



Original Research

External Validation of a Nomogram Developed for Predicting Overall Survival in Gastric Cancer Patients with Insufficient Number of Examined Lymph Nodes

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Abstract

Objectives: Nomograms and scoring systems in gastric cancers have been mainly developed based on adequate lymph node (LN) dissections. This study aimed to perform external validation of a nomogram developed for predicting overall survival (OS) in gastric cancer patients with insufficient number of examined LNs (eLNs) and to evaluate its usability as compared with the 8th American Joint Committee on Cancer (AJCC)'s Tumor-Node-Metastasis staging system.

Methods: Medical records of 262 patients undergoing complete surgical resection for gastric cancers and having pathologically confirmed diagnosis were retrospectively reviewed. The study included 104 (39.7%) patients (82 males, median age, 60.3 years) with insufficient number of eLNs (<16). The 5-year OS rate was calculated using the nomogram and according to the AJCC system.

Results: The median follow-up period was 37.4 months (range: 0.9–122.9). Of the patients, 69 (66.3%) died and 35 (33.7%) achieved 5-year survival within the follow-up period. The nomogram and the AJCC system predicted OS were significantly lower in patients who died than in those who achieved 5-year survival ($p < 0.001$ for both). According to the receiver operative characteristics-curve, the area under the curve for the nomogram (0.801; 95% CI, 0.715–0.887; $p < 0.001$) was larger than that for the AJCC system (0.754; 95% CI, 0.659–0.849; $p < 0.001$).

Conclusion: The nomogram developed for gastric cancer patients with insufficient number of eLNs (<16) was effective in predicting 5-year OS in our cohort and was superior to the AJCC system.

Keywords: Gastric cancer, lymph node dissection, nomogram, survival

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Gastric cancers are currently the 5th most common malignancies and the 3rd leading cause of cancer deaths despite the fact that screening programs and neoadjuvant and adjuvant therapies have contributed to the improvement of prognosis.^[1] Surgical treatment is still considered essential for the removal of disease and for continuity of life in gastric cancers.^[2] Lymph node (LN) metastasis is the most important determinant of survival in patients with

gastric cancer.^[3] Patients need to be informed about survival probability after surgery and choice of additional treatment protocols and should make their decisions.

The Tumor-Node-Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) is considered as the gold standard for staging and predicting survival in patients with gastric cancers. Despite the regulations performed through numerous modifications in the TNM system

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on each revision of the AJCC cancer staging manuals, the 8th edition of which has been published, it is based on the postoperative pathological findings such as number of metastatic LNs (mLNs), depth of tumor invasion, and presence of distant metastasis.^[4,5] For this reason, this staging system has some limitations such that it yields survival predictions that are heterogeneous and broad in range for patients of the same stage. Survival of a patient who is N (+) but in early T stage disease could be predicted better as compared with a patient who is N (0) but in advanced T-stage. Moreover, in the AJCC TNM staging system, the tumor, node, metastasis could not be presented as continuous variables; accordingly, this system leads to an additional predictive accuracy loss by forcing tumor spread to be classified gradually.^[6]

According to the AJCC cancer staging manual, the number of examined LNs (eLNs) must be at least 16 for optimal staging of the gastric cancers.^[4] It has been observed that overall survival (OS) is better in patients with adequate number of eLNs and that dissection of inadequate number of LNs (<16) causes a shift in cancer stage.^[7]

A nomogram is a diagram that shows the relationships between variables, arranged in such a way that the values of the variables can be found with a simple geometric structure. They are the statistics-based scales used to estimate predictions such as survival times and probability of relapse by combining multiple clinical variables and their interdependent relationships. The use of nomograms as prognostic tools in oncology and medicine is gradually becoming more popular.^[6] More than one clinical variable of patients is used in nomograms; therefore, nomograms may provide more precise and tailored predictions as compared to traditional staging or scoring systems.

Numerous nomograms have been proposed for cancer types.^[8,9] There are also many nomograms proposed for prediction of survival and relapse in gastric cancers. However, these nomograms have been mainly prepared for gastric cancer patients with adequate LN dissections.^[9-11] A specific nomogram for gastric patients with inadequate number of eLNs was developed by Wang et al.^[10] in 2017.

The present study aimed to perform external validation of a nomogram prepared for the prediction of OS in gastric cancer patients with insufficient number of eLNs and to evaluate the availability of this nomogram in the present study cohort as compared with the 8th AJCC TNM staging system.

Methods

Study Population

Medical records of patients (n=262) who underwent complete surgical resection (R0) for gastric cancers and in whom

the diagnosis was confirmed by post-operative pathological examinations in the General Surgery Clinics of two separate tertiary hospitals between January 2009 and January 2014 were retrospectively reviewed from the hospital database. Patient selection was based on the criteria defined by Wang et al.^[10] for constructing a nomogram in gastric cancer patients with insufficient eLNs; accordingly, patients who had insufficient number of eLNs (<16) and had no other cancers were eligible for the present study. Of 262 patients evaluated from the medical records, patients with number of eLNs ≥ 16 (n=147), those with non-primary gastric cancers (n=0), those receiving neoadjuvant therapy (n=2), and those having perioperative mortalities (n=7) were excluded from the study. Patients (n=2) with missing data for the variables required for the nomogram prepared by Wang et al.^[10] were also excluded. Thus, the remaining 104 (39.7%) patients were included in the present study.

Patients' data that were collected from the medical records were as follows: Demographic characteristics including age and sex, tumor localization, tumor diameter, macroscopic tumor type (the Borrmann classification), histological type, depth of invasion, lymphovascular invasion status, tumor stage, LN stage, survival status, survival times, follow-up duration, number of mLNs, total number of eLNs, and the AJCC TNM stage. All patients were postoperatively evaluated in the Department of Oncology. Adjuvant treatment protocols were used by the medical oncologists for patients deemed appropriate. The patients were planned to be followed every 3 months in the first 3 years, every 6 months until the postoperative 5th year, and thereafter once in a year. Follow-up assessments included physical examinations, radiologic examinations, endoscopic examinations, and laboratory analyses.

OS was defined as the time from primary surgery to death or to the final follow-up. The probability of 5-year OS was calculated for each patient using the nomogram developed by Wang et al.^[10] Information about mortality was obtained from the Republic of Turkish Ministry of Health National Death Notification System and from the Republic of Turkish Ministry of Interior Central Population Management System for patients who were lost-to-follow-up due to various reasons or for those followed in external centers. For these patients, survival times were calculated as the difference between the time of death obtained from these systems and the time of primary surgery.

All patients were classified according to the 8th AJCC TNM staging system^[4] and their observed OS rates (the 8th AJCC staging system-predicted OS) were calculated. The OS of patients were also calculated using the nomogram defined by Wang et al.^[10]

Statistical Analysis

Data analyses were performed using the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics were expressed as mean, standard deviation (SD), median, minimum (min), maximum (max), frequency, and ratio. The distribution of variables was analyzed using the Kolmogorov–Smirnov test. Quantitative independent variables were analyzed using the independent sample t-test and Mann–Whitney U test, where appropriate. Qualitative independent variables were analyzed using the Chi-square test; when assumptions for the Chi-square test were not fulfilled, the Fisher's exact test was used for the analysis of qualitative independent variables. The receiver operative characteristics (ROC) curves were used to determine the predictive abilities of the nomogram and the 8th AJCC staging system for OS. Univariate and multivariate logistic regression analyses were performed to assess the significant predictors of mortality. The level of efficacy was analyzed by the univariate and multivariate logistic regression analyses. $P < 0.05$ was considered statistically significant.

Ethical Considerations

This study was conducted with the approval of institutional ethics committee (Approval no: 2-13, date:07/02/2019). Since the study was retrospectively designed, consent was not obtained from the patients. Patient data were obtained with the approval of the relevant institutions. All procedures performed in this study were compatible with the ethical standards of the institutional research committee and with those of the Declaration of Helsinki and its comparable ethical standards.

Results

The present study included 104 patients with a median age of 60.3 years (min-max, 32.7–84.4 years) and 82 (78.8%) of the patients were males. The mean follow-up period was 47.7 ± 39.6 months (median, 37.4 months; min-max, 0.9–122.9 months). Of the patients, 69 (66.3%) died within the follow-up period. The number of patients achieving 5-year survival was 35 (33.7%). The demographic and clinicopathologic characteristics of the present cohort as compared with those of the primary cohort in the study by Wang et al.^[10] are presented in Table 1.

Accordingly, the two cohorts were observed to be similar in terms of sex, the ratio of patients achieving 5-year survival, histologic type, tumor invasion, tumor diameter, and the number of mLNs. On the other hand, the two cohorts significantly differed in terms of distribution of patients according to the Borrmann classifications, presence of lymphovascular invasion, and tumor localization.

The patients were also evaluated in two groups as those who achieved and did not achieve 5-year survival (Table 2). Accordingly, the mean age ($p = 0.001$), number of mLNs ($p < 0.001$), total number of eLNs ($p < 0.001$), distributions of patients according to T stage and N stage ($p < 0.001$ for both), and according to the presence of lymphovascular invasion ($p < 0.001$) were significantly higher in those who did not achieve 5-year survival than in those who achieved 5-year survival. The probability of OS calculated by the nomogram and the probability of observed OS calculated according to the 8th AJCC staging system were significantly lower in the patients who did not achieve 5-year survival than in those who achieved (mean OS, 0.20 ± 0.18 and 0.46 ± 0.26 , respectively, for the nomogram-predicted OS; mean OS, 0.51 ± 0.21 and 0.71 ± 0.19 , respectively, for the 8th AJCC staging system-predicted OS; $p < 0.001$ for both).

In the univariate model, age, number of mLNs, total number of eLNs, T stage, N stage, lymphovascular invasion, the nomogram-predicted survival, and the AJCC staging system-predicted survival were found as significantly effective variables in predicting 5-year mortality ($p < 0.05$ for all; [Table 3]). The multivariate regression model demonstrated that age ($p = 0.01$) and the nomogram-predicted survival ($p < 0.001$) were significant and independent predictors of 5-year mortality (Table 3). Distribution of the mean OS rates determined by the nomogram and according to the 8th AJCC staging system in the patients who achieved and did not achieve 5-year survival is presented in Figure 1.

According to the ROC analysis (Fig. 2), the area under the curve (AUC) for the nomogram (AUC, 0.801; 95% CI, 0.715–0.887; $p < 0.001$) and the AUC for the 8th AJCC staging system (AUC, 0.754; 95% CI, 0.659–0.849; $p < 0.001$) demonstrated that both the nomogram and the 8th AJCC staging system had significant predictive ability for OS. The AUC for the nomogram was larger than that of the 8th AJCC staging system.

Discussion

The recommended surgical approach for the treatment of gastric cancer has enhanced survival rates of patients.^[12] Staging is critical for prognosis and treatment planning for both patients and clinicians. Precise staging results in more successful prediction and more individualized treatment. TNM staging is still the gold standard system in oncology; current TNM staging system in gastric cancers has three critical components; tumor invasion, number of mLNs, and presence of distant metastasis.^[4] On the other hand, nomograms, which are used as prognostic tools in oncology and medicine, provide precise, and tailored predictions by combining multiple clinical variables. In gastric

Table 1. Demographic and clinicopathologic characteristics of the present cohort as compared with those of the primary cohort in the study by Wang et al.^[10]

Characteristics	Present study cohort (n=104) mean±SD/n (%)	Primary cohort of Wang et al. ^[10] (n=872) mean±SD/n (%)	p
Age, years			
<40	6 (5.8)	44 (5.0)	0.003*
40-49	10 (9.6)	119 (13.6)	
50-59	33 (31.8)	243 (27.9)	
60-69	25 (24.0)	345 (39.6)	
>70	30 (28.8)	121 (13.9)	
Sex			
Female	22 (21.2)	211 (24.2)	0.571*
Male	82 (78.8)	661 (75.8)	
Tumor localization			
I (upper)	23 (22.1)	184 (21.1)	0.002*
II (middle)	33 (31.7)	155 (17.8)	
III (lower)	48 (46.2)	533 (61.1)	
Macroscopic Type (Borrmann classification)			
Early	9 (8.7)	144 (16.5)	<0.001*
B1	16 (15.4)	29 (3.3)	
B2	40 (38.5)	154 (17.7)	
B3	33 (31.7)	476 (54.6)	
B4	6 (5.8)	69 (7.9)	
Lymphovascular invasion			
Present	71 (68.3)	170 (19.5)	<0.001*
Absent	33 (31.7)	702 (80.5)	
Achieving 5-year survival			
No	63 (60.6)	478 (54.8)	0.311*
Yes	41 (39.4)	394 (45.2)	
Depth of invasion			
Mucosa	3 (2.9)	53 (6.1)	0.271*
Submucosa	6 (5.8)	75 (8.6)	0.422*
Proper muscle	14 (13.5)	123 (14.1)	0.976*
Subserosa	25 (24.0)	347 (39.8)	0.003*
Serosa	39 (37.5)	249 (28.5)	0.075*
Distant organ	17 (16.35)	25 (2.9)	<0.001*
Histologic type			
Differentiated	49 (47.1)	352 (40.4)	0.223*
Undifferentiated	55 (52.9)	520 (59.6)	
Tumor diameter	5.6±2.5	5.25±2.76	0.217**
Number of metastatic LNs	3.5±3.9	2.14±2.92	<0.001**
Total number of eLNs	9.7±4.25	9.45±4.02	0.551**

*Chi-square test, **t-test. SD: Standard deviation, LN: Lymph nodes, eLNs: Examined lymph nodes.

cancers, nomograms have been mainly developed based on patient groups with adequate LN dissections. However, inadequate LN dissection is a quite common condition and is associated with adverse outcomes and stage migration. The present study demonstrated that the nomogram developed by Wang et al.^[10] for gastric cancer patients with a pathologically confirmed diagnosis, an insufficient number

of eLN (<16) and R0 surgical resection, was effective in predicting 5-year OS in the present cohort and compared with the AJCC staging system.

The AJCC cancer staging manual recommends at least 16 LN dissections for optimal evaluation in gastric cancers. However, the recommended number of eLNs for an excellent staging is 30.^[4,13] Many studies have found that

Table 2. Comparison of the characteristics of patients who achieved and did not achieve 5-year survival

Characteristics	Patients who achieved 5-year survival (n=41) mean±SD/n (%)	Patients who did not achieve 5-year survival (n=63) mean±SD/n (%)	p
Age (years) Mean±SD, (median)	57.5±11.0 (56.7)	65.1±11.5 (64.7)	0.001*
Sex, n (%)			
Female	9 (22)	13 (20.6)	0.872**
Male	32 (78)	50 (79.4)	
Tumor diameter Mean±SD, (median)	5.1±2.6 (5.0)	5.9±2.4 (5.5)	0.061***
Number of mLNs			
Mean±SD, (median)	1.7±2.7 (0.0)	4.7±4.2 (4.0)	<0.001***
Total number of eLNs			
Mean±SD, (median)	8.4±4.0 (9.0)	10.5±4.2 (12.0)	0.007***
T stage, n (%)			
T1	8 (19.5)	1 (1.6)	<0.001**
T2	10 (24.4)	3 (4.8)	
T3	6 (14.6)	20 (31.7)	
T4	17 (41.5)	39 (61.9)	
N stage, n (%)			
N0	24 (58.5)	14 (22.2)	<0.001**
N1	8 (19.5)	10 (15.9)	
N2	6 (14.6)	20 (31.7)	
N3	3 (7.3)	19 (30.2)	
Tumor localization, n (%)			
I (upper)	7 (17.1)	16 (25.4)	0.907**
II (middle)	14 (34.1)	19 (30.2)	
III (lower)	20 (48.8)	28 (44.4)	
Lymphovascular invasion, n (%)			
Present	17 (41.5)	54 (85.7)	<0.001**
Absent	24 (58.5)	9 (14.3)	
Surgery			
Subtotal resection	30 (73.2)	42 (66.7)	0.482**
Total resection	11 (26.8)	21 (33.3)	
Nomogram-predicted-OS Mean±SD, (median)	0.46±0.26 (0.50)	0.20±0.18 (0.14)	<0.001***
The 8 th AJCC staging system-predicted OS Mean±SD, (median)	0.71±0.19 (0.68)	0.51±0.21 (0.54)	<0.001***

*t-test, **Chi-square test, ***Mann-Whitney U test. SD: Standard deviation, LN: Lymph nodes, eLNs: Examined lymph nodes, OS: Overall survival, AJCC: The American Joint Committee on Cancer.

increased number of eLNs are associated with improved survival.^[14,15] Japan and Korea are the accepted reference points in gastric cancer surgery. Extended LN dissection is not routinely performed in Europe and the USA. In a study comparing from Korean and US patient groups, in terms of survival after R0 resection for gastric cancer, the proportions of patients with inadequate eLNs (<15) dissection were 3% in Korea and 22% in the USA.^[16] In the present study, the pathology revealed inadequate LN dissections in 39.7% of the patients operated for gastric cancer, which was higher than the rates reported in the literature.^[16] The number of eLNs is related to surgical technique and pathological examination. Accordingly, the high rate of patients with insufficient number of eLNs in the pres-

ent study may be attributed primarily to the fact that our center is not specific to oncological surgery. Coburn et al.^[13] prepared a clinical practice guideline and recommended referral of gastric cancer patients to high-volume hospitals as surgery-related deaths are less likely in these centers. In a study comparing Korean and Italian cohorts, the number of eLNs in the Italian centers specific for gastric cancer surgery was comparable to that in the Korean centers and this finding was reported to be important for surgical quality.^[17] Furthermore, in that particular study, survival in the Italian centers specific to gastrointestinal surgery was found to be equivalent to that in the Korean centers, which was associated with the number of eLNs.^[17] In another study from Korea, it was stated that 15 eLNs would not be adequate

Table 3. Results of univariate and multivariate logistic regression analyses

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.06	1.02–1.11	0.002	1.06	1.01–1.11	0.010
Number of mLNs	1.30	1.11–1.52	0.001			
Total number of eLNs	1.13	1.02–1.25	0.016			
T stage	2.10	1.35–3.27	0.001			
N stage	2.19	1.44–3.33	<0.001			
Lymphovascular invasion	7.12	2.84–17.86	<0.001			
Nomogram-predicted OS	0.01	0.00–0.08	<0.001	0.01	0.00–0.10	<0.001
8 th AJCC staging system-predicted OS	0.01	0.00–0.10	<0.001			

OR: Odds ratio, CI: Confidence interval, mLNs: Metastatic lymph nodes, eLNs: Examined lymph nodes, OS: Overall survival, AJCC: American Joint Committee on Cancer

for further curative surgery and that extended LN dissection should be considered in patients with advanced-stage carcinoma.^[18] In the previous studies, the number of identified LNs <16 in gastric cancer patients was found to be associated with inadequate examination of pathological specimens.^[19] In a retrospective study, the mean number of identified LNs by Japan and American pathologists was reported as 62 and 12 LNs in D2 dissections. Accordingly, it is important for the clinicians to encourage the pathologists for being more sensitive on this issue.

The determined number of mLNs is affected by the number of eLNs. This might lead to false staging, which is called as the Will Rogers phenomenon (stage migration) and was first described by Feinstein et al.^[20] Most of the nomograms from multiple earlier studies used the number of mLNs as the parameter. However, it is known that a decrease in the number of eLNs would result in falsely low numbers of mLNs and would increase the margin of error in predictions. The LN ratio (mLNs/eLNs) has been proposed to minimize the stage migration.^[21]

As is known, patients with the same cancer stage have different genetic, cellular, and clinicopathologic characteristics and do not have similar lifestyles. According to the TNM staging system, prognosis varies significantly between patients having the same stage. The TNM staging system does not include other factors that affect survival; such as age, sex, and tumor morphology. Therefore, instead of using TNM staging-like systems that are based only on pathological findings, nomograms combining the clinical and pathological parameters are used to improve the ability to predict disease prognosis.^[6] Nomograms provide a more individualized prediction of prognosis and are currently the popular research topics. Novel nomograms are continually generated and validated; however, a small number of them has been tested in different cohorts and validated external-

ly.^[6,17] There are numerous nomograms for the prediction of survival and recurrence in gastric cancers. However, these nomograms include patient groups consisting predominantly of those with adequate LN dissections.^[9–11] There are studies demonstrating that patients with the number of eLNs <16 and those with the number of eLNs ≥16 are different in prognosis and survival. Biffi et al.^[22] investigated the prognostic efficacy of the number of eLNs and demonstrated increased number of eLNs to be correlated with better prognosis even in patients without LN metastasis. Biondi et al.^[23] suggested that gastric cancer patients with the number of eLNs <16 showed worse prognosis and that D2 LN dissection would provide survival benefit assuming that extended surgical dissection would give higher number of LNs. On the other hand, Degiuli et al.^[12] associated extended LN dissection with increased perioperative mortality. Accordingly, making the nomograms more individualized and preparing them with more specific groups would improve their ability of prediction. In the present study, the nomogram that was developed and internally validated by Wang et al.^[10] for gastric cancer patients with insufficient number of eLNs (<16 eLNs) was evaluated in our patient group. Comparison of the patients who achieved and did not achieve 5-year survival revealed that age, number of mLNs, and number of eLNs were higher, T stage and N stage were more advanced, and lymphovascular invasion positivity was higher in the patients who did not achieve 5-year survival. Similarly, in a study conducted on more than 100,000 surgically resected gastric cancer patients, advanced age, increased number of mLNs, advanced T and N stages, and presence of lymphovascular invasion were associated with mortality observed within 5 years.^[24] However, the difference observed between males and females in terms of 5-year OS in that particular study^[24] was not observed in the present study. While a positive correlation was reported between increased number of eLNs and

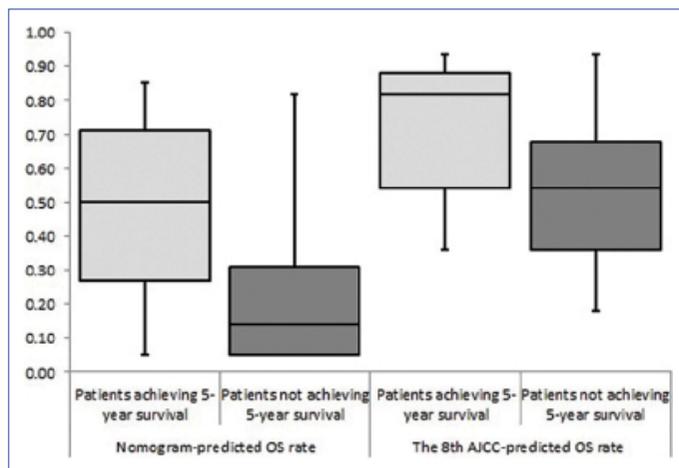


Figure 1. Distribution of the mean overall survival rates determined by the nomogram and according to the 8th American Joint Committee staging system in the patients who achieved and did not achieve 5-year survival.

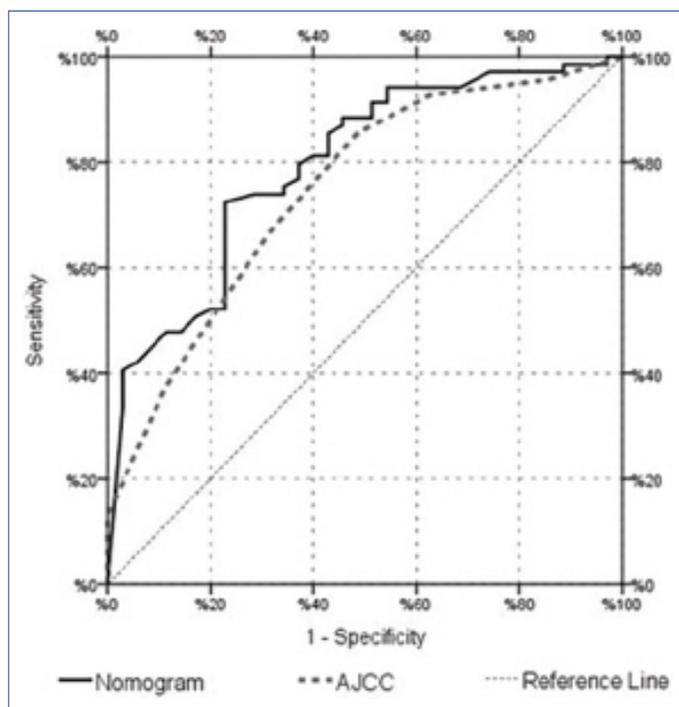


Figure 2. Receiver operating characteristics curves for the nomogram and for the 8th American Joint Committee on Cancer (AJCC) staging system in predicting the overall survival in gastric cancer patients with insufficient number of examined lymph nodes. The area under the curve (AUC) for the nomogram: 0.801 (95% confidence interval [CI], 0.715–0.887; $p < 0.001$); the AUC for the 8th AJCC staging system: 0.754 (95% CI, 0.659–0.849; $p < 0.001$).

survival in the study by Biffi et al.,^[22] the number of eLNs was significantly higher in the patients who did not achieve 5-year survival in the present study.

The concordance index (C - index) is an important outcome in assessing the predictive ability of nomograms. The C-

index of many nomograms ranges between 0.7 and 0.8.^[25] The C - index for the nomogram developed by Wang et al.,^[10] which was used in this study, was 0.742 and 0.743 in development and validation cohorts. In the present cohort, the C - index of the nomogram was found as 0.80, which indicates that the nomogram has a higher predictive value in the present cohort. As compared with the cohort in the study by Wang et al.,^[10] the present cohort has more advanced T stage, mid 1/3 tumor localization, a higher rate of lymphovascular invasion, and a higher number of mLNs. Contrary to the expected result, the higher C - index found for the nomogram was interpreted as the improved efficacy of the nomogram in the present cohort.

The present study has some limitations. First, both the present study and the study^[10] in which the nomogram was developed have retrospective study designs. The efficacy of the nomogram was not evaluated in a patient group receiving preoperative treatment such as neoadjuvant chemotherapy. Moreover, the nomogram was developed in a smaller cohort as compared with the nomograms evaluated in larger cohorts for many other types of cancer. Similarly, the patients evaluated in the present study were also low in number. The major reason for the small number of patients included in the present study was evaluation of only the patients with inadequate LN dissections, which is a non-ideal and unwanted parameter.

Conclusion

The results of this study revealed that the nomogram, which was developed and internally validated by Wang et al.^[10] for gastric cancer patients with insufficient number of eLNs (<16 eLNs), was confirmed to be effective in predicting 5-year OS in the present cohort. Moreover, the nomogram was also found to be superior to the 8th AJCC TNM staging manual in predicting 5-year OS in our cohort. It can be suggested that this nomogram, which provides a more individualized survival prediction, can be safely used by clinicians in the post-operative period while planning therapeutic process in gastric cancer patients and addressing the expectations related to survival probability after surgery.

Disclosures

Ethics Committee Approval: The study was approved by the Alaaddin Keykubat University Clinical Research Ethics Committee (Date: 07/02/2019, No: 2-13).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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