Original Article

Prognostic factors and clinical nomogram predicting survival in high-grade glioma

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ABSTRACT

Background: Genomic-based tools have been used to predict poor prognosis high-grade glioma (HGG). As genetic technologies are not generally available in countries with limited resources, clinical parameters may be still necessary to use in predicting the prognosis of the disease. This study aimed to identify prognostic factors associated with survival of patients with HGG. We also proposed a validated nomogram using clinical parameters to predict the survival of patients with HGG.

Methods: A multicenter retrospective study was conducted in patients who were diagnosed with anaplastic astrocytoma (WHO III) or glioblastoma (WHO IV). Collected data included clinical characteristics, neuroimaging findings, treatment, and outcomes. Prognostic factor analysis was conducted using Cox proportional hazard regression analysis. Then, we used the significant prognostic factors to develop a nomogram. A split validation of nomogram was performed. Twenty percent of the dataset was used to test the performance of the developed nomogram.

Results: Data from 171 patients with HGG were analyzed. Overall median survival was 12 months (interquartile range: 5). Significant independent predictors included frontal HGG (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.40–0.60), cerebellar HGG (HR: 4.67; 95% CI: 0.93–23.5), (HR: 1.55; 95% CI: 1.03–2.32; reference = total resection), and postoperative radiotherapy (HR: 0.18; 95% CI: 0.10–0.32). The proposed nomogram was validated using nomogram's predicted 1-year mortality rate. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and area under the curve of our nomogram were 1.0, 0.50, 0.45, 1.0, 0.64, and 0.75, respectively.

Conclusion: We developed a nomogram for individually predicting the prognosis of HGG. This nomogram had acceptable performances with high sensitivity for predicting 1-year mortality.

KEY WORDS: High-grade glioma, nomogram, validation

INTRODUCTION

The term high-grade glioma (HGG) refers to tumors that are classified as anaplastic astrocytoma (AA) (WHO Grade III) and glioblastoma (GBM) (WHO Grade IV) according to their anaplastic features.[1,2] The treatment strategy for HGG is the highest resection, followed by radiotherapy and temozolomide for GBM or recurrent AA. However, the median survival time of AA and GBM was 2–5 years and 12–18 months, respectively.[2-5] The prognostic factors of the HGG have been reported in the literature. Age of patients, Karnofsky Performance Status (KPS), the extent of resection, postoperative radiotherapy, tumor grade, and histology were associated with outcome.[2-7]

Currently, a nomogram has been used to predict individualized median survival time and survival probabilities each time point in various diseases, particularly GBM. Nomograms which based on O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status were proposed to predict the survival of patients with newly diagnosed GBM.[8-11] Form literature review, accuracy, and precision of nomogram's prediction have been debated. Gittleman *et al.*

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developed an MGMT promoter methylation-based nomogram to estimate individual predicted 6-, 12-, and 24-month survival probabilities from training dataset and validated with independent dataset. The results were that the nomogram provided an individualized estimate of survival time.[9] However, Parks *et al*. studied in the validation of MGMT promoter methylation-based nomogram predicting survival time in patients with GBM. The calculator gives both inaccurate and imprecise predictions that 23% of predictions were within 25% of the actual survival.[12]

Since the estimation of this tool informs as predicted survival time and predicted probability, the individualized validation of survival among patients' challenges for general practice. Interpretation of prediction with continuous results is not simple, whereas the interpretation of a test with binary results is straight forward.[13,14] For example, predicted the 1-year probability of nomogram is 50%, what we should interpret these results for an individual in the real-world applications. Therefore, determining the most appropriate cutoff point of nomogram may be alternative methods for validating outcome as binary classifiers.[15,16] Moreover, genomic technologies and services have been clustered in some centers in a real-world situation. In countries with limited resources, clinical factors have still used for predicting prognosis. Hence, we aimed to develop and validate the clinical-based nomogram to predict survival of patients with HGG for using in the general practice.

METHODS

Study designs and population

The study was a multicenter, retrospective cohort review of medical records of the three university hospitals (Project of Hospital-Based Central Nervous System Tumor Registry: Multicenter study). We enrolled consecutive patients who were newly diagnosed with AA or GBM. The inclusion criteria for the study were patients who had histologically confirmed by a pathologist between January 2009 and December 2017. The data comprised of the demographics, neuroimaging, treatment, and outcome.

Operational definition

The KPS score is a scale for evaluating functional impairment. These scores range from 0 to 100. Therefore, KPS scores which were dichotomized into two groups included KPS score <80 and >80 groups.[17] Magnetic resonance images (MRIs) of the brain were reviewed to estimate tumor size, tumor location, and other characteristics of the tumor by neurosurgeons. The postoperative residual tumor was measured from postoperative MRI or contrast-enhanced computerized tomography of the brain.

According to Vecht *et al*., the extent of resection was postoperatively assessed.[17] Gross total resection was defined as gross macroscopic tumor resection or when the surgeon felt that only a minimal amount of tumor (<5% of residual tumor) was detected on postoperative neuroimaging. Subtotal resection was defined as resection after which 5% to <25% of the residual tumor was visible on postoperative neuroimaging. Partial resection was defined as resection after which more than 25% of the residual tumor was evident on postoperative neuroimaging. Moreover, a biopsy was defined as an operation for tissue diagnosis only, and no attempt was made to remove the tumor.

For outcome assessment, the follow-up data were collected until December 2018 including update status (death or survival) and cause of death. Follow-up data were collected mainly when patients visited outpatient clinics and/or their relatives and death record from the local municipality.

Nomogram development and deployment

Using split methods for validating nomogram, the total data were spat into developing dataset (80%) and deploying dataset (20%) as in Figure 1. Cox proportional hazard regression analyses were used for each fold, and the predictive models were developed from the developing dataset. Using the significant parameters ($P < 0.05$), nomogram from each fold was developed by Zhang and Kattan method[18] for predicting 1-, 2-, and 5-year mortalities. The bootstrap method with 1000 replicates was applied for the internal validity of each model. The "rms" package was used to develop nomogram and analyze the bias-corrected concordance index that evaluated the predictive discrimination of the model.[19] The concordance index is the probability of concordance between predicted probability and response.

From the deploying dataset, the nomogram's performances were evaluated, 1-, 2-, and 5-year mortalities, as binary classifiers (death or survival) with an optimal cutoff total point. Using the receiver operating characteristic (ROC) curve and the largest area under the ROC (AUC) chose the optimal cutoff point in each nomogram. Furthermore, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV),

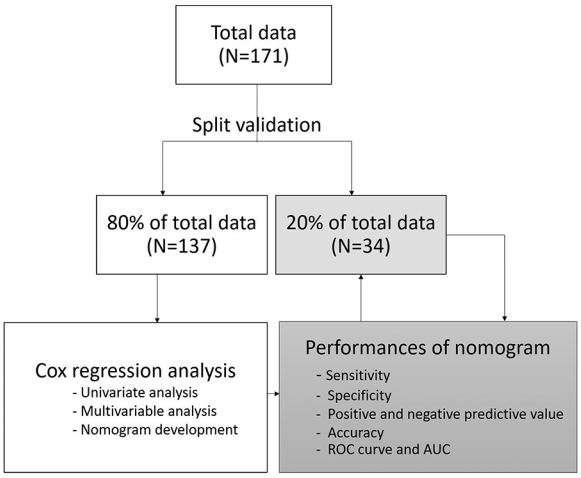

Figure 1: Workflow of nomogram development and deployment. Using split test, 80% of total data (white boxes) were used for developing nomogram from Cox regression analysis, and 20% of total data (Gray box) were used for testing performances of the nomogram

and accuracy were determined in each nomogram.[20] The statistical analysis was performed using the R version 3.4.0 software (R Foundation, Vienna, Austria). Moreover, ROC and AUC were created by "PlotROC" package.[21]

Ethical clearance

The study was performed with permission from the research ethics committee (REC 61-203-10-1).

RESULTS

Clinical characteristics of the 171 patients with HGG are shown in Table 1. Two-third of HGG was dominant in males with the mean age of 50.2 (standard deviation [SD] 15.3) years. Common presentations were hemiparesis, progressive headache, and seizure. The seizure was observed as the first presentation in 30% and 25.5% of patients with AA and GBM, respectively. The common tumor location involved the frontal and temporal lobe in one-third of cases. The periventricular, basal ganglion, and pineal HGG were found in 5.3%, 0.6%, and 0.6%, respectively. In addition, the mean tumor volume was 5.2 (SD 1.7), and multiple HGG was observed in 20.5%. The most common of the extent of resection was partial resection, whereas the rates of total, subtotal, and biopsy were 28.7%, 3.5%, and 13.5%, respectively. Most of the patients (88.3%) underwent radiotherapy after resection. In addition to GBM treatment, temozolomide was used in one-third of cases for concomitant adjuvant therapy. From a mean follow-up of 19.4 months (SD 24.1), the overall median survival time was 26 months (95% confidence interval [CI]: 19.0–41.0), whereas the 1-, 2-, and 5-year survival probabilities were 45.3%, 16.0%, and 3.3%, respectively. The median survival time of AA was 12 months (95% CI: 7–26), whereas GBM was 11 months (95% CI: 9–13) that there was no significant difference by log-rank test ($P = 0.4$).

In univariate analysis, significant independent predictors included frontal HGG (hazard ratio [HR]: 0.56; 95% CI: 0.37–0.85), cerebellar HGG (HR: 6.43; 95% CI: 1.52–27.16), biopsy (HR: 1.54; 95% CI: 1.03–2.30; reference = total resection), and postoperative radiotherapy (HR: 0.15; 95% CI: 0.08–0.26). Therefore, the significant model of the multivariable analysis consisted of frontal HGG (HR: 0.62; 95% CI: 0.40–0.60), cerebellar HGG (HR: 4.67; 95% CI: 0.93–23.5), biopsy (HR: 1.55; 95% CI: 1.03–2.32; reference = total resection), and postoperative radiotherapy (HR: 0.18; 95% CI: 0.10–0.32).

Using split validation, developing dataset was used for Cox proportional hazard regression analysis as shown in Table 2 and nomogram development as shown in Figure 2. Therefore, deploying dataset was used for testing the performance of nomogram. The application of nomogram is simple in general practice. For example, in Figure 3, a 48-year-old male with corpus callosum tumor (25 points from the nonfrontal group) underwent biopsy (15 points). The pathological diagnosis was GBM, and the patient received the concurrent radiotherapy (no point). Consequently, total points equaled 40 points which

Table 1: Demographic data of high-grade astrocytoma (WHO Grade III-IV) (*n*=171)

Factor	*n* (%)
Age (year)	
<60	128 (74.9)
≥60	43 (25.1)
Mean of age-year (SD)	50.2 (15.3)
Gender	
Male	104 (60.8)
Female	67 (39.2)
Weakness	86 (50.3)
Progressive headache	76 (44.4)
Alteration of consciousness	20 (11.7)
Seizure	45 (26.3)
Behavior change	20 (11.7)
Aphasia	14 (8.2)
Ataxic gait	7 (4.1)
Visual disturbance	1 (0.6)
Preoperative KPS	
<80	92 (53.8)
≥80	79 (46.2)
Major location of the tumor	
Frontal	47 (27.5)
Temporal	47 (27.5)
Parietal	29 (17.0)
Corpus callosum	25 (14.7)
Thalamus and basal ganglion	7 (4.1)
Occipital	6 (3.5)
Intraventricular	3 (1.8)
Cerebellum	3 (1.8)
Brainstem	2 (1.2)
Pineal	1 (0.6)
Spinal cord	1 (0.6)
Lateralization of tumor	
Left	74 (43.3)
Right	73 (42.7)
Bilateral	6 (3.5)
Midline	18 (10.5)
Number of tumors	
Single	136 (79.5)
Multiple	35 (20.5)
Preoperative hydrocephalus	13 (7.6)
Positive hypervascular signs	51 (29.8)
Initial leptomeningeal dissemination	18 (10.5)
Eloquent area	91 (53.2)
Mean of diameter, cm (SD)	5.2 (1.7)
Mean of midline shift, mm (SD)	2.6 (2.0)
Treatment	
Total resection	49 (28.7)
Subtotal resection	6 (3.5)
Partial resection	93 (54.4)
Biopsy	23 (13.5)
Histology	
AA	30 (17.5)
GBM	141 (82.5)
Radiotherapy	151 (88.3)
Chemotherapy for GBM (*n*=141)	
No	70 (49.6)
Temozolomide	46 (32.6)
Vincristine with cyclophosphamide	20 (14.2)
Other	5 (3.5)
Postoperative KPS	
<80	105 (61.4)
>80	66 (38.6)

KPS=Karnofsky performance status, SD=Standard deviation, AA=Anaplastic astrocytoma, GBM=Glioblastoma

Table 2: Cox proportional hazard regression analysis for mortality of the highest performance nomogram (*n*=137)

Factor	Univariate analysis OR (95% CI)	*P*	Multivariable analysis OR (95% CI)	*P*
Gender				
Male	Reference			
Female	0.81 (0.24-2.66)	0.73		
Age				
<60	Reference			
≥60	1.37 (0.95-1.96)	0.08		
Aphasia*	1.67 (0.21-13.25)	0.62		
Seizure*	1.91 (0.56-6.55)	0.30		
Motor response of GCS				
Equal 6	Reference			
<6	0.04 (0-1031.67)	0.54		
Preoperative KPS				
<80	Reference			
≥80	0.93 (0.28-3.05)	0.90		
Location				
Frontal lobe*	0.56 (0.37-0.85)	0.006	0.62 (0.40-0.60)	0.03
Temporal lobe*	1.22 (10.86-1.75)	0.25		
Parietal lobe*	1.08 (0.71-1.66)	0.29		
Occipital lobe*	1.62 (0.68-3.99)	0.24		
Intraventricular*	1.45 (0.34-6.10)	0.60		
Brainstem*	0.18 (0.02-1.37)	0.10		
Thalamus*	2.13 (0.98-4.59)	0.053		
Corpus callosum*	0.90 (0.53-1.55)	0.72		
Pineal gland*	3.61 (2.76-52.99)	0.20		
Cerebellum*	6.43 (1.52-27.16)	0.01	4.67 (0.93-23.5)	0.06
Spinal cord*	0.59 (0.08-4.40)	0.61		
Lateralization of tumor				
Left	Reference			
Right	0.86 (0.24-2.99)	0.81		
Bilateral				
Midline	0.71 (0.08-6.28)	0.76		
Eloquent area*,†	1.30 (0.93-1.81)	0.11		
Number of tumor				
Single	Reference			
Multiple	2.2 (0.81-6.39)	0.11		
Positive hypervascular sign*	0.43 (0.09-2.02)	0.29		
Leptomeningeal dissemination*	1.25 (0.15-9.93)	0.82		
Preoperative hydrocephalus*	1.14 (0.46-2.85)	0.76		
Midline shift				
<0.5	Reference			
>0.5	0.81 (0.35-1.84)	0.62		
Maximum diameter, cm				
<3	Reference			
>3	1.55 (0.83-2.88)	0.16		
Extent of resection				
Total resection	Reference		Reference	
Subtotal resection	2.17 (0.84-5.58)	0.10	1.59 (0.57-4.46)	0.37
Partial resection	1.66 (0.74-3.74)	0.21	1.32 (0.58-3.00)	0.50
Biopsy	1.54 (1.03-2.30)	0.03	1.55 (1.03-2.32)	0.03
Histology				
AA	Reference			
GBM	1.21 (0.76-1.92)	0.41		
Postoperative KPS				
<80	Reference			
>80	1.05 (0.32-3.45)	0.93		
Radiotherapy				
No	Reference		Reference	
Yes	0.15 (0.08-0.26)	<0.001	0.18 (0.10-0.32)	<0.001

*Data show only "yes group" while reference groups (no group) are hidden, †Eloquent area defined tumor involved motor cortex, sensory cortex, visual center, speech center, basal ganglion, hypothalamus, thalamus, brainstem, dentate nucleus. KPS=Karnofsky performance status, OR=Odds ratio, AA=Anaplastic astrocytoma, GBM=Glioblastoma, GCS=Glasgow coma scale

approximately corresponds to 50%–60% of 1-year survival probability, 10%–15% of 2-year survival probability, <2% of 5-year survival probability, and 15–20 months of median survival time.

Figure 4 shows the nomogram's performance. For predicting 1-year mortality, the nomogram had good performances showing a sensitivity of 1.0, specificity of 0.50, PPV of 0.45, NPV of 1.0, accuracy of 0.64, and AUC of 0.75 while nomogram's

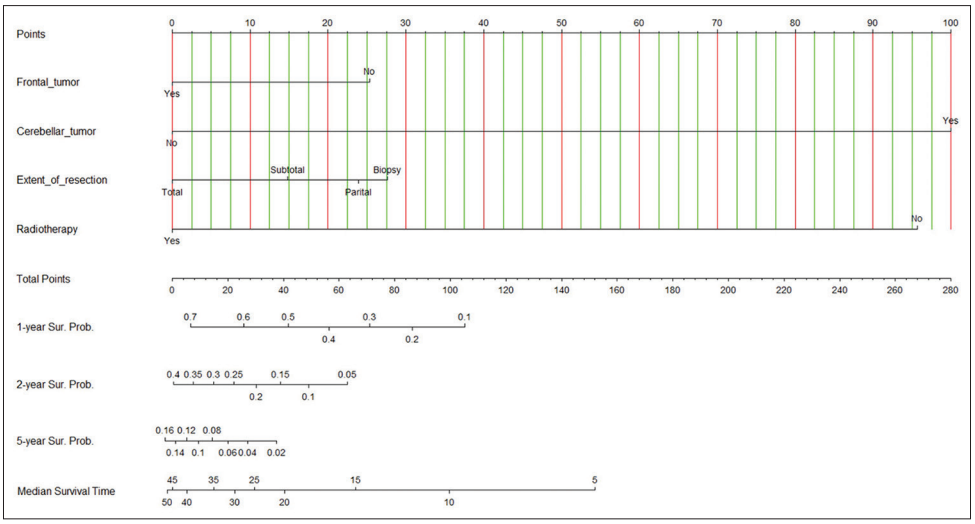

Figure 2: The nomogram predicts 1-, 2-, and 5-year survival probabilities and median survival time (months). To use the nomogram, draw a straight line upward from the patient's characteristics of the frontal tumor, cerebellar tumor, the extent of resection, radiotherapy to the upper points scale, and the sums of the scores of all variables. Then, draw another straight line down from the scale of the total points through the 1-, 2-, 5-year, and median survival time. This is the probability of the presence of prognosis in an individual

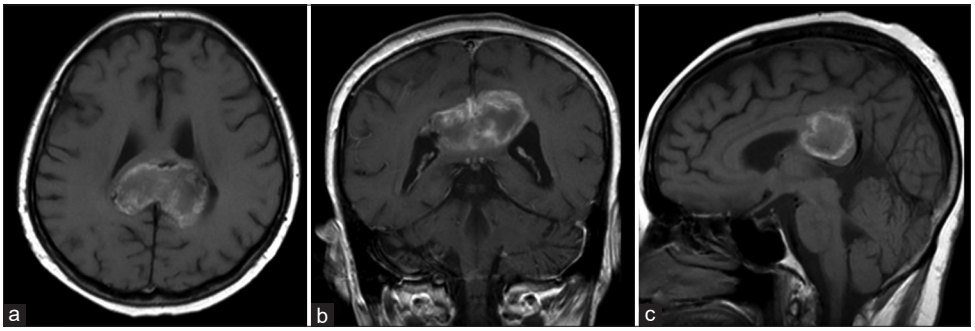

Figure 3: Splenium tumor. A 48-year-old male with infiltrative tumor at the splenium of the corpus callosum. (a) Axial postcontrast T1-weighted image. (b) Coronal postcontrast T1-weighted image. (c) Sagittal postcontrast T1-weighted image. The patient underwent biopsy, and pathological diagnosis was glioblastoma. Therefore, the patient received the radiotherapy and died in 17 months after surgery

Table 3: Performance of nomogram for predicting 1-, 2-, and 5-year mortalities from validation data at cutoff 15-point

Prediction	Sensitivity	Specificity	PPV	NPV	Accuracy
Predicted 1-year mortality	1.00	0.50	0.45	1.00	0.64
Predicted 2-year mortality	0.72	0.66	0.72	0.66	0.70
Predicted 5-year mortality	0.70	0.57	0.86	0.33	0.67

PPV=Positive predictive value, NPV=Negative predictive value

performances dropped for predicting 2- and 5-year mortalities as shown in Table 3.

DISCUSSION

In the present cohort study, we observed poor prognosis of HGG. There was no significant difference between AA and GBM survivals. Similarly, Noiphithak and Veerasarn reported that the survivals of Thai patients with AA and GBM were not different between groups.[6] Equally, prior western studies have been reported median survival time of HGG range 1–5 years. According to histology, AA had survival time significantly longer than GBM depended on each cohort.[2,3,5] For the primary analyses, factors significantly associated with survival were some tumor location, the extent of resection, and postoperative adjuvant therapies.

Paldor *et al*. reported that frontal GBM had a better prognosis than nonfrontal GBM. Similarly, HGG localized to the frontal lobe had a significantly better prognosis than nonfrontal HGG. Because the frontal tumors are generally more amenable to complete surgical resection, these carry a better prognosis.[22] Besides, cerebellar HGGs were reported that these groups had a poorer prognosis than supratentorial HGG. From previous studies, HGG localized in the cerebellum had an independent poor prognostic significance as shown by Cox proportional hazard regression analysis.[23,24] In the present study, the median survival time of cerebellar HGG was 2 months, whereas noncerebellar HGG had median survival time 148 months. The

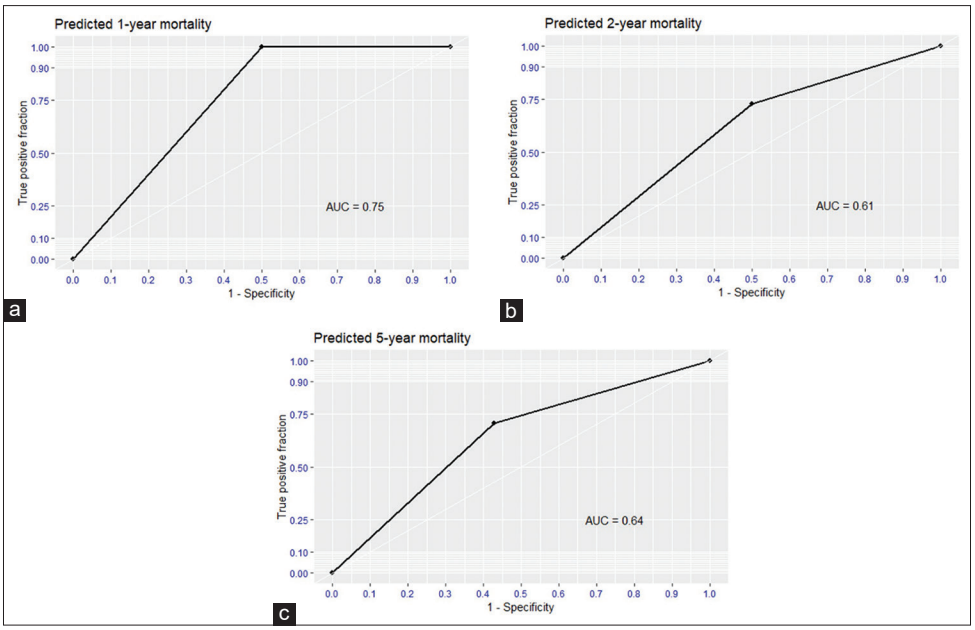

Figure 4: Receiver operating characteristic curve and area under the curve of a nomogram predicting mortality with cutoff 15 points. (a) Predicted 1-year mortality. (b) predicted 2-year mortality. (c) predicted 5-year mortality

results in our cohort showed concordance outcome with the prior study.

The potential effects of treatments on prognosis were the extent of resection, RT in AA, and radiotherapy with temozolomide in GBM.[3-5] However, the present study had shorter survival compared with prior studies. Although the efficacy of chemotherapy significantly prolongs survival, temozolomide has been limited in certain health welfares in Thailand. Accessibility to temozolomide was about 32.6% of GBM. Therefore, survival in the present cohort had poorer than the literature. However, the use of postoperative radiotherapy for AA and GBM was seen to be independent favorable prognostic factors in the present study.

A nomogram is a simple tool which predicts the prognosis. However, biomarker-based nomograms may have limitations for real-world practice because genetic technologies have not still been worldwide available and have increased the cost of treatment. Furthermore, the lack of nomogram's validation has been observed from the literature review.

Parks *et al*. validated MGMT-based nomograms for predicting median survival time in a patient with GBM that there was only a weak-positive correlation between the predicted and actual survival among patients (R2 of 0.07).[12] In addition, Gittleman *et al*. validated nomogram for individualized estimation of survival among patients with newly diagnosed GBM from independent validation datasets that discussed some limitations from switching the training and independent validation datasets for comparisons such as the Cox proportional hazard regression model estimates, the nomogram point assignments, or the concordance indices.[9] Therefore, we proposed nomogram validation as binary classifiers each time point for testing tool's performance. The nomogram of our cohort had acceptable performances for predicting 1-year mortality that had a high level of sensitivity. For general practice, the high-sensitivity nomogram could be applied as a screening tool for decision-making treatment strategies. Because of the high cost in neurooncology treatment such as chemotherapy or genetic technologies, clinical parameters have still been necessary for predicting prognosis in the real-world setting, and cost-effective analysis of genetic technologies are needed to evaluate for the maximum health benefits in countries with limited resources.[25] However, nomogram's performances dropped for predicting 2- and 5-year mortalities that need external validation in the future.

Finally, certain limitations of the present study should be acknowledged. As the retrospective design, the possibility of bias and confounding factors cannot be excluded. However, we presented to adjust the model with multivariable analysis for tackling this limitation.[26] For the future work in this field, the external validation should be prospectively conducted to test this nomogram's performance in the future. In addition, the IDH1mutation of HGGs did not perform in the present study, because these genetic investigations have not routinely estimated in Thailand.

CONCLUSION

Our study proposed nomogram using clinical predictors. This nomogram had acceptable performances and a high level of sensitivity for predicting 1-year mortality. For implication, the high-sensitivity nomogram could be useful to guide health-care workers for decision-making treatment strategies and advising patients.

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Conflicts of interest

There are no conflicts of interest.

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