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Research Article

Down-Regulation of miRNA-217 in Prediction of Poor Prognosis of Glioma as a Potential Therapeutic Target

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Abstract

Background: As other studies in the literature have reported, miRNA-217 could inhibit tumor invasion by directly regulating E2F3.miRNA-217, however, was also confirmed as an oncogene in malignant human B-cell lymphomas, which suppressed the expression of DNA damage response as well as repairing gene network. Therefore, miRNA-217 is closely concerned with the progression and prognosis of tumors. However, its clinical and prognostic value have not been researched in glioma. The purpose of our study was to research miRNA-217 expression and evaluate the clinical value of prognosis.

Methods: We collected glioma specimens including grade II astrocytomas (n=46) and glioblastoma (n=51) from September 2015 to September 2017.Expressions of miRNA-217 in 97 specimens were detected by quantitative real-time PCR (qRT- PCR). The chi-square test was applied to explore the relationship between miRNA-217 expression and clinicopathological characteristics. The overall survival (OS) was estimates by log-rank tests among strata, and the survival curves were drawn by Kaplan-Meier. In addition, univariate and multivariate analysis were utilized to analyze the relationship of prognosis with clinicopathological characteristics including miRNA-217 expression.

Results: We found significantly down-regulated miRNA-217 expression in glioblastoma group, as compared with grade II astrocytomas group (p=0.01).Low expression of miRNA-217 was associated with higher WHO grade (p=0.003),large tumor size (p=0.019), MGMT no methylation (p=0.001) IDH wild (p=0.001) and lower KPS (p=0.001).Moreover, Kaplan-Meier analysis proved that low-expressed miRNA-217 was associated with poor OS (p=0.001).The multivariate analysis suggested that miRNA-217 expression was an independent prognostic factor (p=0.020).

Conclusions: In our study, miRNA-217 had lower expression in glioblastoma and was related with tumor prognosis, which might serve as an independent prognostic factor for patients with glioma.

Keywords: glioma; mirna-217; overall survival; prognosis; clinicopathological characteristics

Introduction

Malignant gliomas remain the most prevalent type of primary intrinsic neoplasms of the CNS in adults[1]. Glioblastoma is the most common type in malignant brain tumour. According to NCCN Guidelines, the standard therapies including surgery, radiotherapy with concomitant temozolomide (TMZ), adjuvant TMZ chemotherapy and TTF therapies. However, patients have poor prognosis with a median survival of only 12-15 months after diagnosis[2, 3].Thus, it is of great urgency to identify novel prognostic biomarkers, thereby providing new therapeutic targets.

An increasing number of molecular markers are being discovered, which improves our understanding of glioma and development mechanism. To date, the final histological diagnosis, final intergrated diagnosis, pathological classification and prognosis assessment are more accurate, which can help develop personalized therapy for glioma. Therefore, it is important to find novel biomarkers which can predict the prognosis, and explore its potential as a therapeutic target for glioma patients.

miRNAs, known as small non-coding RNA molecules, are made up of 19-23 nucleotides, which can regulate gene expression post-transcriptionally through complementary binding to the mRNA3'UTR region[4, 5]. More and more results indicate that miRNAs participate in cellular pathological processes, which included cell proliferation, apoptosis, invasion and metastasis[6, 7].In the meantime, it also has a significant inhibitory effect on carcinogenic cells.

In recent years, miR-217 plays important roles on tumorigenesis and drug resistance[8,9].miR-217 suppressed laryngeal cancer metastasis by inhibiting astrocyte elevated gene-1 and programmed death-ligand[10].The function of miRNA -217 has been widely concerned, and most studies have confirmed that miRNA-217 is down-regulated in a series of tumors[11, 12], such as lung cancer, colon cancer, kidney cancer, glioma and so on. The lower miRNA-217 expression in colorectal cancer (CRC) patients, the worse prognosis and shorter survival time. According to vitro experiments, miRNA- 217 has an obviously inhibitory effect on cells proliferation, which suggests that miRNA-217 may serve as a tumor suppressor gene in colorectal tissues[13].As other studies have reported, miRNA-217 could directly regulate E2F3, thereby inhibiting tumor invasion[14].

In addition, Li J[11] reported that the low expression of miRNA-217 in ovarian cancer was related to pathological stage of tissues and lymph node metastasis. The result suggests that miRNA-217 may be associated with malignant development.

However, the study of miRNA-217 mutation mainly focused on colorectal, ovarian and lung cancer. Therefore, we aim to analyze the clinical value of miRNA-217 in glioma. We focused on the miRNA-217 effect and the expression level in glioma tissue. Subsequently, we analyzed the relation between miRNA-217 expression level and clinicopathological characteristics. In our study, we performed a preliminary analysis between the expression level of miRNA-217 and overall survival risk of glioma among the Chinese people.

Methods

Were devided to high expression and low expression group. Table I summarizes the relation of miRNA-217 expression to clinicopathological parameters in glioma. miRNA-217 low expression was shown to be significantly related with higher WHO grade (p=0.003), large tumor size (p=0.019), MGMT no methylation (p=0.001), IDH wild (p=0.001) and lower KPS (p=0.001), and the coefficients were 0.29,0.25,0.44,0.47 and 0.32 respectively.

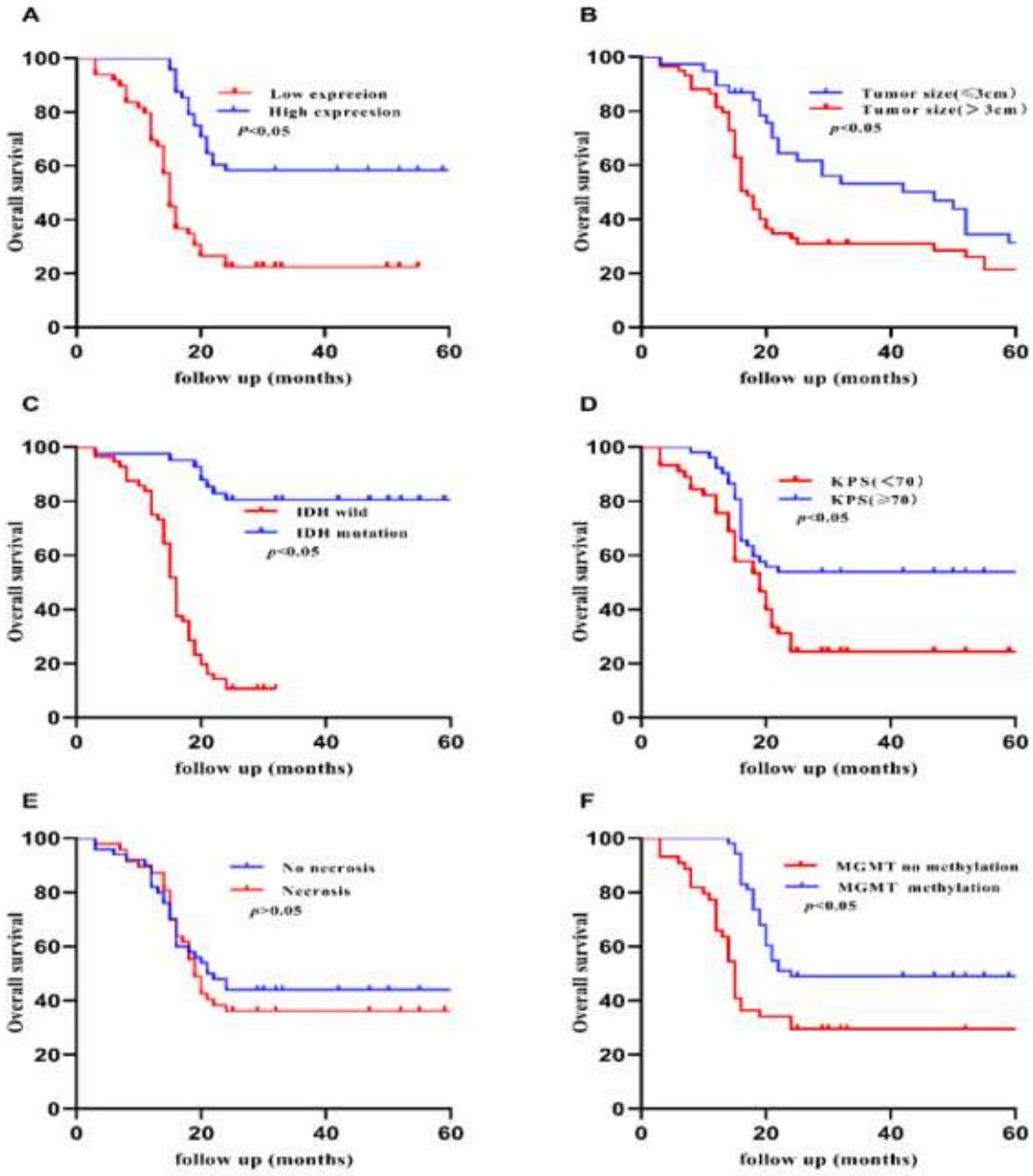
Characteristic	Case percentage	miRNA-217 expression	R_s	*p*-
		Low (n=49)	High (n=48)	
Age(years)				0.580
≤45	36.1%	38.8%	33.3%	
>45	63.9%	61.2%	66.7%	
Gender				0.480
Male	60.8%	61.2%	60.4%	
Female	39.2%	38.8%	39.6%	
umor size(cm)			0.25	0.019
≤3	39.2%	32.7%	45.8%	
>3	60.8%	67.3%	54.2%	
Necrosis				0.609
Yes	48.5%	51%	45.8%	
No	51.5%	49%	54.2%	
WHO grade			0.29	0.003
II	47.4%	32.7%	62.5%	
IV	52.6%	67.3%	37.5%	
IDH status			0.47	0.001
Wide type	57.7%	83.7%	31.3%	
mutation	42.3%	16.3%	68.7%	
MGMT status			0.44	0.001
No methylation	45.4%	69.4%	20.8%	
Methylation	54.6%	30.6%	79.2%	
KPS score			0.32	0.001
< 70	46.4%	63.3%	29.2%	
≧70	53.6%	36.7%	70.8%	

Table I: Relation of miRNA-217 expression level to clinicopathological parameters

Univariate and multivariate analyses were utilized to evaluate the association of OS with various clinic pathological features including miRNA-217 expression level.

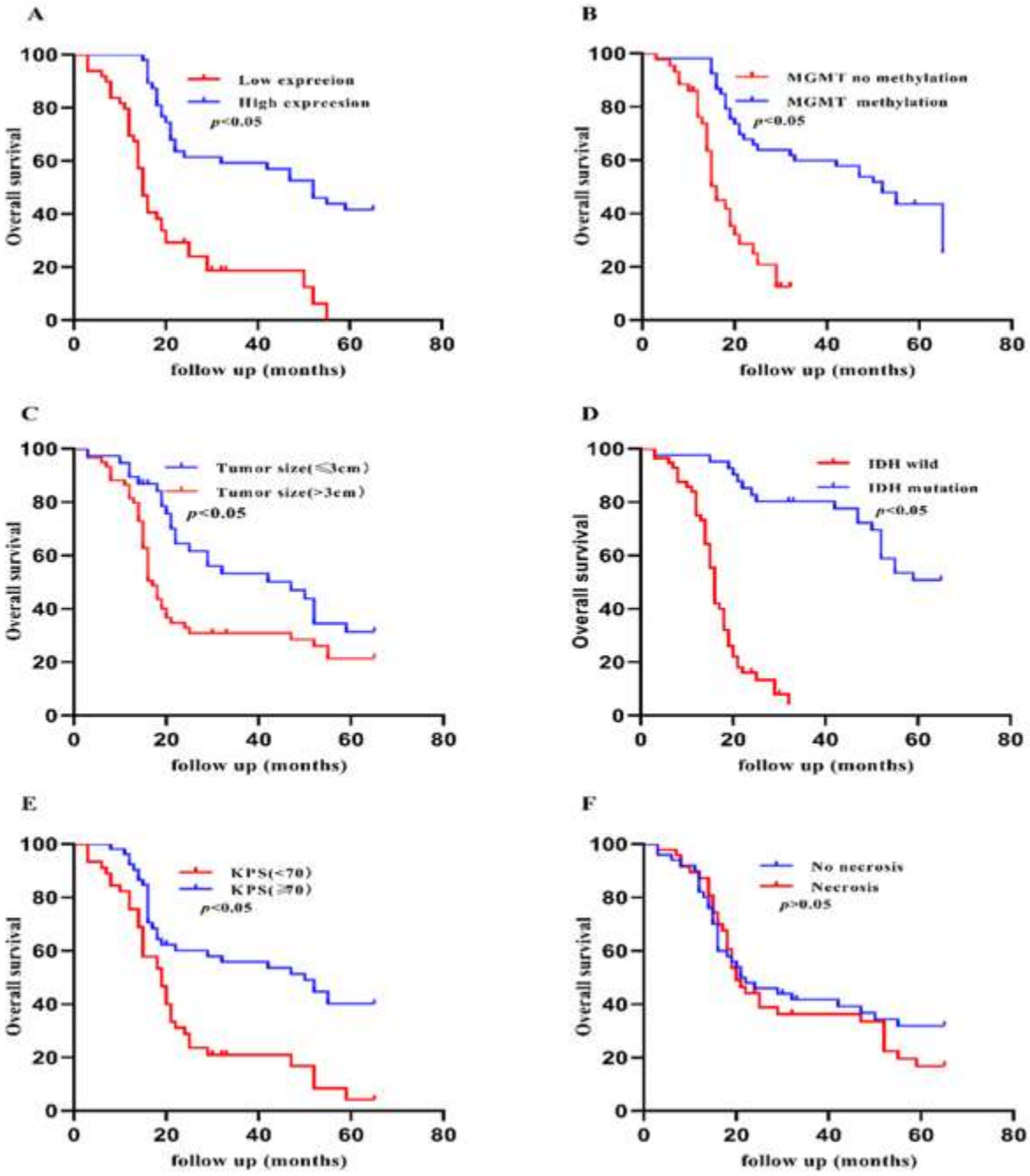
Kaplan-Meier method indicated that the two-year and five-year OS of patients was significantly shorter in patients with miRNA-217 low expression than in those with high miRNA-217 expression (p<0.01). The

OS was significantly longer with small tumor size(≦3cm) compared to those with large tumor size (>3cm) (p<0.01). The OS was significantly shorter in patients with IDH wild type than in those with IDH mutation (p=0.01). The OS was significantly shorter in patients with low KPS than in those with high KPS (p<0.01), The OS was significantly shorter in patients with MGMT no methylation than in those with MGMT methylation (p<0.01) (Figure 1 and Figure 2).



A: miRNA-217 lower expression patients showed worse OS compared with those of higher expression (p=0.001),B: Patients of larger tumor size(>3cm) showed worse OS compared with those of small tumor size(≦3cm)(p=0.002), C:Patients of IDH wild showed worse OS compared with those of IDH mutation (p=0.001),D: Patients of KPS scores(<70) showed worse OS compared with those of KPS scores(≧70)(p=0.008),E: Patients with necrosis showed no significantly differences compared with those with no necrosis (p=0.560),F: Patients with MGMT no methylations showed worse OS compared with those with methylation(p=0.001).

Figure 1: Kaplan-Meier 2-year OS curves of patients with glioma according to clinicopathological features



A: miRNA-217 lower expression patients showed worse OS compared with those of higher expression (p=0.001),B: Patients with MGMT no methylations showed worse OS compared with those with methylation(p=0.001).C:Patients of larger tumor size(>3cm) showed worse OS compared with those of small tumor size(≦3cm)(p=0.02), D:Patients of IDH wild showed worse OS compared with those of IDH mutation (p=0.001),E:Patients of KPS scores(<70) showed worse OS compared with those of KPS scores(≧70)(p=0.001),F: Patients with necrosis showed no significantly differences compared with those with no necrosis (p=0.420).

Figure 2: Kaplan-Meier 5-year OS curves of patients with glioma according to clinicopathological features

As for multivariate cox regression analysis including miRNA- 217 expression, tumor size, IDH status and MGMT status, we found a two-year OS advantage of the high expression vs low expression of miRNA-217 (HR 2.07, 95%CI:1.09-3.91,p=0.026), IDH mutation vs IDH wild type (HR 0.12, 95% CI: 0.05-0.28, p=0.001), large tumor size vs small tumor size (HR 2.44,95%CI: 1.33-4.49, p=0.004), and MGMT methylation vs MGMT no methylation (HR 0.52,95%CI:0.28-0.97, p=0.040) respectively (Table II).

Parameter	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (≦45/>45)	0.72	0.43-1.21	0.213			
Sex (male/femal)	0.69	0.41-1.16	0.16			
Tumor size (≦3cm/>3cm)	2.59	1.43-4.67	0.002	2.44	1.33-4.49	0.004
Necrosis (yes/no)	1.16	0.69-1.95	0.56			
KPS score (<70/≧70)	0.49	0.29-0.83	0.008			
miRNA-217 expression (low/high)	0.26	0.15-0.44	0.001	2.07	1.09-3.91	0.026
IDH status (wide/mutation)	0.09	0.04-0.19	0.001	0.12	0.05-0.28	0.001
MGMT status (no methylation/ methylation	1.90	1.17-3.09	0.001	0.52	0.28-0.97	0.040

Table II: Univariate and multivariate analyses of 2-year OS

Discussion

Several studies reported that miR-217 could be regarded as a potential cancer suppressor. Bo Yu[16]et al found that TCF7L2 increased cell viability, migration and invasion in the colorectal neoplasia cells, however, miRNA-217 could negatively regulate TCF7L2 expression by targeting the transcription factor 7-like 2 (TCF7L2), due to the vital role of TCF7L2 gene in the Wnt/**β**-catenin signaling pathway. Moreover, through targeting Runx2,miR-217 suppressed cell proliferation and invasion in human glioma[12]. miR-217 inhibits proliferation, migration, and invasion in esophageal squamous cell carcinoma[17] by silencing long noncoding RNA MALAT1.

In this study, we focused on the role of miR-217 in glioma, miR-217 expression levels in glioblastoma were significantly decreased compared to the grade II Astro cytomas. Subsequently, Down-regulation of miRNA-217 was significantly related with high grade glioma, large tumor size, MGMT no methylation, IDH wild and lower KPS, our study reported shorter OS in patients with miRNA-217 lower expression, and a significant difference was noted in 2-year and 5-year OS in both groups.

Multivariate analysis revealed that tumor size, IDH status, MGMT methylation status and miRNA-217 expression level were independent prognositic factors for 2-year OS. The hazard ratio in low miRNA-217 expression group was 2.07 times more than high expression group. miRNA-217 expression was independently related with the OS, indicating that low miRNA-217 expression level was an indicator for poor prognosis of patients.

To date, various biological markers have been reported in glioma[18, 19].IDH mutation was found in both low-grade glioma and glioblastoma in our study, suggesting IDH played an important role in the pathogenesis of tumor in glioma. The mutation rate was 15.6%, which was practically in consistent with that reported in the literature[20].The multivariate analysis revealed that the patients of IDH mutation were closely associated with better prognosis, as compared with those of IDH wild.

Previous studies have reported that IDH mutations have been identified as one of the most important diagnostic and prognostic factors of gliomas[21]. Due to intra-group heterogeneity, we need more additional prognostic factors to subdivide the prognosis result in gliomas. There was correlation between IDH status and miRNA-217 expression level, therefore, we would combine IDH status and miRNA- 217 expression to further refine the stratified study and better judge the prognosis in the future study.

Currently, MGMT methylation is a widely accepted biomarker in glioblastoma, which can predict the effect of chemotherapeutic drugs[22]. Patients with MGMT methylation showed a better prognosis than those no methylation.

Patients of KPS (<70) showed worse OS compared with those of KPS (≧70) in 2-year and 5-year OS. We analysed the reasons why the low KPS patients showed poor OS. Patients with the low KPS were mainly those with GBM, who had poor quality of life. Secondly, some patients in the high KPS who underwent standard therapies including concomitant radiotherapy with temozolomide (TMZ), and adjuvant TMZ after surgery. Early rehabilitation exercise was performed in some patients with high KPS.

Old patients (≧45 years) showed worse prognosis compared with those young patients (<45 years) [23]. In this study, old patients showed no significantly differences compared to those young in 2-year and 5-year OS. Since, the proportion of high- grade gliomas in the lower age group was relatively high.

In this study, Patients of larger tumor size(>3cm) displayed worse OS compared to those of small tumor size(≦3cm) in 2-year and 5-year OS. The rate of glioblastoma in the larger tumor size patients was 69.5%, which was apparently higher than 26.3% in the small tumor size patients.

Moreover, the sample size of data was relatively small. Some patients were reluctant to attend follow-up appointments, or the follow-up was

interrupted in our study. We will increase the sample size for detailed study in the future.

miRNA-217 could be a potential prognostic factor and therapeutic target for patients with glioma. The underlying molecular mechanisms of miRNA-217 involvement in the Wnt/β-catenin signaling pathway needs to be investigated in future studies.

Conclusions

miRNA-217 could be a potential prognostic factor in addition to a therapeutic target for glioma patients. Further studies are needed to investigate the molecular mechanisms underlying miRNA-217 involvement in the Wnt/β-catenin signaling pathway in future studies.

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