Prognostic Potential of MicroRNAs in Glioma Patients: A Meta-Analysis

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Abstract

Introduction  MicroRNAs are a noncoding RNA involved in affecting several transcription and translation pathways. Their use has been discussed as potential predictors of several tumors. Their use as potential biomarker in glioma patients is still controversial. The purpose of this meta-analysis is to explore the possible role of such microRNAs in glioma patients.

Methods  After an extensive literature search done on PubMed and Embase, 20 studies were chosen for our analyses with the 9 discussing 11 tumor promoting microRNAs and 11 studies discussing 11 tumor suppressing microRNAs. The data needed was extracted from these studies including the hazard ratio that was used as the effect size for the purpose of our analysis. The needed analysis was performed using Stata and Excel.

Results  The pooled hazard ratio for our analysis with patients having a lower microRNA expression for tumor promoting microRNAs came to be 2.63 ($p < 0.001$), while the hazard ratio for patients with higher expression of tumor promoting microRNA was 2.47 ($p < 0.001$) with both results being statistically significant. However, as significant heterogeneity was observed a random effect model for analysis was used. Subgroup analysis was further performed using grade, cutoff value (mean or median), sample type (Serum or Blood), and Karnofsky performance score, all of them showing a high hazard ratio.

Conclusion  Our results showed that both tumor inhibitory and promoting microRNA can be used as prognostic tool in glioma patients with a poorer prognosis associated with a lower expression in tumor suppressive and higher expression in tumor promoting microRNA, respectively. However, to support this, future studies on a much larger scale would be needed.

Keywords
► glioma
► microRNA

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Introduction

Gliomas comprise a diverse group of central nervous system (CNS) tumors characterized by a pervasive heterogeneity, particularly in terms of their molecular and histological features, as well as their clinical course. Regarded as the most frequent primary neoplasm of the brain and spinal cord, gliomas account for 31% of all CNS tumors, and 81% of malignant CNS tumors within the United States, with men having a greater predisposition to developing these lesions. Traditionally, these tumors have been subdivided according to their semblance to normal glial cells into either astrocytoma, oligodendroglioma, or ependymoma. Since 2007, these lesions were further classified histologically according to morphological features identified on microscopy such as necrosis, mitotic activity, and microvascular proliferation, into grades I through IV as per the 2007 World Health Organization guidelines. Grades I and II are collectively referred to as low-grade gliomas, while grades III and IV are termed as high-grade gliomas.

Recent advances in molecular analytics have facilitated substantial investigation and discovery of genetic, epigenetic, and molecular profiles of these lesions, precipitating the shift from morphological to molecular diagnosis. This paradigm shift was marked in 2016 when the WHO published revised tumor classification guidelines incorporating these genomic characteristics within the diagnostic criteria.

These advancements in molecular profiling have also yielded a more detailed understanding of various oncogenic and tumor-suppressor proteins. Of particular interest among these are the microRNAs and the role they play in tumor progression and suppression as well as their potential use as prognostic indicators and biomarkers.

MicroRNAs are a class of small noncoding RNAs with most being transcribed from DNA sequences. They play an important role in regulating gene expressions by the pathway affecting the 3’ untranslated region of their target mRNA causing its degradation and translation repression. Although not involved directly in protein coding, they can play a role in tumor pathogenesis. Several studies have been conducted to evaluate various microRNA as a prognostic tool, with several these being overexpressed and underexpressed in tumors implying that different microRNA might either promote or suppress tumor suppression, and although still controversial, the possibility of alteration in microRNA expression for cancer treatment has also been discussed.

A meta-analysis done by Li et al. at prognostic role of microRNA-21 and its role in glioma promotion. Several recent studies conducted also highlight microRNAs that play a suppressive role in tumor progression and are downregulated in gliomas especially in those with poorer prognosis; these studies also look at potential role of such microRNA as potential biomarkers for tumor prognosis as well as an option for targeted therapy. Despite all these studies, the prognostic as well as therapeutic role of microRNA with both tumor suppressive and promoter role still remains controversial and studies on it still show inconclusive results.

The aim of our study was to do a meta-analysis of such microRNAs to assess their prognostic and therapeutic value. To our knowledge, an analysis of similar nature has not been conducted before.

Materials and Methods

Search Strategy

The guidelines from meta-analysis for observational studies in epidemiology group (MOOSE) were used to carry out the meta-analysis. For the purpose of this study, literature search was done on PubMed and Embase from January, 2000 till December, 2020. Both Mesh command and simple Boolean terms were used for the literature search; the Mesh term was (“MicroRNAs”[Mesh] AND (“Glioma”[Mesh] OR “GBM”[Mesh] OR “Glioblastoma”[Mesh])) and the simple Boolean terms were “MicroRNA,” “Glioma,” and “Glioblastoma.” For this analysis, only published studies were taken into consideration with the criteria being (a) studies in English, (b) studies on glioma and glioblastoma patients, (c) studies focusing on microRNA with either a tumor suppressing or inhibiting role or microRNA with tumor promoting action. Studies were excluded if they did not match this criterion or if they were (1) reviews or letters, (2) did not include any measurement for survival of patients, (3) had overlapping, duplicate, or insufficient data for the purpose of our analysis.

Quality Assessment

For the purpose of ensuring quality of the studies included in our analysis, a reviewer assessed the studies in accordance with critical review checklist of the Dutch Cochrane Centre proposed by MOOSE the checklist included (1) study population size, (2) type of carcinoma, (3) study design, (4) outcome assessment, (5) sufficient follow-up time, (6) microRNA being studied, (7) method to check microRNA level, and (8) microRNA cutoff value. A study was excluded from our analysis if it failed to provide anyone of the information listed above as to not compromise the validity of our meta-analysis. All the values were double checked by another reviewer to make sure no error occurred during the analysis.

Data Extraction

Data were extracted by a reviewer and then double checked by another reviewer to rule out any discrepancy or errors. The data extracted from the selected studies was as follows: the first author, year of publication, tumor and sample type, grade of tumor, sample size, duration of follow-up, microRNA being studied, method of testing microRNA, cutoff value for the microRNA, hazard ratio (HR) of microRNA as well as the 95% confidence interval and the p-value. In cases where the HR was not provided but the survival was given in terms of Kaplan–Meier survival curve or an appropriate summary statistic, the HR and its associated 95% confidence interval were calculated using the method described by Tierney et al.

Statistical Analysis

For the purpose of our study, a fixed-effect model (Cochran-Mantel-Haenszel method) or the random effect model
(DerSimonian–Laird method) was under consideration in accordance with the heterogeneity of the studies included. Using the hazard risks pooled from our studies and standard error for the HR calculated using the 95% confidence interval, the heterogeneity was verified using Higgins $I^2$ statistic; in cases of heterogeneity being significant with $p < 0.1$ or $I^2 > 50\%$, a random effect model was used for our analysis. If not, then a fixed effect model was utilized. To minimize the influence of heterogeneity, the included studies were further subdivided to carry out subgroup analysis with studies having similar characteristics. To estimate publication bias in our study, Begg's and Egger's tests were performed using funnel plot with log of HR and standard error. In our study, $p$-values were calculated using a two-tailed test with $p$-value $< 0.05$ being statistically significant. To carry out all the statistical analysis, Stata16 (StataCorp LP, College Station, Texas, United States) software and Microsoft Excel (V.2010, Microsoft Corporation, Redmond, Washington, United States) program were used.

**Results**

**Study Characteristics**

A thorough and extensive literature search was performed by the method described in search strategy with 1082 studies being found to be of a potential interest. After the filtration and quality assessment steps mentioned in ► Fig. 1, a total of 20 articles were selected to be included in our meta-analysis. These studies included a total of 2262 patients with their prognosis and survival being compared with the level of microRNA. Out of these 20 studies, 9 were done on 11 microRNAs with tumor promoting action, while 11 of the articles were on 11 microRNA with a tumor suppressive action.

**Correlation between Overall Survival and Expression of Tumor Promoting MicroRNA in Glioma**

Random effect model was chosen for the analysis of the 11 tumor promoting microRNAs that have been shown in ► Table 1.\textsuperscript{11–19} The reason for this was the significant heterogeneity among our selected variable ($I^2 = 0.00\%$). The pooled HR for the overall survival and higher microRNA level was found to be 2.47 (95% CI = 1.98–2.96) as seen in ► Fig. 2, which shows the forest plot for our analysis. After performing a sensitivity analysis, it was seen that none of the included studies caused a significant alteration in the HR when removed.

Further subgroup analysis was performed to compare pooled HR of each subgroup.

**Subgroup Analysis**

Subgroup analysis was as shown in ► Table 2. The studies were divided according to the tumor grade selected for the study, the cutoff value used, and the sample type selected for the study. In all the studies, it was seen that a higher microRNA level was associated with a higher WHO tumor grading in the studies that focused on grade I to IV (HR = 2.31; CI = 1.98–2.64) as well as those focusing on grade IV (HR = 2.82; CI = 2.35–3.29). The overall survival had a significant correlation with higher microRNA expression in both cases when the cutoff was taken as mean (HR = 2.53; CI = 2.41–2.64) or as median (HR = 3.21; CI: 2.80–3.62). Similar results for overall survival and high microRNA expression were found when the sample was collected from serum (HR = 2.52; CI = 2.11–2.93) or by tissue biopsy (HR = 2.61; CI = 2.21–3.01). The expression level of these microRNA was found to be high in patients with low Karnofsky performance score (KPS) as compared with those with a higher KPS (HR = 5.63; CI = –3.12–14.38).

**Publication Bias**

Publication bias in our study was assessed using the funnel plot analysis. As seen by ► Fig. 3, no significant publication bias was observed. Furthermore, the $p$-value for Egger’s test was found to be 0.134 and for Begg’s test, it was found to be 0.178 showing that there was no publication bias in our analysis.

**Correlation between Overall Survival and Expression of Tumor Suppressive MicroRNA in Glioma**

The 11 studies selected for the purpose of this study\textsuperscript{20–30} as seen in ► Table 3 underwent random effect model for the overall survival analysis. This was due to significant heterogeneity being observed in the selected studies ($p < 0.05$, $I^2 = 85.9\%$). After carrying out the analysis, it was found that pooled HR for the overall survival and lower microRNA levels for our selected microRNA was 2.63 (95% CI = 2.44–2.81, $p < 0.01$). This can be seen in ► Fig. 4, showing forest plot for our analysis. Furthermore, a sensitivity analysis was performed to see if any study had a significant influence on our pooled HR. However, no significant alteration could be observed in the pooled HR following exclusion of each study. This showed that no particular study had a greater influence for the purpose of our analysis.

Since significant heterogeneity was observed in our selected studies, subgroup analysis was performed to compare the pooled HR of each subgroup.
Table 4 provides a summary of the subgroup analysis performed. As all these studies were done on Asian population and none on non-Asian population could be found that would fit our criteria for study selection, the difference in overall survival in different populations could not be calculated. Furthermore, the changes in microRNA expression in patients undergoing different therapies could not be observed as the selected studies did not mention it.

Publication Bias
Publication bias in our study was assessed using the funnel plot analysis. As seen by Fig. 5, no significant publication bias was observed. Furthermore, the p-value for Egger’s test was found to be 0.194 and for Begg’s test, it was found to be...
Table 1  Characteristics of studies selected for the meta-analysis for tumor promoting microRNA

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Disease stage</th>
<th>Sample type</th>
<th>MicroRNA</th>
<th>Method</th>
<th>Sample size</th>
<th>Cutoff</th>
<th>Survival analysis</th>
<th>Follow-up (months)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al¹¹</td>
<td>2012</td>
<td>I–IV</td>
<td>Tissue</td>
<td>MicroRNA 17</td>
<td>qRT-PCR</td>
<td>108</td>
<td>Mean</td>
<td>OS</td>
<td>60</td>
<td>5.1</td>
</tr>
<tr>
<td>Jiang et al¹²</td>
<td>2012</td>
<td>I–IV</td>
<td>Tissue</td>
<td>MicroRNA 335</td>
<td>qRT-PCR</td>
<td>166</td>
<td>Mean</td>
<td>OS</td>
<td>24</td>
<td>3.89</td>
</tr>
<tr>
<td>Guan et al¹³</td>
<td>2010</td>
<td>IV</td>
<td>Tissue</td>
<td>MicroRNA 196</td>
<td>qRT-PCR</td>
<td>39</td>
<td>Median</td>
<td>OS</td>
<td>24</td>
<td>3.37</td>
</tr>
<tr>
<td>Jiang et al¹⁴</td>
<td>2010</td>
<td>I–IV</td>
<td>Tissue</td>
<td>MicroRNA 182</td>
<td>qRT-PCR</td>
<td>253</td>
<td>Median</td>
<td>OS</td>
<td>60</td>
<td>3.1</td>
</tr>
<tr>
<td>Zhang et al¹⁵</td>
<td>2016</td>
<td>I–IV</td>
<td>Tissue</td>
<td>MicroRNA 10b</td>
<td>qRT-PCR</td>
<td>128</td>
<td>Median</td>
<td>OS</td>
<td>60</td>
<td>3.28</td>
</tr>
<tr>
<td>Sun et al¹⁶</td>
<td>2016</td>
<td>I–IV</td>
<td>Tissue</td>
<td>MicroRNA 429</td>
<td>qRT-PCR</td>
<td>92</td>
<td>Mean</td>
<td>OS</td>
<td>72</td>
<td>3.67</td>
</tr>
<tr>
<td>Lai et al¹⁷</td>
<td>2015</td>
<td>I–IV</td>
<td>Serum</td>
<td>MicroRNA 210</td>
<td>qRT-PCR</td>
<td>136</td>
<td>Median</td>
<td>OS</td>
<td>60</td>
<td>3.84</td>
</tr>
<tr>
<td>Wang et al¹⁸</td>
<td>2017</td>
<td>IV</td>
<td>Serum</td>
<td>MicroRNA 451a</td>
<td>qRT-PCR</td>
<td>48</td>
<td>Mean</td>
<td>OS</td>
<td>44</td>
<td>1.37</td>
</tr>
<tr>
<td>Li et al¹⁹</td>
<td>2014</td>
<td>I–IV</td>
<td>Tissue</td>
<td>MicroRNA 125b</td>
<td>qRT-PCR</td>
<td>45</td>
<td>Mean</td>
<td>OS</td>
<td>36</td>
<td>2.43</td>
</tr>
<tr>
<td>Li et al¹⁹</td>
<td>2014</td>
<td>I–IV</td>
<td>Tissue</td>
<td>MicroRNA 221</td>
<td>qRT-PCR</td>
<td>45</td>
<td>Mean</td>
<td>OS</td>
<td>36</td>
<td>2.18</td>
</tr>
<tr>
<td>Li et al¹⁹</td>
<td>2014</td>
<td>I–IV</td>
<td>Tissue</td>
<td>MicroRNA 222</td>
<td>qRT-PCR</td>
<td>45</td>
<td>Mean</td>
<td>OS</td>
<td>36</td>
<td>2.13</td>
</tr>
</tbody>
</table>

Abbreviations: OS, overall survival; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

Fig. 2  Forest plot showing microRNA expression of tumor promoting microRNA and overall survival in glioma patients. CI, confidence interval.
0.206 showing that there was no publication bias in our analysis.

### Discussion

The microRNA included in our studies not only affect the progression of glioma but of various other tumors throughout the body with their effects not only being limited to the brain. This suggests the possibility of their application in prognosis and management of a large number of tumors. Several studies have been performed discussing their role in different tumors. A summary of the mechanism of different microRNA and the tumors they affect is provided in Tables 5 and 6.

To our knowledge, this meta-analysis is the first systemic evaluation of the relationship between the levels of several tumor suppressive and promoting microRNA and the prognosis of patients with glioma. Although there have been

### Table 2 Summary of subgroup analysis for tumor promoting microRNA

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Model</th>
<th>Pooled HR (95% CI)</th>
<th>p-Value</th>
<th>Heterogeneity (I²), p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I–IV</td>
<td>7</td>
<td>928</td>
<td>Random</td>
<td>2.31 (1.98–2.64)</td>
<td>&lt;0.001</td>
<td>81.4%, &lt;0.001</td>
</tr>
<tr>
<td>Grade IV</td>
<td>2</td>
<td>87</td>
<td>Fixed</td>
<td>2.82 (2.35–3.29)</td>
<td>&lt;0.001</td>
<td>0.00%, 0.806</td>
</tr>
<tr>
<td>Cutoff value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5</td>
<td>459</td>
<td>Random</td>
<td>2.53 (2.41–2.64)</td>
<td>&lt;0.001</td>
<td>83.4%, &lt;0.001</td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>556</td>
<td>Fixed</td>
<td>3.21 (2.80–3.62)</td>
<td>&lt;0.001</td>
<td>0.00%, 0.842</td>
</tr>
<tr>
<td>Sample type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue</td>
<td>7</td>
<td>831</td>
<td>Random</td>
<td>2.61 (2.21–3.01)</td>
<td>&lt;0.001</td>
<td>79.6%, &lt;0.001</td>
</tr>
<tr>
<td>Serum</td>
<td>2</td>
<td>184</td>
<td>Fixed</td>
<td>2.52 (2.11–2.93)</td>
<td>&lt;0.001</td>
<td>0.00%, 0.821</td>
</tr>
<tr>
<td>KPS (70 &lt; vs. ≥ 70)</td>
<td>4</td>
<td>547</td>
<td>Random</td>
<td>5.63 (-3.12–14.38)</td>
<td>&lt;0.001</td>
<td>72.4%, &lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance score.
individual studies performed on the included microRNAs not only in glioma but also in tumors affecting other parts of the body as well, the prognostic potential of microRNAs in glioma is still unknown. Our study identified that a higher level of tumor promoting microRNA in a patient was predictive of poor survival ($HR = 2.47; 95\% CI = 1.98–2.96$). Similarly, it was seen that a lower level of tumor suppressive microRNA was also associated with a poorer survival ($HR = 2.63; 95\% CI = 2.44–2.81$, $p < 0.01$). Moreover, both tumor promoting and suppressing microRNA
were shown to have a strong association with the WHO grade of the tumor.

Recently several studies have proved that microRNA associated with tumor promoting role in one malignancy can be playing a tumor suppressive role in another. For example, microRNA 210 and 451a that despite being onco-genic in the case of glioma have shown to downregulate cancer cell in esophageal cancer and small cell carcinoma of the lung, respectively.\(^ {31,32}\) As seen in – Tables 5 and 6, all of these microRNAs are involved in pathogenesis of various tumors and thus it shows that their application as a prognostic tool would not only be limited to glioma.

Several studies have already discussed in detail how microRNA can be a prognostic tool for prediction of survival in various tumor. A meta-analysis done by Li et al showed the prognostic potential of microRNA 21 in glioma patients.\(^ {33}\)

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>Model</th>
<th>Pooled HR (95% CI)</th>
<th>(p)-Value</th>
<th>Heterogeneity (I(^2))</th>
<th>(p)-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I/II vs. III/IV</td>
<td>8</td>
<td>821</td>
<td>Random</td>
<td>3.1 (2.87–3.32)</td>
<td>0.021</td>
<td>78.6%, 0.019</td>
<td></td>
</tr>
<tr>
<td>Grade II vs. III/IV</td>
<td>3</td>
<td>426</td>
<td>Fixed</td>
<td>1.72 (1.40–2.03)</td>
<td>0.007</td>
<td>0.00%, 0.806</td>
<td></td>
</tr>
<tr>
<td>Cutoff value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7</td>
<td>699</td>
<td>Random</td>
<td>2.71 (2.41–2.93)</td>
<td>&lt;0.001</td>
<td>88.4%, &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>548</td>
<td>Fixed</td>
<td>2.44 (2.11–2.76)</td>
<td>&lt;0.001</td>
<td>0.00%, 0.714</td>
<td></td>
</tr>
<tr>
<td>Sample type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue</td>
<td>7</td>
<td>894</td>
<td>Random</td>
<td>2.91 (2.67–3.14)</td>
<td>&lt;0.001</td>
<td>82.7%, &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>4</td>
<td>353</td>
<td>Fixed</td>
<td>2.2 (1.91–2.49)</td>
<td>&lt;0.001</td>
<td>0.00%, 0.739</td>
<td></td>
</tr>
<tr>
<td>KPS (70 &lt; vs. ≥ 70)</td>
<td>5</td>
<td>561</td>
<td>Random</td>
<td>7.53 (-13.47–28.54)</td>
<td>&lt;0.001</td>
<td>65.3%, &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance score.

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**Table 4** Summary of subgroup analysis of tumor suppressive microRNA

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![Funnel plot with pseudo 95% confidence interval of tumor suppressive microRNA](image)

**Fig. 5** Funnel plot with pseudo 95% confidence interval of tumor suppressive microRNA. HR, hazard ratio.
### Table 5  The mechanism of action in tumor promoting microRNA

<table>
<thead>
<tr>
<th>MicroRNA</th>
<th>Other cancers</th>
<th>Mechanism of tumor promotion in glioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>MicroRNA 17</td>
<td>Breast cancer, lung cancer, gastric cancer, colon cancer</td>
<td>It has been found to target family of transcription factors like E2F and apoptotic proteins like BIM36–38</td>
</tr>
<tr>
<td>MicroRNA 335</td>
<td>Osteosarcoma, hepatocellular carcinoma, head and neck squamous cell carcinomas (HNSCC), renal cell carcinoma</td>
<td>It targets Rb1 signaling pathway resulting in loss of control over cell cycle arrest in G0/G1 phase39</td>
</tr>
<tr>
<td>MicroRNA 196</td>
<td>Cervical, ovarian, pancreatic, and esophageal cancer</td>
<td>It suppresses the expression of annexin A1 (a mediator of apoptosis) resulting in reduced apoptosis and rapid cell proliferation13</td>
</tr>
<tr>
<td>MicroRNA 182</td>
<td>Melanoma, papillary thyroid, and ovarian Cancer</td>
<td>It reduces the function of FBXW7, which acts to induce apoptosis in cells via ubiquitination mediated degradation40,41</td>
</tr>
<tr>
<td>MicroRNA 10b</td>
<td>Breast, hepatic, pancreatic, and esophageal cancer</td>
<td>The downstream target of Mir-10b is Sirt1, which acts on the PTEN/PI3K/AKT signaling pathway to enhances growth of tumors42</td>
</tr>
<tr>
<td>MicroRNA 429</td>
<td>Ovarian cancer</td>
<td>It targets c-myc and PLGG1 to exert its effects in several tumors43</td>
</tr>
<tr>
<td>MicroRNA 210</td>
<td>Tumor suppressor in esophageal cancer</td>
<td>MicroRNA 210 is known to target to FBXO31 and plays a role in epithelial mesenchymal transition and Wnt/β-catenin signaling31</td>
</tr>
<tr>
<td>MicroRNA 451a</td>
<td>Downregulated in small cell lung cancer and colon cancer</td>
<td>The upregulation of microRNA 451a can reduce the action of BAP31 by binding to its 5’UTR. This gene also has an inhibitory role in myogenesis by inhibiting the C2C12 differentiation.32,44</td>
</tr>
<tr>
<td>MicroRNA 125b</td>
<td>Glioma</td>
<td>It regulates p53 gene and downregulation of mRNA 125b activates p38MAPK apoptotic pathway45</td>
</tr>
<tr>
<td>MicroRNA 221/222</td>
<td>Glioma</td>
<td>In cells with 221/222 gene in effect the bcl-2 is downregulated, while, connexin43, p27, PUMA, caspase-3, PTEN, TIMP3 and Bax is up-regulated46</td>
</tr>
</tbody>
</table>

### Table 6  The mechanism of action in tumor suppressing microRNA

<table>
<thead>
<tr>
<th>MicroRNA</th>
<th>Other cancers</th>
<th>Mechanism of tumor suppression in glioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>MicroRNA-205</td>
<td>Lung cancer, ovarian cancer, bladder cancer, head and neck cancer</td>
<td>Suppresses epithelial–mesenchymal transition and inhibits tumor growth of human glioma through down-regulation of HOXD947,48</td>
</tr>
<tr>
<td>MicroRNA-107</td>
<td>Bladder cancer, gastric cancer</td>
<td>Acts via CDK6 signaling pathway and notch 2 modulation49</td>
</tr>
<tr>
<td>MicroRNA-199a-3p</td>
<td>Renal carcinoma, bladder cancer, hepatocellular carcinoma</td>
<td>Tumor suppression occurs via acting on the AKT/mTOR signaling pathway36,51</td>
</tr>
<tr>
<td>MicroRNA-218</td>
<td>cervical cancer, lung carcinoma, bladder cancer, gastric cancer</td>
<td>Negatively affect the migration and invasiveness of gliomas by targeting NF-kB52,53</td>
</tr>
<tr>
<td>MicroRNA-1231</td>
<td>Nonsmall cell lung cancer</td>
<td>Inhibits glioma progression both in vivo and in vitro by regulation of EGFR/PI3K/AKT pathway44</td>
</tr>
<tr>
<td>MicroRNA-211</td>
<td>Colorectal carcinoma, oral carcinoma, hepatocellular carcinoma, cervical cancer</td>
<td>It targets MMP9, activates the caspase-9/caspase-3 apoptotic cascade, and was found to be hyper methylated in GB55,56</td>
</tr>
<tr>
<td>MicroRNA-124</td>
<td>Head and neck cancer, breast cancer</td>
<td>Restrict the growth of glioma by targeting Smad457,58</td>
</tr>
<tr>
<td>MicroRNA-149</td>
<td>Nasopharyngeal carcinoma, melanoma, hepatocellular carcinoma, colorectal cancer, medullary carcinoma</td>
<td>Tumor suppression occurs by targeting capase-259–61</td>
</tr>
<tr>
<td>MicroRNA-34a</td>
<td>Hepatocellular carcinoma, prostate cancer</td>
<td>Targets c-Met and notch pathway62</td>
</tr>
<tr>
<td>MicroRNA-769–3p</td>
<td>Melanoma, colorectal cancer</td>
<td>Acts on Wnt/β-catenin pathway to inhibit the progression, migration, and invasion of cells53,64</td>
</tr>
</tbody>
</table>
Similarly, another meta-analysis discussed the role microRNA 34a could play in prognosis of gastric cancer.\textsuperscript{34} A review by Lee and Dutta not only discussed the prognostic role of microRNAs in tumor but also the possible role they could play in cancer therapy.\textsuperscript{35} In our meta-analysis, it was seen that both tumor suppressive and promoting microRNAs could be used as prognostic tools; moreover, in the subgroup analysis it was seen that the levels of microRNA obtained from both tumor biopsy and from serum had a clinically significant association with survival thus making liquid biopsy to predict tumor prognosis a possibility. Such a technique would be especially useful in less developed countries where performing a biopsy might not always be an option. It would also have an additional advantage of being less invasive and cheaper.

**Limitations**

At present, our study has some limitations, one of which is the heterogeneity in the results, which is mainly due to the small number of studies, the difference in microRNAs selected, and the variation in their cutoff value. As seen above, some of the studies used mean cutoff values while some used median. Due to these reasons, a random effect model was used in our analysis. Furthermore, the only studies that could be included in the analysis were done on Chinese patients so no comparison could be made with other ethnicities.

Due to a relatively small sample size of glioma patients, the statistical power of the association between microRNA level and glioma is reduced. Also, different microRNA being included with no standard cutoff value further contributes to bias and may deviate the pooled results from accurate findings. Furthermore, there is heterogeneity between overall survival analysis that can be associated with different stage of disease as well as different microRNAs were included; to counter this, future studies would be needed to study each individual microRNA in more detail.

Despite these limitations, the evidence above is sufficient to say with credibility that these microRNA do have possibility to be used as prognosis markers.

**Conclusion**

As evidenced by our analysis, it can be seen that all of our microRNAs selected could be used as potential biomarkers for glioma. However, still further studies are needed to explore their future applications. Prospective studies, which should be multicentric with a large sample size, would still be needed to confirm the validity of the results. Studies in clinical setting focusing on prognostic value of these microRNAs done on different population would further be needed. For now, it can be concluded that these microRNA do play a role in tumor pathogenesis and their expression level could be used as indicator of survival and disease prognosis.

**Availability of Data and Material**

Available.

**Ethics Approval**

This is a meta-analysis; so, no ethical approval or waiver was required.

**Consent to Participate**

The review does not involve human participants.

**Consent for Publication**

Not applicable.

**Authors’ Contributions**

AAL, MN, and SAE supervised and designed the study. ZAS was involved in manuscript writing, literature review, data collection, and data analysis. RA, DAK, and ASK contributed in manuscript writing, literature review, and data collection.

**Funding**

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**Conflict of Interests**

None.

**References**


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