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ORIGINAL ARTICLE

A prognostic model in patients who receive chemotherapy for metastatic or recurrent gastric cancer: validation and comparison with previous models

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Abstract
Purpose To make up for the limitations of previous prognostic models, we developed and validated a model in patients with metastatic or recurrent gastric adenocarcinoma (AGC), and to compare with previous models.
Methods A total of 2,805 patients received chemotherapy for AGC in Asan Medical Center between January 2000 and December 2008 and were randomly split into training and validation sets of 1,870 and 935 patients, respectively. A prognostic model was developed from the training set.
Results The median follow-up duration was 26.5 months (range, 10.8–116.3), during which time 2,495 patients (88.9%) died. Eight factors associated with poor prognosis were identified by multivariate analysis: ECOG performance status $\geq$2 (2 points), no gastrectomy, peritoneal metastasis, bone metastasis (2 points), lung metastasis, alkaline phosphatase $>$ 120 IU/l, albumin $<$ 3.3 g/dL, and total bilirubin $>$ 1.2 mg/dL. A prognostic model was developed by dividing patients into good (0–1 points), moderate (2–3), and poor ($\geq$4) risk groups. The overall survival (OS) curves for three risk groups differed significantly for both the training and the validation sets ($P < 0.001$ each). In the training set, the median OS for the three risk groups was 14.0, 9.4, and 5.1 months, respectively. Application of three previous prognostic models to our validation set showed that the four models, including ours, had similar ability to predict survival outcomes (c-statistics, 0.5520–0.5836).
Conclusion Validation and comparison of prognostic models indicated that our model was as effective as the previous models to stratify the patients with AGC.

Keywords Stomach neoplasms · Prognosis · Tumor burden · Chemotherapy · Validation studies

Introduction

Gastric cancer is the second leading cause of cancer death worldwide, with a median survival time of less than 1 year in patients diagnosed at an advanced stage [1, 2]. In the early 1990s, several randomized clinical trials showed that, compared with best supportive care alone, chemotherapy plus best supportive care could improve median patient survival, from 4–6 to 9–11 months, and quality of life in patients with advanced gastric cancer [3–5]. Survival outcomes remain unsatisfactory despite continuous efforts with various chemotherapy regimens [2, 6–8].

The efficacy of chemotherapy in patients with advanced gastric cancer has been found to depend on patient characteristics and/or disease status (locally advanced, metastatic, recurrent, or resected metastatic) [9, 10]. These factors can be used to construct prognostic models that may help identify patients likely to benefit from current

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chemotherapeutic agents. And these models would also help interpreting and comparing the results of clinical trials.

Although several prognostic factors and models have been evaluated in patients with advanced gastric cancer [9, 11–16], all of these have had limitations. For example, the sample size was found to be too small to produce a reliable model [9, 13, 16], the inclusion criteria were too limited (e.g. stage IV only or long-term survivors only) to generalize from the model, [14, 15] or the patient population analyzed in previous analyses was too heterogeneous, including, for example, patients with locally advanced gastric cancer or those with esophageal cancer or squamous cell carcinoma [11, 12]. Moreover, patients enrolled in clinical trials only may not be representative of all patients treated in practice [11]. Most importantly, all but one report [17] did not validate their prognostic models. In assessing prognostic or predictive factors, there are usually worry about whether the factors found are true or anecdotal only. One of the appropriate ways to admit the results is the validation with different dataset.

We have, therefore, sought to identify factors associated with poor prognosis in patients with recurrent or metastatic gastric cancer, to use these factors to develop a prognostic model and to validate the appropriateness of this model. We also compared our model with previous prognostic models using our validation set of patients with recurrent or metastatic gastric cancer.

Materials and methods

Patients and data collection

We examined the Asan Medical Center Stomach Cancer Registry to identify all patients who were treated for advanced gastric cancer at the Asan Medical Center (Seoul, Korea) between January 2000 and December 2008. We identified a total of 3,107 patients who received front-line palliative chemotherapy for unresectable, metastatic, or recurrent gastric cancer. Patients $\geq$ 18 years of age with histologically confirmed adenocarcinoma of the stomach, who received at least one cycle of chemotherapy and had no history of other malignancies, were included. Patients with locally advanced disease or who underwent R1 resection for microscopic residual tumor just before chemotherapy were excluded; these patients were regarded as having a lower tumor burden than patients with metastatic or recurrent gastric cancer. Of the 3,107 patients screened, 2,805 fulfilled the inclusion criteria. Patients' medical records, stored in a prospectively collected registry, were reviewed for information regarding demographic data, tumor characteristics, treatment types, treatment responses, and survival. The study protocol was approved by the Institutional Review Board of the Asan Medical Center, and all patients provided informed consent.

Statistical analysis

Model development and validation were based on a split-sample method. Two-thirds of the patients were randomly assigned to a training set ($n = 1{,}870$), and one-third were included in an independent validation set ($n = 935$). The predictive model was developed using the training set. The primary endpoint of the analysis was overall survival (OS), which was measured from the date of first-line chemotherapy until death from any cause. The Kaplan–Meier method was used to estimate OS. Clinical variables known to be associated with survival outcome, as well as potential risk factors, were considered. All laboratory variables were dichotomized, with the cutoff points chosen as the normal value for each variable, and survival rates were compared using the log rank test. A prognostic model was established by searching all variables in the univariate analysis, followed by a multivariate analysis using stepwise Cox proportional hazard regression models. Forward and backward stepwise regression analyses were used to test the robustness of the model. A risk score based on hazard ratios was developed from the final multivariate model and validated using the validation set. The predictive accuracy of the model was assessed in terms of discrimination and calibration. Model discrimination performance was evaluated using standard measures of sensitivity, specificity, and positive and negative predictive values. For overall assessment, discrimination was evaluated using c-statistics, with larger areas under receiver operating characteristic (ROC) curves indicating better discrimination. The Hosmer–Lemeshow goodness-of-fit test was used to assess model calibration or its fit to the data based on agreement between predicted risk probabilities using the model and the actual observed probabilities. A two-sided P value < 0.05 was considered significant, and 95% confidential intervals (CIs) were calculated. All statistical analyses were performed using an SPSS software package (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 2,805 patients, of median age 57 years (range, 19–88 years), were followed-up for a median 26.5 months (range, 10.8–116.3 months). Overall, 2,495 patients (88.9%) died, with a median survival time of 10.2 months (95% CI, 9.7–10.6 months). At the time of treatment, 2,512 patients (89.6%) had Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0–1. When we

Table 1 Pretreatment patient characteristics of the training and validation sets

	Training set (n = 1,870)		Validation set (n = 935)		P value by X^2 test
	N	(%)	N	(%)	
Follow-up duration					
Median (month, range)	27.9	10.8–111.7	23.4	10.8–116.3	0.065
Survival					
Death events	1,659	88.7%	836	89.4%	0.580
Median (month, 95% CI)	10.2	9.6–10.7	10.2	9.5–10.8	0.303
Age					
Median (year, range)	56	19–84	57	23–88	0.269
<65	1,381	73.9%	682	72.9%	0.607
Gender					
Male	1,223	65.4%	622	66.5%	0.555
ECOG PS					
0 or 1	1,673	89.5%	839	89.7%	0.887
Gastrectomy					
No	994	53.2%	493	52.7%	0.831
Location of primary tumor					
Cardia	77	4.1%	46	4.9%	0.539
Body	1,253	67.0%	610	65.3%	
NA	540	28.9%	279	29.8%	
Histology					
WD/MD	485	25.9%	236	25.2%	0.614
Undifferentiated	1,131	60.5%	582	62.2%	
NA	254	13.6%	117	12.5%	
Location of metastases					
Peritoneum	818	43.7%	429	45.9%	0.283
Liver	494	26.4%	240	25.7%	0.671
Lung	79	4.2%	49	5.3%	0.222
Bone	122	6.5%	59	6.3%	0.828
≥2 site	561	30.0%	275	29.4%	0.626
Hb					
<12 or 13[a] g/dL	1,288	68.9%	688	73.7%	0.163
Platelet					
<150,000/mm^3	162	8.7%	81	8.7%	0.997
WBC					
<4,000/mm^3	344	18.4%	173	18.5%	0.923
ALP					
>120 IU/L	417	22.4%	205	22.0%	0.850
Creatinine					
>1.4 mg/dL	23	1.2%	7	0.8%	0.242
Albumin					
<3.3 g/dL	524	28.1%	252	27.0%	0.540
Total bilirubin					
>1.2 mg/dL	136	7.3%	58	6.3%	0.301
Clinical trial					
Yes	444	23.7%	220	23.5%	0.900
Entry year					
2000–2004	837	44.8%	409	43.7%	0.610
1st-line regimen					
F	288	15.4%	125	13.4%	0.548

Table 1 continued

	Training set (n = 1,870)		Validation set (n = 935)		P value by X^2 test
	N	(%)	N	(%)	
F + P	997	53.3%	527	56.4%	
T	132	7.1%	58	6.2%	
T + F or P	261	14.0%	128	13.7%	
T + F + P	157	8.4%	76	8.1%	
Other	35	1.9%	21	2.2%	
2nd-line chemotherapy					
Received	944	50.5%	460	49.2%	0.522

ECOG PS Eastern Cooperative Oncology Group Performance Status, *NA* not available, *WD* well differentiated *MD* moderately differentiated, *Hb* hemoglobin, *WBC* white blood cells, *ALP* alkaline phosphatase, *F* fluoropyrimidine, *P* platinum, *T* taxane

[a] Hemoglobin level: <12 for female, <13 for male

Table 2 Univariate analysis of factors predictive of prognosis in the training set

Reference	HR	95% CI	P value
Age			
<65	1.065	0.954–1.188	0.264
Gender			
Male	1.028	0.929–1.137	0.597
ECOG PS			
≥2	1.915	1.635–2.242	<0.001
Location of primary tumor			
Cardia	1.238	0.967–1.583	0.090
Gastrectomy			
No	1.419	1.287–1.564	<0.001
Location of metastases			
Peritoneum	1.285	1.166–1.416	<0.001
Liver	1.097	0.984–1.222	0.096
Bone	2.106	1.746–2.539	<0.001
Lung	1.309	1.036–1.652	0.024
Hb			
<12 or 13[a] g/dL	1.070	0.958–1.196	0.231
Platelet			
<150,000/mm^3	1.143	0.964–1.355	0.123
WBC			
<4,000/mm^3	1.119	0.988–1.267	0.077
ALP			
>120 IU/L	1.571	1.403–1.760	<0.001
Creatinine			
>1.4 mg/dL	1.521	0.989–2.339	0.056
Albumin			
<3.3 g/dL	1.656	1.489–1.841	<0.001
Total bilirubin			
>1.2 mg/dL	1.373	1.145–1.647	<0.001

ECOG PS Eastern Cooperative Oncology Group Performance Status, *Hb* hemoglobin, *WBC* white blood cells, *ALP* alkaline phosphatase

[a] Hemoglobin level: <12 for female, <13 for male

compared the characteristics of the patients in the training and validation sets, we found no significant differences between these two groups (Table 1).

Development of a prognostic model

In the training set of 1,870 patients, 1,659 (88.7%) died. In univariate analysis, the following factors were significantly associated with poor survival outcome: ECOG PS ≥ 2, no previous gastrectomy, peritoneal metastasis, bone metastasis, lung metastasis, serum alkaline phosphatase (ALP) concentration >120 IU/L, serum albumin concentration <3.3 g/dL, and total serum bilirubin concentration >1.2 mg/dL (Table 2). In the subsequent multivariate analysis, all eight factors were independently associated with poor survival outcome. Risk scores were assigned based on hazard ratios (HR) from the final multivariate model, with 2 points for HR > 1.5 and 1 point for HR < 1.5. Based on the scores, patients were assigned to three groups based on risk category: good (0–1 point), moderate (2–3 points), and poor (≥4 points; Table 3). The grouping of patients was based on the area under the ROC curve.

Validation of the prognostic model

We validated our prognostic model using the separate validation set of 935 patients. Of these, 836 (89.4%) died. Because patients missing data on any of the eight prognostic factors were excluded from analysis, 916 patients were included in the validation analysis. At the cutoff point for moderate risk (≥2 points), the model had a negative predictive value (probability of no death in patients designated low risk) of 85.0%, a positive predictive value (probability of death in patients designated moderate to high risk) of 93.0%, a sensitivity (probability of moderate to high risk in those experiencing death) of 57.0%, and a specificity (probability of low risk in those not

Table 3 Multivariate analysis of factors predictive of prognosis in the training set and scoring of these factors

	N	Hazard ratio	95% CI	*P* value	Score
ECOG PS ≥ 2	197	1.701	1.446–2.001	<0.001	2
No gastrectomy	994	1.317	1.189–1.459	<0.001	1
Peritoneal metastasis	818	1.305	1.179–1.444	<0.001	1
Bone metastasis	122	1.718	1.406–2.099	<0.001	2
Lung metastasis	79	1.318	1.038–1.673	0.024	1
ALP > 120 IU/L	417	1.368	1.205–1.552	<0.001	1
Albumin < 3.3 g/dL	524	1.389	1.241–1.554	<0.001	1
Total bilirubin > 1.2 mg/dL	136	1.326	1.095–1.605	<0.001	1

Table 4 Predicted number of deaths from the prognostic model and number of observed deaths by risk group in the validation set

Risk group	No. of patients	Predicted deaths	Observed deaths
Good (0–1)	414	354.3 (85.6%)	352 (85.0%)
Moderate (2–3)	378	345.8 (91.5%)	348 (92.1%)
Poor (≥4)	124	118.9 (95.9%)	119 (96.0%)

Hosmer–Lemeshow test, $P = 0.0752$

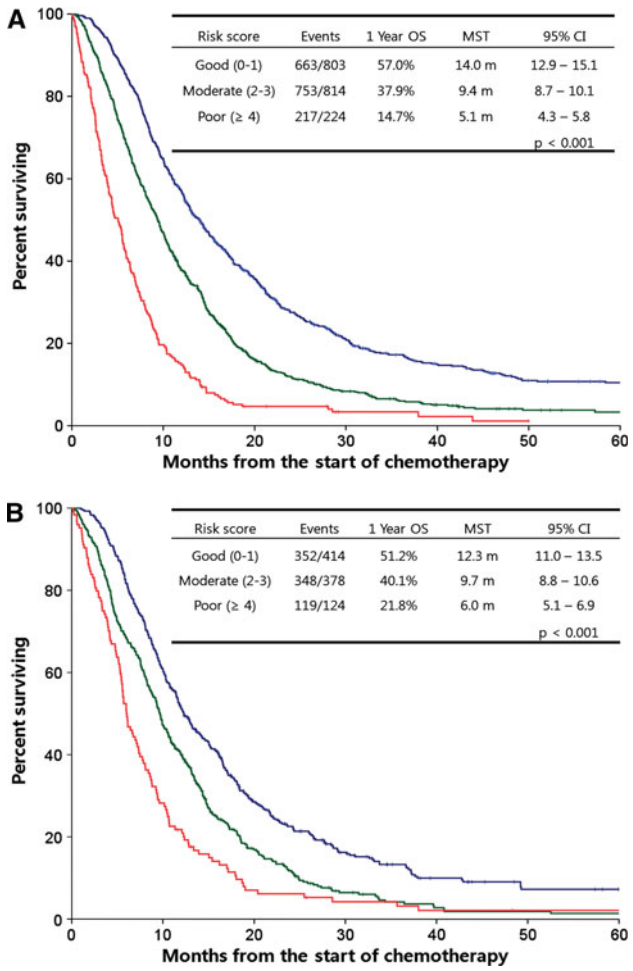

Fig. 1 Survival curves according to risk group in the **a** training set and **b** validation set (*MST* median survival time, *OS* overall survival)

experiencing death) of 63.9%. Using the scoring system, the c-statistic was 0.5836 in the predictive model. The Hosmer–Lemeshow test results in the validation set showed no significant deviation ($P = 0.0752$) between the observed and predicted numbers of patients who died or were alive (Table 4). The proportions of patients classified into each risk category were also similar, and the observed OS curves in patients with various categories of risk showed highly significant OS differences in both the training and validation sets (log rank $P < 0.001$, Fig. 1).

Comparison with previous prognostic models

We applied prognostic models from previous studies to our validation set. One previous model [11] found that four factors were predictive of poor prognosis: poor PS, liver metastasis, peritoneal metastasis, and increased ALP. The second model [12] found that six factors were predictive of poor prognosis: poor PS, no gastrectomy, decreased albumin, increased ALP, bone metastasis, and ascites, the latter of which may reflect peritoneal metastasis. The third model found that five factors were predictive of poor prognosis: poor PS, peritoneal metastasis, elevated total bilirubin, at least two metastatic sites, and bone metastasis, with the latter scored as 2 points due to its high hazard ratio (Table 5). Survival differences were also highly significant among their original risk groups (log rank $P < 0.001$, Fig. 2), and c-statistics were similar for our prognostic index (0.5836) and for the prognostic indices from these three models: 0.5520, [11] 0.5739, [12] and 0.5635 [13].

Discussion

In this study, we evaluated the factors associated with poor prognosis in patients with recurrent or metastatic gastric cancer. And we developed a prognostic model with these factors in a training set randomly selected from the patients' population. Then, we validated the appropriateness of this model using a validation set. Our analysis identified eight factors independently prognostic of poor

Table 5 Factors predictive of poor prognosis in four models

		Our model	Chau et al. [11]	Lee et al. [12]	Kim et al. [13]
Host status	ECOG PS $\geq$ 2	●●*	●	●	●
Tumor burden	No gastrectomy	●		●	
	Peritoneal metastasis	●	●	●	●
	Bone metastasis	●●*		●	●●*
	Liver metastasis		●		
	Lung metastasis	●			
	Metastatic sites $\geq$ 2				●
Laboratory	Increased ALP	●	●	●	
	Decreased albumin	●		●	
	Elevated total bilirubin	●			●

* Two points per factor

OS in patients with metastatic or recurrent gastric adenocarcinoma who received chemotherapy: poor performance status (ECOG PS $\geq$ 2), no previous gastrectomy, presence of bone metastasis, peritoneal metastasis, lung metastasis, increased ALP level, increased total bilirubin level, and decreased albumin level. Combining these factors into a simple prognostic model enabled patients with recurrent or metastatic gastric cancer to be classified, according to risk scores, into three risk groups (good, 0–1 point; moderate, 2–3 points; and poor, $\geq$4 points). The prognostic model was then validated in an independent set of patients from the same cancer registry. Use of the model in the validation set showed that patients in the three risk groups had significantly different OS rates. These prognostic factors can be readily measured in clinical practice, and the model based on these factors can be used to predict patient life expectancy, guide treatment plans, analyze clinical study results, and design future clinical trials.

Characteristics of study design

Although the factors found in the current study seemed similar to those in previous studies [9, 11–15], our study was distinguished by the number of patients enrolled and by the method to manipulate the dataset. The registry from which patients were selected was prospectively collected in a single institution, where there is a consistent strategy that reflects current practice and the management of patients with advanced gastric cancer in Korea. The large number of patients we analyzed strengthens our analysis, as does the survival data on our cohort, of whom more than 90% died. We limited our analysis to patients with adenocarcinoma of the stomach, a histologically and anatomically homogeneous group, to enhance the consistency of the biologic behavior of the tumors and the clinical outcomes of our patients [18, 19]. More than 70% of our patients received first-line chemotherapy in a daily practice setting, which is likely to accurately represent patient status in routine clinical decision making [20, 21]. Although patients with somewhat higher level of bilirubin or creatinine are often excluded from clinical trials, they are usually given chemotherapy, with or without dose adjustment, in practice. We excluded patients with locally advanced gastric cancer because they are considered potentially curable, and in contrast to patients with recurrent or metastatic gastric cancer, the prognosis of patients with locally advanced gastric cancer can be much improved after postchemotherapy surgery [10]. We also excluded patients who underwent R1 resection because their tumor burden is regarded as minimal, and their survival outcomes did not differ from those of patients with node-positive disease who underwent curative surgery [22]. In addition, we developed a prognostic model from a training set of patients and validated the model in an independent validation set.

Characteristics of prognostic factors

Of the eight factors predictive of poor prognosis, seven had previously been reported to be associated with poor prognosis in patients with advanced cancers of the gastrointestinal tract: poor PS [9, 11–13], no gastrectomy [9, 11, 12], peritoneal metastasis [11–14], bone metastasis [12, 13], decreased albumin [12], increased ALP [11, 12], and increased total bilirubin [13]. Although lung metastasis from gastric cancer is not common in clinical practice, the incidence of lung metastasis in patients with recurrent gastric cancer was not infrequent, about 21.1% in patients with hematogenous recurrence [23]. In addition, an autopsy study found that 22.4% of these patients had lung metastases from gastric cancer [24]. In our data, lung metastasis was shown in about 5% of patients with recurrent or metastatic gastric carcinoma. Lung metastasis was reported to be an independent prognostic factor in gastric cancer

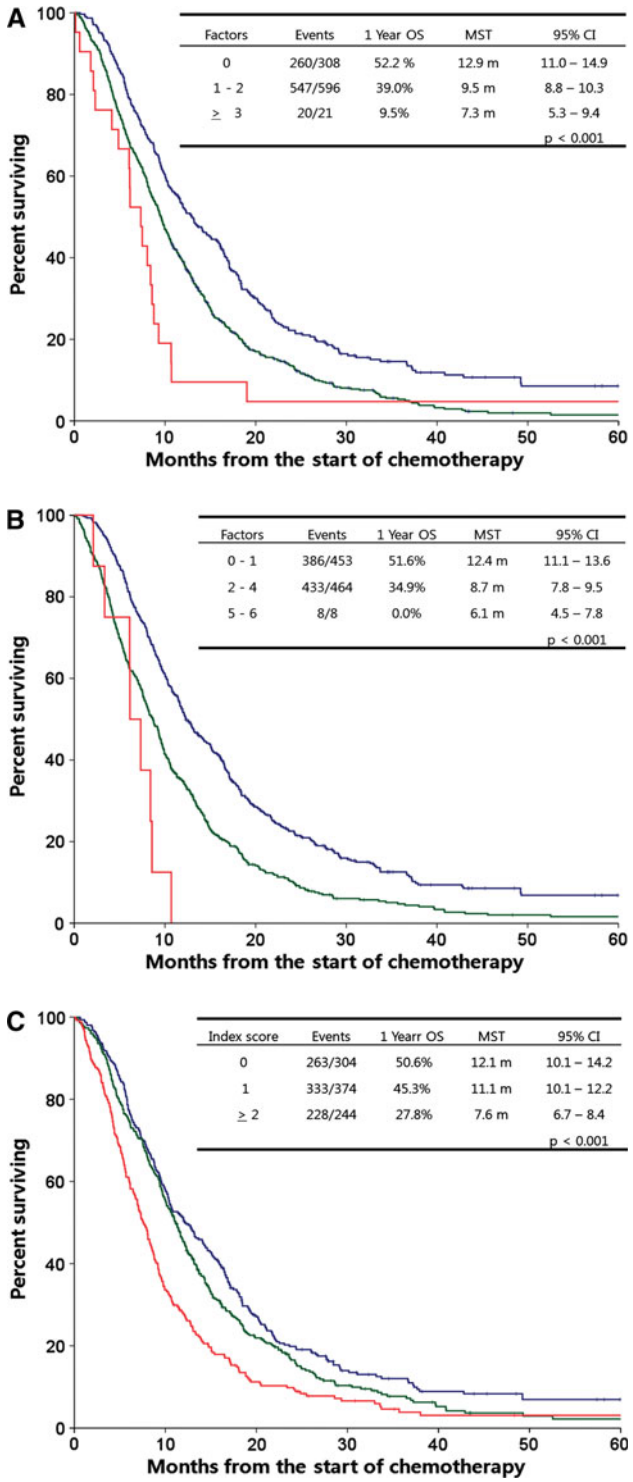

Fig. 2 Survival curves of our validation set according to previously described prognostic models (*MST* median survival time, *OS* overall survival), **a** Chau et al. [11], **b** Lee et al. [12], **c** Kim et al. [13]

patients with bone marrow metastasis [25]. Thus, lung metastasis may be an indicator of more advanced tumor spread or be prognostic in patients with far advanced gastric cancer. The large number of patients in our analysis provided greater statistical power to identify lung metastasis as an independent prognostic factor. Although the number of metastatic sites has been reported to be prognostic in patients with recurrent or metastatic gastric cancer [13, 15, 16], we found that metastasis to certain organs, including bone, peritoneum, liver, and lung, was more predictive of survival outcome.

Characteristics and comparison of prognostic models

We internally validated our model by a random split method, finding that our model performed as well in the validation set as in the training set. Survival differences were significant among the three risk groups, and the observed and predicted numbers of non-surviving patients were similar for each risk group. We also applied prognostic models from previous studies of European and Asian patients with advanced gastric cancer to our validation set (Fig. 2). These models, including ours, showed similar ability to predict survival outcome, with highly significant survival differences among the risk groups and c-statistics indicating that discrimination was similar. These findings indicate that the prognostic factors and models developed from the pretreatment characteristics of Asian and Western patients are similar. However, the models differed in the proportion of patients among the three risk groups. In two models, only 2.3% [11] and 0.9% [12] of patients were included in the poor risk group, whereas the poor risk group in the third model (26.5%) [13] and our model (13.5%) included higher numbers of patients; although patients in the poor risk group had similar median survival times of 6.0–7.6 months. This comparison of the four prognostic models may be meaningful in selecting the most appropriate prognostic model to categorize patients with advanced gastric cancer.

Prospects of prognostic models

Recently, an international phase III study (AVAGAST), comparing capecitabine plus cisplatin with capecitabine plus cisplatin plus bevacizumab as front-line chemotherapy for advanced gastric cancer, reported that efficacies and outcomes were heterogeneous across geographic regions [26]. Differences that may affect patient outcomes, including differences in tumor burden, patient status, practice pattern, or genetics, should therefore be compared across geographic regions. The survival of patients with gastric cancer is affected by race and ethnicity, geographic region, or birthplace [27–29], suggesting that many factors, including tumor histology [30, 31], location [32, 33], initial stage [34], socioeconomics, and treatment [35], may explain survival disparities in patients with gastric cancer. Other factors that may affect survival

include regional differences in patient selection, clinical practice, population genetics, and tumor burden. At present, however, it is unclear whether predictive models to stratify prognostic groups should differ for Asian and Western patient populations. Our results indicate that prognostic factors and models are globally applicable to patients with advanced gastric cancer, especially those with recurrent or metastatic gastric cancer, although survival outcomes may differ between Asian and Western patients. In future, molecular and genetic markers predictive of survival may be combined with these prognostic factors and models to improve predictive accuracy. Further investigation is also needed to develop a prognostic or predictive model for patients who are candidate for the second-line chemotherapy [36].

Conclusion

In conclusion, we have identified eight factors predictive of poor prognosis in patients with recurrent or metastatic advanced gastric cancer. The prognostic model based on a scoring system that incorporated these eight factors could be used to classify patients into three groups with significantly different survival outcomes. This model performed well with a validation set of patients and may therefore help predict life expectancy, guide treatment plans, analyze clinical studies, and design future clinical trials in both Western and Eastern patient populations. Our findings indicate that our model should undergo validation in centers outside Korea or Asia.

Conflict of interest None.

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