Five Genes Associated With Survival in Patients With Lower-grade Gliomas Were Identified by Information-theoretical Analysis

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Abstract. *Background/Aim:* Understanding of the molecular events associated with progression and survival differences in patients with lower-grade gliomas (LGGs) is still unclear. The comparison of findings across studies using different datasets and methods is essential for a new molecular-based classification system. The aim of the study was to identify biomarkers for prognostic classification of patients with LGGs, and furthermore to lay a foundation for future development of targeted therapies for LGGs. *Patients and Methods:* Using information-theoretic and statistical approaches, we analyzed mRNA expression data for 18,413 genes from LGG samples in order to identify candidate biomarkers for survival. The candidate genes were then evaluated for their potential as prognostic biomarkers using multivariable Cox regression analyses that adjusted for the effects of age and grade. *Results:* WEE1, EMP3, E2F7, CD58 and NSUN7 genes were identified as candidate biomarkers of LGGs and their high expression was associated with significantly shorter survival. The hazard ratios for mortality were 5.02 (95% CI=3.40-7.40) for WEE1, 5.45 (95% CI=3.63-8.18) for EMP3, 4.49 (95% CI=3.03-6.66) for E2F7, 4.77 (95% CI=3.22-7.06) for CD58 and 4.38 (95% CI=2.97-6.47) for NSUN7. In addition, the expression pattern of these genes, associated with shorter survival in LGGs, was also observed in glioblastoma multiforme. *Conclusion:* Identification of genes associated with poor outcomes will provide insights into

novel biological mechanisms that may lead to improvement in progression and survival for patients with LGGs.

Low-grade and intermediate-grade gliomas (WHO grades II and III) are less aggressive tumors than high-grade gliomas (WHO grade IV) called glioblastoma multiforme (GBM). Combined grade II and III gliomas have been commonly referred to as lower-grade gliomas (LGGs) (1-3). LGG patients have a better prognosis and longer survival than GBM patients; however, the outcomes of LGG patients are variable; some progress to GBM within months, while others progress slower or remain stable for years (1, 4, 5). Over the years, numerous attempts have been made to identify prognostic biomarkers and to improve survival in LGG patients. Notably, isocitrate dehydrogenase (IDH) mutation status has been recognized as a prognostic biomarker in gliomas (6-8) and has been included in the current WHO 2016 classification (9). However, as regards the prognostic significance of IDH mutation in LGGs, inconsistent results have been reported (4, 10-15). Understanding of the molecular events associated with the progression and survival differences in these patients is an active area of research. The comparison of findings across studies using different datasets and methods is vital for the development of a clinically applicable molecular-based classification system and new targeted therapies as well. At the same time, determining how to handle a huge amount of molecular and clinical data and then how to extract clinically meaningful targets is a significant challenge, not only for gliomas but also for tumors in general.

Herein, we applied an information-theoretic approach to the comprehensive analysis of gene expression patterns in order to identify biomarkers for prognostic classification of LGG patients, and furthermore to lay a foundation for future development of targeted therapies for LGGs. In a previous paper, we showed that the similar information-theoretic analysis is an effective and powerful tool for identifying prognostic factor for survival in patients with estrogen

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Key Words: WEE1, EMP3, E2F7, CD58, NSUN7, lower-grade gliomas, information-theoretical approach.

Table I. Clinical characteristics of the sample datasets.

Characteristic	LGGs, n (n=530)	GBM, n (n=166)
Age ¹ , years	41 (14-87)	60 (21-89)
Gender (Female/Male/NA)	238/291/1	58/107/1
IDH (mutant/wild type/NA)	127/308/95	0/0/166
Grade (II/III/IV/NA)	258/270/0/2	0/0/166/0*
Clinical outcomes		
Overall survival ² , (months)	0-211	0-88
Short-term survival (death<5 years)	104	130
Long-term survival (survival>5 years or censored >5 years)	70	2
Censored <5 years	354	32
NA	2	2

LGGs, Lower-grade gliomas; GBM, glioblastoma multiforme; IDH, isocitrate dehydrogenase. ¹Data presented as median (range). ²Data presented as range. *The grades for GBM cases were not provided in the original TCGA dataset.

receptor-positive breast cancer (16). In information theory, information is quantified using the concept of uncertainty. According to Shannon, information is related to uncertainty in the view that reduction of uncertainty can be regarded as acquisition of information (17). We focus on how the uncertainty of prognosis for LGG patients can be reduced by the acquisition of information on gene expression levels.

Patients and Methods

Method overview. To better understand molecular events associated with the progression and survival differences in LGGs, we used the ‘Brain Lower Grade Glioma’ and ‘Glioblastoma Multiforme’ datasets of The Cancer Genome Atlas (TCGA, Provisional). Data for the LGG and GBM samples were downloaded on July 27, 2019 from the cBioPortal for Cancer Genomics (<http://www.cbioportal.org/>) (18, 19). Clinical details for these samples are given in Table I. The LGG dataset, consisting of 530 samples, included mRNA expression data for 18,413 genes. We analyzed the mRNA expression z-scores of the LGG subgroup using information-theoretic and statistical approaches to identify candidate biomarkers for survival of LGGs. In addition, we investigated the relationships between LGGs and GBM based on the expression of each gene that was identified as a candidate biomarker for LGGs.

Information-theoretic analysis. For 174 patient samples in the TCGA LGG dataset –356 samples were excluded (354 were censored within 5 years after diagnosis and 2 had no clinical information)– the following two events were defined: (x_1), short-term survival (death within 5 years after diagnosis), and (x_2), long-term survival (survival >5 years after diagnosis). The probabilities of these two events are given by $p(x_1)=104/174$ and $p(x_2)=70/174$, respectively. The Shannon entropy of the complete event system $X=\begin{pmatrix} x_1 & x_2 \\ p(x_1) & p(x_2) \end{pmatrix}$ is defined as $S(X)=-\sum_{i=1}^2 p(x_i) \log p(x_i)$, which gives a measure of the uncertainty of X and takes from a minimum value of 0 to a maximum value of $\log 2=1$ (log denotes the binary logarithm throughout our analysis). We used this measure to quantify the uncertainty of prognosis in LGG patients. Moreover, we defined the following two events for

the mRNA expression level of a gene: (y_1), high-expression ($Z\text{-score}>0$), and (y_2), low-expression ($Z\text{-score}<0$). The complete event system Y is denoted by the probabilities $p(y_1)$ and $p(y_2)$ of these two events, such that $p(y_1)+p(y_2)=1$, which are calculated using the z-scores for each gene across the 174 samples (“data_RNA_Seq_v2_mRNA_median_Zscores.txt” file in the TCGA LGG dataset). The dataset included mRNA expression data for 18,413 genes. For each gene, the complete event system Y can be determined. The compound event system $X \times Y$ for X and Y is denoted by the joint probability $p(x_i, y_j)$ for the event x_i ($i=1, 2$) and event y_j ($j=1, 2$), which satisfy $\sum_j p(x_i, y_j)=p(x_i)$ and $\sum_i p(x_i, y_j)=p(y_j)$. Using these event systems, the mutual information is defined as

as $\sum_{i,j} p(x_i, y_j) \log \frac{p(x_i, y_j)}{p(x_i) p(y_j)}$, which is non-negative. The mutual

information measures the reduction in uncertainty of X due to the knowledge of Y . Larger mutual information implies less uncertainty in X . For each gene, the mutual information was calculated. The genes were then ranked based on the mutual information so that the gene with the largest mutual information was number 1. This analysis allowed us to quantify how the uncertainty of the prognosis is reduced through the acquisition of information on gene expression levels, as well as to identify candidate prognostic biomarkers for LGGs.

Statistical analysis. In addition to the information-theoretic analysis, for the 174 LGG samples, we used a chi-square test of independence to assess the association between the expression level (high or low) of each gene for the 18,413 expressed genes and the overall survival (short or long). Thus, we identified candidate genes from both information-theoretic and statistical measures. These candidate genes were then evaluated for their potential as prognostic biomarkers in LGGs. For the 528 LGG samples, including 354 samples censored within 5 years after diagnosis, the Kaplan-Meier method was used to calculate survival rates, and log-rank testing was applied to compare survival differences between expression status. Univariable and multivariable Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for mortality. Univariable analysis was performed for each of the candidate genes and other prognostic variables, including age, gender, IDH1 mutation status and grade, and those variables that were significant ($p<0.05$) were included in multivariable analysis.

Table II. Top 10 genes having potential relevance to the progression and survival differences in lower-grade gliomas.

Information-theoretic analysis*			Chi-square analysis		
Gene	Mutual information	Ranking (chi-square analysis)	Gene	Chi-square value	Ranking (information-theoretic analysis)
WEE1	0.2578	1	WEE1	57.00	1
EMP3	0.2190	4	E2F7	44.32	3
E2F7	0.2070	2	CD58	41.54	4
CD58	0.2005	3	EMP3	41.37	2
NSUN7	0.1933	5	NSUN7	39.15	5
DMRTA2	0.1912	31	EVC2	38.89	8
LNC00669	0.1886	11	ALG6	38.22	19
EVC2	0.1878	6	TNFAP6	37.88	9
TNFAP6	0.1871	8	PTGFRN	37.61	17
PDPN	0.1765	21	TMEM220	37.45	16

*The Shannon entropy, $S(X)=0.9722$.

Furthermore, we investigated the relationships between LGG and GBM samples based on the expression level of each gene that was identified as a candidate biomarker for LGGs, using data (data_RNA_Seq_v2_expression_median.txt) from the two TCGA datasets (530 LGG samples and 166 GBM samples). All statistical analyses were performed using JMP 14 (SAS Institute Inc. Cary, NC, USA), except for the chi-square test for independence which was calculated directly from the number of occurrences of each compound event in the information-theoretic analysis.

Results

The 18,413 genes were sorted in descending order based on their mutual information, and similarly, they were sorted according to their chi-square values. The results for the top 10 genes from each analysis are shown in Table II. Of the top 10 genes selected according to the information-theoretic analysis, 7 were also ranked in the top 10 by the chi-square analysis. The top 5 genes were common in both analyses, although the order of ranking differed. Therefore, these five genes (WEE1, EMP3, E2F7, CD58 and NSUN7) were identified as candidate biomarkers for survival of LGGs. We observed that among the 83, 49, 67, 59 and 54 LGG samples with high expression of WEE1, EMP3, E2F7, CD58 and NSUN7 respectively, 74 cases (89.16%) for WEE1, 48 cases (97.96%) for EMP3, 61 cases (91.04%) for E2F7, 55 cases (93.22%) for CD58 and 51 cases (94.44%) for NSUN7 died within 5 years.

In the survival curves shown in Figure 1, the 528 LGG samples, including 354 samples censored within 5 years after diagnosis, were divided into the two groups based on the expression level ($Z\text{-score}>0$ or $Z\text{-score}<0$) of each gene. High expression levels of WEE1, EMP3, E2F7, CD58 and NSUN7 were associated with shorter survival in LGGs. For WEE1, the 5-year survival rate was 21.8% in high expression (+) *versus* 79.1% in low expression (-); for

Table III. Multivariable analysis of prognostic factors associated with survival differences in lower-grade gliomas (LGGs).

Variable	LGGs (n=527*)	
	HR (95% CI)	p-Value
Age at diagnosis >40/≤40 years	2.97 (2.01-4.45)	<0.0001
Grade III/II	1.73 (1.15-2.65)	0.0078
WEE1 expression level High (+)/low (-)	5.02 (3.40-7.40)	<0.0001
Age at diagnosis >40/≤40 years	2.09 (1.40-3.15)	0.0003
Grade III/II	2.29 (1.54-3.45)	<0.0001
EMP3 expression level High (+)/low (-)	5.45 (3.63-8.18)	<0.0001
Age at diagnosis >40/≤40 years	2.51 (1.71-3.74)	<0.0001
Grade III/II	1.89 (1.24-2.92)	0.0030
E2F7 expression level High (+)/low (-)	4.49 (3.03-6.66)	<0.0001
Age at diagnosis >40/≤40 years	2.51 (1.71-3.72)	0.0003
Grade III/II	2.32 (1.56-3.51)	<0.0001
CD58 expression level High (+)/low (-)	4.77 (3.22-7.06)	<0.0001
Age at diagnosis >40/≤40 years	2.68 (1.82-4.01)	<0.0001
Grade III/II	2.08 (1.40-3.14)	0.0002
NSUN7 expression level High (+)/low (-)	4.38 (2.97-6.47)	<0.0001

HR, Hazard ratio; CI, confidence interval. *Of the 530 LGG samples, 3 cases did not have available overall survival and grade information.

Figure 1. Survival curves for the two lower-grade glioma (LGG) groups based on the expression level [Z-score>0 (+) or Z-score<0 (-)] of each gene, (A) WEE1, (B) EMP3, (C) E2F7, (D) CD58 and (E) NSUN7. *p*-Values were calculated using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were calculated from Cox proportional hazards models.

EMP3, it was 5.1% (+) versus 71.8% (-); for E2F7, it was 17.2% (+) versus 75.3% (-); for CD58, it was 17.5% (+) versus 73.0% (-); for NUSN7, it was 12.0% (+) versus 72.0% (-). In each case, the differences were significant ($p<0.0001$). The univariable hazard ratio (HR) was 6.10 [95% confidence interval (CI)=4.30-8.72] for WEE1, 8.70 (95% CI=5.93-12.65) for EMP3, 6.34 (95% CI=4.44-9.03) for E2F7, 6.62 (95% CI=4.56-9.60) for CD58 and 6.30 (95% CI=4.38-8.97) for NUSN7.

In addition, there were significant differences in survival based on age or grade. The 5-year survival rate was 46.8% in LGG subgroup >40 years and 75.3% in those ≤40 years ($p<0.0001$). The 5-year survival rate was 42.8% in LGG subgroup with grade III and 81.0% in those with grade II ($p<0.0001$). The HR was 2.90 for age (>40/≤40) (95%

CI=2.01-4.23) and 3.35 for grade (III/II) (95% CI=2.31-4.94) in univariable analysis. However, significant differences in survival were not observed based on gender or IDH1 mutation status. The 5-year survival rate was 65.0% in LGG subgroup of women and 59.0% in those of men ($p=0.4482$). The 5-year survival rate was 59.4% in LGG subgroup with IDH1 mutations and 62.1% in those without IDH1 mutations ($p=0.6818$). The HR was 0.87 for gender (female/male) (95% CI=0.61-1.23) and 0.90 for IDH1 (mutant/wild type) (95% CI=0.53-1.45) in univariable analysis.

Multivariable analysis also indicated that age, grade, and each of the 5 candidate genes (WEE1, EMP3, E2F7, CD58 and NSUN7) were significantly associated with differences in survival for LGGs (Table III). Above all, high expression of these genes in LGGs was the main risk factor for

Figure 2. Comparison of mRNA levels of WEE1 (A), EMP3 (B), E2F7(C), CD58 (D) and NSUN7 (E) in the two lower-grade glioma (LGG) groups based on the expression level [Z-score>0 (+) or Z-score<0 (-)] of each gene and the glioblastoma multiforme (GBM) group. Data are shown as box plots. Each box represents the 25th to 75th percentiles. The horizontal line in each box represents the median mRNA level in each group.

increased mortality. The HR adjusted for age and grade was 5.02 (95% CI=3.40-7.40; $p<0.0001$) for WEE1, 5.45 (95% CI=3.63-8.18; $p<0.0001$) for EMP3, 4.49 (95% CI=3.03-6.66; $p<0.0001$) for E2F7, 4.77 (95% CI=3.22-7.06; $p<0.0001$) for CD58 and 4.38 (95% CI=2.97-6.47; $p<0.0001$) for NSUN7.

The pattern of high mRNA expression of these genes associated with shorter term survival in LGGs was also

observed in 166 GBM samples (Figure 2). The respective median values in the GBM group were nearly equal to or higher than those in the LGG subgroup with high expression. In any case, the respective median values in LGG subgroup with low expression were quite low compared to those in the GBM group. These results indicate that high mRNA levels of WEE1, EMP3, E2F7, CD58 and NSUN7 are linked to poor survival in gliomas.

Figure 3. Survival curves for the three lower-grade glioma (LGG) groups based on the expression level [$Z\text{-score} \geq 1$ (++) , $0 < Z\text{-score} < 1$ (+) or $Z\text{-score} < 0$ (-)] of each gene, (A) WEE1, (B) EMP3, (C) E2F7, (D) CD58 and (E) NSUN7. As a reference, the corresponding curve for the GBM group is also depicted. Of the 166 glioblastoma multiforme (GBM) samples, 2 cases did not have available clinical information. The 1-, 3-, and 5-year survival rates were calculated using the Kaplan-Meier method.

For each gene, the LGG samples with high expression were further divided into two subgroups according to the expression level: $Z\text{-score} \geq 1$ (++) and $0 < Z\text{-score} < 1$ (+) (Figure 3). Although there was a significant difference in survival between the CD58(++) and CD58(+) subgroups ($p=0.0001$ by log-rank test), no significant differences were

observed between the subgroups with different expression levels of WEE1, EMP3, E2F7 and NSUN7 ($p=0.0794$, $p=0.4210$, $p=0.8687$ and $p=0.8474$, respectively).

Interestingly, for the LGG(+) group consisting of 54 LGG samples (grade II, $n=3$; and grade III, $n=51$) with high expression ($Z\text{-score} > 0$) of all five genes, the 1-, 3- and 5-

year survival rates were 64.2%, 5.6% and 0%, respectively, while for the LGG(−) group consisting 330 LGG samples (grade II, n=211; grade III, n= 118; and NA, n=1) with low expression ($Z\text{-score}<0$) of all five genes, the 1-, 3- and 5-year rates were 99.3%, 95.5% and 83.2%, respectively. There was a significant difference in survival between the two groups ($p<0.0001$ by log-rank test). The corresponding survival rates for the GBM group were 58.4%, 9.1% and 2.2%, respectively.

Discussion

Information-theoretic and statistical approaches contributed to the identification of WEE1, EMP3, E2F7, CD58 and NSUN7 genes as potential prognostic biomarkers and high expression of these genes was associated with significantly shorter survival in LGGs.

WEE1 is a tyrosine kinase, which has been shown to act as a regulator of the G2 checkpoint in GBM cells (20, 21). Inhibition of this kinase has been indicated to enhance sensitivity to irradiation and temozolomide (20-22). Previous studies have revealed that WEE1 is expressed in all glioma types and grades; while, it is overexpressed in GBM (20-22). Shu *et al.* demonstrated that WEE1 was an independent prognostic biomarker for high-grade gliomas (23).

EMP3 is a transmembrane protein that is involved in cell proliferation and cell-cell interactions, and functions as a tumor suppressor for gliomas (24, 25). Ernst *et al.* have shown that high EMP3 expression was significantly associated with shorter overall survival in astrocytic glioma patients in univariable analysis (26).

E2F7, a member of E2F transcriptional factor, plays an essential role in the regulation of cell cycle progression (27). E2F7 has been reported to be highly expressed in high-grade gliomas compared to low-grade gliomas (28). However, the association between E2F7 expression and overall survival in gliomas has been little studied.

CD58 is a member of the immunoglobulin superfamily, which is a ligand of the T lymphocyte CD2 protein, and functions in adhesion and activation of T lymphocytes (29). CD58 protein is a cell-surface marker as cancer stem cell of colorectal cancer (30). Although there is a study showing differences in CD58 expression level between gliomas and normal brain using small number of samples (31), few studies have reported the involvement of CD58 in the progression of gliomas.

NSUN7 belongs to the methyltransferase superfamily and is essential for sperm motility (32, 33). To our knowledge, no studies have been conducted on the impact of NSUN7 status on the progression in gliomas.

Within our study, there was no significant difference in survival based on IDH1 mutation status, although IDH mutation status has been recognized as a prognostic biomarker for overall survival in gliomas (6-8). More detailed

studies are required to unequivocally determine whether IDH1 mutation status is a prognostic biomarker for LGGs. Nevertheless, our results suggested that the expression levels of WEE1, EMP3, E2F7, CD58 and NSUN7 genes may serve as independent prognostic factors for overall survival in patients with LGGs. Identification of genes associated with poor outcomes will provide insights into novel biological mechanisms that lead to improvement in progression and survival for LGG patients, and lay the foundation for development of novel therapeutic approaches for LGGs. The information-theoretic approach presented here may be an effective and powerful tool for highlighting clinically important genes and can be applied to other tumors.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

K.S. contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting and critical revision of the manuscript. K.T. and K.A. contributed to analysis and interpretation of data, and critical revision of the manuscript.

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