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Prognostic Score in Gastric Cancer: The Importance of a Conjoint Analysis of Clinical, Pathologic, and Therapeutic Factors

Marcelo Leite Vieira Costa, MD, PhD, Karina de Cássia Braga Ribeiro, DDS, PhD, Marcel Autran César Machado, MD, PhD, Ana Carolina Leite Vieira Costa, MD, and André Luis Montagnini, MD, PhD

Hospital do Câncer A.C. Camargo, Fundação Antônio Prudente, Professor Antônio Prudente Street 211, São Paulo, SP Brazil

Background: This study was designed to establish a prognostic score for gastric cancer that takes into account factors related to the tumor, the patient, and the treatment.

Methods: Two hundred thirty patients with gastric adenocarcinoma admitted to the Department of Abdominal Surgery at Hospital do Câncer A. C. Camargo (São Paulo) and treated by gastrectomy from January 1992 until December 1996 were included in this retrospective cohort. The prognostic score was created according to the variables identified in the multivariate analysis and by using the regression coefficients generated by the Cox regression.

Results: The 5-year overall survival rate was 44.5%. The final multivariate model identified six variables with a significant and independent effect on survival: sex, weight loss, lymphocyte count, tumor-node-metastasis staging, lymphadenectomy, and lymph node ratio. Patients were divided into four groups according to their scores, as follows: group 1, 0 to 3.0; group 2, 3.5 to 5.5; group 3, 6.0 to 8.5; and group 4, 9.0 to 14.0. The 5-year survival rates were 91.5%, 49.3%, 20.3%, and .0% for the score groups 1, 2, 3, and 4, respectively ($P < .001$). The score was superior in the assessment of prognosis when compared with tumor-node-metastasis staging alone.

Conclusions: It is possible to create a prognostic score that simultaneously includes factors related to the tumor, patient, and treatment, thus generating a more effective system in predicting the prognosis than the morphology-based staging systems.

Key Words: Stomach neoplasms—Prognosis—Neoplasm staging—Gastrectomy.

Gastric cancer, despite its declining incidence, still ranks second in global cancer mortality.[1] Surgery is the only known potentially curative treatment.[2–4] However, in the West, advances in surgical techniques have only modestly improved survival rates, which remain around 15% to 20%.[5] This is attributable, at least in part, to advanced disease at diagnosis. Indeed, only 30% to 60% of Western patients undergo surgical resections with curative intent,[6–8] some of them with microscopic nodal involvement.[9] The trend toward earlier diagnosis has resulted in a marked decrease in mortality in some countries.[10,11] Therefore, tumor staging, according to the tumor-node-metastasis classification, is considered the most important prognostic factor in gastric cancer.[12,13]

Nevertheless, the consistent discrepancy between the survival rate in Japan and Western countries cannot be solely explained by the earlier disease stage at diagnosis, because this difference persists even in the comparison of groups stratified by stage.[5,14–16] One possible explanation is the better pathologic staging due to routinely performed extended

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Address correspondence and reprint requests to: Ana Carolina Leite Vieira Costa, MD; E-mail: anacaroltavora@hotmail.com.

lymphadenectomies, the so-called staging migration phenomenon. This highlights the idea that different surgical approaches, as well as host characteristics, might be of critical importance in the outcome of gastric cancer patients.

Improving the accuracy of prognostic estimates is exceedingly important for tailoring treatment and facilitates comparisons of therapeutic results from different institutions. The purpose of this study was to establish a realistic and individualized prognostic score for gastric adenocarcinoma that takes into account factors related to the patient, the tumor, and the treatment.

METHODS

This retrospective cohort included patients who underwent resection for primary gastric adenocarcinoma, with curative or palliative intent, between January 1992 and December 1996 at the Department of Abdominal Surgery of Hospital do Câncer A. C. Camargo, São Paulo, Brazil. Patients with malignancies other than gastric adenocarcinoma who received nonsurgical treatments or were treated in other institutions were excluded from the study. This study was approved by the Ethical Committee for Research Projects of Hospital do Câncer A. C. Camargo.

Medical records were reviewed by a specially trained investigator. A standard protocol included, for each patient, data on demographic aspects, clinical picture, preoperative laboratory tests, preoperative risk assessment (American Society of Anesthesiologists), National Cancer Institute comorbidity index,[17] tumor classification (tumor-node-metastasis system, 6th edition), Borrmann macroscopic type, tumor histotype, details on surgical procedure, and other medical conditions. Weight loss was defined as loss of at least 10% of body weight.[18] Some variables were arranged according to percentiles of frequency distribution and literature reference values: age (10th percentile), duration of symptoms (median), National Cancer Institute comorbidity index (25th percentile), serum albumin (25th percentile), hemoglobin level (25th percentile), and total lymphocyte count (25th percentile).

The lymphadenectomy type was retrospectively classified as D1 or D2, according to the criteria described by the Japanese Research Society for Gastric Cancer. Additionally, D2 classification included only procedures with >25 removed lymph nodes. When the operation note did not clearly describe a standard dissection technique, the lymphadenectomy was considered as undone. Curative surgery was defined as complete tumor resection without intracavitary microscopic residual disease or distant metastasis. Postoperative chemotherapy/radiotherapy was considered as adjuvant only when it was conducted after R0 resection.

The histological type was classified in agreement with the World Health Organization and then grouped according to the differentiation degree, as proposed by the Japanese Research Society for Gastric Cancer. Well-differentiated gastric carcinoma included papillary and tubular adenocarcinomas and well-differentiated mucinous carcinoma, whereas poorly differentiated gastric carcinoma included poorly differentiated scirrhous carcinoma, signet ring cell carcinoma, and poorly differentiated mucinous carcinoma.[19]

To calculate metastatic lymph node ratio (LR), the following formula was considered:

LR = number of metastatic lymph nodes/number of resected lymph nodes

The final classification of LR included four categories: $<5\%$, 5% to 20%, 21% to 45% and $>45\%$, according to the mortality risk.

In the last objective analysis, patients were stratified as lost to follow-up, alive and cured, alive with active malignancy, dead from other causes, and dead as a result of their disease, wherein were included deaths that occurred during surgery or until the first 30 days of the postoperative period and those related to surgical complications.

Descriptive analyses were performed with identification of central tendency measures (mean and median) and frequency distribution percentiles that were the yardstick for the posterior categorization of some variables. Survival rates were calculated with the Kaplan-Meier method and differences between groups were assessed with the log-rank test.

Independent variables predicting survival were evaluated by using the Cox proportional hazards model, sharing in all variables with P values $<.20$ in the univariate analysis. The 95% confidence interval was calculated for all hazard ratios (HRs) in Cox regression analysis. The χ^2 linear tendency test was used to find out whether the LR stratified categories corresponded to a gradual increase in the risk of death.

From the final multiple Cox model, a simple and easy applicable prognostic score was constructed. A numerical value was given to each variable according to the relative weight of the independent risk significance shown by each single category in the multivariate analysis.[20] Beta coefficients of each variable

were divided by the lowest β-coefficient, and the results were rounded to .5 multiples. The sum of the single scores gives the overall risk score for each patient. The final score was grouped in quartiles, thus determining a gradual categorization of the mortality risk.

To evaluate the effectiveness of the scoring system in predicting prognosis compared with the tumor-node-metastasis stage grouping, a Cox proportional hazards model was performed. SPSS for Windows software (version 10.0; SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Two hundred thirty patients were included in the study. Some of the descriptive statistics for this cohort are listed in Table 1. Age varied from 31 to 80 years (mean, 60.9 years). The most common symptoms were epigastric abdominal pain (81.3%) and weight loss (68.7%). The duration of symptoms varied from 1 to 84 months (median, 6 months). Hemoglobin levels ranged from 2.5 to 16.4 mg/dL (mean, 11.5 mg/dL), the total lymphocyte count ranged from 288 to 6700/μL, and serum albumin levels ranged from 1 to 5 g/dL (median, 3.5 mg/dL). Most patients had an American Society of Anesthesiologists physical status of II (57.8%), and 24.7% of patients were American Society of Anesthesiologists status III or IV. The National Cancer Institute comorbidity index varied from 0 to 6 (median, 2). The spleen was the organ most frequently resected en bloc with the stomach (14.3%), followed by the pancreas (6.5%), the distal esophagus (6.1%), and other organs (8.3%).

The surgical mortality was 4.3% (10 patients). Adjuvant treatment was rarely applied in this series: chemotherapy in eight patients (3.5%) and radiotherapy in six patients (2.6%).

The four categories of LR were considered adequate for mortality risk stratification, according to the χ^2 linear tendency test ($\chi^2 = 59{,}96$; $P < .001$). Table 2 shows the population's distribution according to the tumor-node-metastasis staging system and LR.

The median follow-up time was 28.3 months. The overall 5-year survival rate was 44.5%. At last follow-up, the recurrence of gastric cancer was detected in 113 (49.1%) patients: 59 patients (27.2%) showed regional recurrence, 53 (24.4%) showed peritoneal dissemination, 32 (14.7%) showed liver metastasis, 17 (7.8%) showed lung or pleural metastasis, and 2 (.9%) showed central nervous system metastasis. In 24 (11.1%) patients, recurrence occurred at other sites. The association between variables and prognosis (univariate analysis) is shown in Table 3.

TABLE 1. *Clinicopathologic and therapeutic features of the 230 cohort patients*

Variable	Category	n (%)
Sex	Male	144 (62.6)
	Female	86 (37.4)
Race	White	165 (71.7)
	Asian	19 (8.3)
	Others	46 (20.0)
Tobacco smoking[a]	No	109 (47.8)
	Yes	119 (52.2)
Alcoholism[a]	No	152 (66.7)
	Yes	76 (33.3)
Family history of cancer[b]	No	116 (50.4)
	Gastric neoplasia	27 (11.7)
	Other neoplasias	48 (20.9)
Tumor location	Proximal	87 (37.8)
	Distal	143 (62.2)
Tumor size (cm)[c]	< 5	77 (40.4)
	≥ 5	146 (56.6)
Macroscopic aspect	Early	23 (10.0)
	Borrmann I	8 (3.5)
	Borrmann II	30 (13.0)
	Borrmann III	154 (67.0)
	Borrmann IV	15 (6.5)
Histotype	Well differentiated	132 (57.4)
	Poorly differentiated	98 (42.6)
Gastrectomy type	Subtotal	143 (62.3)
	Total	87 (37.7)
Lymphadenectomy	D0	38 (16.5)
	D1	108 (47.0)
	D2	84 (36.5)
Residual disease	R0	181 (78.7)
	R1/2	49 (21.3)

[a] Missing values: two patients.
[b] Missing values: 39 patients.
[c] Missing values: seven patients.

The multivariate Cox stepwise proportional hazard model identified male sex (HR, 1.9; $P = .019$); weight loss (HR, 1.9; $P = .025$); preoperative lymphocyte count ≤1.390/μL (HR, 1.3; $P = .027$); tumor-node-metastasis stage IIIa (HR, 4.0; $P = .003$), IIIb (HR, 3.5; $P = .035$), and IV (HR, 5.1; $P = .009$); lymphadenectomy (HR, 4.9; $P < .001$); an LR of 21% to 45% (HR, 3.9; $P = .005$); and an LR >45% (HR, 4.2; $P = .007$) as independent predictors of prognosis (Table 4).

A scoring system based on the final model appears in Table 5. Score values were obtained from 201 of the 230 patients. The overall risk score ranged from 0 to 14 and was stratified in quartiles: group 1, 0 to 3.0; group 2, 3.5 to 5.5; group 3, 6.0 to 8.5; and group 4, 9.0 to 14.0. These groups had statistically significant ($P < .01$) differences in survival curves (Table 6; Fig. 1).

TABLE 2. *Patients' distribution according to tumor-node-metastasis stage and LR*

Variable	Category	n (%)
T stage	T1	34 (14.8)
	T2	28 (12.2)
	T3	141 (61.3)
	T4	27 (11.7)
N stage	N0	65 (28.3)
	N1	66 (28.7)
	N2	52 (22.6)
	N3	16 (7.0)
	NX	31 (13.5)
M stage	M0	205 (89.1)
	M1	25 (10.9)
Tumor-node-metastasis grouped stage	Ia	26 (11.3)
	Ib	19 (8.3)
	II	28 (12.2)
	IIIa	53 (23)
	IIIb	37 (16.1)
	IV	46 (20)
	Ignored	20 (9.1)
LR (%)	< 5	91 (39.6)
	5–20	48 (20.9)
	21–45	45 (19.6)
	> 45	46 (20.0)

LR, lymph node ratio.

The developed prognostic scoring system was compared with tumor-node-metastasis staging. The score was superior in predicting mortality because tumor-node-metastasis categories lost statistical significance in the Cox model when they were analyzed together with prognostic score groups (Table 7; Fig. 2).

DISCUSSION

Standardized tumor classification is an essential tool for an adequate approach in oncology. Staging systems aim to stratify patients according to prognosis, aid the clinician in designing the most suitable treatment, and enable comparisons of interinstitutional treatment results.[21]

This study developed and internally validated a staging system on the basis of the multivariate analysis of this patient series. The score embraces factors related to the patient, the tumor, and the treatment: sex, weight loss, preoperative lymphocyte count, LR, lymphadenectomy, and International Union Against Cancer tumor-node-metastasis stage.

Male sex was related to a worse prognosis in our series. This is in accordance with many authors who have found a significant gain in overall survival associated with a female sex.[22,23] However, the sex influence on gastric cancer patients' prognosis is controversial, and although various hypotheses have been proposed, ranging from genetic to hormonal factors,[24–26] the precise mechanisms for such association remain unknown.

Malnutrition is a frequent component of oncological illness, mainly of gastrointestinal cancers. The pathophysiology includes a combinations of starvation, the stress response to acute or chronic injuries, and abnormal nutrient metabolism. Undernourished patients often present with a diminished body weight and total lymphocyte count. Our study identified that, for gastric cancer patients, these two conditions have an independent negative effect on survival.

The association of weight loss with high morbidity and mortality,[27] as well as with higher toxicity and lower chemotherapy response rates, has already been described among patients with gastric cancer.[28,29] It is also reported that the combination of weight loss and functional abnormalities (serum albumin and immunological parameters) increases the surgical risk even more.[27,30]

The immune system, mainly T-cell mediated, is an important component of the antitumoral activity. It has been suggested that T cells, infiltrating tumor deposits, recognize self-antigens presented by tumor cells and then effect tumor destruction.[31] Unfortunately, the potency of such response is frequently insufficient to alter the course of the disease. Previous reports, however, have found an association between lymphopenia and neoplasia progression.[32,33]

Lymphatic involvement is one of the most important prognostic factors in gastric cancer.[12,34] The prognostic value of LR in the evaluation of lymph node status found in this study confirms the results from previous studies.[1,35,36]

The extent of lymph node dissection to optimize the benefit to the patient is still controversial. Western randomized controlled trials have not shown evidence of a survival benefit for D2 surgery but have reported high operative morbidity and mortality rates, mainly related to pancreatectomy and limited surgical experience.[37,38] Conversely, in Japan, D2 gastrectomy is considered a standard and safe procedure. The Japanese nationwide registry reported an operative mortality of < 2% and, in specialized institutions, < 1% for D2 gastrectomy.[15,39] Nonrandomized Western studies have also reported a distinct therapeutic advantage associated with extended lymphadenectomy (Harrison et al., unpublished data).[40] In our study, the absence of a standardized lymph node dissection independently promoted an adverse clinical outcome, but there was no significant difference in the survival of D1 and D2 lymphadenectomy groups. Nevertheless, the rigorous criteria

TABLE 3. *Variables associated with mortality risk in patients with gastric cancer (univariate analysis)*

Variable	Category	HR_{crude}	95% CI (HR_{crude})	*P* value
Sex	Female	1.0	–	
	Male	1.4	.9–2.1	
Age (y)	≤ 40	1.0	–	
	> 40	2.3	1.0–5.3	.042
Duration of symptoms (mo)	≥6	1.0	–	
	<6	1.7	1.1–2.7	.021
Palpable mass	No	1.0	–	
	Yes	2.6	1.5–4.4	<.001
Weight loss	No	1.0	–	
	Yes	1.9	1.2–2.9	.003
NCI comorbidity index	≤ 1	1.0	–	
	>1	1.8	1.2–2.9	.008
Preoperative hemoglobin (mg/dl)	>9.7	1.0	–	
	≤ 9.7	1.8	1.2–2.6	.003
Preoperative lymphocyte count (per μL)	>1390	1.0	–	
	≤ 1390	1.6	1.1–2.4	.019
Gastrectomy type	Subtotal	1.0	–	
	Total	1.9	1.3–2.6	.001
Splenectomy	No	1.0	–	
	Yes	1.7	1.1–2.6	.022
Pancreatectomy	No	1.0	–	
	Yes	2.0	1.1–3.7	.019
Lymphadenectomy	No	6.6	4.2–10.4	
	Yes (D1/2)	1.0	–	<.001
Intraoperative hemotransfusion	No	1.0	–	
	Yes	2.0	1.4–2.9	< .001
Surgery intent	No	1.0	–	
	Yes	4.0	2.7–5.9	< .001
Duodenal invasion	No	1.0	–	
	Yes	2.9	1.1–7.9	.038
Macroscopic aspect	Early	1.0	–	
	Borrmann I/II	1.8	.7–5.1	.242
	Borrmann III/IV	5.5	2.2–13.7	<.001
Surgical margins	Negative	1.0	–	
	Positive	4.9	2.3–10.2	<.001
Lymphatic invasion	No	1.0	–	
	Yes	3.6	2.2–5.9	<.001
Bloodstream invasion	No	1.0	–	
	Yes	2.5	1.6–3.9	<.001
Perineural invasion	No	1.0	–	
	Yes	2.0	1.3–3.2	.002
T stage	T1	1.0		
	T2	1.5	.5–4.9	.499
	T3	8.2	3.3–20.2	<.001
	T4	21.8	8.2–57.9	<.001
N stage	N0	1.0	–	
	N1	2.4	1.4–4.4	.003
	N2	6.7	3.8–11.9	<.001
	N3	12.4	6.1–25.4	<.001
	NX	5.5	2.8–10.7	<.001
M stage	M0	1.0	–	
	M1	4.6	2.7–7.7	<.001
Tumor-node-metastasis grouped stage	I	1.0	–	
	II	1.9	.7–5.4	.201
	IIIa	6.6	2.9–15.1	<.001
	IIIb	13.3	5.7–30.9	<.001
	IV	28.1	12.2–64.9	<.001
LR (%)	<5	1.0	–	
	5–20	2.9	1.6–5.0	<.001
	21–45	7.8	4.6–13.3	<.001
	>45	10.2	5.9–17.5	<.001

HR, hazard ratio; CI, confidence interval; NCI, National Cancer Institute; LR, lymph node ratio.

TABLE 4. *Independent prognostic factors for patients with gastric cancer*

Variable	Category	HR_{crude}	$HR_{adjusted}$	95% CI ($HR_{adjusted}$)	*P* value
Sex	Female	1.0	1.0	–	
	Male	1.4	1.9	1.1–3.2	.019
Weight loss	No	1.0	1.0	–	
	Yes	1.9	1.9	1.1–3.3	.025
Lymphocyte count (per μL)	> 1390	1.0	1.0	–	
	≤ 1390	1.6	1.8	1.1–3.1	.027
Tumor-node-metastasis grouped stage	I/II	1.0	1.0	–	
	IIIa	4.9	4.0	1.6–10.0	.003
	IIIb	9.9	3.5	1.1–11.0	.035
	IV	20.9	5.1	1.5–17.2	.009
Lymph node resection	No	6.6	4.9	2.5–9.7	
	Yes	1.0	1.0	–	< .001
LR (%)	< 5	1.0	1.0	–	.280
	5–20	2.9	1.6	.7–3.7	.005
	21– 45	7.8	3.9	1.5–10.5	.007
	> 45	10.2	4.2	1.5–12.0	< .001[a]

HR, hazard ratio; CI, confidence interval; LR, lymph node ratio.
[a] Chi-square linear tendency test.

TABLE 5. *Prognostic score for patients with gastric cancer*

Variable	Category	Score
Sex	Female	0
	Male	1.5
Weight loss	No	0
	Yes	1.5
Preoperative lymphocyte count (per μL)	> 1390	0
	≤ 1390	1.5
Tumor-node-metastasis grouped stage	I/II	0
	IIIa	2.0
	IIIb	2.5
	IV	3.0
Lymphadenectomy	No	0
	Yes	3.5
LR (%)	< 5	0
	5–20	1.0
	21–45	3.0
	> 45	3.0

LR, lymph node ratio.

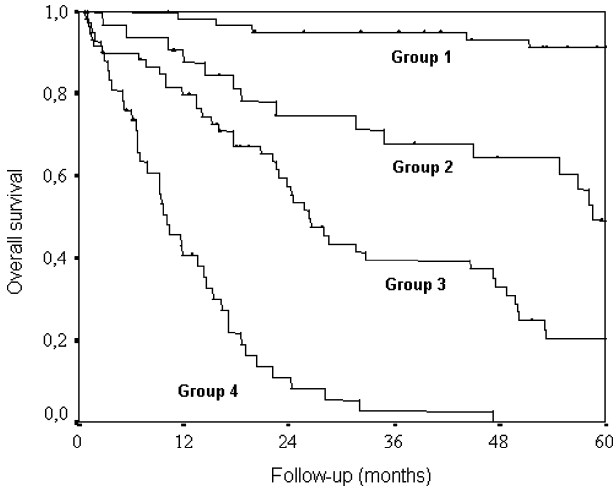

FIG. 1. Survival curves according to prognostic score.

TABLE 6. *Cumulative overall 5-year survival and prognostic group scores*

Prognostic group	Overall 5-y survival (%)
Group 1 (0–3.0)	91.5
Group 2 (3.5–5.5)	49.3
Group 3 (6.0–8.5)	20.3
Group 4 (9.0–14.0)	.0

$P < .001$.

used to classify the D2 category may have underestimated the number and the possible therapeutic benefits of D2 procedures.

Residual disease is a recognized prognostic factor in gastric cancer, and all efforts should be made to achieve a curative resection. The useful prognostic effect of this criterion was indirectly reproduced in our series, given that three of the score variables seem tied into this.

The scoring system developed in this study was more predictive of mortality than the tumor-node-metastasis stage, the malignant tumor staging system most accepted in the world.[41] The tumor-node-metastasis stage comprises the primary tumor extension, the number of regional lymph nodes involved, and the presence of distant metastasis. Tumor-node-metastasis is a strong indicator of prognosis and has been applied to a diversity of human neoplasms. However, it is based only on the morphological aspects of the tumor and considers the anatomical dissemination as an isolated staging criterion.

TABLE 7. *Multivariate Cox stepwise proportional hazard model: comparison of scoring system and grouped tumor-node-metastasis predictive values*

Variable	Category	HR_{crude}	$HR_{adjusted}$	95% CI ($HR_{adjusted}$)	*P* value
Tumor-node-metastasis grouped stage	I/II	1.0	1.0	–	
	IIIa	4.9	1.4	.5–3.7	.462
	IIIb	9.9	1.8	.6–5.1	.300
	IV	20.9	1.9	.6–5.9	.276
Prognostic score	Group 1	1.0	1.0	–	
	Group 2	5.8	4.6	1.7–12.8	.003
	Group 3	14.6	9.4	2.9–30.1	< .001
	Group 4	55.2	31.1	8.4 –114.8	< .001

HR, hazard ratio; CI, confidence interval.

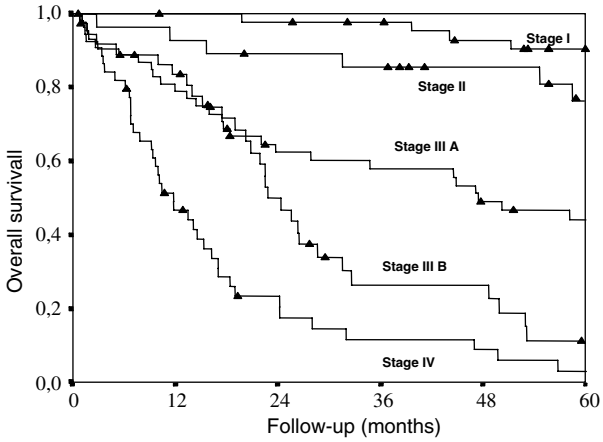

FIG. 2. Survival curves according to tumor-node-metastasis grouped stage.

The morphology-based staging systems embrace neither extremely relevant aspects related to the patient, such as the clinical picture and functional condition, nor a set of variables related to the treatment. This is mainly justified by the difficulty in objectively assessing the effect of these variables. Nevertheless, for gastric cancer, as well as for other cancers, the prognostic value of these factors has been consistently recognized.[1,4,12,34,42,43] Neglecting them may lead to important problems in the interpretation of scientific results, including the difficulty of inferring therapeutic results for each patient individually, in addition to a morphological staging group, and the impossibility of ascribing different survival rates to the treatment, because clinical factors are not taken into account.[44]

Several alternative models designed to improve the accuracy of prognostic estimates of gastric cancer patients are published in the medical literature.[9,21,45–48] Nevertheless, to date, none of them is routinely adopted in clinical setting.

The scoring system developed in this series is simple, reproducible, and feasible. It incorporates in an easily applicable scale widely accepted prognostic factors that are available for all patients at all centers. It combines the objectivity and clinical applicability of the anatomical staging systems with the advantage of analyzing together variables related to the tumor, the patient, and the treatment.

Besides the superiority in predicting prognosis as compared with the tumor-node-metastasis system, the application of this score may also have a greater influence in the clinical management of gastric cancer because it is a dynamic system that may change in accordance to lymph node clearance variables. The clearly demonstrated prognostic effect of LR proposes that surgeons are able to modify the prognosis, thus pointing to a possible therapeutic advantage of extended lymphadenectomies.

A limitation of our prognostic system is that an external validation still needs to be performed. The score application in another group of patients is essential to confirm its actual effectiveness in prognostic stratification and to define its clinical relevance. This study emphasizes the importance of a conjoint analysis of clinical, pathologic, and therapeutic factors for estimating the prognosis of gastric cancer patients.

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