based on the SEER database of a large-scale population, the role of RT in GC is beyond a doubt, and it could improve CSS in GC patients, especially those with positive lymph nodes. In addition, a prognostic nomogram model was constructed to predict survival outcomes for GC patients. The establishment of nomogram in this study can offer a visualized assessment of risk based on each prognostic parameter and an assistance to clinicians in predicting the 1-, 3- and 5-year CSS outcomes of GC patients.

Abbreviations

GC: gastric cancer; SEER: Surveillance, Epidemiology, and End Results; RT: radiotherapy; CSS: cancer-specific survival; C-index: concordance index; DCAs: decision curve analyses; ROC: receiver operating characteristic curve; LNR: lymph node metastasis ratio; PCR: pathological complete remission.

Declarations

Acknowledgments

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Availability of data and materials

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

Authors' contributions

TCJ and TCJ designed the study. TCJ, NL and SHS performed the data analysis and literature searching. TCJ was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no potential conflict of interest.

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Figures

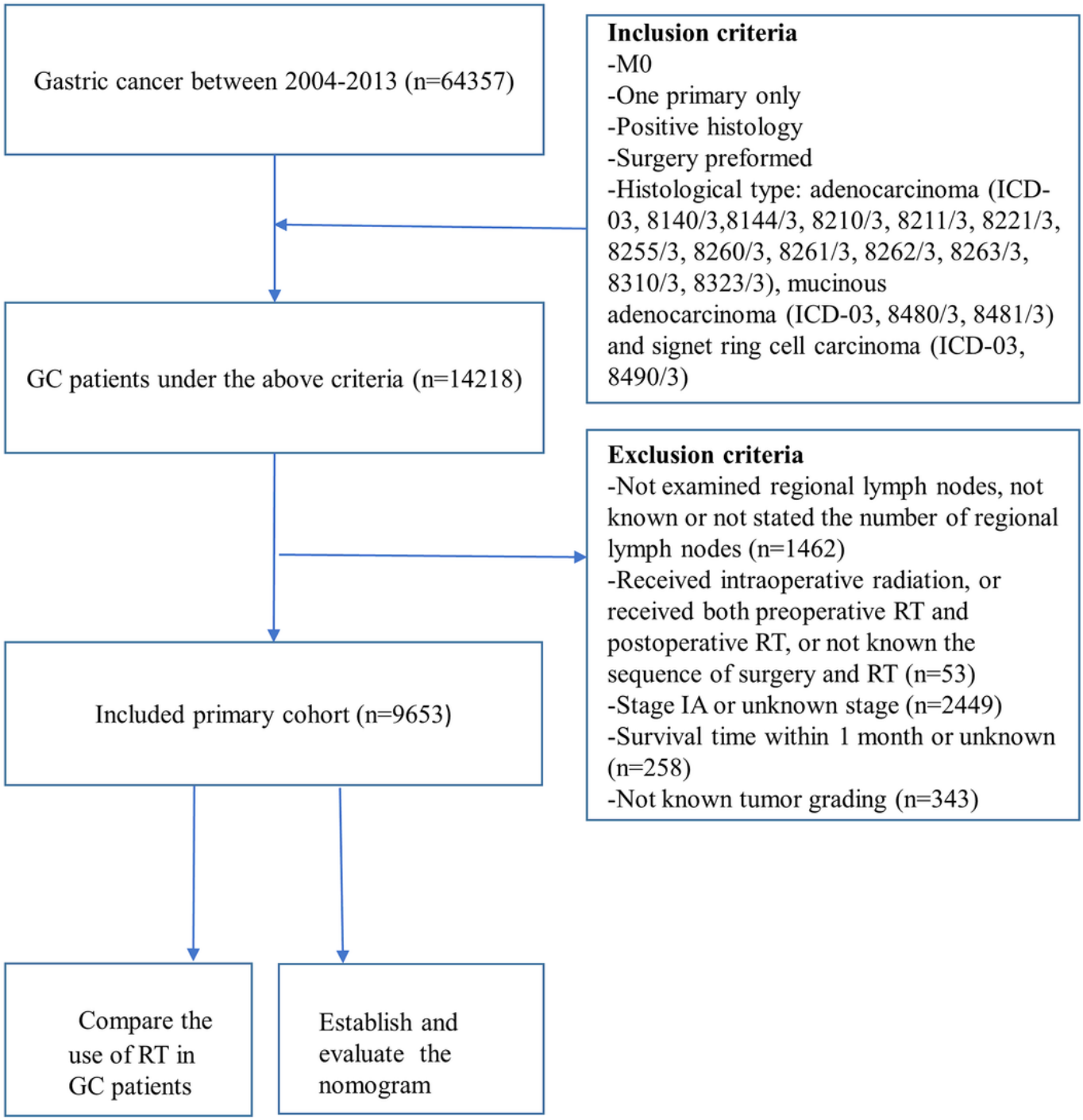

Figure 1

A flowchart for the present study.

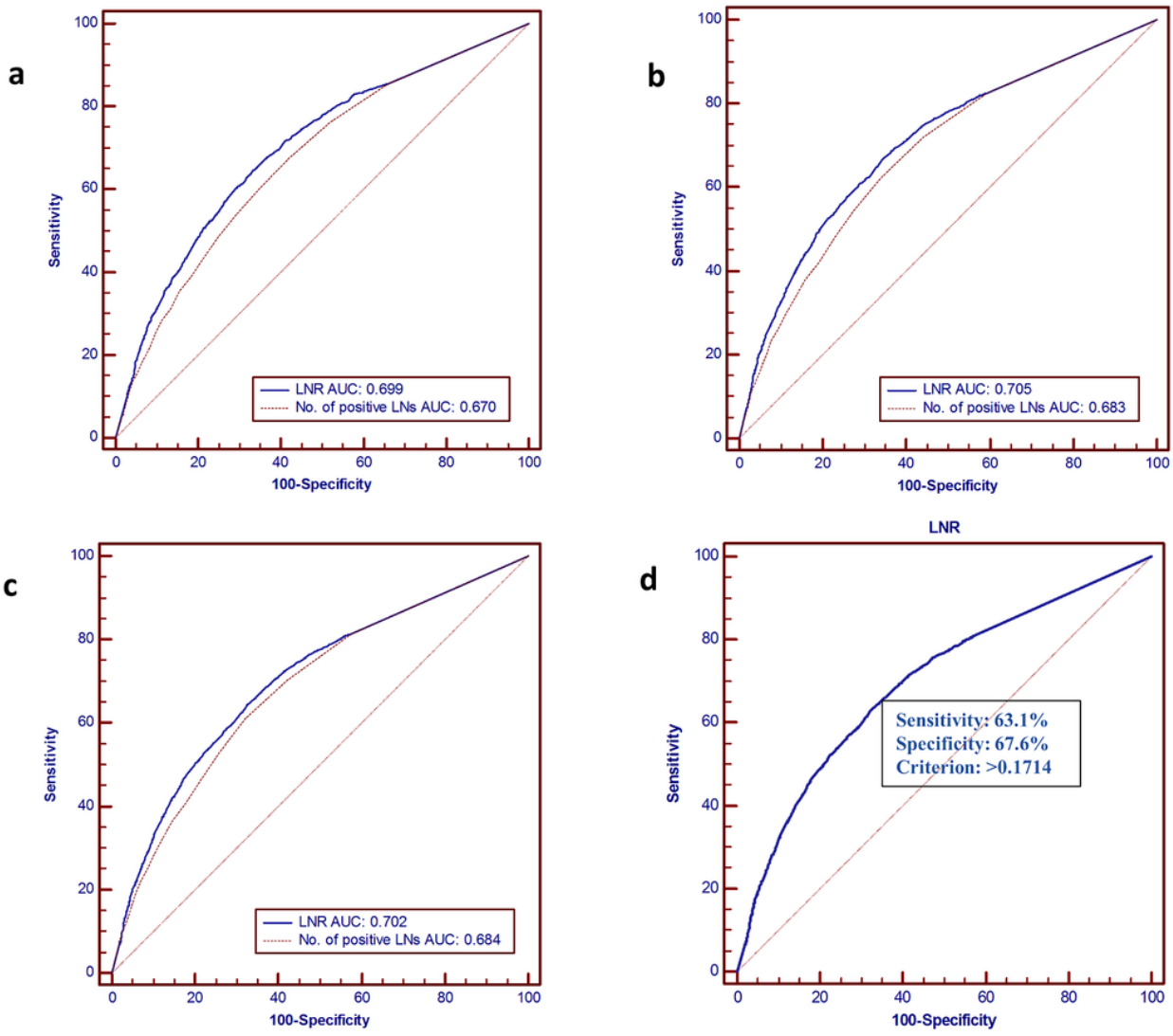

Figure 2

The discrimination using the receiver operating characteristic curve between the LNR and positive lymph nodes number. It was compared for 1- (a), 3- (b) and 5-years (c) CSS, all p values < 0.001; the best cut-off point of the LNR was selected (d).

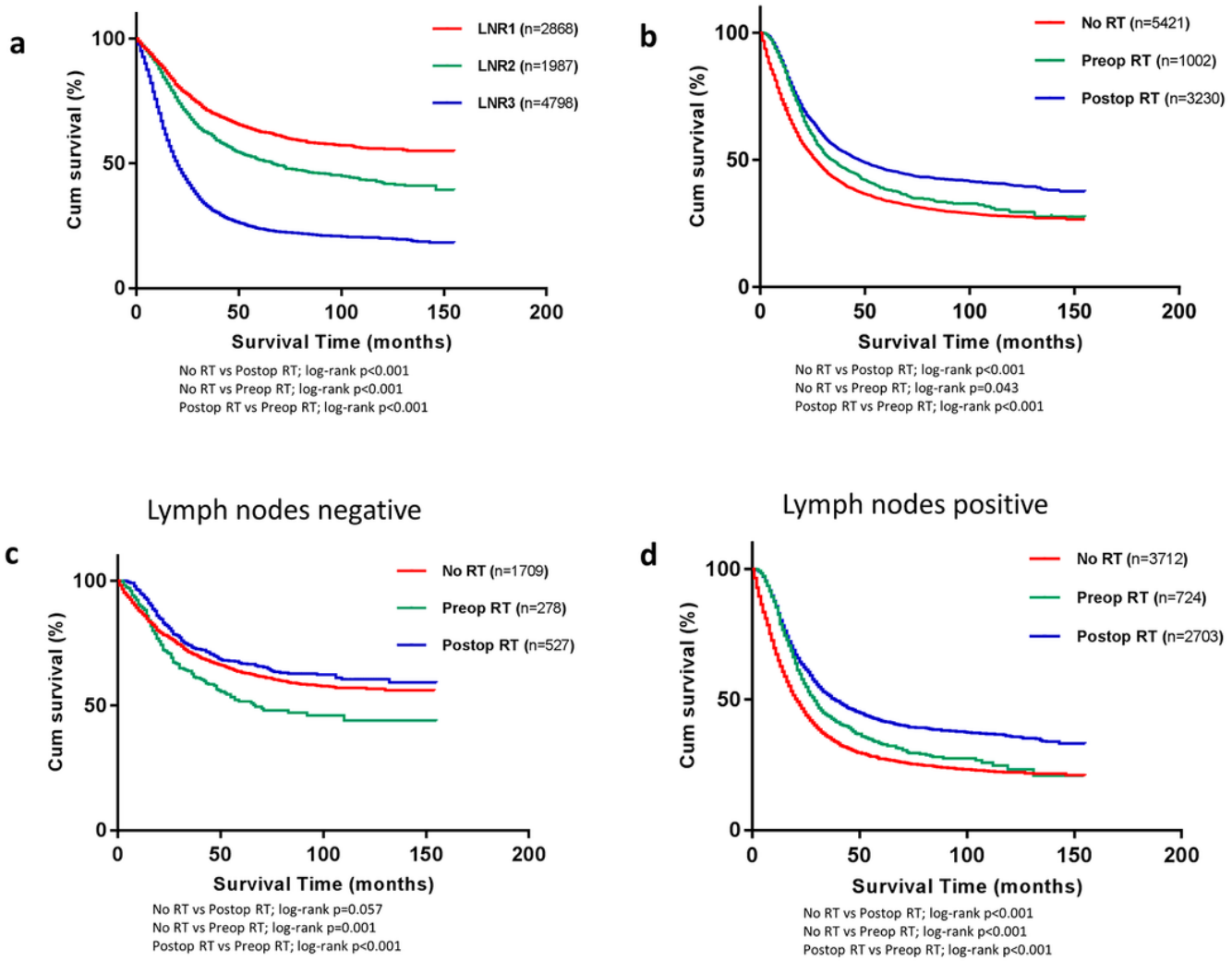

Figure 3

Kaplan-Meier survival curves of LNR grouping (a); Kaplan-Meier survival curves of the No RT, Preop RT and Postop RT groups in the primary cohort (b), in patients with negative regional lymph nodes (c), and in patients with positive regional lymph nodes (d).

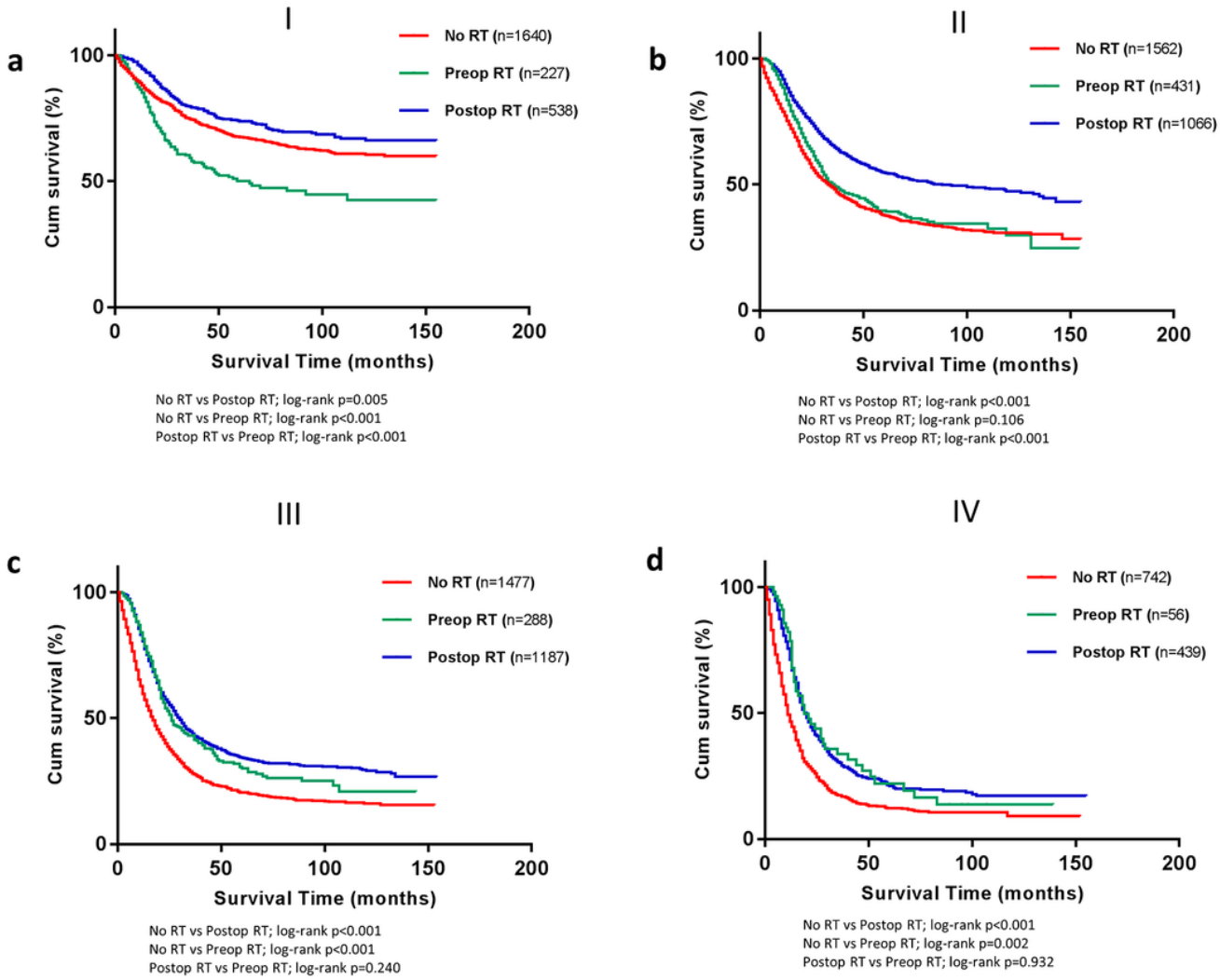

Figure 4

Subgroup survival analysis based on AJCC stage. Kaplan-Meier survival curves of the No RT, Preop RT and Postop RT groups in AJCC I stage (a), AJCC II stage (b), AJCC III stage (c), and AJCC IV stage (d).

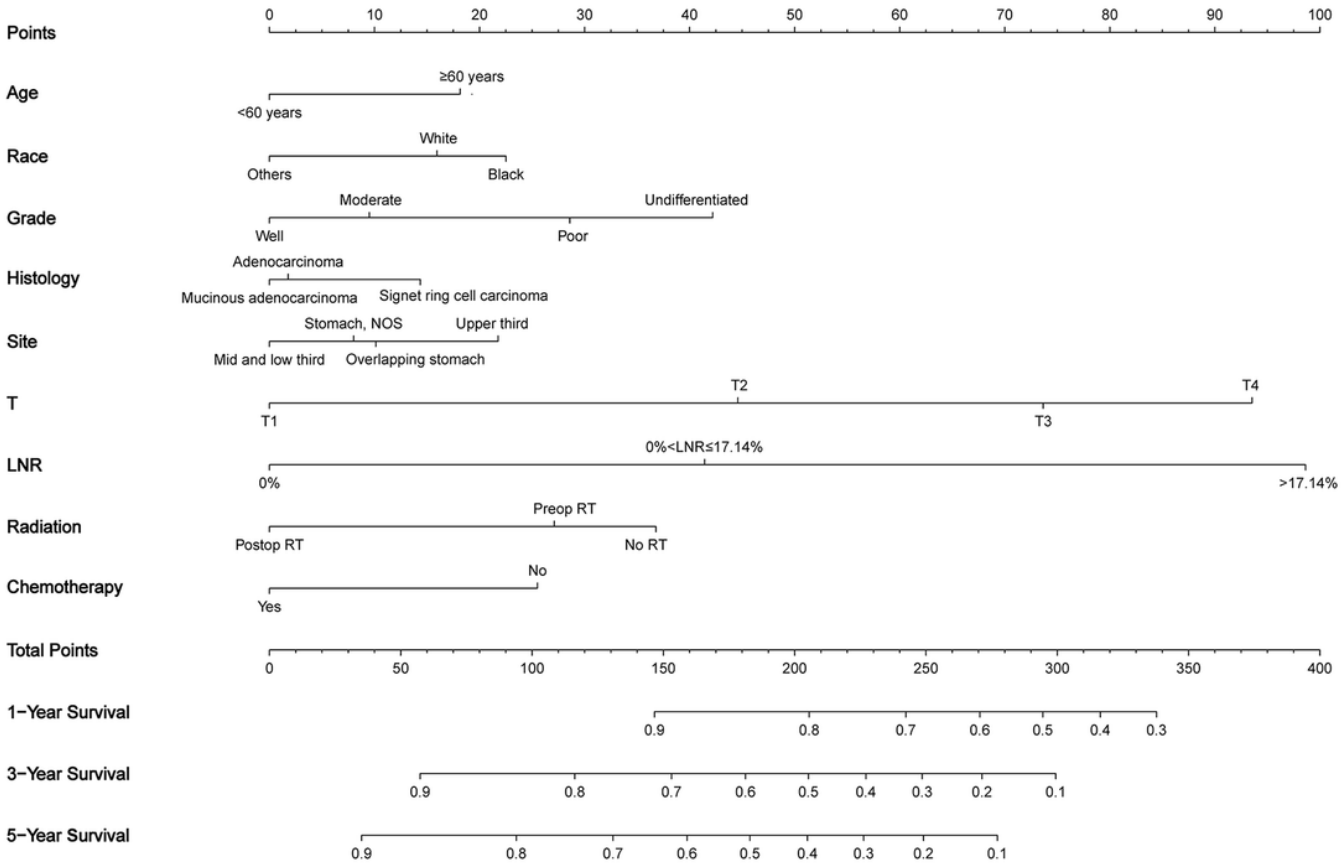

Figure 5

Nomogram of gastric cancer-specific survival at 1-, 3- and 5- years.

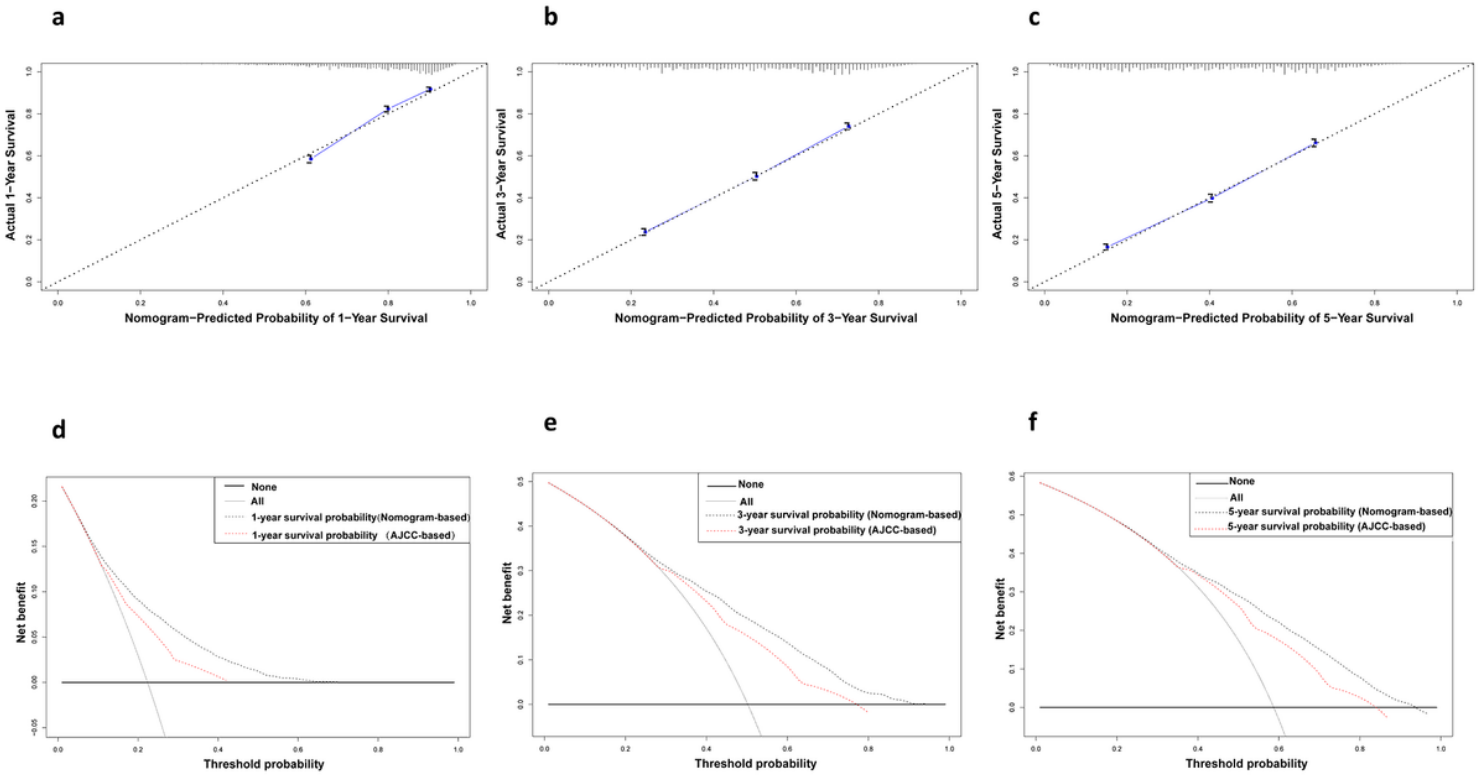

Figure 6

Calibration plots for predicting 1- (a), 3- (b) and 5- years (c) cancer-specific survival (CSS). Decision curve analysis of the novel nomogram and 6th AJCC staging system for predicting 1- (d), 3- (e) and 5- years (f) CSS.