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Development and external validation of a clinical prediction model for survival in patients with *IDH* wild-type glioblastoma

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OBJECTIVE Prognostication of glioblastoma survival has become more refined due to the molecular reclassification of these tumors into isocitrate dehydrogenase (*IDH*) wild-type and *IDH* mutant. Since this molecular stratification, however, robust clinical prediction models relevant to the entire *IDH* wild-type glioblastoma patient population are lacking. This study aimed to provide an updated model that predicts individual survival prognosis in patients with *IDH* wild-type glioblastoma.

METHODS Databases from Germany and the Netherlands provided data on 1036 newly diagnosed glioblastoma patients treated between 2012 and 2018. A clinical prediction model for all-cause mortality was developed with Cox proportional hazards regression. This model included recent glioblastoma-associated molecular markers in addition to well-known classic prognostic variables, which were updated and refined with additional categories. Model performance was evaluated according to calibration (using calibration plots and calibration slope) and discrimination (using a C-statistic) in a cross-validation procedure by country to assess external validity.

RESULTS The German and Dutch patient cohorts consisted of 710 and 326 patients, respectively, of whom 511 (72%) and 308 (95%) had died. Three models were developed, each with increasing complexity. The final model considering age, sex, preoperative Karnofsky Performance Status, extent of resection, O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation status, and adjuvant therapeutic regimen showed an optimism-corrected C-statistic of 0.73 (95% confidence interval 0.71–0.75). Cross-validation between the national cohorts yielded comparable results.

CONCLUSIONS This prediction model reliably predicts individual survival prognosis in patients with newly diagnosed *IDH* wild-type glioblastoma, although additional validation, especially for long-term survival, may be desired. The nomogram and web application of this model may support shared decision-making if used properly.

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KEYWORDS glioblastoma; survival; prediction; oncology

Glioblastoma is the most common primary malignant brain tumor and the third most frequently reported CNS tumor.[1] Its annual age-adjusted incidence rate of 3.21 per 100,000 person-years is the highest among patients with malignant brain and CNS tumors.[1] Patients suffering from glioblastoma face a poor survival prognosis with a 5-year survival rate of less than 10%.[2] Nonetheless, there is substantial interpatient variability in survival, which is partly due to differences in tumor biology.[3]

ABBREVIATIONS CI = confidence interval; EOR = extent of resection; GTR = gross-total resection; HR = hazard ratio; IDH = isocitrate dehydrogenase; KPS = Karnofsky Performance Status.

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In 2016, the revised 4th edition of the WHO classification of CNS tumors introduced two distinct glioblastoma entities according to isocitrate dehydrogenase (*IDH*) mutation status.[4] The vast majority of patients (> 90%) with glioblastoma harbor tumors with an *IDH* wild-type status and these patients have a median overall survival of 1.2 years.[3] In contrast, patients with glioblastoma molecularly labeled with an *IDH* mutation are less common (< 10%), reaching a favorable 3-fold longer median overall survival time when compared to patients with *IDH* wild-type glioblastoma.[3] Despite this categorization, patient survival with *IDH* wild-type glioblastoma remains diverse. Prognostication of individual patient survival times depends on a range of prognostic variables related to patient characteristics, neurosurgical approach, glioblastoma biology, and adjuvant treatment strategies.[5–10]

Accurate prognostication is important, not only to counsel patients on their survival probability, but also to build strong clinical trial cohorts. Nowadays, it is imperative to facilitate shared decision-making, i.e., to inform patients and their relatives so that they understand the risks when making joint decisions on possible choices. Consequently, therapeutic regimens can be better tailored to the individual patient and clinical scenario.

Clinical prediction models and their visualization, especially nomograms, are powerful tools for individualized estimation of patient survival times and for patient counseling. However, since the molecular stratification of glioblastoma,[4] only a few reports have addressed the use of nomograms for patients with newly diagnosed glioblastoma.[9,11] Furthermore, patients undergoing biopsy-only procedures, and patients treated with adjuvant therapy other than the standard radiotherapy with concurrent and maintenance temozolomide chemotherapy, are excluded. These restrictions may make clinical prediction models less relevant to the entire glioblastoma patient population. Therefore, we aimed to develop and externally validate an updated clinical prediction model to better predict survival in patients newly diagnosed with *IDH* wild-type glioblastoma, considering both traditional and modern predictors.

Methods

Study Design and Population

Patients with glioblastoma from three university hospitals were selected for model development and validation: University Medical Centers in Düsseldorf and Frankfurt, Germany, and Erasmus MC, the Netherlands. Patients were eligible for analysis if they were at least 18 years of age on the day of neurosurgical intervention and received a histopathological diagnosis of de novo *IDH* wild-type glioblastoma, according to the WHO 2016 classification of CNS tumors.[4,9] Glioblastomas from patients diagnosed before 2016 were neuropathologically reevaluated and reclassified according to the WHO 2016 criteria. *IDH* mutation status was assessed using immunohistochemistry for analysis of IDH1-R132H as previously recommended.[12,13] Tumors of patients younger than 55 years of age were additionally investigated for less common mutations at codon 132 of IDH1 and codon 172 of IDH2 by Sanger sequencing or pyrosequencing.[12] Patients were excluded from analysis if a resection was performed more than 4 weeks after a biopsy procedure. The development data set included patients from the University Medical Center Düsseldorf (n = 279, treated from 2013 to 2018) and from the University Medical Center Frankfurt (n = 431, treated from 2012 to 2018). The validation data set was derived from Erasmus MC, including 326 patients treated from 2012 to 2018.[14]

Ethics approval for the study was obtained from the IRBs at each center, i.e., the Medical Faculty of Heinrich Heine University Düsseldorf, the University Medical Center Frankfurt, and Erasmus MC. In the German cohort, patients had provided informed consent for the use of their tissue samples and clinical data. In the Dutch cohort, written informed consent from patients was waived by the ethics committee.

Outcome Definition

Overall survival was assessed from the day of the first surgery until death or last follow-up. Patients were censored at the date of last follow-up.[7]

Candidate Prognostic Variables

Based on literature review and subject matter knowledge, we considered predictor variables in the following categories: patient characteristics, surgical results, glioblastoma biology, and adjuvant treatment strategies.

Patient Characteristics

Data on sex, age, and preoperative performance status (Karnofsky Performance Status [KPS]) were collected by patient chart review. KPS score was assessed preoperatively on the day of admission. The KPS score was categorized into four groups: ≤ 70, 80, 90, and 100.

Surgical Results

Extent of resection (EOR) was defined as gross-total resection (GTR), non-GTR, and biopsy.[8] In the German cohort, GTR was defined as complete removal of contrast enhancement on early T1-weighted postoperative MRI (< 72 hours after surgery) by a neuroradiologist blinded to intraoperative and histopathological findings.[8] In the Dutch cohort, glioblastoma segmentation was performed. Contrast-enhanced tumor volumes were quantitatively assessed on pre- and postoperative MRI (< 72 hours after surgery) scans and EOR was calculated; GTR was defined as > 97% EOR.[14] All tumor volumes were assessed while blinded to patient clinical outcomes.[14]

Glioblastoma Biology and Adjuvant Treatment Strategies

O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation status was determined by pyrosequencing of sodium bisulfite-treated DNA and/or methylation-specific polymerase chain reaction, as previously reported.[6,15,16] Adjuvant therapeutic regimen was defined as Stupp, non-Stupp, and no therapy.[8] The Stupp category consisted of radiotherapy plus concomitant and maintenance temozolomide.[5] The non-Stupp category consisted of subparts/modifications of the Stupp protocol and experimental designs.[8] The no-therapy group included patients

who were not assigned to postsurgical therapy. Decisions on therapy were rendered by the local multidisciplinary tumor boards and analyzed according to an intention-to-treat principle.

Sample Size

Conventional sample size recommendations require at least 10–20 events per candidate prognostic variable, a target that was easily met.[17] In addition, we performed a more advanced calculation.[18] Using the observed C-statistic from Gittleman et al. (C-statistic 0.76 with 163 events),[9] we would need more than 200 patients to ensure a heuristic shrinkage slope > 0.9 for the prediction model. For models with a lower C-statistic, at least 300–500 patients would be required for reliable modeling.

Statistical Analysis

For continuous data we show means, standard deviations, and ranges. For categorical data we used counts and percentages. Generation of the clinical prediction model was performed in accordance with recent methodology[17,19] and reported according to the TRIPOD guidelines.[20,21]

Model Development

Cox regression analysis was used to develop a clinical prediction model estimating survival. Age and preoperative KPS score were kept as continuous prognostic variables in the analysis to avoid loss of prognostic information.[22] In addition, we explored nonlinearity for the association of age and preoperative KPS score with mortality, using restricted cubic splines.[23] Missing values were assumed to be missing at random and multiple imputation was performed using the mice algorithm.[24] Missing values were imputed 10 times. Statistical analyses were performed on the 10 imputed data sets and results were pooled using Rubin rules.[25] The modeling procedure consisted of three models of increasing complexity: 1) a clinical model, including patient sex, age, and KPS score; 2) a surgical model, adding EOR to the clinical model; and 3) a treatment model, consisting of the surgical model plus *MGMT* promoter methylation status and adjuvant treatment regimen. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were estimated as measures for association of the prognostic variables with survival.

Model Performance

We assessed the quality of the prediction model by evaluating calibration and discrimination measures.[17] Model calibration gauges the agreement between the predictions of the model with the observed survival probability.[17] Model calibration was graphically assessed using calibration plots.[26] Differences in baseline risk were studied by adding cohort as a factor in the model. Furthermore, the calibration slope was calculated.[27]

Harrell's concordance statistic (C-statistic) was used to quantify discriminative ability.[28] Model discrimination demonstrates how well the constructed prediction model identifies, for two randomly chosen patients, the patient who died first with a higher probability of dying. An uninformative model will have a C-statistic of 0.5, whereas a model with perfect discrimination will have a C-statistic of 1.0.[17] Furthermore, we quantified the heterogeneity in case-mix in the development and validation populations to aid the interpretation of the observed C-statistic at validation.[29]

Model Validation

We first developed models in the German cohort with validation in the Dutch cohort. We then reversed this procedure, conducting development in the Dutch cohort and validation in the German cohort. This cross-validation procedure between the national data sets shows the external validity of the prediction model.[30] Subsequently, the final model was developed using the combined data from the cohorts, provided that no major between-cohort heterogeneity was found. The performance of this final model was estimated by a bootstrap (1000 samples) internal validation procedure.[30]

Model Presentation

Nomograms were created to define an individual patient's anticipated 1-year, 2-year, and median predicted survival time. Descriptive analysis and prediction modeling analysis were performed using R software (version 3.5.2). The significance level was set at 5% for all analyses.

Results

Study Population

The combined German cohort consisted of data from 713 patients. We excluded 3 patients in whom a resection was performed 4 weeks after the initial biopsy. Thus, after imputation, 710 complete cases were analyzed. The Dutch cohort did not have any missing values and consisted of 326 patients. Overall survival as assessed by the Kaplan-Meier method is shown in Fig. 1. In both cohorts, age at diagnosis was comparable and more than half of the patients were male (Table 1). Eighty-five percent of the German cohort had a preoperative KPS score > 70, compared with 64% of the Dutch cohort. A minority of patients had GTR (approximately one-fifth in the German cohort and one-tenth in the Dutch cohort), whereas most patients had non-GTR followed by the biopsy-only procedure. Approximately half of the patients had *MGMT* promoter-methylated tumors. The majority of the patients received the Stupp regimen as postsurgical therapy. However, in the German cohort more patients were assigned to a non-Stupp regimen (32% vs 17%). Nearly one-fifth of the patients were not assigned to postoperative therapy.

The median duration of survivor follow-up was almost the same in both cohorts (0.89 vs 0.84 years; Table 1). Three hundred eight patients died in the cohort from the Netherlands compared to 511 in the German cohorts. Univariable HRs between the predictors and mortality are shown in Table 2. Supplemental Table 1 lists more details on patient characteristics stratified according to the respective academic center.

Model Development

Age and preoperative KPS score could be modeled

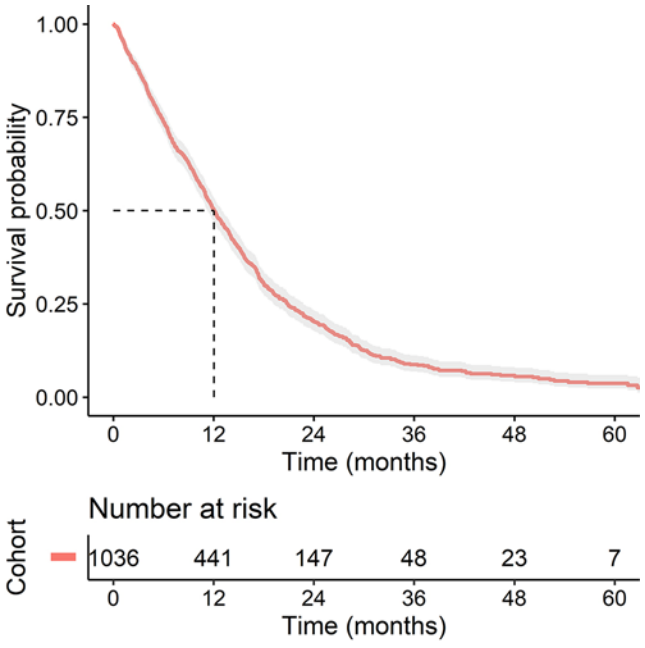


FIG. 1. Kaplan-Meier estimate of survival. The *red line* is the Kaplan-Meier estimate of survival probabilities of the cohort and the *gray area* is the associated 95% CI. Figure is available in color online only.

well assuming a linear association. Other than patient sex (HR 0.94, 95% CI 0.79–1.11), all candidate prognostic variables showed statistically significant associations with survival in the developed model (Fig. 2). Younger patients at diagnosis with a higher preoperative KPS score had better survival (age per decade HR 1.32, 95% CI 1.22–1.42; preoperative KPS score HR 0.85, 95% CI 0.76–0.94). Incomplete tumor resection (partial resection HR 1.30, 95% CI 1.04–1.64; biopsy-only HR 1.95, 95% CI 1.52–2.49) and deviations from standard adjuvant therapy (non-Stupp HR 1.29, 95% CI 1.06–1.58; no therapy HR 2.38, 95% CI 1.85–3.07) were statistically significantly associated with worse survival. Patients determined to have an *MGMT* promoter-methylated tumor confer a favorable survival prognosis compared to those with an *MGMT* promoter-unmethylated tumor (HR 0.50, 95% CI 0.41–0.62; Supplemental Table 2).

The direction of the predictor effects was the same in both the German and Dutch cohorts (Fig. 2, Supplemental Table 2). The treatment model had somewhat larger regression coefficients in the Dutch cohort (interaction by cohort: $p < 0.001$), but not for the clinical and surgical models ($p = 0.068$ and $p = 0.248$), without any obvious reason. The apparent C-statistic of the developed prediction models in the development set (i.e., the German cohort) was promising: the treatment model had the highest discriminative ability (C-statistic 0.74, 95% CI 0.71–0.76; Supplemental Table 2).

Model Validation

At cross-validation by country, we confirmed an increasing C-statistic with increasing model complexity (Table 3). The C-statistic for the treatment model was 0.70 (95% CI 0.67–0.73). The calibration plots showed some miscalibration, especially for predicting long-term survival probabilities (Fig. 3). The calibration plots suggested that the clinical model underestimated survival while the

TABLE 1. Patient characteristics of the data used at model development

Variable	German Cohort	Dutch Cohort	p Value*
No. of patients	710	326	
Median duration of survivor follow-up (IQR), yrs	0.89 (0.37–1.49)	0.84 (0.37–1.43)	0.684
Died, n (%)	511 (72.0)	308 (94.5)	<0.001
Median age (IQR), yrs	64 (55–73)	65 (57–72)	0.862
Male sex, n (%)	385 (54.2)	206 (63.2)	0.008
Preop KPS score, n (%)			<0.001
≤70	88 (15.1)	119 (36.5)	
80	93 (16.0)	92 (28.2)	
90	218 (37.4)	85 (26.1)	
100	184 (31.6)	30 (9.2)	
EOR, n (%)			<0.001
GTR	158 (22.4)	34 (10.4)	
Non-GTR	321 (45.5)	214 (65.6)	
Biopsy	227 (32.2)	78 (23.9)	
MGMT promoter-methylated, n (%)	291 (47.2)	177 (54.3)	0.044
Adjuvant therapy, n (%)			<0.001
No therapy	117 (16.8)	61 (18.7)	
Non-Stupp	220 (31.6)	56 (17.2)	
Stupp	360 (51.6)	209 (64.1)	

IQR = interquartile range.
* Calculated using the t-test, Mann-Whitney U-test, or chi-square test.

TABLE 2. Univariable association between predictors and mortality (n = 1036)

Predictor	HR (95% CI)
Age per decade	1.33 (1.25–1.41)
Male vs female	1.10 (0.96–1.26)
Preop KPS score per 10-point increase	0.75 (0.70–0.80)
EOR	
GTR	Ref
Non-GTR	1.50 (1.24–1.81)
Biopsy	2.38 (1.94–2.92)
MGMT promoter status, unmethylated vs methylated	0.65 (0.56–0.75)
Adjuvant therapy	
Stupp	Ref
Non-Stupp	1.48 (1.26–1.73)
No therapy	3.90 (3.23–4.71)

Ref = reference.

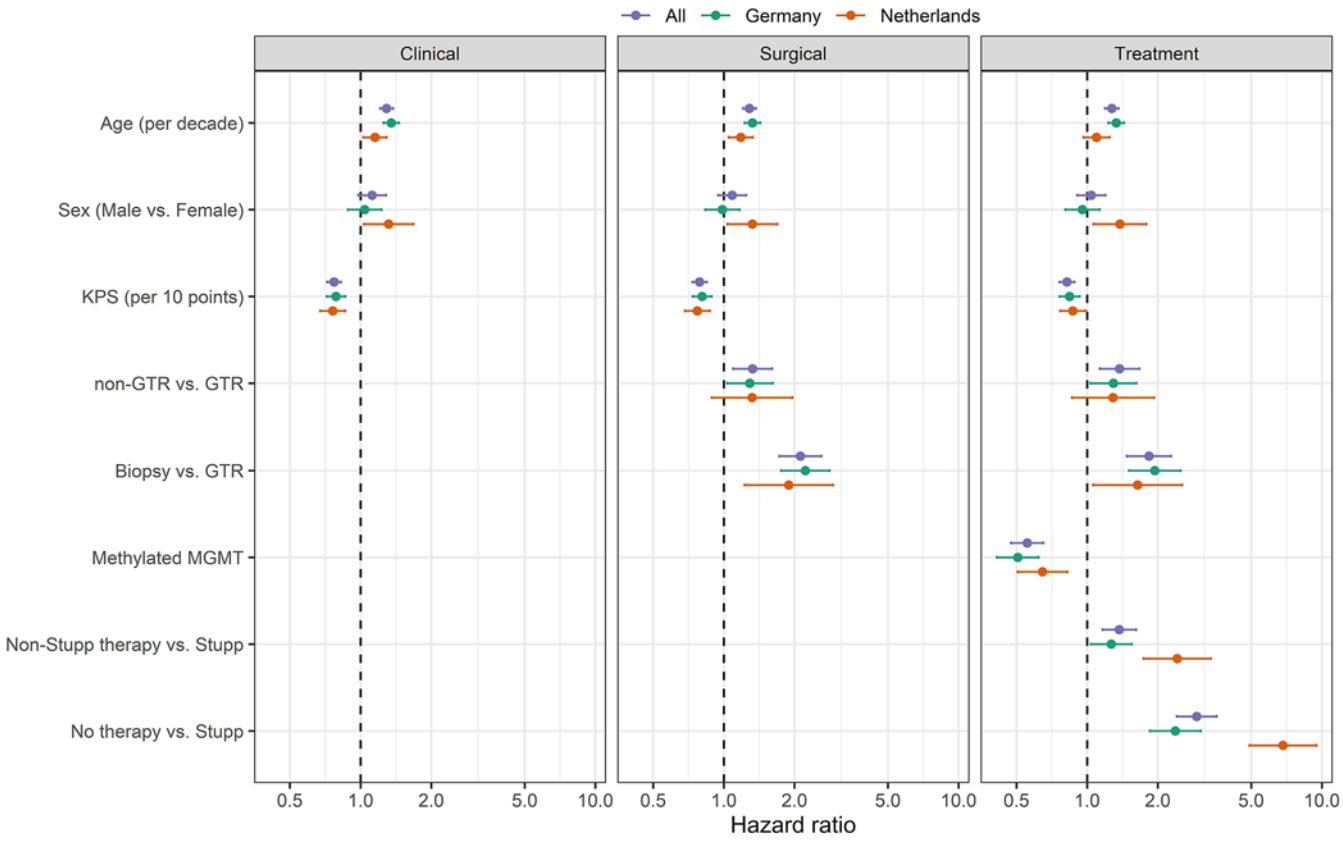


FIG. 2. Association of the prognostic variables with survival in each model. Figure is available in color online only.

surgical and treatment model overestimated survival (Fig. 3). More specifically, beyond 1 year of survival follow-up, the predicted curve deviated more from the observed curve. The calibration slope was approximately 1 for all models: < 1 for the clinical and surgical models, and > 1 for the treatment model (Table 3).

After refitting the models in the Dutch cohort, the apparent C-statistics were 0.62, 0.64, and 0.73, respectively (Supplemental Table 2). When we reversed the validation procedure, the validated C-statistics in the German cohort were 0.65 (95% CI 0.62–0.67), 0.68 (95% CI 0.66–0.71), and 0.72 (95% CI 0.69–0.74) for the clinical, surgical, and treatment models, respectively (Table 3). The calibration plot for the clinical model showed an excellent agreement between observed and survival probability (Fig. 3). The surgical and treatment models again overestimated survival, this time even more pronounced, especially for predicting long-term survival (Fig. 3).

The spread between the predictions (standard deviation of the linear predictor) increased with model complexity and was smaller in the Dutch cohort for all models (Supplemental Table 3). This indicates that the decrease in C-statistic was partly due to a decrease in case-mix heterogeneity from the German to the Dutch cohort.

Model Presentation

The final model combined all data from the German and Dutch cohorts, yielding comparable associations of the prognostic variables with survival (Table 4, Fig. 2). The C-statistic was 0.73 (95% CI 0.71–0.75). We developed nomograms to predict an individual patient's survival for several time periods (Fig. 4). In addition, an online prognostic calculator based on the model algorithms and including error margins (95% CI for prediction) is accessible at https://www.evidencio.com/models/show/2384 and shown in the box in Supplemental Fig. 1. Supplemental

TABLE 3. Performance of the developed prediction models at external validation

Model	Performance Measure (95% CI)	
	Calibration Slope	C-Statistic
Clinical		
Netherlands	0.73 (0.43–1.03)	0.61 (0.58–0.65)
Germany	1.02 (0.78–1.26)	0.65 (0.62–0.67)
Surgical		
Netherlands	0.81 (0.52–1.09)	0.62 (0.59–0.66)
Germany	1.01 (0.82–1.20)	0.68 (0.66–0.71)
Treatment		
Netherlands	1.12 (0.87–1.36)	0.70 (0.67–0.73)
Germany	0.67 (0.57–0.76)	0.72 (0.69–0.74)

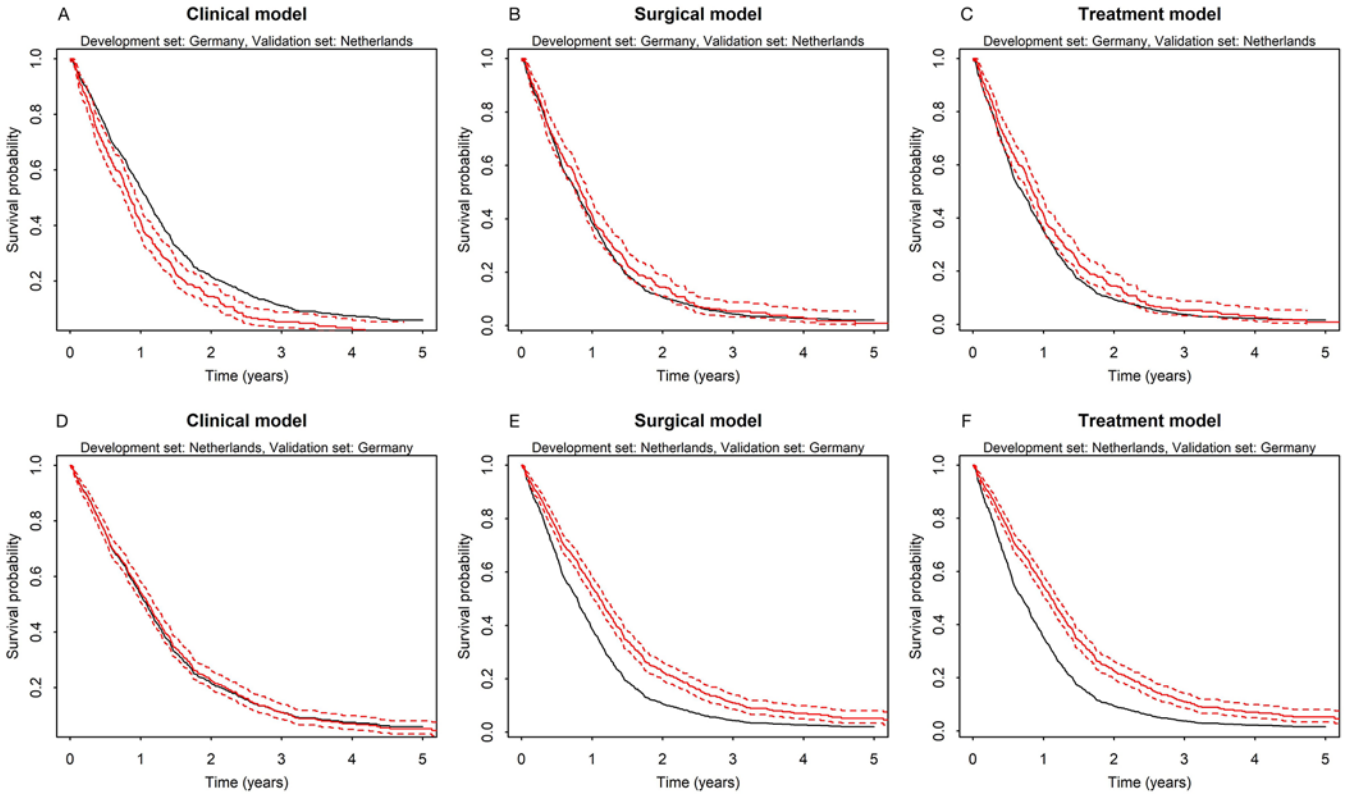


FIG. 3. Calibration plots of the developed models (**A–F**) at cross-validation. The *black line* denotes the average of the predicted survival probabilities of all patients. The *solid red line* is the Kaplan-Meier estimate of survival probabilities of the validation cohort, and the *dashed red lines* are the associated 95% CIs. Figure is available in color online only.

Table 4 provides the baseline hazard and predictor coefficients for the different models to allow for independent external validation studies by independent researchers.

Discussion

Individualized estimates of survival time can be obtained with reasonable accuracy from the proposed clinical prediction model in patients newly diagnosed with *IDH* wild-type glioblastoma. The model is cross-validated in large institutional patient cohorts from Germany and the Netherlands. Considering updated conventional predictors and new predictor variables including current relevant molecular biomarkers, our prediction model reached a promising discriminative model performance (C-statistic 0.73). The web-based prognostic calculator will help to facilitate clinical implementation.

Before publication of the revised 4th edition of the WHO classification of CNS tumors in 2016, most literature reporting on prediction models for patients with glioblastoma was confounded by omitting information on prognostically important molecular biomarkers in the analyses, particularly *IDH* mutation status and *MGMT* promoter methylation status.[7,31] Recently, Gittleman et al. developed and validated a clinical prediction model in *IDH* wild-type glioblastoma in an American population that does take into account these biomarkers.[9] We found similar predictor effects for age at diagnosis, patient sex, and preoperative KPS score, although we avoided dichotomizing preoperative KPS score to prevent loss of data. About half of the patients had *MGMT* promoter-methylated tumors, consistent with previous evidence.[6] The predictor effect of *MGMT* promoter methylation status was also consistent with the work by Gittleman et al.[9] Furthermore, as recently recommended, we expanded and updated the model with an additional surgical intervention (the biopsy-only group) and an additional adjuvant treatment option (the non-Stupp alternative). As expected, patients undergoing a biopsy-only procedure had a worse prognosis. Patients allocated to the non-Stupp treatment confer a favorable survival prognosis compared to patients without adjuvant therapy. To address the addition of multiple parameters to the model, a more robust effective sample size was achieved to provide accurate predictions. Nonetheless, the work by Gittleman et al. presented a higher C-statistic of 0.76.[9] This difference could be due to a lower case-mix heterogeneity in the present Dutch cohort. The lower C-statistic may also be explained by measurement error that might have emerged in the present study. The assessment of EOR differed between the German and Dutch cohorts. In the former cohort, EOR was defined by a qualitative approach,[8] whereas in the latter, a quantitative approach (volumetric segmentation analysis) was used.[14] Consequently, the measurement error in the Dutch cohort is likely lower, possibly resulting in a different association between EOR and

TABLE 4. Hazard ratios and associated 95% CIs in the final prediction models (n = 1036) including the discriminative ability

Predictor	Model		
	Clinical	Surgical	Treatment
Age per decade	1.29 (1.21–1.37)	1.28 (1.20–1.37)	1.27 (1.19–1.35)
Male vs female	1.11 (0.97–1.27)	1.08 (0.94–1.24)	1.02 (0.89–1.18)
Preop KPS score per 10-point increase	0.78 (0.72–0.83)	0.79 (0.74–0.85)	0.82 (0.76–0.89)
EOR			
GTR		Ref	Ref
Non-GTR		1.34 (1.11–1.62)	1.38 (1.14–1.68)
Biopsy		2.11 (1.71–2.59)	1.84 (1.48–2.27)
MGMT promoter status, unmethylated vs methylated			0.55 (0.47–0.65)
Adjuvant therapy			
Stupp			Ref
Non-Stupp			1.39 (1.18–1.64)
No therapy			2.92 (2.39–3.55)
C-statistic	0.66 (0.64–0.68)	0.68 (0.66–0.70)	0.73 (0.71–0.75)

mortality. Furthermore, we found a stronger effect of the adjuvant treatment on patient survival in the Dutch cohort compared to the patients from the German cohort, which was a puzzling result. Local patient allocation to the adjuvant treatment groups according to local principles and the non-Stupp option might have introduced heterogeneity between the data sets in the adjuvant treatment variable. Other unknown factors not captured in this study might have affected patient allocation to adjuvant treatment.

Implications for Patient Management

Patients newly diagnosed with *IDH* wild-type glioblastoma need to be well informed about the prognosis of this devastating disease, as do their families and significant others. To participate adequately in shared decision-making, patients and their relatives need to understand their prognosis to make preference-sensitive decisions. Since the 2016 WHO classification, an updated prediction tool is inevitable for providing reliable predictions within the group of patients with *IDH* wild-type glioblastoma. The proposed prediction model is particularly useful for shared decision-making. The nomograms and online calculator presented here are intuitive and freely available to facilitate shared decision-making in the clinical setting. The different models can be used pre- and postoperatively by health care professionals to explain the anticipated outcome of treatment. Consequently, patient-tailored treatment guidance and future planning become more feasible. For example, addressing existential distress (fear of dying or disease recurrence) may be an important upcoming issue for these patients.[32] Also, the plight of advanced cancer patients puts family members at risk for psychological morbidity.[33] Based on anticipated patient survival time, adequate (dyadic) coping strategies can be planned in time for the individual patient and/or their spouse/caregivers. It is recommended to include couples interventions if possible, to treat the hidden psychological morbidity in spouses/caregivers in time.[33]

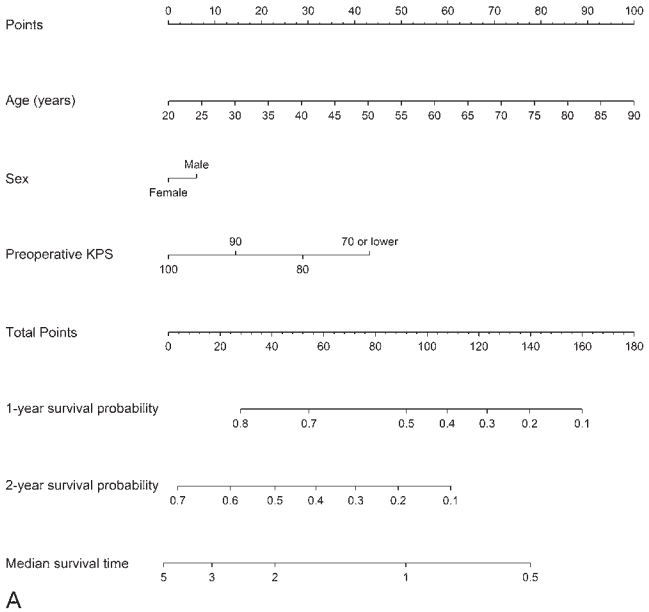
Implications for Future Work

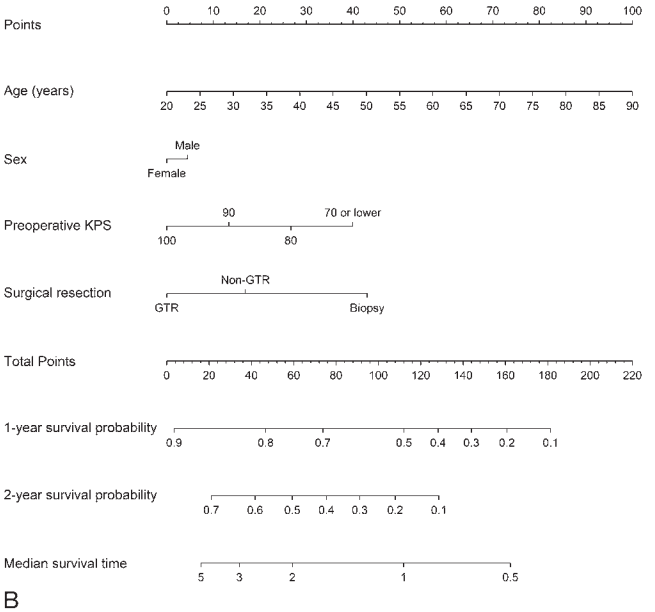
Although the presented model addresses glioblastoma as a molecular heterogeneous entity, future model updating is likely necessary. These updates will need to take into account newly defined molecular subgroups of *IDH* wild-type glioblastoma characterized by distinct DNA methylome profiles, or other potential biomarkers such as tumor mutation burden or total copy number aberration.[34] Along with this basic scientific research, ensuing clinical therapies are designed and tested. Tumor-treating fields concurrent with temozolomide have been suggested to be effective.[35] Immunotherapies and precision oncological approaches have so far not been shown to increase survival.[36] If those therapies become standard care, model updating will likely further increase the predictive performance of the model. Furthermore, the presented model enables the identification of specific patients for enrollment in a clinical trial. Strong clinical trial cohorts can subsequently be built; for example, selecting high-risk patients who may potentially benefit most from experimental treatment becomes feasible.

Strengths and Limitations

A strength of the current study is the development and validation in geographically distinct settings. Other centers may have different case-mix and different local care pathways, which may threaten external validity of the results. The generalizability of the model to nonacademic centers needs to be tested in future work.

Second, although the present model updated some conventional prognostic variables and did consider relevant molecular biomarkers, the model performance was not perfect. Other predictors may need to be considered such as corticosteroid use, seizures, and hospital complications, including venous thromboembolism.[37–39] These events may be associated with outcome and hence affect the accuracy of the presented models. However, including such events may make a clinical prediction very difficult to apply be-





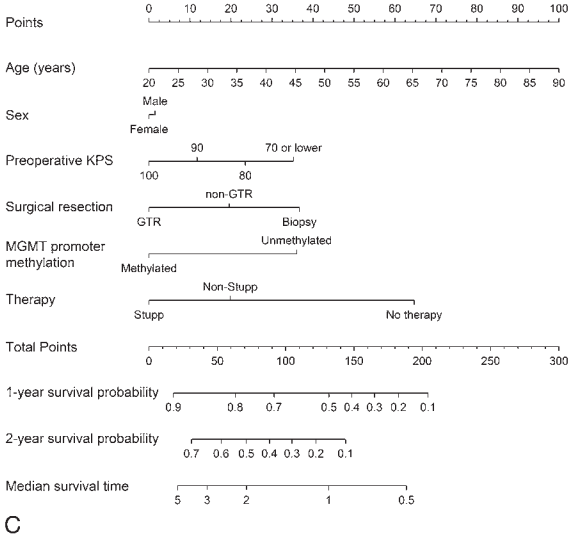


FIG. 4. Nomograms for the clinical (**A**), surgical (**B**), and treatment models (**C**). To use the nomograms, locate the patient's preoperative KPS score on the KPS axis. Draw a line straight upward to the Points axis to determine how many points the patient obtains. Repeat this for each prognostic variable, then sum the achieved points. Locate the final sum of the points on the Total Points axis. Draw a line straight down to find the patient's anticipated 1-year, 2-year, and median predicted survival time. The median predicted survival time denotes the time at which there is a 50% probability that the patient will survive until this time.

cause these data are generally not available at baseline. Adding more variables such as patient morbidity and details on tumor location might increase the performance of the proposed models. These variables may be considered surrogate markers for treatment decisions, e.g., performing a biopsy in a deeply located tumor and the no-therapy regimen for a patient with multiple comorbidities and poor neurological status. We refrained from putting these surrogate markers into the clinical model because of model complexity and sample size considerations. Furthermore, we aimed to use clearly defined variables that are easily accessible and measurable with a low probability for error.

Third, we cannot rule out the possibility of information bias because some variables were collected retrospectively. Machine-learning techniques were not explored, assuming that the limited predictors in our model could adequately be modeled by regression techniques.[40–42] Fourth, a causal relationship between treatment and prediction cannot be shown due to a lack of a comparative design in the data sets. Therefore, the model should not be used for treatment decision-making. However, the model should be used for patient, family, and significant other clarification on the anticipated survival given that a particular treatment is chosen. Therefore, this work is especially useful for shared

decision-making and has the potential to be a basis for impactful studies on personalized decision-making.

Fifth, the Dutch cohort did not have any missing data, and the German cohort was nearly complete for all cases. Multiple imputation is advisable to prevent loss of prognostic information.[19] Nevertheless, some level of inaccuracy of the imputed data cannot be ruled out. Finally, the model was developed and validated within a large sample size. However, internal-external validation of the developed model in Germany and the Netherlands showed some miscalibration of prediction for long-term survival probabilities, especially beyond the 1st year of survival. This may be due to a drop in the sample size as a substantial number of patients died during the 1st year after diagnosis, given the median survival time of < 12 months. Long-term predictions made by the model should be used with caution.

Conclusions

The proposed clinical prediction model reliably predicts individual survival prognosis in patients with newly diagnosed *IDH* wild-type glioblastoma. The model may support shared decision-making if used properly and may be used to select patients for enrollment in a clinical trial. In addition, it provides a framework that can be used for future updating. For clinical implementation, free software is available at https://www.evidencio.com/models/show/2384.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Mijderwijk, Nieboer, Steyerberg, van den Bent, Reifenberger, Hänggi, Smits, Kamp. Acquisition of data: Mijderwijk, Incekara, Berger, Voss, Forster, Kamp. Analysis and interpretation of data: Mijderwijk, Nieboer, Incekara, Steyerberg, van den Bent, Reifenberger, Smits, Senft, Forster, Kamp. Drafting the article: Mijderwijk, Steyerberg, van den Bent, Reifenberger. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mijderwijk. Statistical analysis: Mijderwijk, Nieboer, Steyerberg, van den Bent, Reifenberger. Administrative/technical/material support: Kamp. Study supervision: Nieboer, Steyerberg, van den Bent, Reifenberger, Hänggi, Smits, Senft, Sabel, Kamp.

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