Clinical Study

Oncology

Oncology 2018;95:344–352
DOI: 10.1159/000491753

Received: April 6, 2018
Accepted after revision: July 2, 2018
Published online: August 21, 2018

Estimating Survival Probabilities of Advanced Gastric Cancer Patients in the Second-Line Setting: The Gastric Life Nomogram

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Keywords
Advanced gastric cancer · Prognosis · Stomach

Abstract
Objective: We built and externally validated a nomogram for predicting the overall survival (OS) probability of advanced gastric cancer patients receiving second-line treatment. ***Methods:*** The nomogram was developed on a set of 320 Italian patients and validated on two independent sets (295 Italian and 172 Korean patients). Putative prognostic variables were selected using a random forest model and included in the multivariable Cox model. The nomogram's performance was evaluated by calibration plot and C index. ***Results:*** ECOG performance status, neutrophils to lymphocytes ratio, and

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peritoneal involvement were selected and included into the multivariable model. The C index was 0.72 (95% CI 0.68–0.75) in the development set, 0.69 (95% CI 0.65–0.73) in the Italian validation set, but only 0.57 (95% CI 0.52–0.62) in the Korean set. While Italian calibrations were quite good, the Korean one was poor. Regarding 6-month OS predictions, calibration was best in both Caucasian cohorts and worst the in Asian one. ***Conclusions:*** Our nomogram may be a useful tool to predict 3- or 6-month OS in Caucasian gastric cancer patients eligible for second-line therapy. Based on three easy-to-collect variables, the Gastric Life nomogram may help clinicians improve patient selection for second-line treatments and assist in clinical trial enrollment.

Introduction

The treatment algorithms of metastatic gastric cancer (mGC) patients have notably evolved in recent years thanks to second-line chemotherapy or ramucirumab-based therapy, and their further implementation is awaited as a consequence of the introduction of novel treatment options such as targeted strategies and immunotherapy [1–5].

Currently, the use of second-line therapy is supported by five randomized clinical trials [6–10], two of which tested ramucirumab alone or in combination with paclitaxel. Although still limited, the median overall survival (OS) of pretreated mGC patients is improving over time, reaching nearly 10 months with the paclitaxel/ramucirumab combination [10]. At present, no predictive biomarker – other than HER2 for the use of trastuzumab – is recommended to guide the overall clinical management. Since a consistent percentage of patients with mGC actually derive no or marginal benefit from second-line treatment, appropriate clinical selection may improve the benefit/risk ratio and minimize the individual toxicity and financial expenditures of second-line treatments.

Regarding this clinical challenge, the variability of disease aggressiveness as assessed by the combination of several prognostic biomarkers and the availability of better treatment options has increased the heterogeneity of the life expectancy in this patient population. Even though prognostic variables or specific second-line scores have been proposed [11–13], no evidence-based tools are available to estimate single patient life expectancy in the second-line setting, so that clinicians need to rely on their subjective experience both for trial enrollment and treatment decisions.

Here, our aim was to build and externally validate a nomogram for predicting the OS probability of mGC patients deemed eligible for second-line treatment, thus potentially impacting their clinical management.

Methods

Study Design and Cohort Description

The nomogram was developed on a cohort of Italian patients and externally validated on two independent cohorts of Italian and Korean patients. The inclusion criteria were age ≥18 years, ECOG performance status (PS) ≤2, histologically confirmed diagnosis of mGC, and failure of first-line treatment (including trastuzumab for patients with known HER2-positive tumors) or disease relapse within 6 months from the completion of postoperative combination chemotherapy. All patients had to receive at least one dose of second-line treatment; those patients who had previously experienced unacceptable toxicity warranting treatment discontinuation and were unable to receive the same treatment again were eligible. Patients had to be followed for at least 6 months from the start of second-line treatment.

The developing cohort included two previously investigated Italian series of patients treated with ramucirumab-based therapy (RAMoss study) [14] or with any second-line treatment [13]; the patients were treated at 38 institutions between 2004 and 2016. The Italian validation set included patients consecutively treated at 16 Italian institutions between 2008 and 2017, and the Korean set included patients treated at Samsung Medical Center (Seoul, Korea) between 2008 and 2010.

The nomogram endpoint was OS; we would predict the 3- and 6-month OS probability, the former because life expectancy of 3 months is required for enrollment in clinical trials and the latter being more similar to the median OS in second-line trials. The candidate prognostic variables were baseline clinical and pathological parameters derived in the two Italian studies [13, 14], i.e., age, sex, ECOG PS, primary tumor site (gastroesophageal junction or stomach), Lauren's histotype (intestinal, diffused, other), primary tumor resection (yes, no), presentation of metastases (metachronous, synchronous), number of metastatic sites (1, 2, ≥3), specific sites of metastases (peritoneal, extraregional lymph nodes, liver, lung), laboratory tests (neutrophils to lymphocytes [N/L] ratio, lactate dehydrogenase), first-line objective response, and first-line progression-free survival.

Statistical Methods

The survival time was calculated from the start of second-line treatment to the date of death from all causes, with censoring at the date of last follow-up in living patients. OS curves were estimated by the Kaplan-Meier method.

In the development set, a multivariable random forest procedure [15] including all the above-mentioned a-priori chosen candidate predictors was used for variable selection. The random forest model allows handling of many predictor variables without overfitting and quantifies their relative importance, higher figures indicating stronger prognostic value. Variable selection was performed according to relative importance *p* values calculated by applying a permutation procedure (with 20,000 permutations of the initial dataset) after false discovery rate *p* value adjustment [16, 17].

Table 1. Patients and disease characteristics as well as type of second-line treatment received

Variables	Development set (n = 320)	Italian validation set (n = 295)	Korean validation set (n = 172)
Age, years	62 (52–70)	63 (54–71)	NA
Sex			
Female	111 (34.7%)	99 (33.6%)	51 (29.7%)
Male	209 (65.3%)	196 (66.4%)	121 (70.3%)
ECOG PS			
0	122 (38.1%)	115 (39.0%)	61 (35.5%)
1	131 (40.9%)	155 (52.5%)	91 (52.9%)
2	67 (20.9%)	25 (8.5%)	20 (11.6%)
Primary tumor site			
Gastric	211 (65.9%)	218 (73.9%)	151 (87.8%)
GEJ	109 (34.1%)	77 (26.1%)	21 (12.2%)
Histotype			
Diffuse	114 (35.6%)	121 (44.0%)	118 (68.6%)
Intestinal	182 (56.9%)	141 (51.3%)	45 (26.2%)
Other	24 (7.5%)	13 (4.7%)	9 (5.2%)
NA	–	20	–
Primary tumor resection			
No	123 (38.4%)	151 (51.2%)	93 (54.1%)
Yes	197 (61.6%)	144 (48.8%)	79 (45.9%)
Number of metastases			
1	173 (54.1%)	124 (42.0%)	52 (30.2%)
2	104 (32.5%)	115 (39.0%)	106 (61.6%)
≥3	43 (13.4%)	56 (19.0%)	14 (8.2%)
Presentation of metastases			
Metachronous	127 (39.7%)	99 (33.6%)	66 (38.4%)
Synchronous	193 (60.3%)	196 (66.4%)	106 (61.6%)
Liver metastases			
No	195 (60.9%)	156 (52.9%)	108 (62.8%)
Yes	125 (39.1%)	46 (15.6%)	64 (37.2%)
Lung metastases			
No	274 (85.6%)	249 (84.4%)	147 (85.5%)
Yes	46 (14.4%)	16 (15.6%)	25 (14.5%)
Peritoneal metastases			
No	198 (61.9%)	165 (55.9%)	67 (39.0%)
Yes	122 (38.1%)	130 (44.1%)	105 (61.0%)
Response to first-line treatment			
Complete response	11 (3.4%)	6 (2.1%)	–
Partial response	104 (32.5%)	109 (38.7%)	–
Stable disease	98 (30.6%)	93 (33.0%)	–
Progressive disease	107 (33.4%)	74 (26.2%)	–
NA	–	13	–
LDH, U/L	260 (181–353)	293 (205–395)	325 (241–494)
N/L ratio	2.6 (1.8–4.2)	2.9 (1.9–4.7)	4.4 (2.1–7.5)
Type of second-line treatment			
Irinotecan-based	81 (25.3%)	62 (21.0%)	57 (33.1%)
Taxane-based	104 (32.5%)	85 (28.8%)	115 (66.9%)
Ramucirumab-based	97 (30.3%)	100 (33.9%)	–
Other	38 (11.9%)	48 (16.3%)	–

Values are presented as median (IQR) or n (%). GEJ, gastroesophageal junction; LDH, lactate dehydrogenase; N/L, neutrophils to lymphocytes; NA, not available; PS, performance status.

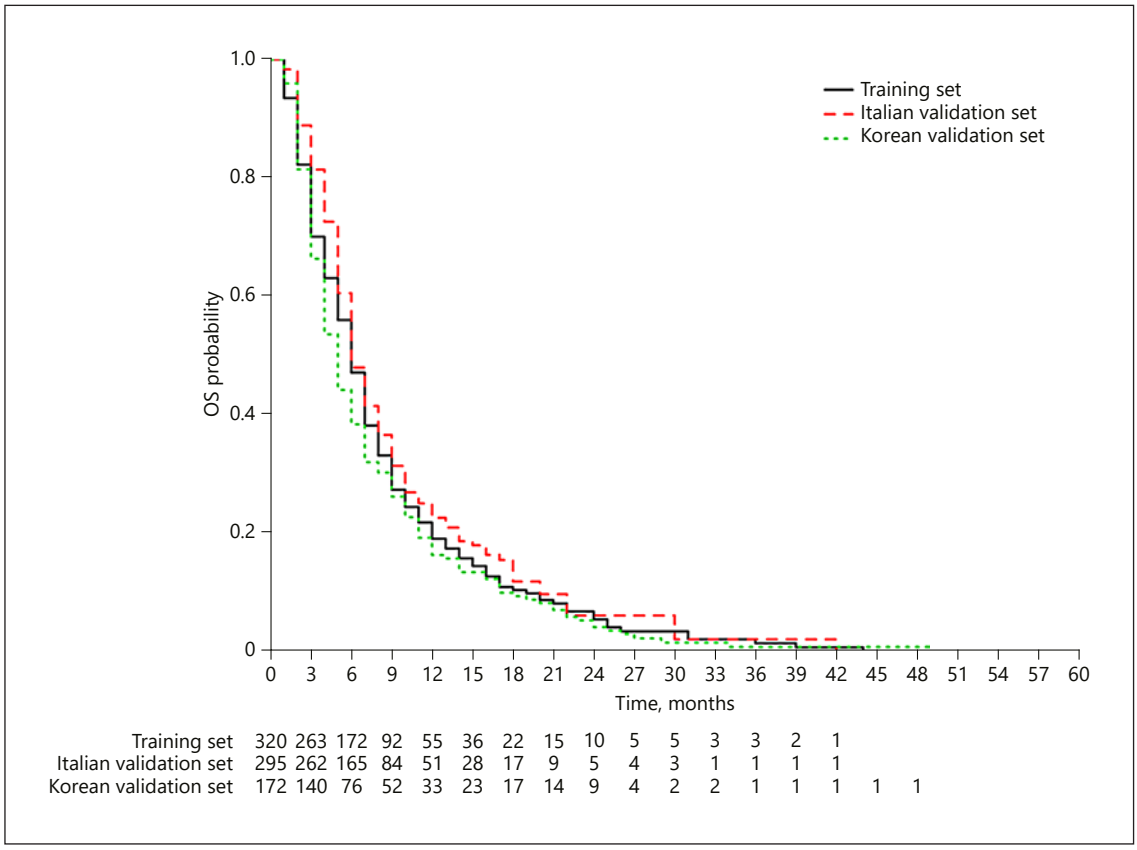

Fig. 1. Kaplan-Meier OS curves in the training set as well as the Italian and Korean validation sets. OS, overall survival.

The selected variables were included in a multivariable Cox model used to develop the nomogram to predict patients' 3- and 6-month OS. The categorical covariates were modeled by using dummy variables, whereas continuous by means of three-knots restricted cubic splines to assess flexible fit [18], excluding the nonlinear term of the latter when not significant. Nomogram model performance was evaluated both in the development and validation sets assessing the calibration by means of calibration plots (how close the predictions were to the actual outcome) and discriminative ability (Harrell C index) [19] together with its 95% CI [20]. Moreover, to assess the general external validity of the nomogram model, we followed van Houwelingen [21] and for each validation set, we fitted a Cox model including the linear predictor calculated based on the nomogram model regression coefficients. If the linear predictor regression coefficient β was equal to 1, the covariates effect estimated by the nomogram model was valid in the validation set. To perform external validation, we should exclude from the validation sets those patients with nomogram covariate values not compatible with those observed in the development set (for instance ECOG = 3 or N/L ratio >26).

The analyses were carried out using the SAS® and R software; in particular, random forest was fitted using the rfsrc function in randomForestSRC package. We considered a statistical test as significant when the corresponding p value was <0.05.

Results

Online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000491753) shows the patients' flowchart leading to their inclusion in the present study. The development set included 320 out of 1,037 evaluable patients treated at 26 Institutions between 2006 and 2016. The Italian and Korean validation sets included 295 and 172 evaluable patients, respectively, after excluding 5 and 9 patients, respectively, with values of the nomogram covariates not compatible with those observed in the development set.

Table 1 summarizes patients' baseline characteristics and the type of second-line treatments received in the development, Italian, and Korean validation sets, whereas online supplementary Figure S2 depicts the time period distribution of treatment start. Interestingly, patients in the Italian validation set were registered before and after ramucirumab introduction, whereas all those in the Korean set were treated in the chemotherapy era.

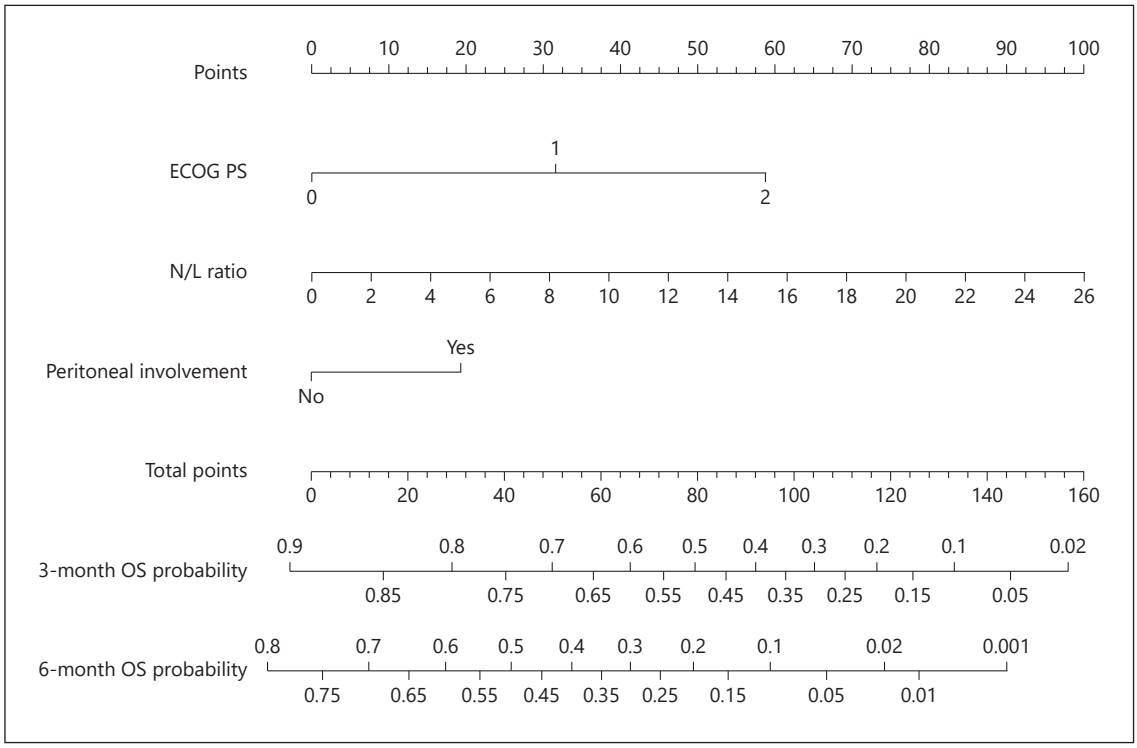

Fig. 2. Nomogram to predict the 3- and 6-month OS in mGC patients receiving second-line treatment. For nomogram use, see explanation in the text. mGC, metastatic gastric cancer; N/L, neutrophils to lymphocytes; OS, overall survival; PS, performance status.

Table 2. Multivariable Cox model results used to develop the nomogram on training set patients

Variable	HR	95% CI	*p* value
ECOG PS			<0.001
1 vs. 0	2.03	1.54–2.68	
2 vs. 0	3.74	2.68–5.22	
N/L ratio			<0.001
4.2 vs. 1.8*	1.23	1.13–1.35	
Peritoneal involvement			<0.001
Yes vs. no	1.54	1.21–1.97	

N/L, neutrophils to lymphocytes; PS, performance status. * The reported values are the third and first quartiles of the variable distribution.

As depicted in Figure 1, the median (IQR) OS was similar in the training, Italian, and Korean validation sets, i.e., 25 (12–43), 26 (17–48), and 20 (10–45) weeks. Three- and 6-month OS (95% CI) reached 70% (65.2–75.2%) and 47.1% (41.9–53.0%), 81.4% (77.0–85.9%) and 48.0% (42.5–54.2%), and 65.7% (59.2–73.0%) and 38.7% (32.2–46.5%) in the training, Italian, and Korean validation sets, respectively.

When applying the random forest procedure, ECOG PS and N/L ratio achieved very low *p* values (<0.0001), both without and with false discovery rate adjustment (online suppl. Table S1) and were selected as predictors. The peritoneal involvement *p* value was as low as 1.3% without adjustment and increased to 6.9% after adjustment, being slightly higher than the 5% threshold; thus, based on *p* value results in conjunction with clinical consideration, we decided to retain also this covariate in the multivariable Cox model (Table 2) to develop the nomogram (Fig. 2). The nomogram scoring system is reported in online supplementary Figure S3. To estimate the 3- or 6-month probability for a given patient, locate the N/L ratio level and draw a line straight up to the points axis to determine the score associated to that level. Repeat the process for ECOG PS level and peritoneal involvement, sum the scores, and locate this sum on the total points axis. Then draw a line straight down to the 3- or 6-month probability axis and read off the probability. The nomo-

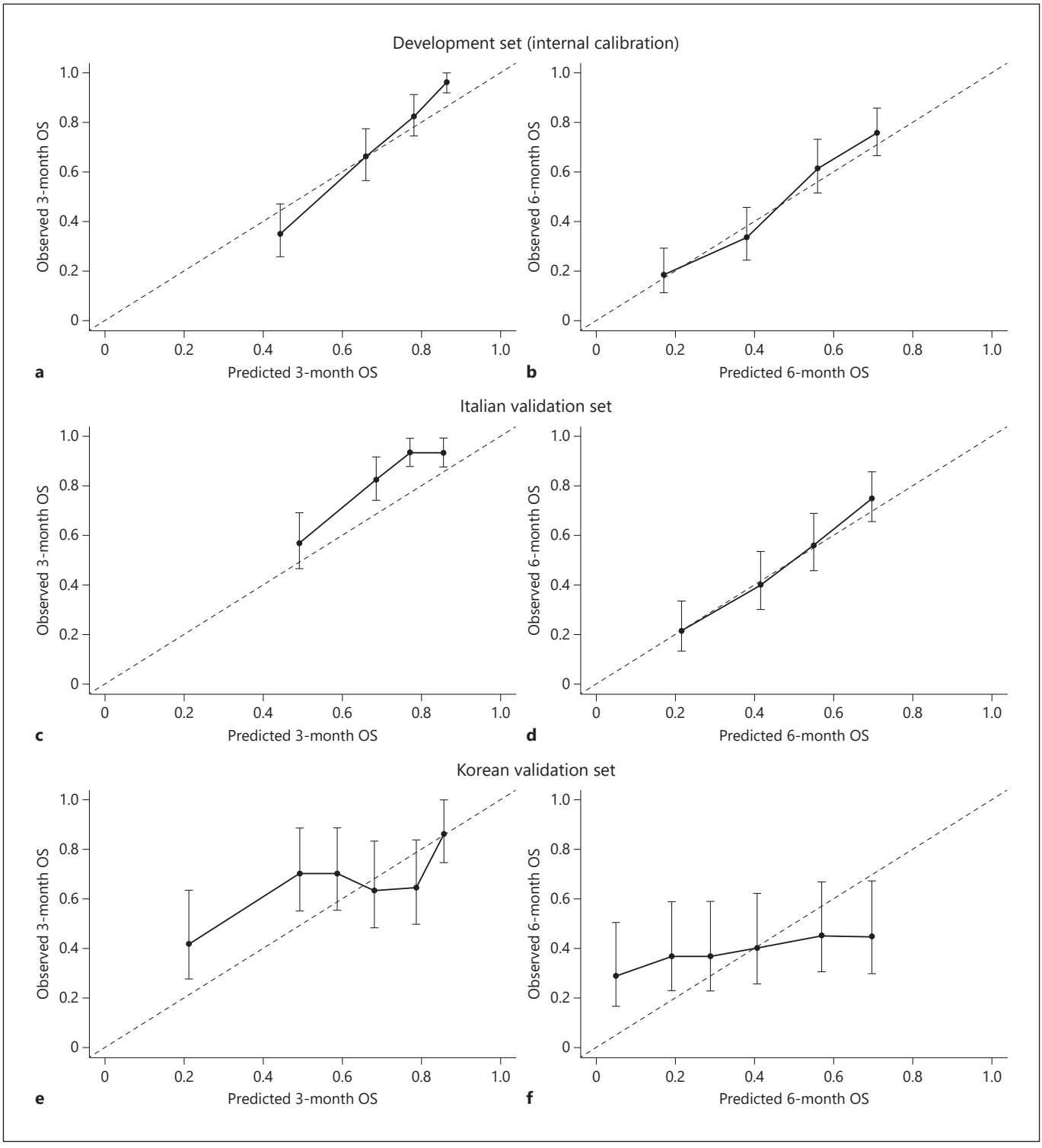

Fig. 3. Plots for internal and external calibration of the nomogram. **a**, **b** Internal calibration (development set) of the 3- and 6-month OS probabilities. **c**, **d** External calibration of the 3- and 6-month OS probabilities in the Italian validation cohort. **e**, **f** External calibration of the 3- and 6-month OS probabilities in the Korean validation cohort. In each plot, the Kaplan-Meier OS probability in equal-sized groups was plotted (*y* axis) against the corresponding predicted probability (*x* axis). The error bars are Kaplan-Meier 95% CIs. The dashed diagonal line is the reference line indicating the probability of an ideal prognostic classification (accordance between predicted and observed probabilities). OS, overall survival.

gram Harrell C index was 0.72 (95% CI 0.68–0.75), indicating good discriminative ability of the model. The C index was similar in the Italian validation set (0.69; 95% CI 0.65–0.73), whereas it was only 0.57 (95% CI 0.52–0.62) in the Korean validation set, indicating poor discriminative ability in the second validation set. As regards model calibration (Fig. 3), while the internal calibration was very good as expected (Fig. 3a, b), the nomogram slightly underestimated the 3-month observed OS (Fig. 3c), but the external calibration in the Italian cohort was perfect at 6 months (Fig. 3d). In the Cox model for assessing the nomogram validity in the Italian external set, the covariate effect was slightly lower than that estimated by the nomogram, as indicated by the $\beta = 0.78$ (95% CI 0.61–0.96) somewhat below 1 (even if significant, as indicated by the 95% CI not including 1). On the contrary, the calibration on the Korean external cohort was poor in that the nomogram underestimated the 3-month observed OS in the first three subsets with OS predictions <60%, with a greater concordance in the remaining three subsets (Fig. 3e). The calibration was even worse when considering 6-month predictions (Fig. 3f), in which the calibration line crossed the perfect calibration diagonal line, and this is a clear indicator of a different nomogram covariate effect in such an external set. This was confirmed in the specific Cox model for assessing the external validity: the $\beta = 0.24$ (95% CI 0.02–0.47) was very far and significantly lower than 1, indicating that the covariate effect in the Korean set was much lower than that estimated by the nomogram. To better explain to readers such a result, we fitted a multivariable Cox model on the Korean set, in which all the nomogram covariates but ECOG were not significantly associated with OS, and their estimated hazard ratios were considerably lower than those reported in Table 2 for the nomogram multivariable model (data not shown).

Discussion

In the last decade, the OS of mGC patients has improved due to the availability of newer treatment options such as chemotherapy, targeted therapies including antiangiogenic agents, and immunotherapy [22]. Regarding the evidence specifically available for second-line therapies, both single-agent chemotherapy with irinotecan/taxanes [6–8] and ramucirumab [9] provided a significant OS benefit as compared to best supportive care or placebo, whereas the addition of ramucirumab to paclitaxel allowed reaching an unprecedented median OS of 9.6 months [10]. Although the rate of mGC patients treated with at least two treatment lines is increasing, life expectancy in the second-line setting remains poor, and the median OS gain derived from active treatments (around 2 months) should be evaluated in light of potential toxicities, treatment costs, and overall life expectancy. No molecular biomarker is expected on the horizon in order to refine patient selection for both chemotherapy and antiangiogenic treatments. On the other side, other promising agents – among others several immune checkpoint inhibitors [23] and the VEGFR-2 inhibitor apatinib [24] – are almost ready to enter the therapeutic landscape of mGC. For instance, both the anti-PD1 monoclonal antibody nivolumab [25] and apatinib [26] conferred a significant OS gain over placebo in the third-line setting in Asian phase III trials. Finally, third-line chemotherapy may confer additional disease control in routine clinical practice [27].

In this scenario, it is clear that more and more active agents will be available for pretreated mGC patients, whereas the overall disease prognosis in the second-line setting and beyond still remains highly unsatisfactory. Therefore, some questions are arising: can we predict a relatively short-term life expectancy (i.e., 3 or 6 months) at the beginning of second-line treatment in order to potentially assign individual patients to best supportive care versus active treatment or to treatment sequences versus the potentially last treatment line? As already shown in refractory metastatic colorectal cancer [28], prognostic tools such as nomograms may assist clinicians in accurately assessing their patients' life expectancy by means of easy-to-collect clinical or pathological variables, therefore providing an objective information able to usefully support the subjective experience. In the Gastric Life nomogram, three variables (ECOG PS, N/L ratio, and peritoneal involvement) are able to predict the 3- and 6-month OS probability in mGC patients deemed eligible for second-line therapy. Noteworthy, a recent nomogram was developed to predict the 1- and 2-year OS probability in mGC patients receiving first-line chemotherapy, and again both ECOG PS and N/L ratio were among the seven variables used to build the model [29].

A limitation of the present analysis is that some patients in the development set had not HER2 status assessed (14%), therefore forcing us to exclude this variable from the putative ones. Moreover, while the nomogram's performance was satisfactory in an independent Italian series, it was very poor when the nomogram was applied to an external and independent validation set represented by Korean patients treated at a single tertiary cancer cen-

ter, in terms of low discriminative ability (Harrell C = 0.57), poor calibration (observed OS not in agreement with predictions), and reduced prognostic effect of the nomogram covariates. This is not surprising given the marked biological and prognostic differences observed in Caucasian versus Asian patients. It should be pointed out that, in the past literature, it was not possible to validate the Memorial Sloan Kettering Cancer Center nomogram of Kattan et al. [30] in Asian patients undergoing D2 gastrectomy [31]. Therefore, an Asian-specific nomogram was built and validated in Korea [32] with regard to the same setting, i.e., the postoperative estimation of survival in patients with radically resected gastric cancer.

The Gastric Life nomogram may be used to accurately predict OS probability in the second-line setting, thus helping clinicians in the management of their Caucasian patients. In conclusion, while the predictive ability of our nomogram should be further assessed in prospective trials, the Gastric Life nomogram may represent a useful tool for selecting patients for second-line treatments in daily clinical practice, but also for assisting researchers in a more evidence-based fashion during the inclusion of mGC patients in clinical trials.

Acknowledgments

The authors would like to thank all the patients included in this study and their families as well as the RAMoss study investigators.

Statement of Ethics

The study was approved by the Institutional Ethics Committee of the Coordinating Center, Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy; Institutional Study Protocol INT 117/15). Approval for data collection was obtained independently by each institution involved as per local practice.

Disclosure Statement

The authors have no potential conflicts of interest.

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