

Original Article



Performances of Prognostic Models in Stratifying Patients with Advanced Gastric Cancer Receiving First-line Chemotherapy: a Validation Study in a Chinese Cohort

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ABSTRACT

Purpose: While several prognostic models for the stratification of death risk have been developed for patients with advanced gastric cancer receiving first-line chemotherapy, they have seldom been tested in the Chinese population. This study investigated the performance of these models and identified the optimal tools for Chinese patients.

Materials and Methods: Patients diagnosed with metastatic or recurrent gastric adenocarcinoma who received first-line chemotherapy were eligible for inclusion in the validation cohort. Their clinical data and survival outcomes were retrieved and documented. Time-dependent receiver operating characteristic (ROC) and calibration curves were used to evaluate the predictive ability of the models. Kaplan-Meier curves were plotted for patients in different risk groups divided by 7 published stratification tools. Log-rank tests with pairwise comparisons were used to compare survival differences.


Results: The analysis included a total of 346 patients with metastatic or recurrent disease. The median overall survival time was 11.9 months. The patients were different into different risk groups according to the prognostic stratification models, which showed variability in distinguishing mortality risk in these patients. The model proposed by Kim et al. showed relative higher predicting abilities compared to the other models, with the highest χ^2 (25.8) value in log-rank tests across subgroups, and areas under the curve values at 6, 12, and 24 months of 0.65 (95% confidence interval [CI]: 0.59–0.72), 0.60 (0.54–0.65), and 0.63 (0.56–0.69), respectively.

Conclusions: Among existing prognostic tools, the models constructed by Kim et al., which incorporated performance status score, neutrophil-to-lymphocyte ratio, alkaline phosphatase, albumin, and tumor differentiation, were more effective in stratifying Chinese patients with gastric cancer receiving first-line chemotherapy.

Keywords: Gastric cancer; Chemotherapy; Survival analysis; Validation study

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Author Contributions

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Gastric cancer is the fifth most common and third leading cause of cancer-related deaths worldwide [1]. It has been estimated that more than 40% of patients with gastric cancer live in China [1], with approximately 70,000 new cases annually in China [2]. Data from the Surveillance, Epidemiology, and End Results (SEER) showed that more than one-third of all newly diagnosed gastric cancer cases have distant metastatic disease and the overall prognosis for these patients remains poor, despite great advances in chemotherapy and targeted therapy [3].

Chemotherapy is the cornerstone of first-line treatment for patients with metastatic gastric cancer. However, among patients receiving first-line chemotherapy, the survival times vary according to multiple characteristics. However, there are no generally accepted tools for identifying patients at high or low risks of death. As early as 2004, scholars from the Royal Marsden Hospital (RMH) developed a prognostic model for patients with advanced gastric cancer using data from 3 multicenter, randomized, controlled trials in Caucasians, in which the patients were stratified into good, moderate, and poor risk groups according to performance status, liver metastases, peritoneal metastases, and alkaline phosphatase levels [4]. However, the Japan Clinical Oncology Group (JCOG) model, which is also derived from data from clinical trials, incorporates a different set of variables; namely, performance status, number(s) of metastatic sites, prior gastrectomy, and alkaline phosphatase levels [5]. In recent years, several other prognostic models have also been developed for Korean populations, such those from Lee et al. [6], Kim et al. [7], Koo et al. [8], and Kim et al. [9]. These models were based on data from clinical practice, and the parameters included in each model were not unified. Moreover, none of these models have been validated in Chinese patients. In 2016, Wang et al. [10] constructed a model using a dataset from Chinese patients, but only those with a good performance status (PS: 0–1). Thus, the present study aimed to validate these 7 prognostic models in a Chinese cohort of patients with advanced gastric cancer receiving first-line chemotherapy and to determine the performance of these models in stratifying Chinese patients.

MATERIALS AND METHODS

Patient cohort

The patients included in this validation study were derived among those who visited the First Affiliated Hospital of Anhui Medical University (Anhui Province, People's Republic of China) between 2009 and 2018. The protocol for this retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Quick-PJ2021-05-19). The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and the requirement for consent to participate was waived. All patients were histopathologically diagnosed with gastric or esophagogastric junction adenocarcinoma, with pathologically or radiologically confirmed distant metastatic disease, irrespective of the primary staging. First-line chemotherapy with single, doublet, or triplet combination regimens was acceptable. Anti-Her-2 antibody trastuzumab or angiogenesis inhibitors (apatinib, endostatin, or bevacizumab) could be added to the regimens; however, patients who received only trastuzumab or angiogenesis inhibitors were not included in the analysis. We referred to the case files to obtain information on the essential parameters. Vital status was determined by telephone contact with the patients or their relatives. The dates of

death were obtained from the Vital Statistic Information System of the Center for Disease Prevention and Control. Overall survival (OS) was defined as the period between the date of first metastasis and the date of death or the last follow-up date (August 1, 2018).

Stratification models and patient scoring

This study validated 7 published stratification models for patients with advanced gastric cancer receiving first-line chemotherapy. Of these, the RMH model was the first developed model. It was derived from patients enrolled in 3 multicenter, prospective, randomized controlled trials in the United Kingdom from 1992 to 2001 [4] and validated using individual patient data from the REAL 2 Study [11]. The JCOG model was developed in 704 Japanese patients enrolled in the JCOG 9912 trial between 2000 and 2006 and validated using data from the SPIRITS and G-SOX trials [5,12]. Lee et al. [6] developed a model using data from 1,455 patients with gastric cancer (1994–2005) at the Samsung Medical Center, Korea. Kim et al.'s model [7] was derived from 304 consecutive patients at the Korea Cancer Center Hospital. Koo et al.'s model [8] was derived from patients at the Asan Medical Center in Korea. Kim et al. [9] developed a model using data from 1,733 patients with gastric cancer (2008–2018) at the Samsung Medical Center, Korea. Wang et al.'s model [10] was based on 310 patients at the First Hospital of China Medical University (2007–2013). According to the rules for score assignment for the variables in each model (**Tables 1** and **2**), the patients in our cohort were scored and assigned to the high (poor), intermediate (moderate), or low (good) risk groups, respectively.

Statistical analysis

Categorical variables in the validation dataset were described as numbers (%). Numerical variables are shown as medians (25th–75th percentile) and were transformed into categorical variables by the respective cut-off values of the variables in the stratification models. The discriminative abilities of the models were evaluated by time-dependent receiver operating characteristic curve (ROC) analysis in R 4.0.3 using the “timeROC” package. Calibration curves were plotted to measure the discrepancies between the predictions and the actual outcomes (1-year survival probabilities). Kaplan-Meier survival analyses were used to estimate the survival curves for different risk subgroups. Survival times were compared using log-rank tests with pairwise comparisons. $P < 0.05$ was considered statistically significant. Survival analysis was performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Survival curves were drawn using GraphPad Prism software version 5.01 (GraphPad Software, Inc., San Diego, CA, USA).

RESULTS

Patient characteristics

The validation cohort included 346 cases with advanced gastric adenocarcinoma. The baseline characteristics of these patients are shown in **Table 3**. The median age was 61 years and there were twice as many males as females. In this study, 82.7% of patients had good performance scores and more than half of the tumors were poorly differentiated or undifferentiated. Regarding metastatic sites, distant lymph nodes were the most common site of the first episode of metastasis (56.1%), followed by the liver (30.9%). Approximately two-thirds of the patients had single-organ involvement. The medians of alkaline phosphatase (ALP), total bilirubin (TBIL), and albumin (ALB) levels, as well as the neutrophil-to-lymphocyte ratio (NLR), are also shown in **Table 3**. More than two-thirds of the patients

Validation of GC Prognostic Models

Table 1. Distributions of patients and allocated scores for variables assessed in 7 prognostic models

Variables	RMH model		JCOG model		Kim et al.'s model [7]		Kim et al.'s model [9]		Koo et al.'s model [8]		Lee et al.'s model [6]		Wang et al.'s model [10]	
	Score	No. (%)	Score	No. (%)	Score	No. (%)	Score	No. (%)	Score	No. (%)	Score	No. (%)	Score	No. (%)
PS*														
0-1	0	286 (82.7)	0	3 (0.9)	0	286 (82.7)	0	286 (82.7)	0	286 (82.7)	0	286 (82.7)	-	-
2-3	1	60 (17.3)	1	343 (99.1)	1	60 (17.3)	2	60 (17.3)	2	60 (17.3)	1	60 (17.3)	-	-
Liver metastasis														
Absent	0	239 (69.1)	-	-	-	-	-	-	-	-	-	-	0	239 (69.1)
Present	1	107 (30.9)	-	-	-	-	-	-	-	-	-	-	2	107 (30.9)
Peritoneal metastases														
Absent	0	295 (85.3)	-	-	-	-	-	-	-	-	-	-	-	-
Present	1	51 (14.7)	-	-	-	-	-	-	-	-	-	-	-	-
No. of metastatic sites														
1	-	-	0	264 (76.3)	0	264 (76.3)	-	-	-	-	-	-	0	264 (76.3)
≥2	-	-	1	82 (23.7)	1	82 (23.7)	-	-	-	-	-	-	1	82 (23.7)
Prior gastrectomy														
Yes	-	-	0	197 (56.9)	-	-	-	-	-	-	0	197 (56.9)	0	197 (56.9)
No	-	-	1	149 (43.1)	-	-	-	-	-	-	1	149 (43.1)	1	149 (43.1)
Bone metastasis														
Absent	-	-	-	-	0	324 (93.6)	-	-	0	324 (93.6)	0	324 (93.6)	0	324 (93.6)
Present	-	-	-	-	2	22 (6.4)	-	-	2	22 (6.4)	1	22 (6.4)	2	22 (6.4)
Peritoneal metastasis														
Absent	-	-	-	-	0	295 (85.3)	-	-	0	295 (85.3)	-	-	-	-
Present	-	-	-	-	1	51 (14.7)	-	-	1	51 (14.7)	-	-	-	-
Lung metastasis														
Absent	-	-	-	-	-	-	-	-	0	311 (89.9)	-	-	-	-
Present	-	-	-	-	-	-	-	-	1	35 (10.1)	-	-	-	-
ALP (U/L)[†]														
Low	0	217 (62.7)	0	338 (97.7)	-	-	0	282 (81.5)	0	257 (74.3)	0	157 (45.4)	-	-
High	1	129 (37.3)	1	8 (2.3)	-	-	2	64 (18.5)	1	89 (25.7)	1	189 (54.6)	-	-
ALB (g/L)[‡]														
High	-	-	-	-	-	-	0	272 (78.6)	0	303 (87.6)	0	251 (72.5)	-	-
Low	-	-	-	-	-	-	2	74 (21.4)	1	43 (12.4)	1	95 (27.5)	-	-
NLR[§]														
≤3	-	-	-	-	-	-	0	195 (56.4)	-	-	-	-	0	173 (50.0)
>3	-	-	-	-	-	-	2	151 (43.6)	-	-	-	-	1	173 (50.0)
TBIL														
Normal	-	-	-	-	0	332 (96.0)	-	-	0	325 (93.9)	-	-	-	-
>Normal	-	-	-	-	1	14 (4.0)	-	-	1	21 (6.1)	-	-	-	-
Differentiation														
Well/moderately	-	-	-	-	-	-	0	62 (17.9)	-	-	-	-	-	-
Poor/signet/other	-	-	-	-	-	-	1	284 (82.1)	-	-	-	-	-	-
Gastrectomy														
Yes	-	-	-	-	-	-	-	-	0	197 (56.9)	-	-	-	-
No	-	-	-	-	-	-	-	-	1	149 (43.1)	-	-	-	-
Ascites														
Absent	-	-	-	-	-	-	-	-	-	-	0	295 (85.3)	-	-
Present	-	-	-	-	-	-	-	-	-	-	1	51 (14.7)	-	-

RMH = Royal Marsden Hospital; JCOG = Japan Clinical Oncology Group; PS = performance status; ALP = alkaline phosphatase; ULN = upper limit of normal; TBIL = total bilirubin; NLR = neutrophil-to-lymphocyte ratio; ALB = albumin.

*PS criteria of Lee et al.'s model is 0-1 and ≥2. †ALP criteria (low, high) is different with each models: RMH model (<100, ≥100); JCOG model (<ULN, ≥ULN); Kim et al.'s model [9] (<140, >140); Koo et al.'s model [8] (<120, >120); Lee et al.'s model [6] (<85, >85). ‡ALB criteria (high, low) is different with each models: Kim et al.'s model [9] (>35, ≤35); Koo et al.'s model [8] (≥33, <33); Lee et al.'s model [6] (≥36, <36). §NLR criteria of Wang et al.'s model [10] is ≤50 and >50 percentile. ||TBIL criteria of Koo et al.'s model [8] is ≤1.2 and >1.2 mg/dL.

Table 2. Rules for risk stratification according to the total scores in different models

Risk	RMH model	JCOG model	Kim et al.'s model [7]	Kim et al.'s model [9]	Koo et al.'s model [8]	Lee et al.'s model [6]	Wang et al.'s model [10]
Low (good)	0	0–1	0	0–1	0–1	0–1	0
Intermediate (moderate)	1–2	2–3	1	2–3/4–5	2–3	2–4	1–3
High (poor)	3–4	4	2–	6–9	4–	5–6	4–

RMH = Royal Marsden Hospital; JCOG = Japan Clinical Oncology Group.

received a doublet combination of chemotherapy of either platinum plus fluoropyrimidines or other combinations (platinum or fluoropyrimidines with added anthracenes, taxanes, or irinotecan); single- and 3-drug regimens accounted for approximately 10% and 20% of cases, respectively. Targeted drugs were added to the first-line chemotherapy only in 3.4% of patients (7 patients with trastuzumab and 5 patients with angiogenesis inhibitors). The estimated median overall survival (mOS) of this group of patients was 11.9 months (95% confidence interval [CI], 10.3–13.4). The survival curves are shown in **Fig. 1A**.

Performance of prognostic models

The time-dependent ROCs for the 7 models in the validation cohorts are shown in **Fig. 2**, while the areas under the curves (AUCs) are shown in **Table 4**. None of the models showed good ability in discriminating the prognoses of patients with advanced gastric cancer in our Chinese cohort with an AUC of no more than 0.7 and the calibration curves deviated from the 45-degree lines. Among the models, that from Kim et al. [9] showed relatively higher predicting abilities than those for the other models, with AUC values at 6, 12, and 24 months of 0.65 (95% CI, 0.59–0.72), 0.60 (95% CI, 0.54–0.65), and 0.63 (95% CI, 0.56–0.69), respectively. By applying the rules of stratification for the different models (**Table 2**) to our cohort, the patients were repeatedly divided into low (good), intermediate (moderate), and high (poor) risk groups (4 groups in the Kim et al.'s model) [9]. The Kaplan-Meier estimated survival curves for patients in the different risk groups are shown in **Fig. 1**. All the models were workable in the Chinese cohort. For each validation, the P-values for the pooled comparisons in the log-rank tests across subgroups were statistically significant, with the maximum χ^2 observed in the validation of the model from Kim et al. [9], followed by that from Koo et al. [8], which indicated its potential superiority to others in stratifying our patients. However, different models showed varying abilities to distinguish patient mortality risks. In summary, the models from the RMH, Kim et al. [7], and Koo et al. [8] showed relatively higher performance in identifying patients with a poor prognosis. The mOS times of the poor-risk group in these 3 validations were 5.0 (95% CI, 1.5–8.4), 7.3 (95% CI, 5.2–9.3), and 6.4 (95% CI, 4.8–8.1) months, respectively. Compared to the respective mOS of the good- and moderate-risk groups, all P-values in pairwise comparisons were <0.05. However, the 3 models were unable to distinguish the good-risk group from the moderate-risk group (P-values of pairwise comparisons: 0.171, 0.241, and 0.143 for the validation of the RMH, Kim JG et al., and Koo et al. models, respectively). In contrast, the other 3 models [6,9,10] were all good at separating low-risk patients but failed to identify high-risk patients. The corresponding mOS times of the low-risk patients in the 3 validations were 14.5 (95% CI, 11.7–17.3), 14.5 (95% CI, 10.1–18.9), and 15.8 (95% CI, 12.8–18.9) months, respectively, longer than their partners in each validation cohort (P<0.05) except for the low-risk vs. high-risk groups (only 1 case left) in the validation of the model from Lee et al. [6]. The JCOG model was not valuable in identifying high-risk patients (only 3 patients were identified in the validation cohort) and showed unremarkable performance for the identification of low-risk patients. The survival times kept pace with patients in the moderate-risk group (13.4 vs. 11.0 months, $\chi^2=8.89$), although the P-value was 0.003.

Table 3. Characteristics of patients in the validation cohorts (n=346)

Clinical characteristics	Values
Age (yr)	61 (53, 68)
Sex	
Male	235 (67.9)
Female	111 (32.1)
Gastrectomy	
Yes	197 (56.9)
No	149 (43.1)
ECOG score at first episode of metastasis	
0	3 (0.9)
1	283 (81.8)
≥2	79 (17.3)
Tumor grade	
G1-2	62 (17.9)
G3-4	199 (57.5)
Unknown	85 (24.6)
Her-2 status	
Negative	36 (10.4)
Positive	15 (4.3)
Unknown	295 (85.3)
Original AJCC7th staging	
I	11 (3.2)
II	34 (9.8)
III	149 (43.1)
IV	152 (43.9)
Metastatic to (first episode of metastasis)	
Liver	107 (30.9)
Lung	35 (10.1)
Bone	22 (6.4)
Distant lymph node	194 (56.1)
Peritoneal/malignant ascites	51 (14.7)
Number of involved organs in the first episode of metastasis	
1	264 (76.3)
≥2	82 (23.7)
ALP (U/L)	89 (72, 122)
TBIL (mg/dL)	0.53 (0.40, 0.74)
ALB (g/L)	38.8 (35.5, 42.9)
NLR	2.61 (1.79, 4.12)
First-line regimens	
Single chemotherapy drug	32 (9.2)
Fluoropyrimidines (p.o. or i.v.)	26 (7.5)
Others	6 (1.7)
Doublet chemotherapy combination	236 (68.2)
Platinum plus fluoropyrimidines	125 (36.1)
Other combinations	111 (32.1)
Triplet chemotherapy combination	78 (22.5)
Anthracenes-contained regimens	12 (3.5)
Taxanes-contained regimens	61 (7.6)
Irinotecan-contained regimens	5 (1.4)
In combination with targeted therapy	
Trastuzumab	7 (2.0)
Angiogenesis inhibitors	5 (1.4)
No	334 (96.5)

Values are expressed as number (%) or median (25th, 75th percentile).

ECOG = Eastern Cooperative Oncology Group; ALP = alkaline phosphatase; TBIL = total bilirubin; NLR = neutrophil-to-lymphocyte ratio; ALB = albumin; p.o. = per oral; i.v. = intravenous.

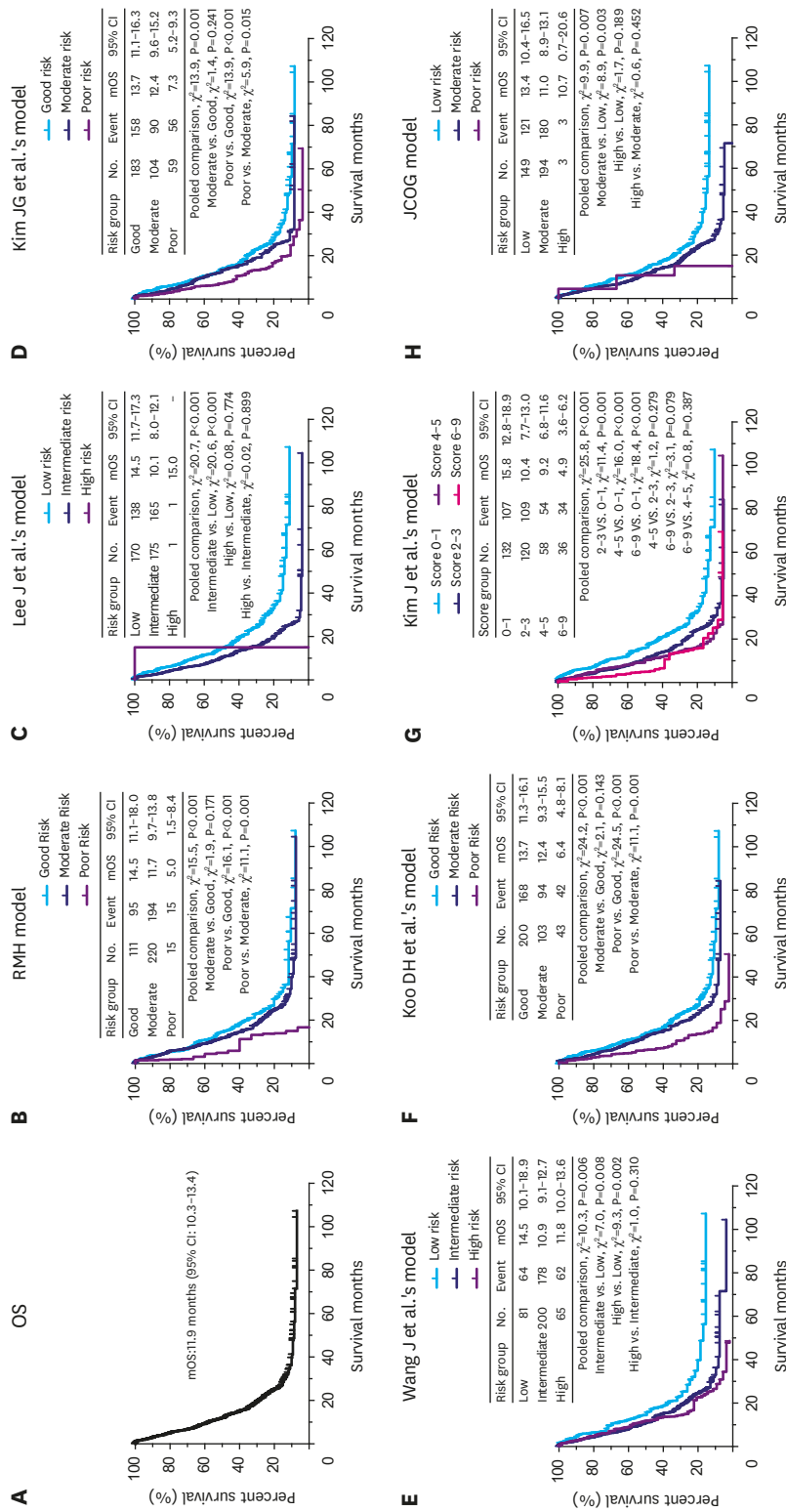


Fig. 1. Kaplan-Meier estimated survival curves of 346 patients with metastatic gastric cancer. (A) OS curve of the pooled population. (B-H) 346 patients were allocated into risk subgroups according to the rules of the respective models. Log-rank tests with pairwise comparisons were used to compare the survival times of patients in different subgroups. OS = overall survival; mOS = median overall survival; CI = confidence interval; RMH = Royal Marsden Hospital; JCOG = Japan Clinical Oncology Group.

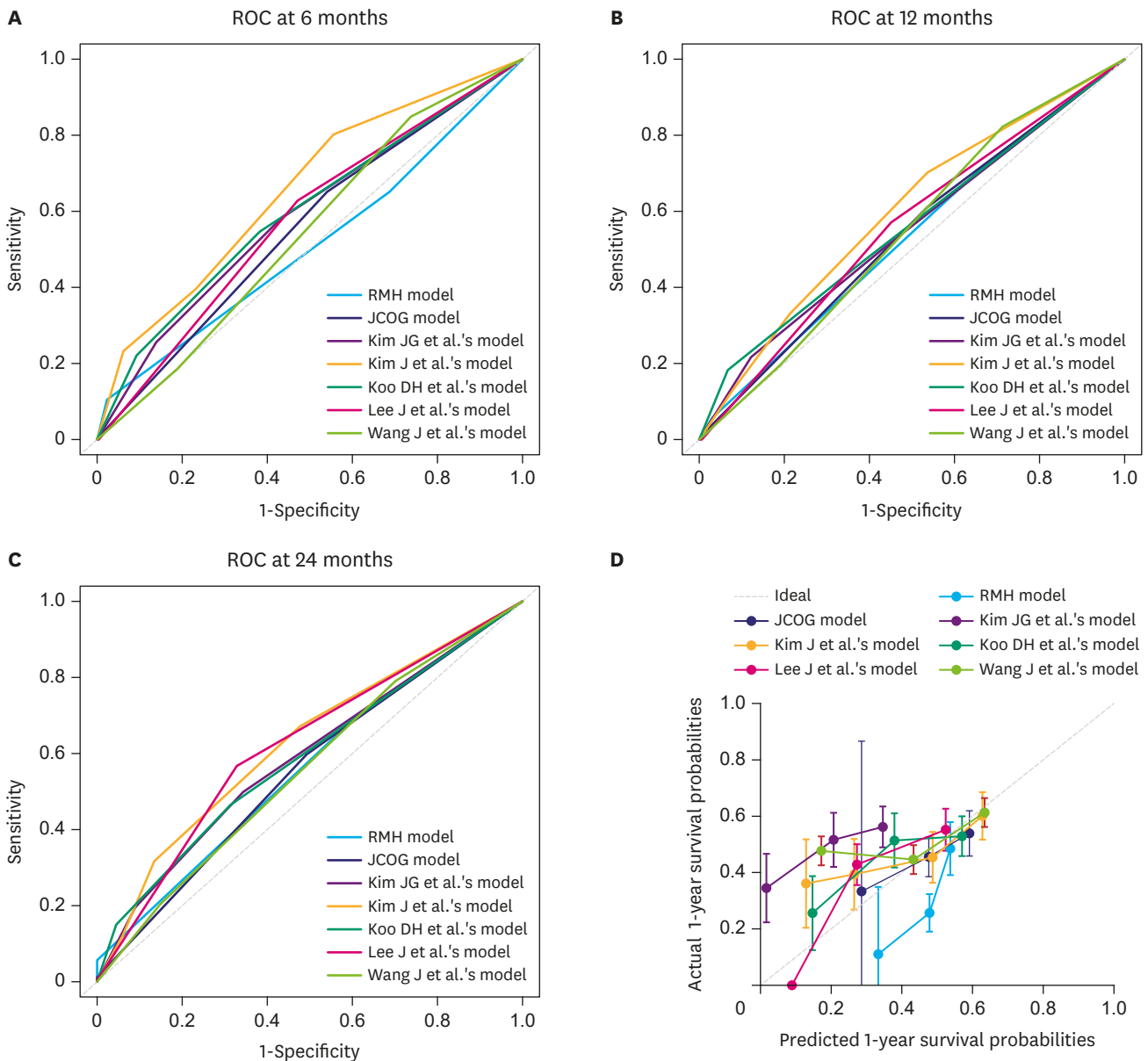


Fig. 2. Time-dependent ROC and calibration curves in the validation cohort for different prognostic models. (A-C) ROCs at 6, 12, and 24 months, respectively. (D) Calibration curves of different models. The patients were grouped by risk scores for the respective models. The 1-year survival probabilities with their respective 95% confidence intervals are indicated in the graph. ROC = receiver operating characteristic; RMH = Royal Marsden Hospital; JCOG = Japan Clinical Oncology Group.

Table 4. Abilities of 7 prognostic models to predict survival patients with advanced gastric cancer in the validation cohort

Model	AUROC (95% CI)		
	6-month	12-month	24-month
RMH	0.51 (0.45–0.58)	0.53 (0.48–0.58)	0.56 (0.50–0.62)
JCOG	0.56 (0.50–0.62)	0.54 (0.49–0.59)	0.56 (0.49–0.62)
Kim et al. [7]	0.59 (0.52–0.65)	0.55 (0.50–0.61)	0.59 (0.52–0.65)
Kim et al. [9]	0.65 (0.59–0.72)	0.60 (0.54–0.65)	0.63 (0.56–0.69)
Koo et al. [8]	0.60 (0.53–0.66)	0.56 (0.51–0.62)	0.59 (0.53–0.65)
Lee et al. [6]	0.58 (0.52–0.64)	0.56 (0.51–0.61)	0.62 (0.56–0.68)
Wang et al. [10]	0.54 (0.49–0.60)	0.55 (0.49–0.60)	0.56 (0.49–0.63)

AUROC = area under receiver operating characteristic curve; CI = confidence interval; RMH = Royal Marsden Hospital; JCOG = Japan Clinical Oncology Group.

DISCUSSION

Although chemotherapy is usually recommended for patients with metastatic or recurrent gastric cancer, the prognosis for these patients remains poor, with the median survival time of patients with advanced gastric cancer receiving first-line chemotherapy in clinical trials of approximately 8–14 months [13–20]. In the setting of clinical decision-making, it is important to identify patients at high or low risk of death. In this study, we established a retrospective cohort of Chinese patients with gastric cancer who received first-line chemotherapy, with a median overall survival time of 11.9 months, which was consistent with those in previous reports. The results of our validation of 7 published prognostic models in our cohort showed that the ability to distinguish mortality risk of patients varied across models, with Kim et al.'s model [9] showing relatively higher performance in stratifying Chinese patients with gastric cancer receiving first-line chemotherapy.

There were also some limitations to the 7 prognostic models used in this study. First, only the RMH and JCOG models were validated using independent datasets [11,12]; the others were either not validated or validated only with the inner dataset. More importantly, to our knowledge, none of these models have been tested in Chinese patients. Second, because most models were developed in the last few decades, the chemotherapy regimens were out-of-date. For example, the RMH was derived from pooled datasets of clinical trials of first-line chemotherapy for advanced gastric cancer in the United Kingdom conducted between 1992 and 2001, including ECF (epirubicin, cisplatin, and 5-Fu), FAMTX (methotrexate, 5-Fu followed by doxorubicin), and MCF (mitomycin C, cisplatin and 5-Fu). Kim et al.'s model [7] was derived from data of patients treated with cisplatin-based chemotherapy during 1992 and 1996, before taxanes were introduced. Third, these models did not include some clinicopathological parameters such as Lauren subtype and Her-2 status, which are now considered important prognostic factors.

The ability to distinguish the mortality risk of patients varied across models for the following reasons. First, heterogeneity existed between the training datasets of the models and our cohort. For example, the dataset derived by Kim et al. [7] had higher proportions of patients with PS 2–3 and peritoneal metastasis (26.6% and 20.7%, respectively) compared to those in our cohort (17.3% and 14.7%, respectively), both of which indicated poor prognosis for gastric cancer patients. Thus, we speculated that Kim et al.'s model [7] was more suitable for high-risk patients, as demonstrated in the current study. Similarly, the training dataset used to develop Koo et al.'s model [8] included more patients with peritoneal metastasis (43.7% vs. 14.7%) and low (<33 g/L) ALB levels (28.1% vs. 12.4%). In contrast, the training dataset in Kim et al.'s model [9] included lower proportions of patients with adverse prognostic factors compared to the proportions in our validation dataset (24.9% vs. 43.6% for patients with high NLR, and 76.9% vs. 82.1% for patients with poorly differentiated subtype). In Lee et al.'s model [6], the median ALB and ALP levels were also lower in the training dataset than in the validation dataset. These factors contributed to their higher ability to identify patients at low risk of death. In addition, the first-line regimens for patients in the training cohort were outdated compared to those in our cohort, with newly developed regimens containing oxaliplatin, capecitabine, S1, paclitaxel, docetaxel, or irinotecan extensively adopted in our cohort, especially taxane-containing triplet regimens, which provided a survival benefit compared to doublet platinum and fluoropyrimidines [13,21]. Thus, it was reasonable that models derived from patients with “poor prognosis” were good at distinguishing high-risk patients.

Our study has some limitations. First, the limitations inherent to outdated models are unavoidable. Second, the data from the patients in our cohort were retrospectively collected and the most common parameter in the prognostic models “PS score” was not evaluated uniformly, which may have influenced the performance of validation. Moreover, the sample size of the validation cohort was not large enough. For the high-risk subgroups for stratification in the JCOG and Lee et al.'s models [6], too few patients resulted in less precise prediction. In addition, this was a single-center validation study; thus, referral bias was unavoidable.

In conclusion, among existing prognostic tools, the models constructed by Kim et al. [9], which incorporated PS score, NLR, ALP, ALB, and tumor differentiation, were more effective than others in stratifying Chinese patients with gastric cancer receiving first-line chemotherapy.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.
[PUBMED](#) | [CROSSREF](#)
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115-132.
[PUBMED](#) | [CROSSREF](#)
3. Ebinger SM, Warschkow R, Tarantino I, Schmiech BM, Güller U, Schiesser M. Modest overall survival improvements from 1998 to 2009 in metastatic gastric cancer patients: a population-based SEER analysis. *Gastric Cancer* 2016;19:723-734.
[PUBMED](#) | [CROSSREF](#)
4. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *J Clin Oncol* 2004;22:2395-2403.
[PUBMED](#) | [CROSSREF](#)
5. Takahari D, Boku N, Mizusawa J, Takashima A, Yamada Y, Yoshino T, et al. Determination of prognostic factors in Japanese patients with advanced gastric cancer using the data from a randomized controlled trial, Japan Clinical Oncology Group 9912. *Oncologist* 2014;19:358-366.
[PUBMED](#) | [CROSSREF](#)
6. Lee J, Lim T, Uhm JE, Park KW, Park SH, Lee SC, et al. Prognostic model to predict survival following first-line chemotherapy in patients with metastatic gastric adenocarcinoma. *Ann Oncol* 2007;18:886-891.
[PUBMED](#) | [CROSSREF](#)
7. Kim JG, Ryoo BY, Park YH, Kim BS, Kim TY, Im YH, et al. Prognostic factors for survival of patients with advanced gastric cancer treated with cisplatin-based chemotherapy. *Cancer Chemother Pharmacol* 2008;61:301-307.
[PUBMED](#) | [CROSSREF](#)
8. Koo DH, Ryoo BY, Kim HJ, Ryu MH, Lee SS, Moon JH, et al. A prognostic model in patients who receive chemotherapy for metastatic or recurrent gastric cancer: validation and comparison with previous models. *Cancer Chemother Pharmacol* 2011;68:913-921.
[PUBMED](#) | [CROSSREF](#)
9. Kim J, Hong JY, Kim ST, Park SH, Jekal SY, Choi JS, et al. Clinical scoring system for the prediction of survival of patients with advanced gastric cancer. *ESMO Open* 2020;5:E000670.
[CROSSREF](#)

10. Wang J, Qu J, Li Z, Che X, Zhang J, Liu J, et al. A prognostic model in metastatic or recurrent gastric cancer patients with good performance status who received first-line chemotherapy. *Transl Oncol* 2016;9:256-261.
[PUBMED](#) | [CROSSREF](#)
11. Chau I, Ashley S, Cunningham D. Validation of the Royal Marsden hospital prognostic index in advanced esophagogastric cancer using individual patient data from the REAL 2 study. *J Clin Oncol* 2009;27:e3-e4.
[PUBMED](#) | [CROSSREF](#)
12. Takahari D, Mizusawa J, Koizumi W, Hyodo I, Boku N. Validation of the JCOG prognostic index in advanced gastric cancer using individual patient data from the SPIRITS and G-SOX trials. *Gastric Cancer* 2017;20:757-763.
[PUBMED](#) | [CROSSREF](#)
13. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol* 2006;24:4991-4997.
[PUBMED](#) | [CROSSREF](#)
14. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;9:215-221.
[PUBMED](#) | [CROSSREF](#)
15. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36-46.
[PUBMED](#) | [CROSSREF](#)
16. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. *Ann Oncol* 2009;20:666-673.
[PUBMED](#) | [CROSSREF](#)
17. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-697.
[PUBMED](#) | [CROSSREF](#)
18. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. *J Clin Oncol* 2010;28:1547-1553.
[PUBMED](#) | [CROSSREF](#)
19. Koizumi W, Kim YH, Fujii M, Kim HK, Imamura H, Lee KH, et al. Addition of docetaxel to S-1 without platinum prolongs survival of patients with advanced gastric cancer: a randomized study (START). *J Cancer Res Clin Oncol* 2014;140:319-328.
[PUBMED](#) | [CROSSREF](#)
20. Yamada Y, Higuchi K, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. *Ann Oncol* 2015;26:141-148.
[PUBMED](#) | [CROSSREF](#)
21. Wang J, Xu R, Li J, Bai Y, Liu T, Jiao S, et al. Randomized multicenter phase III study of a modified docetaxel and cisplatin plus fluorouracil regimen compared with cisplatin and fluorouracil as first-line therapy for advanced or locally recurrent gastric cancer. *Gastric Cancer* 2016;19:234-244.
[PUBMED](#) | [CROSSREF](#)