Prognostic Factors and Nomogram Predicting Survival in Diffuse Astrocytoma

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Abstract

Background   Prognosis of low-grade glioma are currently determined by genetic markers that are limited in some countries. This study aimed to use clinical parameters to develop a nomogram to predict survival of patients with diffuse astrocytoma (DA) which is the most common type of low-grade glioma.

Materials and Methods   Retrospective data of adult patients with DA from three university hospitals in Thailand were analyzed. Collected data included clinical characteristics, neuroimaging findings, treatment, and outcomes. Cox's regression analyses were performed to determine associated factors. Significant associated factors from the Cox regression model were subsequently used to develop a nomogram for survival prediction. Performance of the nomogram was then tested for its accuracy.

Results   There were 64 patients with DA with a median age of 39.5 (interquartile range [IQR] = 20.2) years. Mean follow-up time of patients was 42 months (standard deviation [SD] = 34.3). After adjusted for three significant factors associated with survival were age ≥60 years (hazard ratio [HR] = 5.8; 95% confidence interval [CI]: 2.09–15.91), motor response score of Glasgow coma scale < 6 (HR = 75.5; 95% CI: 4.15–1,369.4), and biopsy (HR = 0.45; 95% CI: 0.21–0.92). To predict 1-year mortality, sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and area under the curve our nomogram was 1.0, 0.50, 0.45, 1.0, 0.64, and 0.75, respectively.
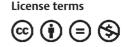
Conclusions   This study provided a nomogram predicting prognosis of DA. The nomogram showed an acceptable performance for predicting 1-year mortality.

Keywords
► diffuse astrocytoma
► nomogram
► survival analysis

Introduction

Diffuse astrocytoma (DA) is one type of low-grade glioma (LGG) and classified as WHO (World Health Organization) grade II. DA is a relatively slow-growing brain tumor with a median survival time of 3.9 to 10.8 years.[1-6] However, DA infiltrates brain parenchyma, making it hard for total resection. The rate of gross-total resection is only 14 to 17%.[2,3] Therefore, residual tumors become the burden of patients with DA in the long-term follow-up.

Low-grade glioma (LGG) comprised of several types of tumor, that is, astrocytoma, oligodendroglioma, and mixed oligoastrocytoma. Associated factors for poor outcomes in patients with LGG are older age, Karnofsky's performance status (KPS) < 70, prior neurological deficits, tumor size >6 cm, tumor crossing midline, and nonhemispheric/noncerebellar tumor.[6-8] Postoperative radiotherapy (RT) is yet a debatable predicting factor for prognosis of LGG. In a study, postoperative conventional RT tends to shorten time to progression and prolonged progression-free survival but not the overall survival.[9] Another study shows no significant difference in survival between pediatric patients with LGG who received postoperative RT and those who did not.[8] Nonetheless, there has been limited data about prognosis among subpopulation of patients with LGG including patients with DA.

Nomogram has been used to predict clinical outcome in various groups of diseases, such as malignancies,[10,11] degenerative diseases,[12] and metabolic diseases.[13] From the literature review, there is the heterogeneity of histology in the group of LGG and lack of evidence of the prognostic factors that focuses on diffuse astrocytoma. We aimed to identify prognostic factors associated with survival of patients with diffuse astrocytoma. This study developed the nomogram to predict survival of DA hoping to use in the clinical practice.

Subjects and Methods

Study Designs and Population

We reviewed data from three university hospitals in Thailand (Central Nervous System Tumor Registry). Patients who were newly diagnosed with DA within the study period (January 2009 and December 2017) were included. DA was histologically-confirmed by certified pathologists using World Health Organization Classification.[14] Data collected included demographics, neuroimaging, treatment, and outcome.

The Karnofsky performance status (KPS) score is an assessment tool for functional impairment. Scores run from 100 to 0 (the lowest KPS score has the worst survival probability). KPS scores were also dichotomized into two groups, according to the ability to carry on normal activities (KPS ≥80).[15]

Magnetic resonance images (MRI) of the brain were reviewed prospectively by trained neurosurgeons to demonstrate tumor location, tumor size, and other characteristics of the tumor. The postoperative residual tumor was quantified from postoperative MRI or contrast-enhanced computerized tomography (CT) of the brain. The hypervascularization of the tumor defined as the visualizing vascular structures inside a tumor (flow void sign) was reviewed.[16]

The extent of resection was defined using the same definition by Vecht et al.[17] Gross-total resection was defined as residual tumor seen in postoperative neuroimaging less than 5%. Subtotal resection was defined as residual tumor 5 to 25% seen in postoperative neuroimaging. Partial resection was defined as visible residual tumor more than 25%. Biopsy was defined as an operation for tissue diagnosis only, and no attempt was made to remove the tumor.

The follow-up data were collected until December 2018. Survival duration was duration from the time of surgery to death or censor (still survived) in December 2018. Follow-up data were collected mainly when patients visited outpatient clinics. Patients (or caregivers) who did not come to the hospital were interviewed by phone. We also checked death records from the local municipality. The study got clearance from the institutional review board of each collaborator (REC number 61–203–10–1).

Nomogram Development and Performance Test

From the multivariable analysis, the prediction model was constructed from the significant parameters that affect the mortality. A nomogram was developed using the significant parameters ($p < 0.05$) of the method by Zhang et al.[18] The bootstrap method with 1,000 replicates was used for the internal validity of the model. The validated function in the "rms" package was used to analyze the bias-corrected c-index that evaluated the predictive discrimination of the model.[19] The concordance index is the probability of concordance between predicted probability and response.

For the individual prediction, the performances of nomogram were evaluated as the binary classifiers (death or living) instead of the death-probability prediction by the self-consistency validation.[20] The nomogram's sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were determined for death in various cut-off point of the total scores. Therefore, the highest performance nomogram with optimal cut-off points was chosen by the receiver operating characteristic (ROC) curve and the area under the receiver operating characteristic (AUC) were plotted. Additionally, AUCs were determined that values ≥0.9 are "excellent," ≥0.80 "good," ≥0.70 "fair," and <0.70 "poor."[21]

Statistical Analysis

Clinical characteristics and therapeutic factors were first described using descriptive statistics. Survival curve was constructed using the Kaplan–Meier method. The Cox proportional hazard regression model was used to identify the univariate and multivariate predictors of survival. A p-value less than 0.05 was considered statistically significant. The statistical analysis was performed using the R version 3.4.0 software (R Foundation, Vienna, Austria). In details, the "rms" package was used for establishing nomogram.[19] Moreover, ROC and AUC were created by "PlotROC" package.[22]

Results

The clinical manifestations of the 64 patients with DA are shown in ►**Table 1**. More than half of the DA was slightly dominant in males. The mean age was 39.4 years (SD = 17.3). The patients usually presented with a seizure and a progressive headache. Additionally, 96.9% of patients had the Glasgow coma scale (GCS) score 15, while 3.1% had a GCS score of less than 15. The common tumor location involved the frontal and temporal lobe in 37.5 and 23.4%, respectively. The thalamic tumor was found in 1.6% of cases. Moreover, the mean tumor volume was 5.6 (+SD = 1.8) and 92.2% of the DA was solitary tumors while 7.8% was multiple tumors.

Table 1   Clinical characteristics of patients (*n* = 64)

Factor	n (%)
Age (y)	
<60	55 (85.9)
≥60	9 (14.1)
Median of age (y)(IQR)	39.5 (20.2)
Gender	
Male	34 (53.1)
Female	30 (46.9)
Seizure	34 (53.1)
Progressive headache	21 (32.8)
Weakness	16 (25.0)
Visual disturbance	3 (4.7)
Alteration of consciousness	2 (3.1)
Ataxic gait	2 (3.1)
Preoperative Karnofsky's performance status	
<80	22 (34.4)
≥80	42 (65.6)
Major location of the tumor	
Frontal	24 (37.5)
Temporal	15 (23.4)
Corpus callosum	7 (10.9)
Parietal	5 (7.8)
Brainstem	3 (4.7)
Pineal	2 (3.1)
Spinal cord	2 (3.1)
Occipital	1 (1.6)
Periventricular	1 (1.6)
Basal ganglion	1 (1.6)
Thalamus	1 (1.6)
Sellar/suprasellar	1 (1.6)
Cerebellum	1 (1.6)
Lateralization of tumor	
Left	24 (37.5)
Right	27 (42.2)
Bilateral	1 (1.6)
Midline	12 (18.8)
Number of tumors	
Single	59 (92.2)
Multiple	5 (7.8)
Preoperative hydrocephalus	15 (23.4)
Positive hypervascular signs	20 (31.3)
Initial leptomeningeal dissemination	3 (4.7)
Eloquent area	26 (40.6)
Mean of diameter (cm) (SD)	5.6 (1.8)
Mean of midline shift (mm) (SD)	3.3 (3.7)

(continued)

Table 1 *(continued)*

Factor	n (%)
Type of operation	
Total resection	8 (12.5)
Subtotal resection	7 (10.9)
Partial resection	27 (42.2)
Biopsy	22 (34.4)
Radiotherapy	53 (82.8)
Postoperative Karnofsky's performance status	
< 80	29 (45.3)
≥ 80	35 (54.7)

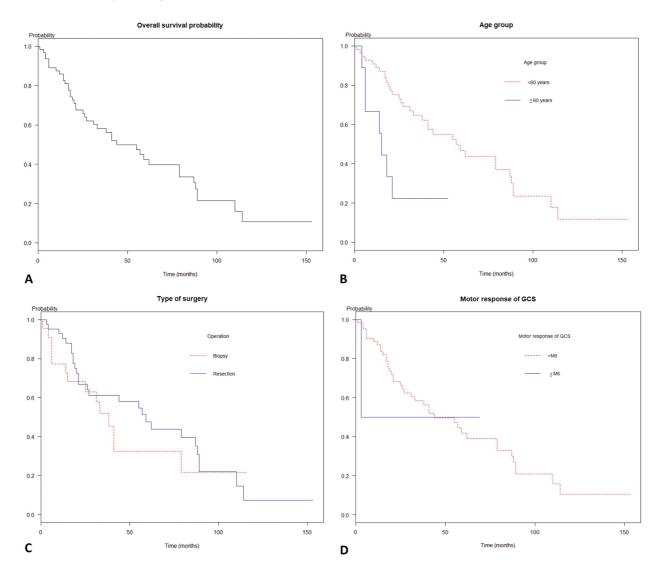Abbreviations: IQR, interquartile range; SD, standard deviation.

Fig. 1 Survivals of patients with diffuse astrocytoma glioma by predictors. (**A**) The overall median survival time was 26 months (95% confidence interval [CI]: 19.0–41.0). (**B**) A comparison of survival times among age groups (log-rank test, $p = 0.004$). (**C**) A comparison of survival times among patients according to motor response groups (log-rank test, $p < 0.001$). (**D**) A comparison of survival times among biopsy and resection operations (log-rank test, $p = 0.04$).

In this study, the total resection rate was 12.5%, while the rates of subtotal, partial resection, and biopsy were 10.9, 42.2, and 34.4%, respectively. Most of the patients (82.8%) underwent radiotherapy after resection.

Survival Analysis

The prognosis of the diffuse astrocytoma was pitiable as the Kaplan–Meier curve in ►**Fig. 1A** Mean follow-up time was 42 months (SD = 34.3). Also, the overall median survival time

was 44 months (95% confidence interval [CI]: 31.0–87.0), while the 1-, 2-, and 5-year survival probability were 85.9, 67.6, and 42.3%, respectively. Moreover, the malignant transformation was observed in 17.2% of cases.

According to Cox's proportional hazard regression analysis as shown in ►**Table 2**, the significant parameters for increased death were age 60 years or more group (hazard ratio [HR] = 4.83, *p* = 0.001), motor response of GCS score less than 6 in groups (HR 39.49, *p* = 0.009), positive hypervascular sign (HR = 2.05, *p* = 0.03), biopsy (HR = 0.47, *p* = 0.03) in univariate analysis. By multivariable analysis, the significant model consisted of age 60 years or more (HR = 5.76, *p* < 0.001), the motor response score of GCS less than 6 (HR = 75.47, *p* = 0.003), and biopsy (HR = 0.45, *p* = 0.02).

As the Kaplan–Meier curve in ►**Fig. 1B–D**, the median survival time of age less than the 60-year group was 34 months, whereas age 60 or above group was 7 months (log rank test, *p* < 0.01). The patients with motor response score of GCS less than 6 had median survival time at 40 months while motor response score of GCS equal to 6 had median survival time at a month (log-rank test, *p* = 0.005). Additionally, the median survival time of biopsy and tumor resection was 22 months and 27 months, respectively (log rank test, *p* = 0.04).

Nomogram Development and Performance Test

The nomogram was developed using the significant parameters in the multivariable analysis as shown in ►**Fig. 2**. Additionally, the calibrate plot revealed that the model was nearby the ideal and had a bias-corrected concordance-index value of 0.933. The nomogram is simple in general practice. For example, a 58-year-old patient (no point) had six scores in the motor response of GCS (no point), and the MRI of the brain showed a left frontal diffuse astrocytoma with positive of the hypervascular sign, and he underwent to total tumor resection (no point) as ►**Fig. 3**. Therefore, total points equal to 0 points which approximately corresponds to more than 90% of 1-year survival probability, more than 70% of 2-year survival probability, 35 to 40% of 5-year survival probability, and 80 to 90 months of predicted-survival time.

For validation, the performances of nomogram were evaluated as the binary classifiers instead of survival probability. Therefore, nomogram needed to find the optimal cut-off point for highest performance. At an optimal cut-off point of 18, the nomogram was validated by self-consistency test that sensitivity, specificity, PPV, NPV, accuracy, and AUC were 0.77, 0.61, 0.25, 0.94, 0.70, and 0.70, respectively for predicting 1-year mortality as ►**Fig. 4**. Nevertheless, nomogram performance gradually dropped in 2-year and 5-year prediction as ►**Table 3**.

Discussion

Overall median survival time have been reported between 3.9 and 10.8 years in the LGG which composed of astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas.[1-6] Spych et al reported LGG had the median survival times of 26.9 months (range: 25.4–46.8 months), whereas the median survival times was 48 months

(range: 30 months–138 months) according to the study by Kumthekar et al.[2,3] Moreover, The 1-year, 3-year, and 5-year overall survivals of LGG were 88.3, 55.1, and 43.3%, respectively.[2] As the present results, the prognosis of our cohort was poorer than prior studies that the median survival time of the cohort was 26 months and the 5-year probability was 22.0%. Since the heterogeneity of the LGG population limits to comparison with the present cohort.

For negative prognostic factors, Pignatti et al reported that age >40 years, whereas Okamoto et al reported age >50 years associated with the poor prognosis.[6] Similarly, the present study found the elderly patients had a poor prognosis. Furthermore, the presence of neurologic deficit before surgery was one of the significant prognostic factors, while motor response score of GCS was less than 6, as well as the poor performance status of the patients was associated with worse outcome in the present study.

Several studied reported that tumor resection significantly impacts the survival of LGGs.[23-25] The result in the present study concordances the prior studies that biopsy was significantly associated with increased mortality. Furthermore, the effect of RT is controversial for improving outcome and prognosis. LGGs treated with postoperative RT which was highly correlated with overall survival[3,9] in prior studies, whereas other studies reported that postoperative RT was no statistically significant difference in survival was seen between the postoperative RT and non-RT groups.[2,8,26] However, the heterogeneity of the study population of LGGs was observed in previous studies. In the present cohort of DA, the radiotherapy following surgery was no statistically significant association with overall survival rate. From the literature review, a few studies focused on the prognosis of the DA group since the limitation of sample size were considered. Nevertheless, the present study, which focused on the specific DA group, had the strength in the homogeneity of the study population. To the best of our knowledge, this is the first study mentioned to evaluate and validate nomogram which is specific to DA.

Gorlia et al proposed nomogram for predicting survival of patients with LGGs including astrocytoma, oligodendroglioma, and mixed oligoastrocytoma. The final overall survival model, independent prognostic factors were identified as time since first LGG symptoms (HR = 0.67, *p* = 0.009), Medical Research Council (MRC) neurological score (HR = 1.51, *p* = 0.0001), independent confirmation of astrocytoma (HR = 1.96, *p* < 0.001), and tumor size (HR = 1.74, *p* = 0.001). However, there is a limitation of validation because the prediction of nomogram is probability at each time point and survival time.[27] 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, we proposed nomogram validation as binary classifiers each time point with the optimal cut-off point in the present study. The nomogram of our cohort had acceptable performances for predicting 1-year mortality that had a high level of sensitivity and accuracy. For general practice, the nomogram could be applied as the screening tool for advising patients and managing treatment strategies. However, nomogram's

Table 2 Factors associated with the death of patients with diffuse astrocytoma

	Univariate analysis		Multivariable analysis	
Factor	Odds ratio (95%CI)	*p*-Value	Odds ratio (95%CI)	*p*-Value
Gender				
Male	Ref.			
Female	1.16 (0.61–2.20)	0.63		
Age (y)				
< 60	Ref.			
≥ 60	4.83 (1.86–12.55)	0.001	5.76 (2.09–15.91)	< 0.001
Aphasia[a]	4.50 (0.56–36.0)	0.15		
Seizure[a]	1.08 (0.56–2.08)	0.80		
Motor response of GCS				
Equal 6	Ref.		Ref.	
Less than 6	39.49 (2.47–631.49)	0.009	75.47 (4.15–1369.4)	0.003
Preoperative Karnofsky performance status				
< 80	Ref.			
≥ 80	1.29 (0.67–2.51)	0.43		
Location				
Frontal lobe[a]	1.06 (0.55–2.05)	0.84		
Temporal lobe[a]	0.83 (0.49–1.68)	0.69		
Parietal lobe[a]	0.67 (0.20–2.28)	0.52		
Brainstem[a]	1.17 (0.15–8.71)	0.87		
Thalamus/basal ganglion[a]	2.85 (0.65–12.32)	0.16		
Corpus callosum[a]	2.20 (0.63–7.71)	0.21		
Sellar/suprasellar region[a]	0.20 (0.02–1.75)	0.14		
Spinal cord[a]	2.59 (0.32–20.52)	0.36		
Lateralization of tumor				
Left	Ref.			
Right	1.45 (0.73–2.88)	0.28		
Midline	1.36 (0.53–3.48)	0.51		
Eloquent area [a,b]	0.87 (0.46–1.65)	0.68		
Number of tumors				
Single	Ref.			
Multiple	2.18 (0.75–6.28)	0.14		
Positive hypervascular sign[a]	2.08 (1.04–4.12)	0.03	1.81 (0.88–3.75)	0.10
Leptomeningeal dissemination[a]	1.59 (0.37–6.73)	0.52		
Preoperative hydrocephalus[a]	1.09 (0.51–2.30)	0.81		
Midline shift				
< 0.5	Ref.			
≥ 0.5	1.20 (0.59–2.45)	0.59		
Maximum diameter (cm)				
< 3	Ref.			

(continued)

Table 2 *(continued)*

	Univariate analysis		Multivariable analysis	
Factor	**Odds ratio (95%CI)**	***p*-Value**	**Odds ratio (95%CI)**	***p*-Value**
≥ 3	0.73 (0.30–1.78)	0.49		
Type of operation				
Biopsy	Ref.		Ref.	
Resection	0.47 (0.23–0.95)	0.03	0.45 (0.21–0.92)	0.02
Postoperative Karnofsky's performance status				
< 80	Ref.			
≥ 80	0.98 (0.52–1.85)	0.95		
Radiotherapy				
No	Ref.			
Yes	0.86 (0.35–2.06)	0.73		

Abbreviations: CI, confidence interval; Ref., reference.
[a]Data show only "yes group" while reference groups (no group) are hidden.
[b]Eloquent area defined tumor involved motor cortex, sensory cortex, visual center, speech center, basal ganglion, hypothalamus, thalamus, brainstem, dentate nucleus.
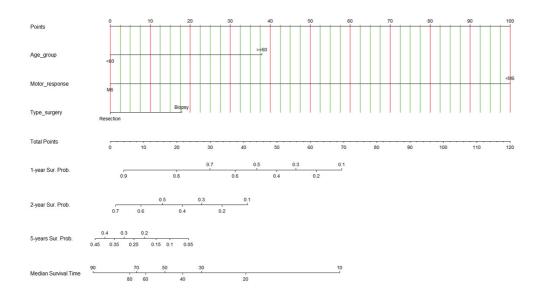

Fig. 2 Nomogram predicting 1-year, 2-year, 5-year survival probabilities (Sur. Probs.) and median survival time (months). To use the nomogram, draw a straight line upward from the patient's characteristics of age group, motor response, type of surgery to the upper points scale, the sums of the scores of all variables. Then, draw another straight line down from the scale of the total points through the 1-year, 2-year, 5-year, and median survival times. This is the probability of the presence of prognosis in an individual.

performances dropped for predicting 2- and 5-year mortality that needs external validation in the future.

Limitations

Certain limitations of the present study should be acknowledged. The *IDH1* mutation of DAs did not perform in the present study because these genetic investigations have not routinely estimated in Thailand. Moreover, the possibility of bias and confounding factors cannot be excluded from the retrospective study. However, we presented to adjust the model by multivariable analysis for controlling this limitation[28]

Conclusion

We provided nomogram predicting prognosis of a patient with DA. The nomogram was acceptable performance for predicting 1-year mortality. The tool is a good clinical utility for optimizing therapeutic approaches and counseling patients.
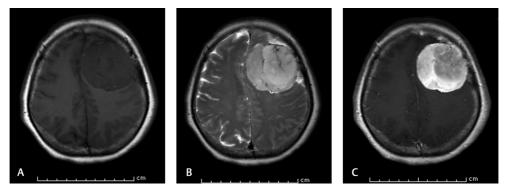
Fig. 3 Brain MRI of a 58-year-old patient who survived at 4-year-follow-up. (**A**) Axial T1-weighted image shows left hypointense frontal mass. (**B**). Axial T2-weighted image demonstrates the intratumoral flow void sign. (**C**). Axial T1-weighted image shows vivid enhancement after contrast injection. MRI, magnetic resonance imaging.
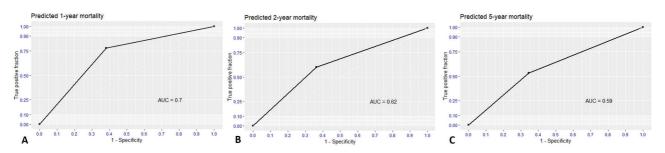

Fig. 4 Receiver operating characteristic (ROC) curve and area under the curve (AUC) of predicted mortality as binary classifiers using cut-off-point of 18. (**A**) 1-year predicted mortality, (**B**) 2-year predicted mortality, and (**C**) 5-year predicted mortality.

Table 3 Performance test of a nomogram predicting 1-, 2-, and 5-year mortality of diffuse astrocytoma at cut-off 18 points

Prediction	Sensitivity	Specificity	PPV	NPV	Accuracy
1-year mortality	0.77	0.61	0.25	0.94	0.70
2-year mortality	0.60	0.63	0.42	0.77	0.62
5-year mortality	0.53	0.65	0.60	0.58	0.59

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Key Messages

To the best of authors' knowledge, this article is the first one to mention the nomogram predicting prognosis of diffuse astrocytoma. Moreover, we proposed that nomogram can be used in the binary outcome for simplifying nomogram application in the clinical practice.

Authors' Contributions

T.T., S.R., U.I., A.K., and T.V. participated in study design and data collection plan. T.T., S.S., T.O., I.S., A.K., S.R., A.K., and T.V. supervised data collection. T.T., S.R., A.K., and T.V. contributed in data extraction, data management, and quality control. T.T. analyzed the data and drafted the manuscript. All authors contributed substantially to manuscript revision. T.T. takes responsibility for this paper as a whole.

Conflict of Interest

None declared.

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