Systematic Review

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Effect of PIMREG Expression on Prognosis in Glioma Patients: A Meta-Analysis

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Background: The phosphatidylinositol binding clathrin assembly protein interacting mitotic regulator (PIMREG) is highly expressed in osteosarcoma, cholangiocarcinoma, breast cancer, pancreatic cancer, and other cancer types, with its high expression being associated with poor cancer survival. At the same time, some studies have explored the association between PIMREG expression and glioma, but the results are controversial. Therefore, this study aimed to conduct a meta-analysis to systematically evaluate the effect of PIMREG expression on the prognosis of glioma patients.

Methods: The relevant literature published in English was accessed through various databases, including PubMed, Embase, Web of Science, and The Cochrane Library from September 2023. The research articles were screened based on the predetermined inclusion and exclusion criteria. The quality of the literature was assessed using the Newcastle-Ottawa Scale (NOS). Furthermore, hazard ratio (HR) and its corresponding 95% confidence interval (CI) for overall survival (OS) were either directly obtained from the original sources or derived from the Kaplan-Meier survival graphs using Engauge Digitizer 4.3. STATA 15.0 was selected for meta-analysis. Moreover, sensitivity analysis was performed to evaluate the stability of the included studies. Additionally, the Begg rank correlation method and Egger regression method were employed to evaluate the publication bias of the included literature.

Results: Following a thorough screening process, 6 research articles were included in this study. Meta-analysis results showed that patients with high PIMREG expression had poorer OS (HR = 2.77, 95% CI: 1.83–3.71). The subgroup analysis revealed that the HR of OS was 2.32 (95% CI: 1.59–3.06) in the Asian population and 3.12 (95% CI: 0.80–5.44) in the non-Asian population. In subgroups of tumor types, the HR for OS was 2.71 (95% CI: 1.88–3.54) for patients with glioma type and 2.60 (95% CI: 0.87–4.34) for those with glioblastoma type. Furthermore, sensitivity analysis revealed that the stability of the included studies was good. Begg and Egger tests showed that in the meta-analysis, publication bias of the included literature was not significant ($p = 0.630$).

Conclusion: The high expression of PIMREG is associated with poor prognosis of glioma patients, indicating its application as a potential prognostic indicator for these patients.

Keywords: glioma; high expression of PIMREG; prognosis; meta-analysis

Introduction

Glioma is the most common type of primary brain tumor, with a 5-year survival rate of lower than 10% [1]. Despite the current advancements in the treatment approaches for glioma, some patients experience tumor recurrence or metastasis after treatment, resulting in minimal improvement in their prognosis [2]. According to the World Health Organization (WHO), gliomas are classified into grades 1 to 4. However, grades 1 to 3 are designated as low-grade gliomas, while grade 4 is known as glioblastoma. Glioblastoma is characterized by its higher proliferation rate and aggressive nature [3]. Presently, the pathogenesis of glioma remains unclear, although studies suggest an association between the occurrence and development of glioma and both genetic and environmental factors [4,5]. Therefore, continued research on the identification of potential therapeutic targets for glioma holds immense significance in enhancing the prognosis of patients.

Phosphatidylinositol binding clathrin assembly protein interacting mitotic regulator (PIMREG), also known as regulator of chromosome segregation (RCS1), cathepsin S (CATS), and family with sequence similarity 64, member A (FAM64A), is a mitotic regulatory protein involving phosphatidylinositol binding clathrin assembly (PICALM) interaction. It is located on chromosome 17 at band P13, and serves as a marker for tumor cell proliferation [6]. PIM-

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

REG regulates cells by relying on cell periodicity, controlling the transition of mitotic cells from metaphase to the late stage [7,8]. Studies conducted by Jiang *et al*. [9], Zhang *et al*. [10], Yao *et al*. [11], and Jiao *et al*. [12]. showed significantly elevated expression of PIMREG in osteosarcoma, bile duct cancer, breast cancer, pancreatic cancer, and various other cancers, with its higher expression being associated with poor survival rate. Wei *et al*. [13] demonstrated that reduced expression levels of PIMREG could reverse the epithelial-to-mesenchymal transformation induced by transforming growth factor-β (TGF-β), accelerating the turnover of tight junction protein triggered by TGF-β, thereby reducing the mobility of glioblastoma cancer cells. Zhu *et al*. [14] indicated a negative correlation between the high expression levels of PIMREG and the survival rates of glioma patients. However, no studies have systematically evaluated whether the expression levels of PIMREG correlate with the survival time of glioma patients. Hence, this study conducted a meta-analysis to assess the impact of PIMREG expression on the survival of glioma patients, aiming to explore whether PIMREG could be a potential target for predicting poor prognosis in glioma patients.

Materials and Methods

Literature Search

All relevant research articles published in English language, from the establishment of PubMed, Embase, Web of Science, and The Cochrane Library databases up to September 2023, were reviewed for the following specific terms: ("Glioma" [Mesh] OR ((((((((((((((((((((Gliomas [All Fields]) OR Glial Cell Tumors [All Fields]) OR Glial Cell Tumor [All Fields]) OR Tumor, Glial Cell [All Fields]) OR Tumors, Glial Cell [All Fields]) OR Mixed Glioma [All Fields]) OR Glioma, Mixed [All Fields]) OR Gliomas, Mixed [All Fields]) OR Mixed Gliomas [All Fields]) OR Malignant Glioma [All Fields]) OR Glioma, Malignant [All Fields]) OR Gliomas, Malignant [All Fields]) OR Malignant Gliomas [All Fields]) OR glioblastoma [All Fields]) OR anaplastic astrocytoma [All Fields]) OR diffuse astrocytoma [All Fields]) OR anaplastic oligodendroglioma [All Fields]) OR oligodendroglioma [All Fields]))) AND (((((((PIMREG) OR (CATS protein)) OR (family with sequence similarity 64, member A protein, human)) OR (cathepsin S)) OR (PICALM interacting mitotic regulator protein, human)) OR (FAM64A)) OR (FLJ10491 protein, human))). After retrieval of the researcher's articles, they were manually screened to avoid excluding those that met the inclusion criteria.

Inclusion Criteria

The articles meeting the following criteria were included in this analysis: (1) The articles published only in English, (2) those reporting histopathologically confirmed glioma, and (3) the articles reporting the hazard ratio (HR) of PIMREG expression level to overall survival (OS) and their corresponding 95% confidence interval (CI), with Kaplan-Meier survival graphs provided in the data.

Exclusion Criteria

For these analyses, the exclusion criteria were set as follows: (1) Those with repetitive published data, (2) case reports, meeting minutes, clinical guidelines, experience sharing, reviews, etc., (3) those with no provided HR and their corresponding 95% CI, or Kaplan-Meier survival curve, and (4) the research articles involving animal experimentations.

Data Extraction and Quality Assessment

Data extraction and quality evaluation were conducted independently by two researchers. Each researcher reviewed these research articles and selected the literature according to the predetermined inclusion and exclusion criteria. If there is a conflict in the selected literature, the third researcher was assigned to determine whether to include it, or the two researchers would discuss the literature to decide on its inclusion.

The data extraction process included: the author's name, year of publication, type of cancer, number of patients, and OS data. The HR and the corresponding 95% CI for OS were directly obtained from the literature or achieved from the Kaplan-Meier survival curve through Engauge Digitizer 4.3. Furthermore, for assessing literature quality, the Newcastle-Ottawa Scale (NOS) [15] was employed, including 9 items across 3 aspects: representation of the exposed cohort, selection of the unexposed cohort, determination of exposure, absence of outcome of interest at baseline, adjustment for age and sex, adjustment for other potential confounding factors, outcome evaluation, sufficient duration of follow-up, and adequacy of cohort follow-up.

These research manuscripts were evaluated using categories of "unclear", "no", and "yes", where "yes" represents low-risk bias and "no" indicates high-risk bias. The total NOS score is 9, and if the score is >6, the included documents are considered high quality.

Statistical Methods

We utilized Stata 15.0 for meta-analysis. The heterogeneity among the data was analyzed using the χ^2 test. In the case of heterogeneity ($p < 0.1$, $I^2 \geq 50\%$), a random effects model was selected. However, in the case of no heterogeneity ($p \geq 0.1$, $I^2 < 50\%$), a fixed-effect model was selected. For the time variable of OS, HR was selected as the effect size, and its 95% CI was calculated. Additionally, the sources of heterogeneity were further explored through subgroup analysis. Moreover, sensitivity analysis was performed for the included literature. The Begg rank correlation and Egger regression methods were employed

Table 1. Basic features of the included literature.

Author	Year	Country	Number of patients	Cancer type	Outcome	HR evaluation sources	WHO pathological grades	Follow-up time	NOS
Fu M [16]	2023	China	767	glioma	OS	survivorship curve	II∼IV	200 months	6
Lyu W [17]	2020	China	675	glioblastoma	OS	survivorship curve	IV	200 months	7
Zhu H [14]	2022	China	676	glioma	OS	survivorship curve	II∼IV	200 months	7
Serafim RB [18]	2022	Brazil	660	glioblastoma	OS	survivorship curve	II∼IV	240 months	7
Zhu H [19]	2021	China	168	glioma	OS	survivorship curve	I∼IV	144 months	6
Flannery T [20]	2006	England	88	glioblastoma	OS	survivorship curve	I∼IV	30 months	8

Note: OS, overall survival; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; WHO, World Health Organization.

to evaluate the publication bias of the included literature. The threshold of the meta-analysis was set at $\alpha = 0.05$ and $p < 0.05$, indicating statistical significance in the comparative difference between the results of each study.

Results

Research Design

This meta-analysis follows the preferred reporting items for systematic review and meta-analysis (PRISMA) statements (See **Supplementary Material**).

Literature Screening Results

A total of 432 research articles were retrieved using various databases, including 82 accessed from PubMed (https://pubmed.ncbi.nlm.nih.gov/), 245 from Embase (https://www.embase.com/landing?status=grey), 6 from Web of Science (https://www.webofscience.com/wos/woscc/basic-search) and 99 from The Cochrane Library (https://www.cochranelibrary.com/), were excluded. The remaining 19 articles underwent the preliminary screening. After reading the full text, a total of 13 pieces of literature were excluded because their survival outcomes were unknown, or their observational indicators were not relevant to the analysis. Finally, only 6 pieces of literature, meeting the predetermined inclusion criteria, were included in this analysis. The flow chart of literature screening is shown in Fig. 1.

The six research papers were published between 2006 and September 2023, including four from China, one from Brazil, and one from the United Kingdom. Among them, there were 2 cases of glioma WHO grades I–IV, 3 cases of glioma WHO grades II-IV, and 1 case of glioma WHO grades IV. Furthermore, the NOS score was determined to evaluate the quality of the literature and was found higher than 6 points for all included articles (Table 1, Ref. [14,16–20]).

Relationship between PIMREG Expression and OS

The effect of PIMREG expression on the OS of patients was compared among all 6 included articles (Fig. 2). We observed that these six research articles exhibited a high heterogeneity ($I^2 = 67.0\%$, $p = 0.010$), rendering the selection of the random effects model. Furthermore, the meta-analysis revealed that high PIMREG expression would lead to shorter OS in patients (HR = 2.77, 95% CI: 1.83–3.71).

Subgroup Analysis

We investigated the relationship between PIMREG expression and the prognosis of OS in glioma patients using subgroup analysis based on the demography and tumor type. As shown in Fig. 3, the findings from the meta-analysis indicated that high expression of PIMREG in both the Asian population (HR = 2.32, 95% CI: 1.59–3.06) and the non-Asian population (HR = 3.12, 95% CI: 0.80–5.44) was associated with shortened OS ($p < 0.05$). Moreover, within subgroups of different tumor types, the expression of PIMREG in patients with tumor-type glioma (HR = 2.71, 95% CI: 1.88–3.54) and those with glioblastoma (HR = 2.60, 95% CI: 0.87–4.34) was correlated with OS ($p < 0.05$). The correlation between PIMREG expression and different tumor types is shown in Fig. 4.

Publication Bias and Sensitivity Analysis

The publication bias of the included studies was evaluated using the Begg and Egger tests. The p value obtained from the Begg and Egger tests was 0.630, which was greater than 0.05, suggesting the absence of publication bias within the included studies. The funnel diagram of publication bias is depicted in Fig. 5. Additionally, we conducted a sensitivity analysis of the impact of stability of PIMREG expression on OS. By deleting each independent study to assess the impact on the overall results, the findings from sensitivity analysis (HR = 2.83, 95% CI: 1.99–4.01) and the results of PIMREG expression on OS (HR = 2.77, 95% CI: 1.83–3.71) showed no significant difference, indicating the robustness of the meta-analysis outcomes (Fig. 6).

Discussion

In recent years, many studies have confirmed the role of PIMREG in the occurrence and development of various tumors, such as angiogenesis, tumor growth, and metastasis. It has been shown that PIMREG can interact with Breast cancer susceptibility gene 1 (*BRCA1*), cleavage

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

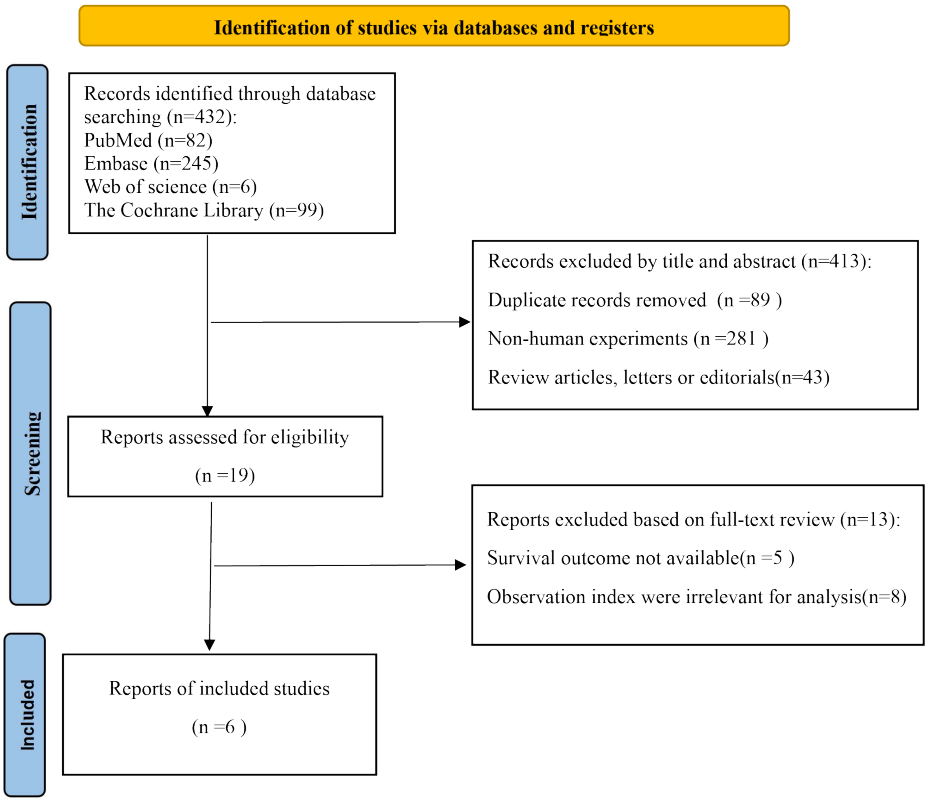

Fig. 1. PRISMA literature screening flow chart.

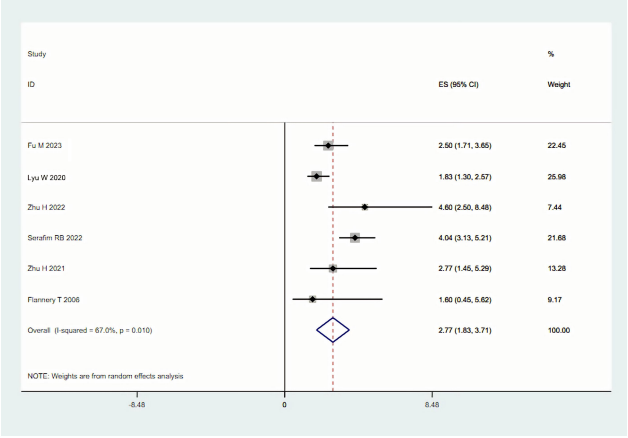

Fig. 2. The expression of PIMREG and the forest diagram of OS. ES, effect size; OS, overall survival; CI, confidence interval; PIMREG, phosphatidylinositol binding clathrin assembly protein interacting mitotic regulator.

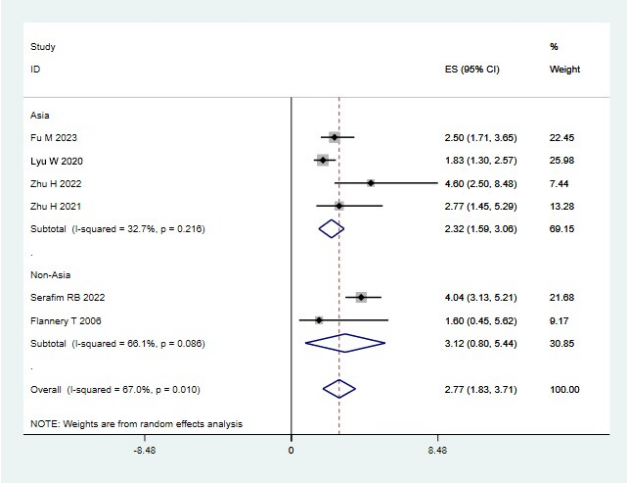

Fig. 3. Forest map of PIMREG expression and OS in patients of different ethnicities. ES, effect size; OS, overall survival; CI, confidence interval.

BRCA1 carboxyl terminal (BRCT) domain, accelerate the degradation of *BRCA1* mediated by ubiquitin, reduce the damage response of DNA and accelerate the repair defect activity, thus accelerating the progression of breast cancer [21]. Furthermore, the expression of PIMREG shows a significant association with the tumor stage in triple-negative breast cancer patients, with high expression of PIMREG in epithelial tissues correlated with improved prognosis of patients [22]. In prostate cancer, the PIMREG promoter can directly bind to dihydrotestosterone (DHT) through the androgen receptor (AR), thereby increasing the expression level of PIMREG. Consequently, this upregulation contributes to the elevated proliferation, invasion, migration, and cell cycle progression in androgen-dependent cell pop-

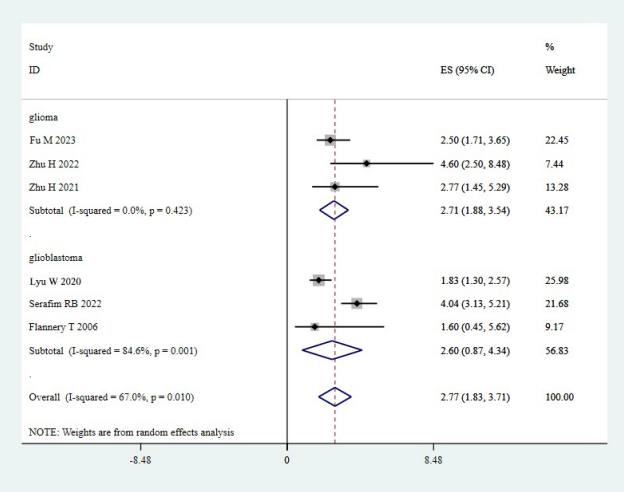

Fig. 4. Forest map of PIMREG expression and OS in patients with different tumor types. ES, effect size; OS, overall survival; CI, confidence interval.

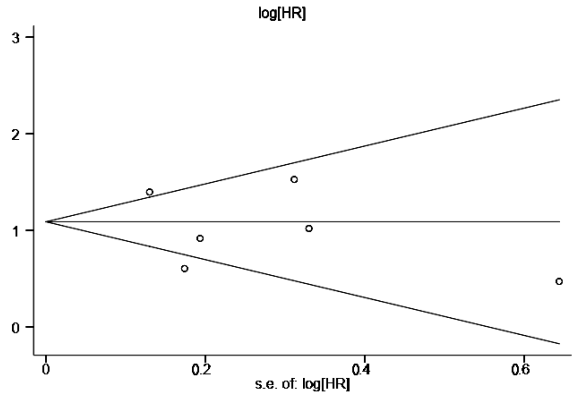

Fig. 5. Publication bias funnel plot for assessing OS. HR, hazard ratio.

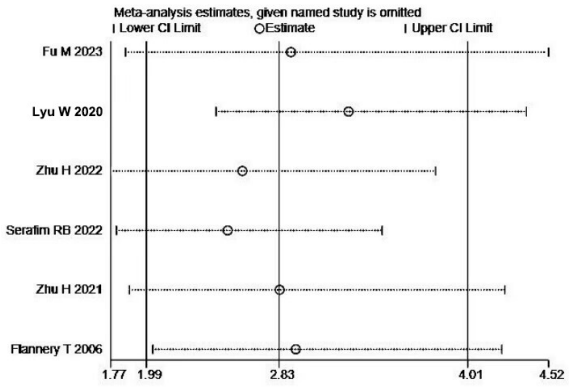

Fig. 6. Sensitivity analysis of PIMREG expression to OS. CI, confidence interval.

ulations during endocrine therapy. Meanwhile, the high expression of PIMREG inhibits the immune function of cells and disrupts the interferon signaling pathway, exhibiting a positive correlation with poor prognosis among prostate cancer patients [23]. Subsequently, Yao *et al*. [24] revealed that decreased expression of PIMREG reduces the proliferation, migration, and invasion capabilities of clear renal cell carcinoma, and inhibits the expression of cyclin D1, cyclin-dependent kinase 4 (CDK4), and CDK6. These findings highlight the role of PIMREG in the immune microenvironment of clear renal cell carcinoma. Moreover, these findings also suggest the potential of PIMREG as a prognostic factor in cancer patients. Additionally, a study conducted by Wang *et al*. [25] indicated that the high expression of PIMREG activates the β-catenin signaling pathway in glioma cells, increasing invasion and proliferation, thereby promoting the progression of glioma cells. Similarly, Fu *et al*. [16] reported that increased PIMREG expression in glioblastoma is indicative of poor prognosis for patients, while decreased expression of PIMREG leads to decreased cell proliferation and migration capabilities along with increased cell accumulation in the G2 / M phase. Furthermore, Zhu *et al*. [19] investigated the expression of PIMREG across various malignant tumors and its effect on patient prognosis. These outcomes demonstrated that in malignant tumors such as breast cancer, cholangiocarcinoma, and sarcoma, patients with high expression of PIMREG experienced shorter OS. In contrast, elevated PIMREG expression in glioma patients did not affect their OS. Therefore, in glioma patients, the adverse effects of PIMREG expression on patients' OS remain controversial. Therefore, this study aims to include eligible literature for meta-analysis to further explore the significance of PIMREG expression in determining the prognosis of glioma patients.

To our knowledge, this study is the first meta-analysis to investigate the effect of PIMREG expression on OS in glioma patients. Through literature screening, a total of 6 research investigations met the predetermined inclusion criteria and were selected for subsequent meta-analysis. The heterogeneity analysis of these 6 studies revealed higher heterogeneity (I^2 = 67.0%, p = 0.010), leading to the selection of a random model. Furthermore, the meta-analysis showed that elevated PIMREG expression would lead to shorter OS in patients (HR = 2.77, 95% CI: 1.83–3.71). Similarly, studies conducted by Lyu *et al*. [17] and Serafim *et al*. [18] substantiated that increased PIMREG expression would lead to poor prognosis of glioma patients, which aligns with the outcomes of our study, suggesting that elevated PIMREG expression might be a potential prognostic marker for glioma patients. Furthermore, in subgroup analysis, increased PIMREG expression indicated poor OS in both subgroups of ethnicity and tumor type, further supporting the potential of high PIMREG expression as a prognostic marker for glioma patients. Additionally, sensitivity analysis revealed that the findings of the meta-analysis were stable, and the funnel plot demonstrated minimal publication bias.

Journal of
BIOLOGICAL REGULATORS
and Homeostatic Agents

Despite certain encouraging findings, the limitation of this study should be acknowledged:

(1) In the six literatures included in this study, the prognostic HR and 95% CI were primarily derived from survival curve rather than directly reported in the literature, so the results may be biased to some extent.

(2) There is heterogeneity among the included studies. Despite using the random effects model in this study, complete elimination of the heterogeneity was not obtained due to incomplete data, potentially causing certain biases in the research findings.

(3) Positive results are more likely to be published compared to negative. This may exaggerate the relationship between high PIMREG expression and the prognosis of glioma patients.

(4) We included only literature published in English, which may have influenced the findings by excluding the data available in other languages.

(5) Finally, we included only 6 research articles in these analyses, indicating a small number of available studies on the subject. Therefore, additional large-scale, high-quality studies are needed to further elucidate the role of PIMREG in glioma patients.

Conclusion

In summary, the elevated PIMREG expression is associated with poor OS in glioma patients, indicating its application as a potential biomarker to determine the prognosis of glioma patients. However, due to certain limitations in this study, multi-center and high-quality studies on the correlation between PIMREG and the prognosis of glioma patients are needed in the future.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Author Contributions

TG and DJL designed the research study. QQZ, CYZ and ZXZ performed the research. HFC and XFP analyzed the data. TG and DJL draft the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.23812/j.biol.regul.homeost.agents.20243806.366.

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