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Development and validation of prognostic nomograms for metastatic gastrointestinal stromal tumour treated with imatinib

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Abstract ***Purpose:*** Metastatic gastrointestinal stromal tumour (GIST) is generally an incurable disease with variable response to imatinib. We aimed to develop prognostic nomograms to predict overall survival (OS) and progression-free survival (PFS) for patients treated with imatinib.

Methods: Nomograms were developed in a training cohort ($n = 330$) of patients treated in a randomised trial (EORTC-ISG-AGITG 62005 phase III study) using Cox regression models, and validated in patients ($n = 236$) treated in routine clinical care from six referral centres.

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Nomogram performance was assessed by calculating the *c* statistic. A classification based on the nomograms' scores was generated to group patients according to risk.

Results: Nomogram risk factors for OS and PFS were size of the largest metastasis, tumour genotype, primary tumour mitotic count, haemoglobin and blood neutrophil count at commencement of imatinib. The nomograms predicted survival with a *c* statistic of 0.75 (training) and 0.62 (validation) for OS, and 0.69 (training) and 0.62 (validation) for PFS. When tested in the validation cohort, the nomograms discriminated well the high and intermediate risk from low risk patients (hazard ratio [HR] for OS 3.83, 95% confidence interval [CI] 1.71–8.56; and 2.48, 95% CI 1.12–5.50; for PFS 2.84, 95% CI 1.66–4.87; and 1.45, 95% CI 0.87–2.41, respectively).

Conclusion: The nomograms predicted the risk of GIST progression and death with good discrimination of risk groups, and may be of value for patient counselling and risk stratification.

1. Introduction

Gastrointestinal stromal tumour (GIST) is a distinct subtype of sarcoma characterised commonly by mutations in the *KIT* and *PDGFRA* (encodes the platelet-derived growth factor receptor alpha) proto-oncogenes [1,2]. Although metastatic GIST is generally incurable, treatment with imatinib causes tumour regression or stabilisation in the majority of patients, with a median overall survival (OS) of at least 5 years [3]. However, assessment of the risk of cancer progression and death in an individual remains challenging, as GIST is a genetically heterogeneous disease and patient response to imatinib is variable [4].

In patients with localised resectable GIST, risk of disease recurrence after surgery alone and in those who receive adjuvant imatinib can be estimated based on tumour size, mitotic activity, tumour location and rupture [5–8] but not tumour genotype [9,10]. Risk stratification schemes combining these prognostic factors have been developed to help quantify the likelihood of recurrence-free survival (RFS) and OS [11,12].

It is unclear whether stratification systems developed in a localised GIST population are applicable to patients with metastatic disease – a population with substantially poorer prognosis. Different factors may be important in the metastatic setting, for example, tumour genotype has been reported as having major prognostic significance in imatinib treated patients [13]. Tools to help classify risk of death and cancer progression in this population would be valuable for patient counselling and treatment decisions. For these reasons, we developed prognostic nomograms to group stratify and to provide individualised predictions of OS and progression-free survival (PFS) in these patients with metastatic GIST treated with imatinib.

2. Methods

2.1. Patients

We developed the nomograms using data from the 'training' cohort of a subset of patients who participated in the EORTC-ISG-AGITG 62005 phase III study comparing a daily dose of 400 mg versus 800 mg imatinib [14]. These patients had metastatic GIST, and the *KIT* and *PDGFRA* genotype status were available [13]. We validated the nomograms using data from the 'validation' cohort of patients undergoing routine clinical treatment for metastatic GIST at six large tertiary referral institutions in Warsaw, Helsinki, New York, Sydney, Melbourne and Canberra in 2000–2013. Patients included had metastatic GIST, histological confirmation of GIST diagnosis, known *KIT* genotype status, had received first-line therapy with imatinib for metastatic GIST, and did not participate in any first-line treatment clinical trials were included. The local institutional review board of each participating institution approved this study.

2.2. Statistical methods

We estimated OS and PFS probabilities using the Kaplan–Meier method [15]. From the training cohort, we developed two multivariate models using Cox proportional hazards regression for OS and PFS outcomes, respectively. Each patient was assigned a score (scaled to range from 0 to 100) for each outcome; the score was based on the weighted sum of the relative importance of each variable in the multivariate models. We performed logarithmic transformation whenever appropriate for continuously measured variables with skewed distributions. The proportional hazards assumption was verified [16]. All statistical tests were two-sided, and *P* values less than .05 were considered to be statistically significant.

A risk stratification scheme consisting of low-, intermediate-, and high-risk groups was developed based on the nomogram scores. This was done by grouping the scores from all patients into quartiles: the first quartile formed the low-risk (good-prognosis) group; the middle two quartiles were combined to form the intermediate-risk group; and the final quartile formed the high-risk (poor prognosis) group.

We quantified the discriminatory ability of the nomograms in the training cohort by calculating the *c* statistic

[17]. We also computed and compared the *c* statistics when the nomograms were applied to the validation dataset. We further illustrated the discriminatory ability of the nomogram-derived classification systems using Kaplan–Meier curves and log-rank tests.

The nomograms were also assessed for their calibration, which is a measure of how closely the predicted survival outcomes agree with the observed outcomes. We compared the nomogram-predicted probabilities for PFS at 1 and 2 years, and for OS at 3 years, with the corresponding observed PFS and OS probabilities. Plots that resemble a 45-degree line indicate that the nomogram predictions are well calibrated. We also computed the χ^2 statistic [18] to test for goodness-of-fit of the observed and predicted outcomes. A P value <0.05 for this test indicates poor calibration of the model (that is, a significant difference between expected and observed outcomes).

We recalibrated the nomograms whenever there was systematic underestimation or overestimation of OS and PFS risks in the validation cohort. Recalibration allows the prediction function of the nomograms developed in a training cohort to be transportable to the validation cohort or other populations with different baseline risk.

We performed sensitivity analyses to assess the performance of the nomograms when the following variables were excluded: tumour genotype, blood haemoglobin concentration and blood neutrophil count. We further assessed the performance of the nomograms when tumour site was added as an additional variable.

3. Results

The training cohort consisted of 330 patients. The median follow-up was 34 months (range, 0–43 months). A total of 216 patients (65%) had disease progression and 123 (37%) had died. The validation cohort consisted of 236 patients. The median follow-up was 70 months (range, 1–159 months). A total of 142 (60%) patients had disease progression and 107 (45%) had died. Patients in the training cohort had significantly shorter OS than those in the validation cohort (median, OS 40.3 versus 66.7 months, respectively, $P < .001$) and shorter PFS (median, PFS 22.4 versus 34.0 months, $P < .001$; Fig. 1). The baseline characteristics of patients are summarised in Table 1. Supplementary Fig. 1 shows the included and excluded patients in the training and validation cohorts.

3.1. Nomogram for overall survival

Fig. 2A shows the nomogram to predict the probability of 3-year OS. A web-based version of this nomogram, Advanced GIST Online, is available at http://advancedgistonline.ctc.usyd.edu.au to provide individualised estimates of OS. The predictors were the longest

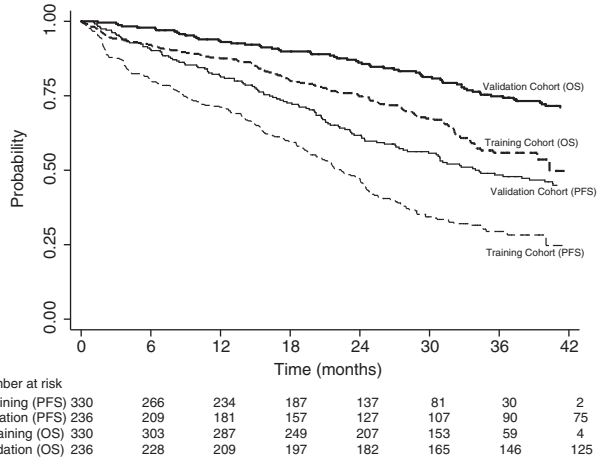

Fig. 1. Overall survival and progression-free survival in the training and validation cohorts. Kaplan–Meier estimates of overall survival and progression-free survival of patients with metastatic gastrointestinal stromal tumour (GIST) treated with imatinib in the EORTC-ISG-AGITG phase III study (training cohort) and in routine clinical care from six institutions (validation cohort). OS = overall survival. PFS = progression-free survival.

diameter of the largest metastasis (millimetres, logarithmic scale), the absolute blood neutrophil count at imatinib initiation ($\times 10^9$/L, logarithmic scale), tumour genotype, blood haemoglobin concentration at imatinib initiation (g/dL), and the primary tumour mitotic count per 50 high-power fields (per 50 HPFs, logarithmic scale). All variables were statistically significant predictors in univariable and multivariable analyses (Supplementary Table 1). The *c* statistic value was 0.75 (95% confidence interval (CI), 0.71–0.80). Therefore, 75% of the time the nomogram correctly predicted the ordering of the outcome of two randomly selected patients.

Fig. 3A illustrates the good discriminatory value of the nomogram when the patients were stratified into low risk (nomogram score less than 32.67, $n = 84$), intermediate risk (nomogram score 32.67–55.72, $n = 164$) and high risk (nomogram score higher than 55.72, $n = 82$) prognostic groups (log-rank $P < .001$). When compared with the low-risk group, the high-risk group was associated with a 13.2-fold increase in risk of death (hazard ratio (HR) 13.22, 95% confidence interval (CI) 6.00–29.17), and in the intermediate-risk group, a 5.4-fold increase in risk of death (HR 5.43, 95% CI 2.48–11.86).

When the nomogram was applied to the validation cohort, the *c* statistic was 0.62 (95% CI 0.56–0.67). Fig. 3B illustrates the discriminatory value of the nomogram when the patients in the validation cohort were stratified into three prognostic groups (log-rank $P < .001$). When compared with the low-risk group, the high-risk group was associated with a 3.8-fold increase in risk of death (HR 3.83, 95% CI 1.71–8.56) and the intermediate-risk group was associated with 2.5-fold increase in risk of death (HR 2.48, 95% CI 1.12–5.50).

Table 1
Baseline patient characteristics and clinicopathological variables.

Characteristic	Training cohort $N = 330$	Validation cohort $N = 236$	P^*
Median age (range) (years)	61 (18–84)	56 (17–87)	.004
Sex			
Male	206 (62)	133 (56)	.15
Female	124 (38)	103 (44)	
Primary site of the disease			
Stomach	108 (39)	83 (36)	<.001
Small bowel	84 (30)	115 (49)	
Duodenum	35 (13)	3 (1)	
Omentum	13 (5)	1 (<1)	
Rectum	18 (6)	4 (2)	
Colon	10 (4)	13 (5)	
Other	62(19)	16 (7)	
Unknown	0 (0)	1 (<1)	
Median time, primary diagnosis to initiation of imatinib (range) (month)	11.3 (0–208)	6 (0–286)	.001
Imatinib starting dose (mg)			
200	0 (0)	1 (<1)	<.001
300	0 (0)	9 (4)	
400	160 (48)	207 (88)	
600	0 (0)	7 (3)	
800	170 (52)	9 (4)	
Median size of largest metastasis (mm) (range)	80 (10–306)	80 (10–350)	.20
Median primary tumour mitotic count (range)†	5 (1–62)	20 (1–250)	<.001
GIST genotype			
KIT exon 11	208 (63)	161 (68)	.29
KIT exon 9	52 (16)	30 (13)	
Wild-type	51 (15)	27 (11)	
Other	19 (6)	18 (8)	
Median blood neutrophil count (range) (×109/L)	4.9 (1.5–30.6)	4.3 (1.1–15.7)	.001
Median blood haemoglobin (range) (g/dL)	12.7 (7.6–17.6)	12.8 (6.4–16.3)	.70

Data are number (%) or median (range).
* P for differences in distributions between training and validation cohorts.
† Mitotic count = number of mitoses per 50 high-power fields of the microscope. Other tumour genotypes include *KIT* exon 13 ($n = 7$), *KIT* exon 17 ($n = 3$), *PDGFRA* mutations ($n = 9$) in the training cohort. Other tumour genotypes in the validation cohort include *KIT* exon 13 ($n = 5$), *KIT* exon 18 ($n = 1$), *KIT* exon 17 ($n = 1$), *PDGFRA* mutations ($n = 11$).

3.2. Nomogram for progression-free survival

Fig. 2B shows the nomogram to predict the probabilities of 1-year and 2-year PFS. A web-based version of this nomogram is available at http://advancedgistonline.ctc.usyd.edu.au to provide individualised estimates of PFS. In multivariable analyses (Supplementary Table 1), the same predictors for OS were also significant predictors of PFS except for size of the largest metastasis. Although it was not statistically significant ($P = .11$), size of the largest metastasis was considered to be a clinically relevant variable and was reintroduced into the model. The c statistic was 0.69 (95% CI 0.65–0.73).

Fig. 3C illustrates the discriminatory value of the nomogram when patients were stratified into low-risk (nomogram score less than 27.54, $n = 83$), intermediate-risk (nomogram score 27.54–56.30, $n = 165$), and high-risk (nomogram score greater than 56.30, $n = 82$) prognostic groups (log-rank $P < .001$). When compared with the low-risk group, the high-risk group was associated with a 4.8-fold increase in risk of disease progression or death (HR 4.75, 95% CI 3.15–7.21), and the intermediate-risk group with 2.3-fold increase in risk of disease progression or death (HR 2.30, 95% CI 1.55–3.39).

When the nomogram was applied to the validation cohort, the c statistic was 0.62 (95% CI 0.58–0.68). Fig. 3D illustrates the discriminatory value of the nomogram when the patients in the validation cohort were stratified by prognosis groups (log-rank $P < .0001$). When compared with the low-risk group, the high-risk group was associated with a 2.8-fold increase in risk of disease progression or death (HR 2.84, 95% CI 1.66–4.87), and the intermediate-risk group with a 1.5-fold increase in risk of disease progression or death (HR 1.45, 95% CI 0.87–2.41).

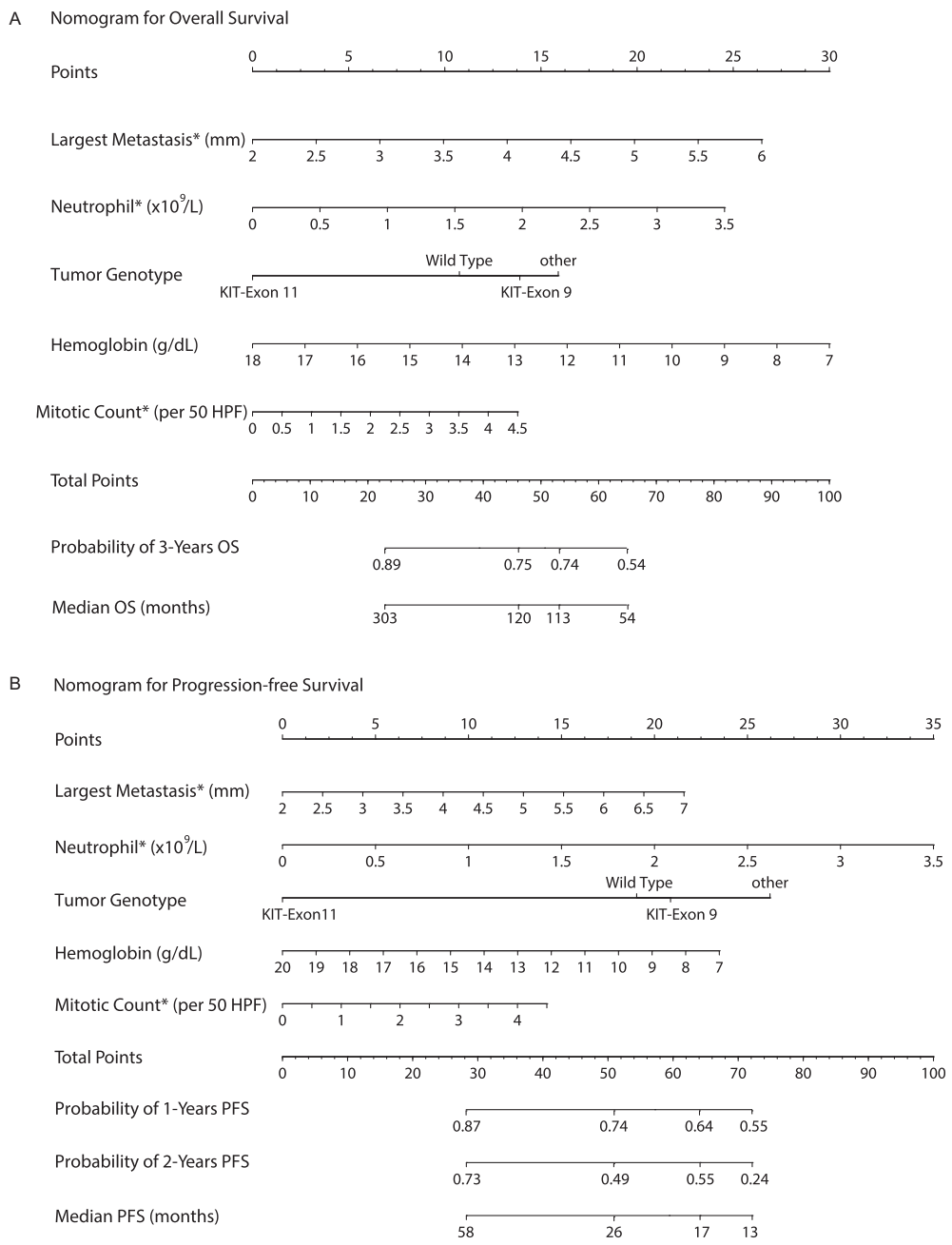

Fig. 2. Nomograms to predict the probabilities of 3-year overall survival, and 1-year and 2-year progression-free survival. Points are assigned for largest tumour size, blood neutrophil count, tumour genotype, blood haemoglobin and tumour mitotic count, by drawing a line upward from the corresponding values to the 'Points' line. The sum of these five points, plotted on the 'Total points' line, corresponds to predictions of (A) probability of 3-year overall survival (OS) and median overall survival, and (B) probability of 1-year progression-free survival (PFS) and 2-year PFS, and median PFS. *Largest metastasis, neutrophils and mitotic count are measured on a logarithmic scale.

Supplementary Table 2 also summarised the univariable analyses of all other variables considered but were not included in the final multivariable models for OS and PFS.

3.3. Calibration

When the nomograms were applied to the validation cohort, the predicted OS and PFS systematically underestimated the observed survival outcomes. Recalibration with multiplication with a single scaling factor (0.547 for OS and 0.739 for PFS) on all the regression coefficients substantially improved the performance of the nomograms in the validation cohort (Fig. 4). The predicted probabilities of OS and PFS illustrated in Fig. 2 and on the website (http://advancedgistonline.ctc.usyd.edu.au) have been scaled to better represent patients in routine care.

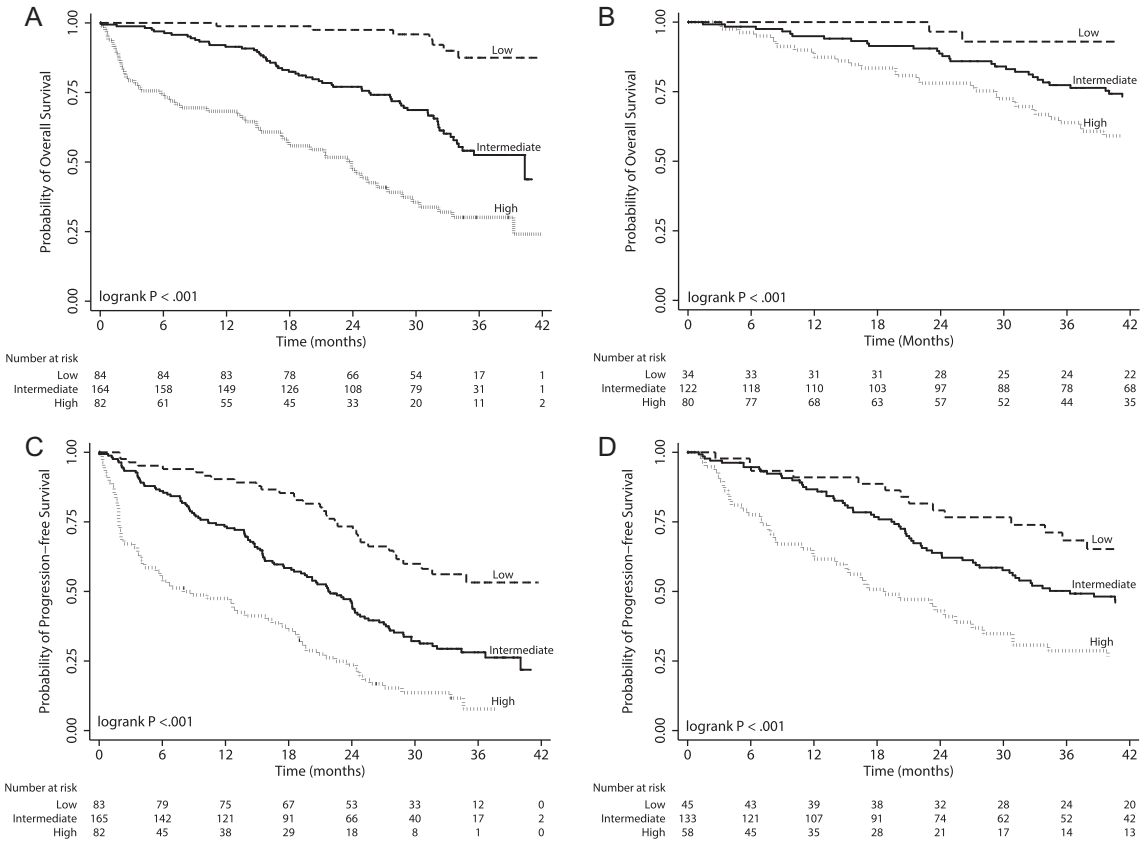

Fig. 3. Overall survival and progression-free survival of training and validation cohorts according to risk groups. Kaplan–Meier estimates according to low-, intermediate- and high-risk groups of metastatic gastrointestinal stromal tumour (GIST) patients treated with imatinib, based on subset of patients enrolled in the (A) training cohort and (B) validation cohort for overall survival, and (C) training cohort and (D) validation cohort for progression-free survival.

3.4. Sensitivity analyses

When tumour genotype was excluded in the multivariable models, the performance of the models was significantly poorer (Supplementary Table 3). Exclusions of blood haemoglobin concentration and the blood neutrophil count also reduced the performance of the multivariable models. Inclusion of the primary tumour site did not improve the models significantly.

4. Discussion

The nomograms were developed as pragmatic tools that combine readily available clinical information to provide rapid and simple prognostic information from otherwise complex statistical estimates. To our knowledge, this study provides the first prognostic classification for metastatic GIST patients treated initially with imatinib.

Despite differences in the baseline characteristics in the training and validation cohorts (Table 1), the prognostic nomograms provided good discrimination for OS (*c* statistic 0.75 and 0.62, respectively) and PFS (*c* statistic 0.69 and 0.62, respectively) in both cohorts. Similarly, there is also good discrimination of survival outcomes based on a classification system of low, intermediate and high risk (Fig. 3).

Recalibration was necessary when the nomograms were applied to the validation cohort as the patients had significantly longer median OS and PFS times than the training cohort. At the time when the EORTC-ISG-AGITG 62005 study was initiated, there was no effective systemic therapy for advanced GIST, and hence patients enrolled in that trial likely had more advanced disease with a greater tumour bulk than most current patients. The validation cohort, on the other hand, includes patients with more recent diagnoses and access to multiple lines of tyrosine kinase inhibitors. The differences between these two populations probably accounted for the lower *c* statistics observed in the validation cohort. The systematic underestimation of the survival in the validation cohort was hence recalibrated with a single simple scaling factor on the weights (regression coefficients) of the individual factors in the nomograms. Notably the calibration process does not affect hazard ratio comparisons and hence does not affect the discrimination performance. OS times likely will continue to improve with increasing therapeutic options and earlier detection of advanced disease by improved imaging

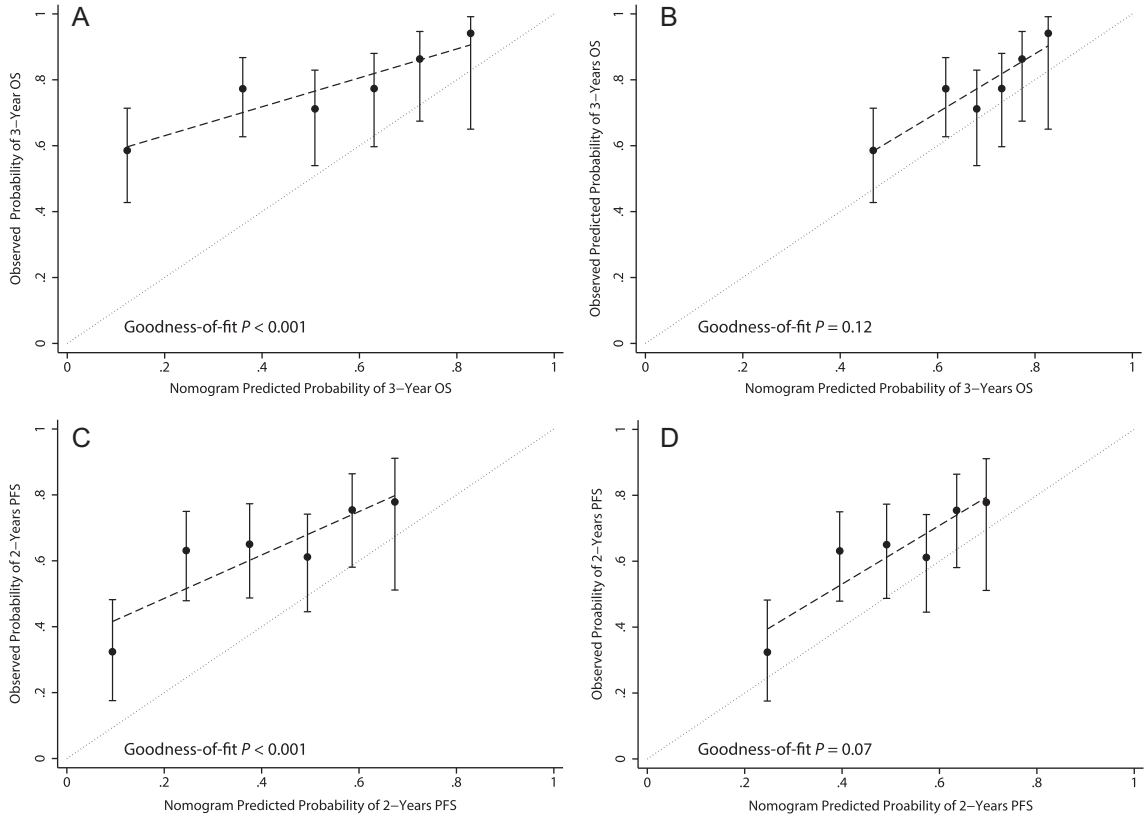

Fig. 4. Calibration of nomogram-predicted overall survival and progression-free survival. Observed overall survival compared with nomogram-predicted at 3 years (A) uncalibrated and (B) recalibrated plot for the validation cohort. Observed progression-free survival compared with nomogram-predicted survival at 2 years (C) uncalibrated and (D) recalibrated plot for the validation cohort. OS = overall survival. PFS = progression-free survival. A significant goodness-of-fit P value ($P < .05$) indicates lack of calibration of the model.

modalities. Using this recalibration process with future patient cohort data may allow the nomograms to remain contemporary.

These nomograms identified predictors of survival in metastatic patients treated with imatinib, distinct from those with localised GIST. Tumour genotype has a major impact in the metastatic population, but evidence remains conflicting in localised GIST even with adjuvant imatinib [9,10]. This may partly relate to use of 400 mg imatinib in an adjuvant study where there might be poorer outcomes in those with exon 9 *KIT* mutations [13]. On the other hand, tumour site has minimal effect in metastatic GIST (Supplementary Table 3), in contrast to its large impact on prognosis in localised GIST [8]. Although not a statistically significant variable, size of the largest metastasis was included in the PFS nomogram as it is widely regarded as an important prognostic factor.

Nomograms offer an alternative to current practice, where estimates of prognosis rely on individual clinician experience or published median survival times. Another popular alternative would be to use single prognostic factors, such as GIST tumour genotype, or a simple summation of factors to predict good versus poor outcomes. This latter approach fails to account for interactions and assumes that all prognostic factors are of equal weight, potentially underestimating survival outcomes [19]. Nomograms provide more accurate estimates by combining clinical predictors into single summary measures. Our online nomogram can also be used to communicate the level of uncertainty surrounding individual estimates of survival outcomes for the typical (half to double the median survival), best-case (triple the median) and worst-case (one quarter of the median) scenarios using the approach developed for use in advanced breast cancer [20]. In addition to providing improved prognostic information for counselling, they also have a role in guiding clinical follow-up assessment frequency based on risk of relapse, and to stratify future patients for clinical trials especially if adaptive strategies based on prognostic factors are being investigated.

This study has several strengths. The nomograms utilised variables that are widely available in clinical practice. Their performance has been assessed in an independent dataset of patients undergoing routine clinical treatment for metastatic GIST from institutions located in five different countries. There are also potential limitations. The predictive ability of the nomograms (c statistic of 0.62 in validation dataset for PFS and OS) remains modest and further work is required to identify other factors that impact on survival. The assessment of mitotic count was variable and not standardised [21].

Furthermore, we have examined mitotic count using the standard per 50 HPFs instead of the recent recommendation of number of mitoses on a total area of 5 mm^2 [22] as comparative data of whether this new approach will improve prediction accuracy remains limited. We have also not looked for all possible prognostic factors in metastatic GIST such as gene expression profiling [23]. Despite these limitations, the present nomograms represent a useful advancement, and could act as a platform to incorporate new prognostic factors as our understanding of the biology of GIST progresses and new treatment strategies emerge.

In summary, the nomograms developed in a clinical trial population predicted the risk of GIST progression and death with good discrimination of risk groups in routine-care populations. This work also generates new risk stratification schemes for patients with metastatic GIST treated with imatinib.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2015.02.015.

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