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ORIGINAL ARTICLE

A prognostic model based on lymph node metastatic ratio for predicting survival outcome in gastric cancer patients with N3b subclassification

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Summary *Background:* Determining the survival outcome for gastric cancer patients with metastases to more than 15 regional lymph nodes is difficult. This study aims to develop a lymph node metastatic ratio (LNR)-based prognostic model to predict the survival outcome after D2 surgery in such patient groups.
Methods: Our study retrospectively enrolled 139 gastric cancer patients with metastases to more than 15 regional lymph nodes who underwent D2 surgery between 2007 and 2014. Clinicopathologic variables to predict overall survival (OS) using multivariate Cox regression were selected to create a prognostic model.
Results: The prognostic model for predicting OS was developed based on five independent factors, namely, T-classification (T2 or T3 vs. T4), LNR (<0.80 vs. ≥0.80), carcinoembryonic antigen level (<5 vs. ≥5 ng/ml), Eastern Cooperative Oncology Group performance scale (scale 0–1 vs. ≥2), and adjuvant chemotherapy (yes vs. no). Using the prognostic score, patients were stratified into good, intermediate, and poor prognostic groups. The median OS in the good, intermediate, and poor prognostic risk groups was 32.0 months (95% confidence interval [CI]: 22.3–41.7), 12.4 months (95% CI: 8.5–16.3), and 5.4 months (95% CI: 2.1–8.7), respectively. The c-index of the prognostic model was 0.79 (95% CI: 0.71–0.87).

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Conclusion: This study developed an accurate LNR-based prognostic model for predicting the survival outcome after D2 surgery in gastric cancer patients with metastasis to more than 15 regional lymph nodes. This model might assist clinicians in prognostic stratification of such patients and convince eligible patients to receive adjuvant chemotherapy.

1. Introduction

Gastric cancer is the fourth most common cancer and also the fourth most common cause of cancer-related mortality worldwide.[1] The prevalence rate and mortality rate of gastric cancer is particularly higher in Eastern Asia, including Taiwan, than in Western Europe and North America.[2] Surgical resection is the primary choice for curative treatment of gastric cancer[3,4]; however, approximately only 33—55% of patients survive more than 5 years after gastrectomy and extended lymph node dissection (D2 surgery).[4,5]

Patients with metastases to more than 15 regional lymph nodes such condition were categorized to have stage IV disease in the 6th edition of the AJCC staging system, implying an extremely poor prognosis of this disease similar to distant metastases.[6,7] In the 7th AJCC staging system, patients with metastases to more than 15 regional lymph nodes were classified as N3b and categorized as stage III.[8] Finally, the prognostic value of metastases to more than 15 regional lymph nodes was modified to stage IIIB or IIIC and was separated from those with 7—15 regional lymph node metastases in the latest version of AJCC (8th edition).[9]

Determining the survival outcome for patients with metastases to more than 15 regional lymph nodes is difficult due to the following reasons. First, although removing more than 30 regional lymph nodes is desirable,[10] the optimal number of regional lymph nodes that should be retrieved is still debated.[11] The inevitable increase in the number of dissected lymph nodes dissected results in a high incidence of postoperative morbidities and mortalities.[5] Although the high number of metastatic regional lymph nodes implied poor outcome, the prognostic value of more than 15 metastatic regional lymph nodes is yet to be completely established. Therefore, the numbers of metastatic regional lymph nodes alone have no further clinical value in patients classified as N3b. Recently, a high lymph node metastatic ratio (LNR) had been described as a poor prognostic factor in several gastric cancer studies.[12—16] In line with previous reports, the present study aimed to identify the prognostic value of LNR and to develop an LNR-based prognostic model for predicting the survival outcome after D2 surgery in patients with gastric cancer and metastases to more than 15 regional lymph nodes.

2. Material and methods

2.1. Patients and treatment

The present study included 139 gastric cancer patients with metastasis to more than 15 regional lymph nodes who underwent radical gastrectomy and D2 lymph node dissections between 2007 and 2014 at the Chang Gung Memorial Hospital Linkou Branch. All patients received curative surgery with no residual tumor resection (R0) or microscopic residual tumor resection (R1). Patients who had recurrent tumors, metastatic tumors, grossly residual tumor (R2 resection), or prior chemotherapy or radiotherapy were excluded. All patients were advised to receive adjuvant chemotherapy within 6 weeks after the radical surgery. However, the final decision to receive or decline such therapy was made by the patient. Adjuvant chemotherapy was a 5-fluorouracil-based regimen, which included 5-fluorouracil administered intravenously,[17] uracil-tegafur (UFT),[18] titanium silicate (TS)-1,[19] or capecitabine plus oxaliplatin (XELOX),[20] and was determined according to the physician's discretion. The 5-fluorouracil or XELOX regimen was administered for 6 months, whereas the UFT or TS-1 regimen was administered for up to 1 year. Patient characteristics were analyzed to identify the variables associated with survival outcome. The study complied with the 1996 Helsinki Declaration and was approved by the institutional review board of the hospital.

2.2. Data collection and follow-up

Administrative and clinical data consisted of patient demographics collected retrospectively, including clinical features with age, sex, and Eastern Cooperative Oncology Group performance status (ECOG PS); American Society of Anesthesiologists (ASA) score; history of previous cancer; pre-existing comorbidities; stump cancer or not; family history of gastric cancer; preoperative body mass index (BMI); preoperative carcinoembryonic antigen (CEA) level; preoperative cancer antigen 19-9 (CA19-9) level; and pathological results, including *Helicobacter pylori* infection; surgical margin; perineural, lymphatic, or vascular invasion; Lauren classification[21]; lymph node retrieval ratio; LNR; and tumor (T) classification. Data were recorded by the primary care clinicians using an electronic patient record form at the time of cancer diagnosis. Comorbidities were represented by modified Charlson Comorbidity Index (CCI),[22] excluding patient age and cancer diagnosis. The overall survival (OS) and disease-free survival (DFS) rates were calculated from the time of surgery to the time of death and tumor recurrence, respectively. Data on the dates of the surgery, tumor recurrence, and the death of each patient were obtained from the institutional cancer center registry or the National Register of Death Database in Taiwan. All of the included patients were followed-up until the date of death or June 30, 2016.

2.3. Statistical analysis

Basic demographic data were summarized as *n* (%) for categorical variables and median with a range of 95% confidence interval (CI) for continuous variables. Distribution of clinical variables was tabulated as *n* (%) and compared between the two groups using the Pearson chi-square test. Possible clinical and pathologic variables for OS after cancer surgery were examined via univariate and multivariate logistic regressions. A prior statistical analysis plan was approved in univariate analysis, and variables with *P* values < 0.10 in univariate analysis were included for analysis in the multivariate model. A multivariate, proportional hazard Cox model with backward selection was performed to determine which factors were independently predictive of survival. A risk model was developed from a multivariate logistic regression model. The β-coefficients from the risk model were used to generate the points of the prognostic score for calculating survival time. Patients were further stratified into 3 prognostic groups according to the total score obtained from the prognostic score. Survival time was analyzed using the Kaplan–Meier method. Log-rank tests were used to determine significant differences between the survival curves. The prognostic model was internally validated by using bootstrapping method (200 repetitions) to obtain a relatively unbiased estimate of the models' performance. The monotonicity of each variable was assessed using the linear trend chi-square test. The linear trend test, homogeneity likelihood ratio, and c-index of each independent variable within the multivariate analysis and the full model were calculated to determine the model performance. All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) and R version 2.9.1 (The R Foundation for Statistical Computing, Vanderbilt University, Nashville, TN) using the Hmisc and Design libraries. All statistical assessments with $P < 0.05$ were considered significant.

3. Results

Table 1 shows the demographic data of the 139 patients. The median age was 64 years (range, 36–90), and 66.9% of the patients were men. The distribution of the T-classification was 1.4%, 28.1%, and 70.5% for stages T2, T3, and T4, respectively. The most common Lauren histological classification was diffuse type (48.2%), followed by intestinal type (39.7%), and mixed or unclassified type (12.2%). Before surgery, 31 (22.3%) and 28 (20.1%) patients had elevated serum CEA level and CA19-9 level, respectively. Sixty-four patients (46.0%) received total gastrectomy, whereas the other 75 patients (54%) received subtotal gastrectomy. The median number of retrieved lymph nodes and metastatic lymph nodes was 43 (range, 17–135) and 22 (range, 16–67), respectively. Accordingly, the distributions of LNR 0–0.39, 0.40–0.59, 0.60–0.79, and 0.80–1.0 were 18.7%, 36.0%, 23.0%, and 22.3%, respectively. In total, 31 patients (22.3%) had microscopic residual tumor, and 86 (61.9%) received adjuvant chemotherapy. No patient received adjuvant radiotherapy in our patient cohort. In total, 86 (61.9%) and 53 (38.1%) patients were categorized into the adjuvant and non-adjuvant chemotherapy groups, respectively. Patients in the non-adjuvant chemotherapy group were generally older, poorer ECOG status, and higher ASA class.

At the end of the study, 99 patients (73.3%) had died, and 95 (68.3%) had recurrent tumor. The median OS and DFS were 17.9 months (95% CI: 11.8–24.0) and 10.9 months (95% CI: 7.2–14.7), respectively. The results of univariate analyses for clinical variables associated with OS and DFS are presented in Table 2. Five variables, namely, T-classification, LNR, CEA, ECOG PS, and adjuvant chemotherapy, showed a statistically significant effect on OS and DFS in univariate analysis. Age and CCI were two additional significant variables affecting OS in univariate analysis. The variables identified via univariate analysis to be significantly associated with OS were included in the multivariate analysis. T-classification, LNR, CEA, ECOG PS, and adjuvant chemotherapy were the only independent prognostic factors for OS in multivariate analysis. The hazards ratios for each variable in multivariate analysis are shown in Fig. 1.

The risk model and scoring system of prognostic score generated from β-coefficients of multivariate analysis for OS are shown in Table 3. The total prognostic scores ranged from 0 to 5. Using the prognostic score, patients were stratified into good (total score: 0–1), intermediate (total score: 2–3), and poor (total score: 4–5) prognostic groups. Based on the prognostic score, 46.8%, 40.3%, and 12.9% of the patients were categorized under good, intermediate, and poor prognostic groups, respectively. The median OS in the good, intermediate, and poor prognostic risk groups was 32.0 months (95% CI: 22.3–41.7), 12.4 months (95% CI: 8.5–16.3), and 5.4 months (95% CI: 2.1–8.7), respectively (Fig. 2). The hazard ratios were 2.67 (95% CI: 1.71–4.18; $P < 0.001$) when comparing the intermediate and good prognostic groups and 10.3 (95% CI: 5.50–19.2; $P < 0.001$) when comparing the poor and good prognostic groups. Accordingly, the median DFS rate in the good, intermediate, and poor prognostic risk groups was 29.3 months (95% CI: 14.4–44.3), 8.7 months (95% CI: 6.60–10.9), and 5.5 months (95% CI: 5.19–5.79), respectively, with a hazard ratio of 2.70 (95% CI: 1.74–4.20; $P < 0.001$) when comparing the intermediate and good prognostic groups and 4.79 (95% CI: 2.40–9.55; $P < 0.001$) when comparing the poor and good prognostic groups (Supplementary Fig. 1).

Supplementary Table 1 shows the prognostic stratification performance among each independent variable in multivariate analysis and the entire model. The performance of the entire model is superior to each variable in terms of monotonicity, homogeneity, and discriminatory capability of prognostic prediction. The c-index of the model for OS and DFS was 0.79 (95% CI: 0.71–0.87) and 0.68 (95% CI: 0.59–0.77), respectively.

The impact of type of adjuvant chemotherapy regimen on survival outcome was further analyzed in Supplementary Fig. 2. Among 86 patients who received adjuvant chemotherapy, 35 patients (40.7%) received the XELOX regimen and 51 patients (59.3%) received 5FU or TS-1 or UFT regimen. In general, patients who received any regimen of chemotherapy had better overall survival outcomes in terms than those treated without adjuvant chemotherapy. There was no statistical difference in overall survival between patients receiving XELOX or other chemotherapy regimens ($P = 0.13$).

Table 1 Basic characteristics of patients.

Variable	Category	Overall, $n = 139$ (%)	Adjuvant group, $n = 86$ (%)	Non-adjuvant group, $n = 53$ (%)	*P* value
Age, years	Median, range	64 (36–90)	60.6 (36–90)	74.0 (40–87)	<0.001
Gender	Male	93 (66.9)	56 (65.1)	37 (69.8)	0.58
Body mass index, kg/m^2	<18.5	13 (9.4)	6 (7.0)	7 (13.2)	0.33
	18.5–25	96 (69.1)	59 (68.6)	37 (69.8)	
	>25	30 (21.6)	21 (24.4)	9 (17.0)	
Charlson comorbidity index	0	60 (43.2)	43 (50.0)	17 (32.1)	0.11
	1	43 (30.9)	24 (27.9)	19 (35.8)	
	>1	26 (25.9)	19 (22.1)	17 (32.1)	
Admission mode	OPD	99 (71.2)	64 (74.4)	35 (66.0)	0.34
	ER	48 (22.8)	22 (25.6)	18 (34.0)	
T-classification	2	2 (1.4)	1 (1.2)	1 (1.9)	0.52
	3	39 (28.1)	27 (31.4)	12 (22.6)	
	4	98 (70.5)	58 (67.4)	40 (75.5)	
Tumor grade	Moderate	25 (18.0)	15 (17.4)	10 (18.9)	0.84
	Poorly	114 (82.0)	71 (82.6)	43 (81.1)	
Lauren classification	Diffuse	67 (48.2)	41 (47.7)	26 (49.1)	0.32
	Intestinal	55 (39.7)	37 (43.0)	18 (34.0)	
	Mixed or unclassified	17 (12.2)	8 (9.3)	9 (17.0)	
Serum CEA, ng/dL	>5	31 (22.3)	18 (20.9)	13 (24.5)	0.68
Serum CA19-9, ng/dL	>37	28 (20.1)	17 (19.8)	11 (20.8)	1.0
ECOG PS	0–1	95 (68.3)	71 (82.6)	24 (45.3)	<0.001
	2–4	44 (31.7)	15 (17.4)	29 (54.7)	
ASA score	2	64 (46.0)	45 (52.3)	19 (35.8)	0.023
	>2	75 (54.0)	41 (47.7)	34 (64.2)	
Gastrectomy method	Total	64 (46.0)	38 (44.2)	26 (49.1)	0.61
	Subtotal	75 (54.0)	48 (55.8)	27 (50.9)	
Lymph node retrieved number	Median, range	43(17–135)	44.5 (19–135)	40 (17–91)	0.38
Metastatic lymph node number	Median, range	22 (16–67)	22.5 (16–62)	22.0 (16–67)	0.49
Lymph node metastatic ratio	0–0.39	26 (18.7)	16 (18.6)	10 (18.9)	0.08
	0.40–0.59	50 (36.0)	37 (43.0)	13 (24.5)	
	0.60–0.79	32 (23.0)	19 (22.1)	13 (24.5)	
	0.80–1.0	31 (22.3)	14 (16.3)	17 (32.1)	
Perineural invasion	Yes	110 (79.1)	67 (77.9)	43 (81.1)	0.83
Vascular invasion	Yes	53 (38.1)	30 (34.9)	23 (43.4)	0.37
Lymphatic invasion	Yes	131 (94.2)	80 (96.2)	51 (93.0)	0.71
H. pylori infection	Yes	23 (16.5)	14 (16.3)	9 (17.0)	1.00
Surgical margin	Positive	31 (22.3)	15 (17.4)	16 (30.2)	0.10

OPD, outpatient department; ER, emergency room; CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists.

4. Discussion

In this study, LNR was shown to be an independent prognostic factor of OS and DFS after D2 surgery in gastric cancer patients with metastasis to more than 15 regional lymph nodes. We developed an LNR-based prognostic model for predicting survival outcomes in patients with locally advanced gastric cancer. The model accurately predicted survival outcome and was internally validated with a bootstrapped corrected c-index of 0.79. All the five independent variables of this prognostic model are accessible and are available during preparation for adjuvant chemotherapy. Therefore, this model is widely applicable. This study showed that the LNR-based model might enable prognostic stratification of locally advanced gastric cancer patients after surgical resection and might assist clinicians in counseling patients appropriately.

High numbers of metastatic regional lymph nodes imply a poor prognosis.[13] Unfortunately, no prognostic stratification model that considers the number of metastatic lymph nodes in patients with metastases to more than 15 regional lymph nodes is available in literature. The LNR, calculated by dividing the number of metastatic lymph nodes with the total number of retrieved lymph nodes, might replace the number of metastatic lymph nodes as a prognostic factor in such circumstance. High LNR denotes either extensive metastases of regional lymph nodes or few numbers of lymph node retrieved, thus indicating either more locally advanced tumor stage or less extensive lymph node dissection. LNR is consistently associated with poor prognosis in several types of gastrointestinal cancers, including gastric cancer,[12–16] colorectal cancer,[23] pancreatic cancer,[24] and ampulla of Vater cancer,[25] as well as in other non-gastrointestinal tract malignancies.[26] Komatsu

Table 2 Univariate analysis for overall survival and disease-free survival.

Variable	Category	No (%)	Overall survival		Disease-free survival	
			Median survival (95% CI)	Univariate *p*	Median survival (95% CI)	Univariate *p*
Total		139	17.9 (11.8–24.0)		10.9 (7.2–14.7)	
Age, year	≤65	75	24.6 (18.3–30.9)	<0.001	15.5 (8.0–22.9)	0.096
	>65	64	12.3 (6.8–17.8)		10.4 (6.7–14.0)	
Gender	Male	93	16.8 (13.1–20.5)	0.14	10.9 (7.5–14.4)	0.74
	Female	64	24.5 (15.1–36.4)		10.4 (2.1–18.8)	
Body mass index, kg/m^2	<18.5	13	16.8 (11.3–22.3)	0.39	10.3 (7.4–13.1)	0.45
	18.5–25	96	17.7 (8.6–26.8)		10.5 (8.3–12.6)	
	>25	30	26.1 (1.6–50.6)		15.7 (6.4–25.0)	
Stump cancer	No	135	18.6 (12.4–24.8)	0.13	11.0 (6.6–15.5)	0.60
	Yes	4	10.9 (9.6–12.3)		5.6 (0–12.6)	
Family history of gastric cancer	No	131	18.6 (12.2–25.1)	0.88	11.0 (6.8–15.2)	0.86
	Yes	8	13.7 (8.90–18.6)		8.9 (6.3–11.5)	
Charlson comorbidity index	0	60	25.3 (20.8–29.8)	0.002	14.1 (2.7–25.6)	0.54
	1	43	16.8 (10.6–23.0)		9.4 (5.4–13.4)	
	>1	36	8.1 (3.8–12.4)		11.0 (1.0–21.0)	
Admission mode	OPD	99	18.7 (11.8–25.7)	0.70	11.5 (6.2–16.8)	0.94
	ER	40	17.7 (8.5–26.8)		10.5 (7.6–13.3)	
T-classification	2–3	41	31.9 (24.3–39.5)	0.005	20.1 (9.5–30.7)	0.018
	4	98	13.7 (10.7–16.8)		9.8 (7.9–11.7)	
Lymph node metastatic ratio	<0.40	26	24.0 (20.4–27.5)	0.004	11.0 (3.1–18.9)	0.008
	0.40–0.59	50	18.7 (10,5–26.9)		14.1 (2.6–25.6)	
	0.60–0.79	32	26.1 (11.2–41.0)		19.7 (7.1–32.2)	
	0.80–1.0	31	11.0 (8.5–13.5)		7.4 (6.2–8.7)	
Tumor grade	Well/moderate	25	17.7 (5.2–30.1)	0.56	11.0 (6.8–15.2)	0.84
	Poorly	114	17.9 (10.7–25.2)		10.8 (5.9–15.8)	
Lauren classification	Diffuse	51	17.9 (8.8–27.0)	0.43	11.5 (6.4–16.6)	0.31
	Intestinal	71	18.6 (9.4–27.8)		12.2 (4.2–120.2)	
	Mixed or unclassified	17	15.8 (4.9–26.8)		10.0 (5.7–14.3)	
Serum CEA, ng/dL	<5	108	24.5 (19.9–29.1)	0.001	15.5 (9.1–21.8)	0.005
	≥5	31	11.3 (9.2–13.3)		7.1 (5.2–9.0)	
Serum CA19–9, ng/dL	<37	111	18.6 (11.9–25.4)	0.61	11.5 (7.0–16.0)	0.44
	≥37	28	13.7 (4.9–22.5)		7.7 (5.4–10.0)	
ECOG PS	0–1	95	26.9 (22.0–31.8)	<0.001	15.7 (8.4–23.0)	<0.001
	>1	44	7.9 (5.6–10.2)		7.1 (5.6–8.6)	
ASA score	2	64	24.0 (17.0–30.9)	0.23	10.8 (3.7–18.0)	0.38
	>2	75	16.7(14.2–19.1)		10.9 (8.2–3.6)	
Gastrectomy method	Total	64	17.9 (13.5–22.4)	0.34	9.6 (7.4–11.9)	0.29
	Partial	75	23.6 (13.2–34.0)		13.5 (5.4–21.6)	
Perineural invasion	No	29	17.7 (7.9–27.5)	0.55	10.0 (5.7–14.2)	0.32
	Yes	110	18.6 (11.7–25.5)		11.5 (6.6–16.4)	
Vascular invasion	No	86	23.9 (14.5–33.4)	0.072	14.1 (6.6–21.6)	0.25
	Yes	53	14.7 (9.2–20.2)		9.6 (7.9–11.4)	
Lymphatic invasion	No	8	n/a	0.14	7.1 (n/a)	0.44
	Yes	131	17.7 (11.7–23.6)		10.9 (7.3–14.5)	
Resection margin	No	108	18.7 (11.7–25.7)	0.15	10.8 (7.1–14.6)	0.77
	Yes	31	12.4 (10.1–14.7)		12.2 (0.1–25.2)	
H. pylori infection	No	116	17.9 (11.2–24.7)	0.48	11.5 (6.7–16.3)	0.92
	Yes	23	18.6 (3.8–33.5)		10.4 (9.0–11.7)	
Adjuvant chemotherapy	No	53	10.9 (8.7–13.2)	<0.001	7.8 (4.8–10.7)	0.002
	Yes	86	24.6 (18.3–30.9)		15.7 (7.1–24.4)	

OPD, outpatient department; ER, emergency room; CEA, carcinoembryonic antigen; CA19-9, cancer antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; ASA, American Society of Anesthesiologists.

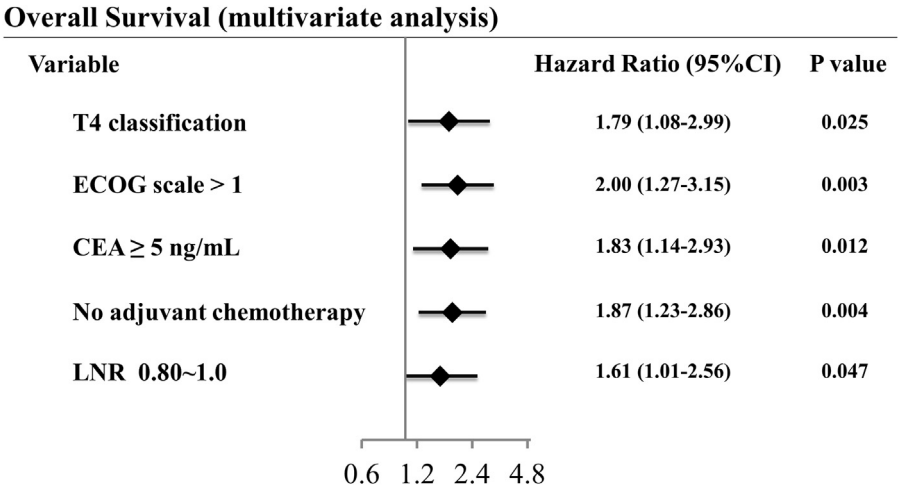

Figure 1 Multivariate analysis for overall survival.

Table 3 Prognostic score.

Variable	β-Coefficients	SE	Point	
			0	1
T-classification	0.84	0.26	2—3	4
CEA, ng/mL	0.87	0.24	<5	≥5
ECOG PS	1	0.23	0—1	≥2
LNR	0.69	0.23	<0.80	≥0.80
Adjuvant chemotherapy	0.91	0.22	Yes	No
Total score				0—5

SE, standard error; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; ASA, American Society of Anesthesiologists; LNR, ratio of metastatic lymph nodes to total retrieved lymph nodes.

et al conducted a study that included 1069 consecutive gastric cancer patients and reported that high LNR is a significant factor for high lymphatic invasion, vascular invasion, and undifferentiated cancer.[27] In the molecular level, high LNR was closely associated with epidermal growth factor receptor expression,[28] which was associated with poor patient outcomes after curative resection of gastric cancer.[29,30] However, the optimal cutoff value of LNR as a prognostic factor for gastric cancer has not been established. Kilic et al identified LNR $\geq$ 0.75 as a prognostic factor for DFS based on 71 gastric cancer patients with metastases to more than 15 regional lymph nodes who underwent D2 lymph node dissection.[31] Similarly, our study identified LNR $\geq$ 0.80 as a prognostic factor for both DFS and OS. The high cutoff value of LNR as the prognostic factor for survival outcome indicates the severity of this disease entity. In line with previous studies, we identified the prognostic value of LNR in gastric cancer patients with metastasis to more than 15 regional lymph nodes after D2 surgery. As an essential result in pathological reports, we recommend the incorporation of LNR as a prognostic tool in clinical practice for patients with gastric cancer with metastasis to more than 15 lymph nodes.

The consensus for administering adjuvant chemotherapy for gastric cancer was mainly reached through reports from meta-analysis[32,33] before 2007. The Adjuvant

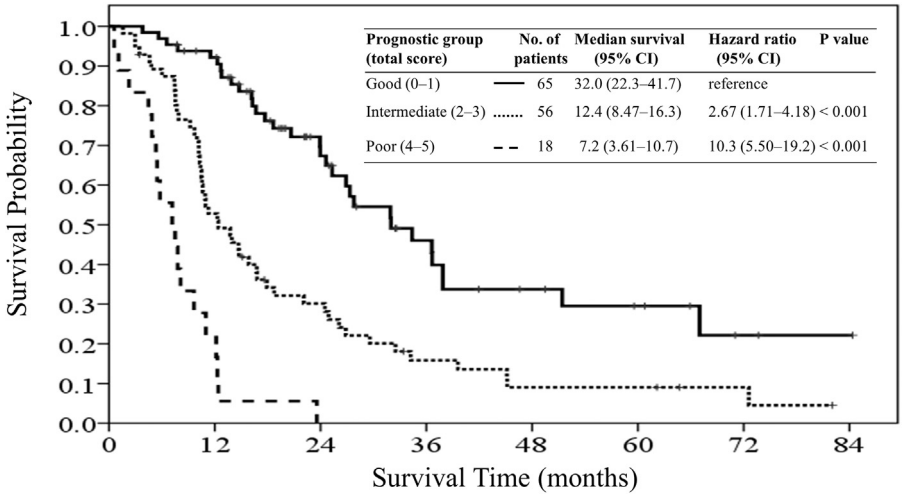

Figure 2 Overall survival curves according to the prognostic model.

Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) was the first well-designed phase III study that showed the significant benefit of adjuvant chemotherapy for Japanese patients with stage II and III gastric cancer who had undergone D2 surgery.[19] Subsequently, another positive result of a phase III study examining the benefit of capecitabine and oxaliplatin combination treatment (CLASSIC study) in patients with stage II to III gastric cancer after D2 resection was reported in 2012.[20] Based on these two positive phase III studies, the clinical benefit of adjuvant chemotherapy was agreed upon. Unfortunately, the ACTS-GC trial included patients categorized using the Japanese Gastric Cancer staging system,[34] which categorized N-classification according to anatomic location of metastatic lymph nodes rather than the numbers of lymph nodes metastases like that in the AJCC staging system. In the CLASSIC trial, patients with metastasis to more than 15 regional lymph nodes were excluded. As such, the clinical value of adjuvant chemotherapy in patients with more than 15 metastatic lymph nodes was uncertain. In real-world practice, our study identified adjuvant chemotherapy as an independent prognostic factor in this disease. D2 surgery alone was inadequate to achieve long-term survival for gastric cancer patients with metastasis to more than 15 regional lymph nodes, as the median OS and DFS was only 10.9 and 7.8 months, respectively. Based on our study, adjuvant chemotherapy should be mandatory after radical surgery for gastric cancer patients with metastasis to more than 15 regional lymph nodes.

Our model also identified T-classification, CEA level, and ECOG PS to be independent prognostic factors for advanced gastric cancer patients who underwent curative surgery. High T-classification[35] and elevated preoperative CEA level[36] reflected advanced tumor status, whereas ECOG PS indicated the patient's fitness for radical surgery.[37] Patients with better ECOG PS may have speedy recovery after surgery, can receive adjuvant chemotherapy on schedule, and tolerate the adverse events of adjuvant chemotherapy.[38] Using these well-documented clinical variables in conjunction with LNR and adjuvant treatment, we developed a prognostic model and demonstrated its superior performance to using single variables in terms of monotonicity, homogeneity, and high capability of discrimination.

In the current study, the survival outcome can be further stratified into 3 different prognostic groups based on clinicopathologic variables of each patient. To our knowledge, this is the first study to construct a prognostic model for predicting survival outcome after D2 surgery in gastric cancer patients with metastasis to more than 15 regional lymph nodes. However, this study has several limitations. First, a selection bias might exist because of the retrospective nature of the study. In our series, a high ratio of total gastrectomy (46%) was noted, which was due to the large size and bulk of the tumors (70.5% of patients had T-4 classification in our cohort) found preoperatively rather than a high prevalence of several body tumors. To achieve free and adequate length of gross sectional margin, a higher number of total gastrectomy was performed compared with other earlier stage gastric cancer patients. Even with aggressive surgical resection, the margin-positive rate is as high as 22.3% in stage IIIc gastric cancer patients, which is much higher than the value in our usual practice in less locally advanced stage patients.[36] Second, we included adjuvant treatment as a prognostic factor; as such there was selection bias regarding which patients were offered the treatment. The decision of receiving adjuvant chemotherapy and which regimens to administer might vary and depend on the patient's postoperative fitness and economic status, availability of adjuvant medications, and physician's preference. However, adjuvant chemotherapy still affected survival after adjustment for other confounding factors in the multivariate model. Third, because of the lack of a standard duration for image follow-up in all of the patients, the actual DFS might be overestimated in our study. Finally, and most importantly, even though our prognostic model showed good accuracy to predict postoperative survival outcomes, all data were available from a single medical center and internally validated. An external validation of the model is essential before it can be widely used.

5. Conclusions

This study developed an accurate LNR-based prognostic model for predicting the survival outcome after D2 surgery in gastric cancer patients with metastasis to more than 15 regional lymph nodes. This model might assist clinicians in the prognostic stratification of such patients and convince eligible patients to receive adjuvant chemotherapy.

Conflict of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2017.10.001.

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