AJNR

Effect of Piezo1 Overexpression on Peritumoral Brain Edema in Glioblastomas

S. Qu, T. Hu, O. Qiu, Y. Su, J. Gu and Z. Xia

AJNR Am J Neuroradiol 2020, 41 (8) 1423-1429
doi: https://doi.org/10.3174/ajnr.A6638
http://www.ajnr.org/content/41/8/1423

This information is current as of June 5, 2025.

Effect of Piezo1 Overexpression on Peritumoral Brain Edema in Glioblastomas

S. Qu, T. Hu, O. Qiu, Y. Su, J. Gu, and Z. Xia

ABSTRACT

BACKGROUND AND PURPOSE: Previous studies have suggested that increased mortality and disability in patients with brain tumor are associated with peritumoral brain edema. However, the mechanism of peritumoral brain edema in brain tumors is unknown. This study aimed to investigate the effect of Piezo1 overexpression on peritumoral brain edema in glioblastomas.

MATERIALS AND METHODS: The Piezo1 expression in cell lines and paired samples was detected by quantitative reverse transcription polymerase chain reaction, Western blot, and immunohistochemistry. Sixty-four patients with glioblastomas were analyzed retrospectively. The Piezo1 expression of tumor tissue was detected by immunohistochemistry. The diameters of tumor and edema were measured by preoperative MR imaging, and the edema index value was calculated.

RESULTS: Western blot and quantitative reverse transcription polymerase chain reaction showed that Piezo1 expression was higher in 6 glioma cell lines than in the normal astrocyte cell line. Compared with peritumoral tissues, Piezo1 was up-regulated in tumor tissues. Sixty-four patients with glioblastomas were enrolled in further study. Piezo1 was higher in the moderate edema group than in the mild edema group ($P < .001$), higher in the severe edema group than in the moderate edema group ($P < .001$), and correlated with the edema index ($r = 0.73$; $P < .001$). Receiver operating characteristic curve analysis showed that the edema index yielded an area under the curve of 0.867 (95% CI, 0.76–0.97; $P < .001$), with a sensitivity of 100% and a specificity of 70%.

CONCLUSIONS: Piezo1 overexpression is positively correlated with the degree of peritumoral brain edema in glioblastomas. Predicting high Piezo1 expression in tumor tissues based on the edema extent shows good sensitivity and specificity.

ABBREVIATIONS: EI = edema index; GBM = glioblastoma; IHC = immunohistochemistry; IRS = immunoreactivity score; PTBE = peritumoral brain edema; qRT-PCR = quantitative reverse transcription polymerase chain reaction; ROC = receiver operating characteristic; WHO = World Health Organization

Human glioma is the deadliest primary tumor of CNS cancers. The incidence of CNS tumors in America from 2011 to 2015 shows that gliomas account for 26% of all intracranial tumors and 81% of intracranial malignant tumors.[1] Gliomas are usually classified into 4 grades (World Health Organization [WHO] grades I–IV).[2] Among them, glioblastoma (GBM) is a very invasive tumor[3] and common cause of death. Even after standardized treatment, the survival rate of patients with GBMs is still very low. The median overall survival is approximately 15 months, and the 5-year survival rate is only 5.6%.[1,4] The poor prognosis of patients is related not only to age, pathologic features, the extent of resection, radiation therapy, chemotherapy, and targeted therapy but also to the extent of peritumoral brain edema (PTBE).[5,6] PTBE can result in many potential hazards, such as epilepsy, additional neurologic dysfunction, and an increase in intracranial pressure, which may cause cerebral herniation.[7,8] In addition, it can affect the exposure of tumors during an operation and increase the difficulty of surgical resection.[9] However, the mechanism of PTBE has not been fully clarified.

Piezo1 is a calcium ion (Ca^{2+}) permeable transmembrane ion channel protein that is activated by mechanical force and consists of 3 pore-forming units.[10] Friedrich et al[11] observed that deletion of Piezo1 in the lung tissue of mice could significantly decrease fluid exudation of lung tissue for the first time. More interesting, Chen et al[3] reported that compared with normal tissues, Piezo1 expression was up-regulated in gliomas on the basis of an analysis of The Cancer Genome Atlas data. Despite these discoveries,

Received March 18, 2020; accepted after revision May 1.

From the Department of Neurosurgery (S.Q., T.H., O.Q., Y.S., Z.X.), First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; and Department of Neurosurgery (J.G.), Cancer Center, Sun Yat-sen University, Guangzhou, China.

S. Qu, T. Hu and O. Qiu contributed equally to this study.

This work was supported by the National Natural Science Foundation of China (81971663) and the Science and Technology Program Key Project of Guangzhou (201604020004).

Please address correspondence to Zhibo Xia, MD, PhD, Department of Neurosurgery, First Affiliated Hospital, Sun Yat-sen University, 58 Zhongshan Rd II, Guangzhou 510080, China; e-mail: xiazhb@mail.sysu.edu.cn

Indicates open access to non-subscribers at www.ajnr.org

Indicates article with supplemental on-line appendix.

http://dx.doi.org/10.3174/ajnr.A6638

however, to date, the clinical relevance between Piezo1 overexpression and PTBE has not been documented.

Thus, we hypothesized that the extent of PTBE in patients with GBMs is correlated with Piezo1 overexpression in tumor tissues. Furthermore, we studied other relevant factors of PTBE.

MATERIALS AND METHODS

Cell Lines and Tumor Samples

A normal astrocyte line (HA1800) and human glioma cell lines (HS683, SW1783, U251, LN319, SNB19, and U373) were obtained. All human glioma cell lines and normal astrocyte lines were cultured in the same manner as reported previously.[12] All clinical samples were obtained from tumor tissue after surgical resection in our neurosurgery center.

Quantitative Reverse Transcription Polymerase Chain Reaction and Western Blot Analysis

We used quantitative reverse transcription polymerase chain reaction (qRT-PCR) and Western blot methods to evaluate the Piezo1 expression in clinical samples and cell lines. The detailed protocols of qRT-PCR and Western blot are specified in the On-line Appendix.

Inclusion and Exclusion Criteria of Patients

We initially collected patients with gliomas who underwent surgical resection in the first affiliated hospital of Sun Yat-sen University between January 2013 and December 2019. All included patients met the following inclusion criteria: pathologically confirmed to be primarily diagnosed with GBM; the tumor located above the tentorium of the cerebellum, not in the ventricle; and preoperative MR imaging and an enhancement examination performed. The exclusion criteria were as follows: tumors located under the tentorium of the cerebellum or in the ventricle; multiple tumors; no MR imaging or an enhanced examination; patients with recurrent gliomas; patients with gliomas with tumor hemorrhage; and patients with gliomas undergoing radiation therapy, chemotherapy, and other drug treatments for edema before an operation. This study received approval from the Medical Ethics Committee of our hospital. Each patient gave their written consent.

MR Imaging Examination and Edema Index Measurement

All patients underwent a preoperative brain 3T MR imaging scan and an enhancement examination. All MR imaging data were measured with a computer workstation. Tumor volume was measured with a preoperative MR imaging T1-enhanced TSE sequence. Briefly, the first step was to measure the GBM axial maximum diameter (A), the coronal maximum diameter (B), and the sagittal maximum diameter (C) in the MR imaging T1-enhanced TSE sequence (TR = 2000 ms; TE = 9 ms; section thickness = 6 mm; FOV = 230 × 187 mm; voxel size = 0.7 × 0.7 × 6.0 mm) of each patient. To reduce artificial bias, 1 senior neurosurgeon and 1 senior radiologist independently measured the scans of each patient. Additionally, the scans of the same patient was re-examined after an interval of 2 weeks by the same 2 physicians, and the average value was recorded.

The second step was to calculate the tumor volume. The formula used to calculate tumor volume was $V = 4/3\pi \times A/2 \times B/2 \times C/2$.[13] PTBE volume was measured with the T2-weighted and FLAIR TSE sequences (TR = 9000 ms; TE = 81 ms; section thickness = 6 mm; FOV = 230 × 200 mm; voxel size = 0.7 × 0.7 × 6.0 mm). Similarly, we measured the maximum diameter of tumor edema in the axial, coronal, and sagittal scanning images and calculated the edema volume. The edema index (EI) was used to evaluate the degree of PTBE. Next, we calculated the EI of each patient as follows: $EI = (V_{tumor+edema})/(V_{tumor})$. PTBE is usually classified by the EI value, which can be classified as follows: no edema (EI = 1), mild edema ($1 < EI \leq 1.5$), moderate edema ($1.5 < EI \leq 3$), and severe edema ($EI > 3$).[14]

Immunohistochemistry

All tumor tissues were examined by histopathology and immunohistochemistry (IHC) after surgical resection. The detailed IHC protocols of Piezo1, Ki-67, *isocitrate dehydrogenase* (*IDH1*), and p53 are specified in the On-line Appendix. The immunoreactivity score (IRS) is equal to the product of the staining intensity score and the positive staining tumor cell score. According to the IRS value, Piezo1 expression was divided into low ($IRS < 4$) and high ($IRS \geq 4$) expression.[12] The *IDH1* status was based on *IDH1* R132H staining, which was divided into positive reactions and negative reactions.[15] The p53 status was based on the nuclear staining cell rate. Specimens with nuclear staining cell rates of at least 10% were considered positive for p53, and those with <10% were considered negative for p53.[16]

Statistical Analysis

Statistical analysis was performed using statistical software (SPSS, Version 23; IBM). Because continuous data were not normally distributed, the Mann-Whitney *U* test was used for comparisons. For variables that did not conform to a normal distribution or for ordered classification variables, Spearman correlation analysis was performed. The correlation between binary variables was tested with the χ^2 test. The sensitivity, specificity, and accuracy of the EI for high Piezo1 expression was determined by receiver operating characteristic (ROC) analysis. The difference was statistically significant ($P < .05$ for a 2-tailed test). The Bonferroni correction was used to control the type I error rate for multiple testing.

RESULTS

Screening and Clinical Characteristics of Patients

We initially searched 325 patients with gliomas. After the exclusion of 205 patients with WHO grades I-III, the remaining 120 patients were further reviewed. Among them, 15 gliomas were located below the tentorium of the cerebellum, 9 gliomas involved the ventricle, 1 patient did not undergo a preoperative MR imaging examination, 27 patients had recurrent GBMs, and 4 patients with tumor hemorrhage were excluded. Finally, 64 patients with a primary diagnosis of GBM were enrolled. The Table shows characteristics of the included patients.

High Piezo1 Expression in Human Gliomas

To evaluate Piezo1 expression, we performed both qRT-PCR and Western blot in 7 cell lines. Both the messenger RNA and protein

The correlation between Piezo1 expression and clinicopathologic characteristics in 64 patients with glioblastomas

Characteristics	Cases (No.)	Expression of Piezo1		*P* Value
		Low[a] (No.)	High[b] (No.)	
Cases (No.)		20	44	–
Age (yr)				
60 or older	12	4	8	.86
Younger than 60	52	16	36	
Sex				
Male	36	12	24	.68
Female	28	8	20	
Peritumoral brain edema				
No edema	0	0	0	.00
Mild edema	9	9	0	
Moderate edema	16	5	11	
Severe edema	39	6	33	
Ki-67 index				
≥40%	42	10	32	.08
<40%	22	10	12	
IDH1 mutation				
No	50	16	34	.54
Yes	14	4	10	
p53 status				
Negative	27	7	20	.43
Positive	37	13	24	

Note:—indicates not applicable.
[a] "Low" means low Piezo1 expression.
[b] "High" means high Piezo1 expression.

levels of Piezo1 were increased in 6 glioma lines compared with the HA1800 line (Fig 1*A*). Next, 8 paired tumor samples were used for qRT-PCR, and 4 paired WHO grade I–IV tumor samples were used for the Western blot. Consistent with these findings, the results showed that the messenger RNA and protein levels of Piezo1 were also up-regulated in tumor tissues compared with peritumoral tissues (Fig 1*B*). Furthermore, IHC staining of the above 4 paired samples was separately performed on normal brain tissue ($n = 1$) and tumor tissue ($n = 4$, WHO grades I–IV). Compared with normal tissue, the cell staining intensity and Piezo1-positive cell rate of tumor tissues were higher and increased with the increase of the WHO grade (Fig 1*C*).

Piezo1 Expression in 64 Patients with GBMs

To identify the Piezo1 expression in GBMs, qRT-PCR and Western blot were conducted in the 14 paired GBM samples. qRT-PCR and Western blot results indicated that Piezo1 was highly expressed in tumor tissues compared with normal tissues (Fig 2). IHC was also performed on these 64 patients' paraffin-embedded slides. According to the IRS value, 64 patients were divided into a low Piezo1 group (20 patients) and a high Piezo1 group (44 patients). The Table shows the correlation between Piezo1 and clinicopathologic parameters. Piezo1 overexpression is only significantly related to PTBE.

PTBE Grading in 64 Patients with GBMs

According to the EI, we performed PTBE grading in 64 patients with GBMs.[17] The median EI was 4.09 (range, 1.06–12.02): 0 with no edema, 9 (14.1%) with mild edema, 16 (25.0%) with moderate edema, and 39 (60.9%) with severe edema.

Correlation between Piezo1 Overexpression and PTBE in 64 Patients with GBMs

Figure 3*A–I* shows the preoperative MR imaging of patients with different grades of edema and the corresponding Piezo1 immunohistochemical staining results. The higher the extent of edema, the higher was the expression of Piezo1. Furthermore, we analyzed the Piezo1 levels in different edema groups. The Piezo1 expression level in the moderate edema group was higher than that in the mild edema group ($P < .001$), and the expression level in the severe edema group was higher than that in moderate edema group ($P < .001$) (Fig 3*J*).

To explore whether there was a positive correlation between the Piezo1 levels and the EI, we performed a χ^2 test and a Spearman correlation analysis. First, we compared the number of patients with mild, moderate, and severe edema between the low and the high Piezo1 expression groups. A χ^2 test revealed that Piezo1 overexpression was significantly related to the grade of PTBE ($P < .001$). Second, compared with the low Piezo1 group, the EI of the high Piezo1 group was significantly higher ($P < .001$) (Fig 3*K*).

Next, by calculating the correlation coefficients, we observed a significant positive correlation between Piezo1 expression levels and the EI ($r = 0.73$; $P < .001$). Linear regression analysis was further performed. The correlation between Piezo1 expression levels and the EI was linear ($R^2 = 0.47$, $P < .001$) in the 64 patients (Fig 3*L*).

Correlation Analysis of Other Indexes

Furthermore, we also investigated other correlative factors related to the EI and Piezo1 expression by Spearman correlation analysis. We observed a positive correlation between the EI and Ki-67 ($r = 0.46$, $P < .001$). The EI was significantly different between patients with low (<40%) and high (≥40%) Ki-67 ($P = .002$). The correlation between Ki-67 expression and the EI was linear ($R^2 = 0.23$, $P < .001$).

Next, we further observed whether the Piezo1 overexpression was still positively correlated with PTBE in the Ki-67 subgroup. As shown in Fig 4, the results have not changed. However, Piezo1 was not significantly related to Ki-67 ($r = 0.22$, $P = .08$). Also, the EI and Piezo1 were not significantly related to age ($r = 0.24$, $P = .054$; $r = 0.20$, $P = .12$, respectively), sex ($r = 0.12$, $P = .33$; $r = 0.05$, $P = .69$, respectively), the *IDH1* status ($r = 0.06$, $P = .64$; $r = 0.03$, $P = .83$, respectively), or the p53 status ($r = -0.06$, $P = .65$; $r = 0.13$, $P = .31$, respectively).

ROC Analysis of the EI for High Piezo1 Expression

We assessed the predictive ability of PTBE for high Piezo1 expression on preoperative MR imaging using ROC analysis. The

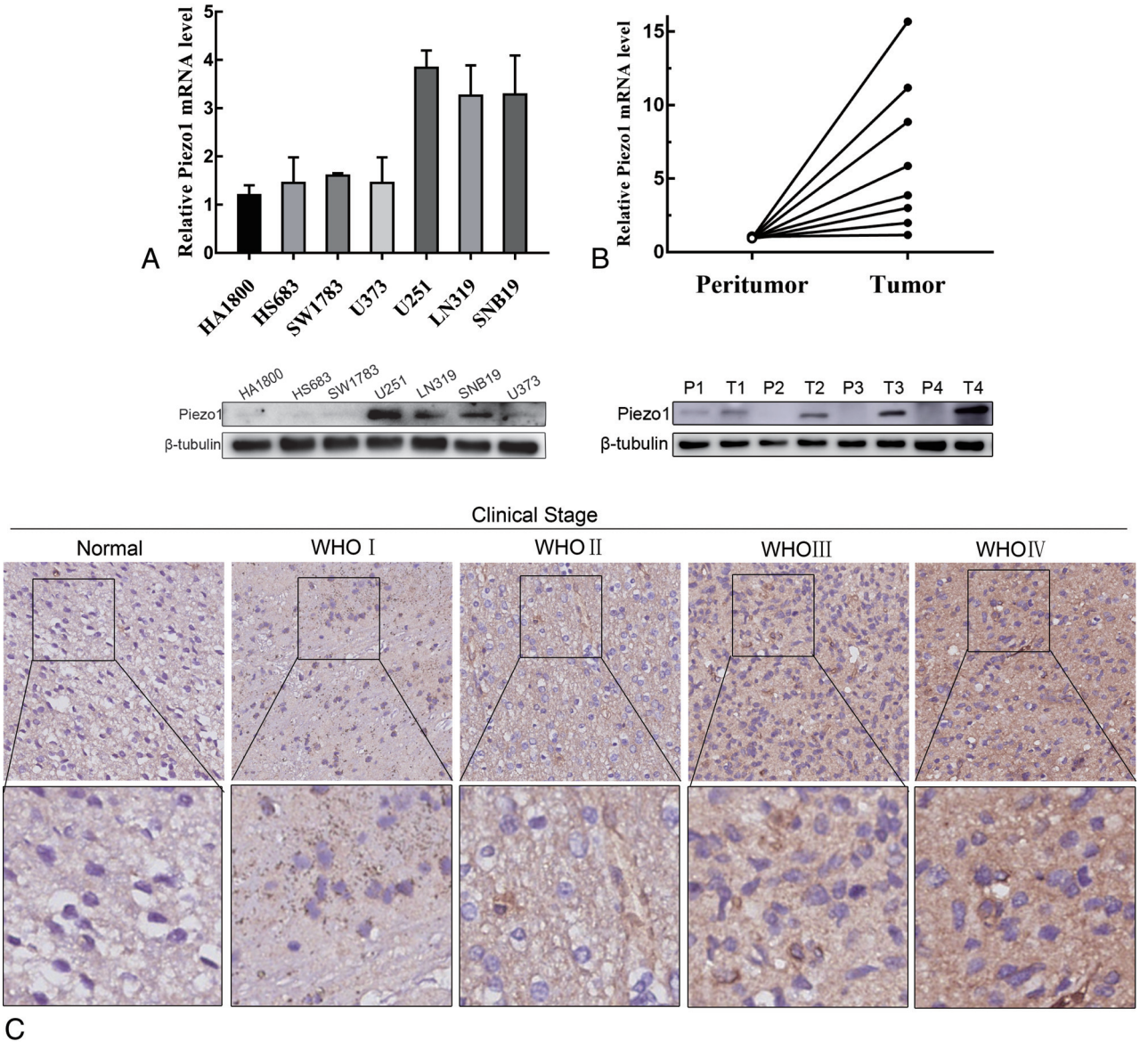

FIG 1. Piezo1 overexpression in glioma cell lines and human gliomas. *A*, Piezo1 expression was detected by qRT-PCR and Western blot in 1 normal astrocyte line (HA1800) and 6 glioma cell lines (HS683, SW1783, U373, U251, LN319, and SNB19). *B*, qRT-PCR analysis of Piezo1 in 8 paired tumor samples and Western blot analysis of Piezo1 in 4 paired tumor samples (WHO grades I–IV). P indicates peritumoral tissues; T, tumor tissues; mRNA, messenger RNA. *C*, Piezo1 was analyzed in normal brain tissue and glioma tissue (WHO grades I–IV) by IHC.

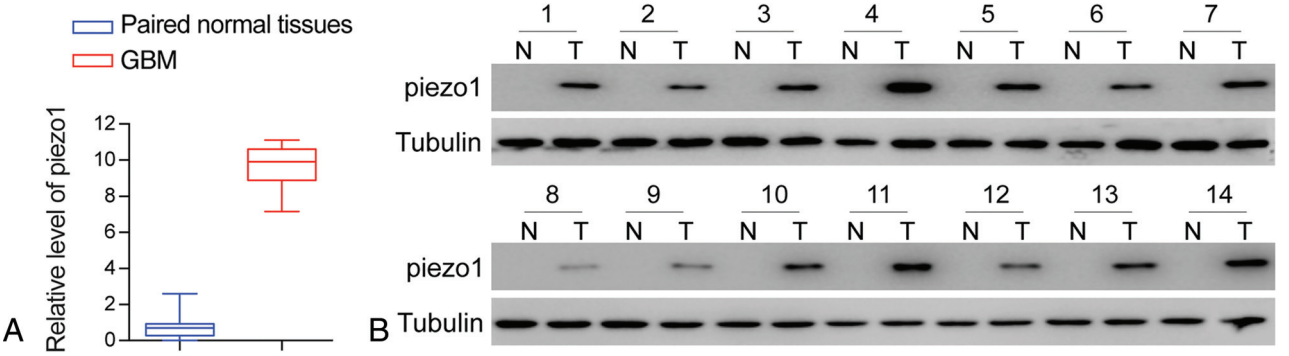

FIG 2. *A*, Relative Piezo1 levels in clinical samples of GBM and paired adjacent normal tissues in a cohort of 64 patients with GBMs with WHO grade IV. *B*, Piezo1 expression was detected in several representative paired GBM samples. N indicates adjacent normal tissues; T, tumor tissues.

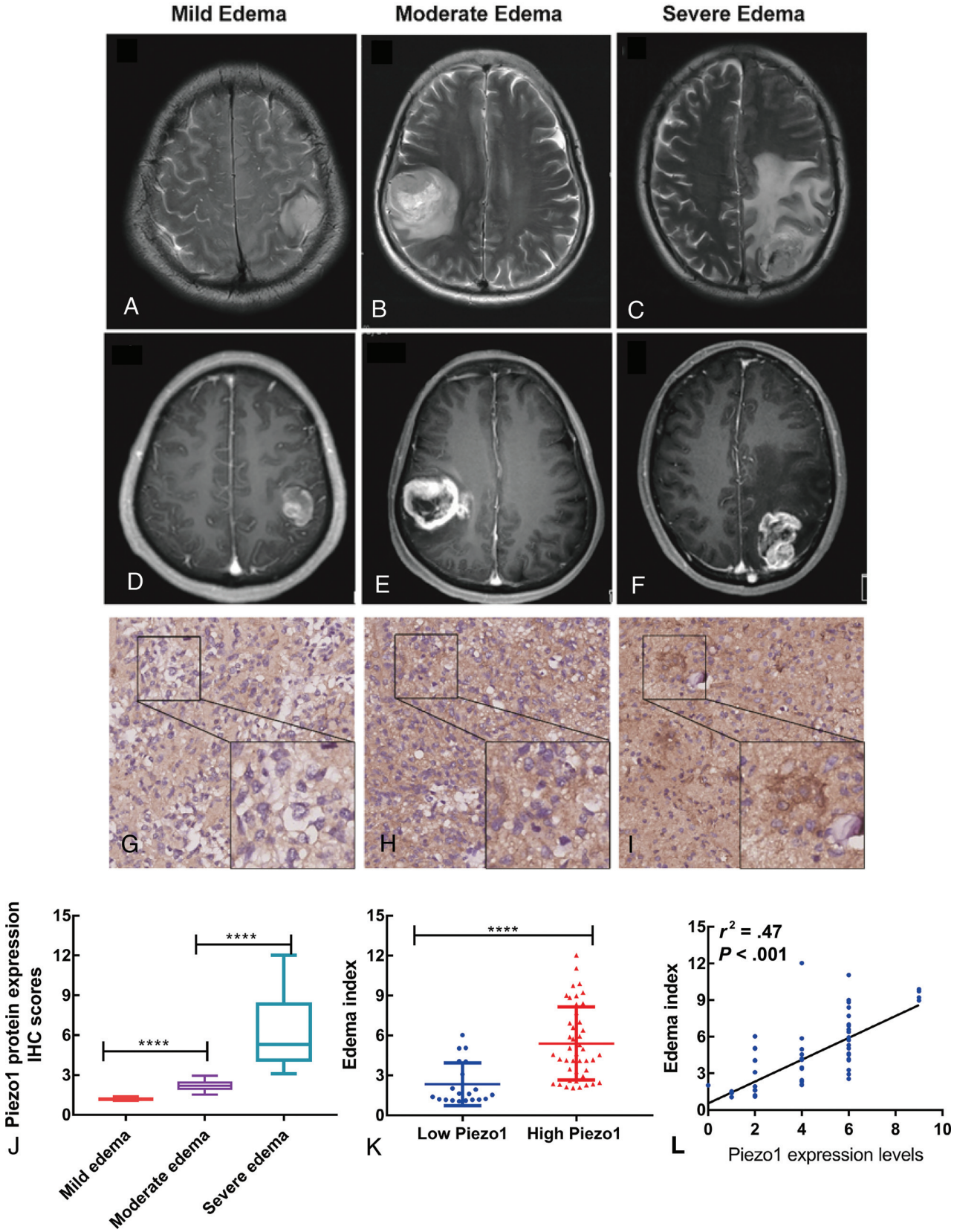

FIG 3. *A–I*, MR imaging (T2-weighted scan and T1-enhanced scan) and Piezo1 immunohistochemical staining of tumors with different grades of brain edema (mild edema, moderate edema, and severe edema). *J*, Piezo1 expression levels in the mild edema group ($n = 9$), moderate edema group ($n = 16$), and severe edema group ($n = 39$) were assessed by IHC. *K*, The EI was compared between the high Piezo1 expression group ($n = 44$) and the low Piezo1 expression group ($n = 20$). *L*, Scatterplot of Piezo1 expression and its corresponding EI based on linear regression analysis ($R^2 = 0.47$, $P < .001$). *The asterisk* indicates $P < .05$, 4 *asterisks*, $P < .001$ using a 2-tailed Student *t* test.

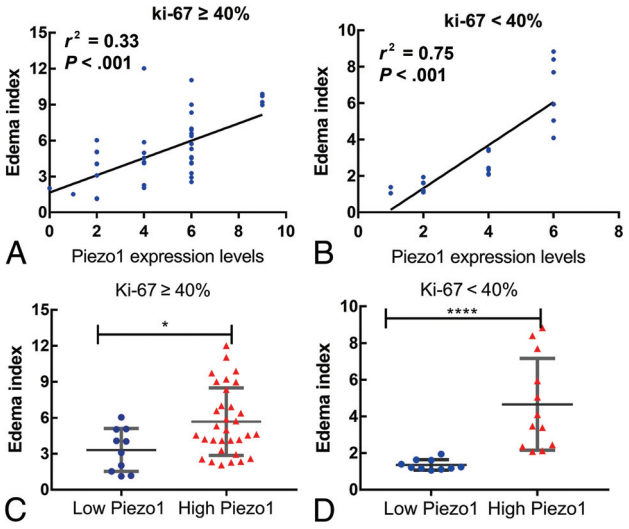

FIG 4. *A* and *B*, Scatterplot of Piezo1 expression and its corresponding EI based on linear regression analysis in the high- and low-expression subgroups of Ki-67 ($R^2 = 0.33$, $P < .001$; $R^2 = 0.75$, $P < .001$; respectively). *C* and *D*, In the subgroup analysis of Ki-67, the EI was compared between the high-Piezo1 and low-Piezo1 expression groups. *The asterisk* indicates $P < .05$; *4 asterisks*, $P < .001$ using a 2-tailed Student *t* test.

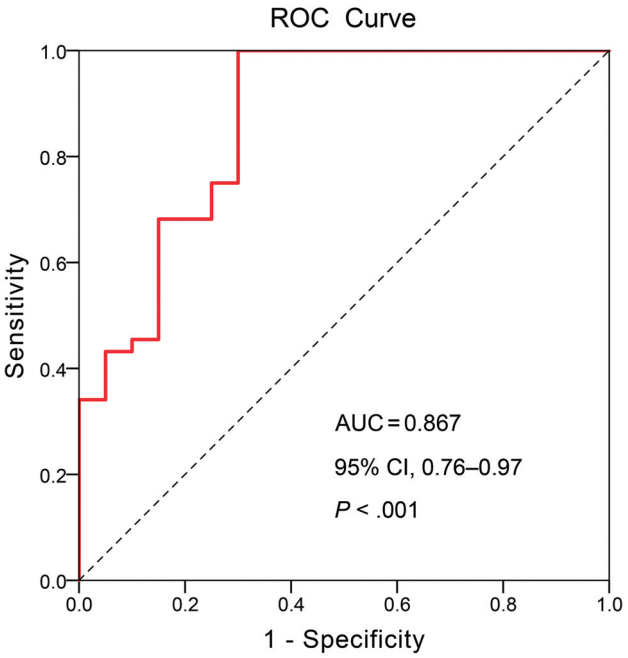

FIG 5. ROC curves of the extent of PTBE (*red line*) for the prediction of high Piezo1 expression in patients with GBMs.

EI yielded an area under the curve of 0.867 (95% CI, 0.76–0.97; $P < .001$) (Fig 5). At the optimal cutoff value, an EI of ≥2.04 predicted high Piezo1 expression, with a sensitivity of 100% and a specificity of 70%.

DISCUSSION

Our results indicate that Piezo1 expression is up-regulated in gliomas, especially high-grade gliomas. In patients with GBMs, the amount of PTBE is positively correlated with the expression of Piezo1 and Ki-67, but not with age, sex, *IDH1* status, or p53 status. The relationship between PTBE and Piezo1 overexpression may be linear. When we defined the value of EI (EI = 2.04), the EI had great clinical value for predicting high Piezo1 expression with good sensitivity and specificity.

So far, it has been accepted that both vasogenic edema and cytotoxic edema are involved in the formation of PTBE.[18,19] The relationship between vasogenic edema and cytotoxic edema is not only mutual influence but also mutual independence. However, the exact mechanism has not been fully elucidated. Vasogenic edema is usually due to the degradation of tight junctions (eg, E-cadherin, N-cadherin, and β-catenin) between endothelial cells, which increases vascular permeability.[20] Then, intravascular fluid exudates into the tissue space and further causes tissue edema. Most interesting, we are the first to find the correlation between PTBE and Piezo1 overexpression in GBMs. Of note, Friedrich et al[11] first confirmed that Piezo1 protein as a calcium channel promotes the influx of calcium ions into vascular endothelial cells and then activates calcium-dependent calpain. Calpain could further promote the degradation of tight junctions between vascular endothelial cells and increase vascular permeability.[11] High vascular permeability increases the extravasation of protein-rich fluid, resulting in brain edema. Therefore, the Piezo1 protein may mediate vasogenic edema by the degradation of tight junctions in GBMs. On the other hand, whether Piezo1 protein is related to cytotoxic edema remains to be further studied.

PTBE is a common GBM-associated phenomenon, which aggravates the patient's symptoms. Some studies have shown that it is an important factor affecting the prognosis and recurrence in patients.[6] It is not yet known whether Piezo1 will become a new drug target for the molecular therapy or prevention of brain edema. If Piezo1 can be used as a new drug target, its high expression might be predicted by the EI, which can be calculated on preoperative MR imaging.

Moreover, our findings suggest that the EI is positively related to the Ki-67 index. Indeed, Yu et al[21] observed a similar result, that Ki-67 expression increased with increasing PTBE in 74 patients with gliomas. Ki-67 is a marker that is commonly used to determine the degree of malignancy of tumors and is closely related to tumor cell proliferation and invasion, which could contribute to PTBE.[22]

Our findings suggest that PTBE is not significantly correlated with age, sex, *IDH1* status, or p53 status. These results agreed with those of previously reported studies.[23,24]

Due to the absence or partial presence of MR imaging T1 enhancement in the patients with WHO grade I–III gliomas, it is very difficult to distinguish PTBE from the tumor; therefore, our study subjects were limited to patients with primary GBM. Thus, it is not known whether our results are applicable to patients with other pathologic types of gliomas (WHO grades I–III) or other types of brain tumors. Additionally, the study was limited by its sample size. The results must be confirmed in a larger study. At present, there is no unified method that can be used to measure the true volume of PTBE or tumor. In this study, the volume was reflected by the maximum diameter of tumor or PTBE. The

formula used to calculate volume was $V = 4/3\pi \times A/2 \times B/2 \times C/2$. Other researchers also recognized this method as a valid way to calculate the volume.[17,25]

CONCLUSIONS

Piezo1 overexpression is positively correlated with the degree of PTBE in GBMs. In addition, the PTBE is also correlated with Ki-67 expression but not with age, sex, *IDH1* status, or p53 status. Predicting high Piezo1 expression in tumor tissues according to the amount of edema has good sensitivity and specificity.

REFERENCES

1. Ostrom QT, Gittleman H, Truitt G, et al. **CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015.** *Neuro Oncol* 2018;20:iv1–86 CrossRef Medline
2. Louis DN, Perry A, Reifenberger G, et al. **The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary.** *Acta Neuropathol* 2016;131:803–20 CrossRef Medline
3. Chen X, Wanggou S, Bodalia A, et al. **A feedforward mechanism mediated by mechanosensitive ion channel PIEZO1 and tissue mechanics promotes glioma aggression.** *Neuron* 2018;100:799–815.e7 CrossRef Medline
4. Ho VK, Reijneveld JC, Enting RH, et al. **Changing incidence and improved survival of gliomas.** *Eur J Cancer* 2014;50:2309–18 CrossRef Medline
5. Hammoud MA, Sawaya R, Shi W, et al. **Prognostic significance of preoperative MRI scans in glioblastoma multiforme.** *J Neurooncol* 1996;27:65–73 CrossRef Medline
6. Schoenegger K, Oberndorfer S, Wuschitz B, et al. **Peritumoral edema on MRI at initial diagnosis: an independent prognostic factor for glioblastoma?** *Eur J Neurol* 2009;16:874–78 CrossRef Medline
7. Wang P, Ni RY, Chen MN, et al. **Expression of aquaporin-4 in human supratentorial meningiomas with peritumoral brain edema and correlation of VEGF with edema formation.** *Genet Mol Res* 2011;10:2165–71 CrossRef Medline
8. Hou J, Kshettry VR, Selman WR, et al. **Peritumoral brain edema in intracranial meningiomas: the emergence of vascular endothelial growth factor-directed therapy.** *Neurosurg Focus* 2013;35:E2 CrossRef Medline
9. Sindou M, Alaywan M. **Role of pia mater vascularization of the tumour in the surgical outcome of intracranial meningiomas.** *Acta Neurochir* 1994;130:90–93 CrossRef Medline
10. Coste B, Mathur J, Schmidt M, et al. **Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels.** *Science* 2010;330:55–60 CrossRef Medline
11. Friedrich EE, Hong Z, Xiong S, et al. **Endothelial cell Piezo1 mediates pressure-induced lung vascular hyperpermeability via disruption of adherens junctions.** *Proc Natl Acad Sci U S A* 2019;116:12980–85 CrossRef Medline
12. Guo L, Ding Z, Huang N, et al. **Forkhead Box M1 positively regulates UBE2C and protects glioma cells from autophagic death.** *Cell Cycle* 2017;16:1705–18 CrossRef Medline
13. Osawa T, Tosaka M, Nagaishi M, et al. **Factors affecting peritumoral brain edema in meningioma: special histological subtypes with prominently extensive edema.** *J Neurooncol* 2013;111:49–57 CrossRef Medline
14. Chinese Neurosurgical Society. **Consensus on the drug treatment of peritumoral brain edema** (in Chinese). *Zhonghua Yi Xue Za Zhi* 2010;90:5–9 Medline
15. Capper D, Weissert S, Balss J, et al. **Characterization of R132H mutation-specific IDH1 antibody binding in brain tumors.** *Brain Pathol* 2010;20:245–54 CrossRef Medline
16. Kobayashi T, Masutomi K, Tamura K, et al. **Nucleostemin expression in invasive breast cancer.** *BMC Cancer* 2014;14:215 CrossRef Medline
17. Gawlitza M, Fiedler E, Schob S, et al. **Peritumoral brain edema in meningiomas depends on aquaporin-4 expression and not on tumor grade, tumor volume, cell count, or Ki-67 labeling index.** *Mol Imaging Biol* 2017;19:298–304 CrossRef Medline
18. Zhang Y, Wang J, Zhang Y, et al. **Overexpression of long noncoding RNA Malat1 ameliorates traumatic brain injury induced brain edema by inhibiting AQP4 and the NF-kappaB/IL-6 pathway.** *J Cell Biochem* 2019;120:17584–92 CrossRef Medline
19. Liang D, Bhatta S, Gerzanich V, et al. **Cytotoxic edema: mechanisms of pathological cell swelling.** *Neurosurg Focus* 2007;22:E2 CrossRef Medline
20. Heiss JD, Papavassiliou E, Merrill MJ, et al. **Mechanism of dexamethasone suppression of brain tumor-associated vascular permeability in rats: involvement of the glucocorticoid receptor and vascular permeability factor.** *J Clin Invest* 1996;98:1400–08 CrossRef Medline
21. Yu H, Yong Z, Yonggang W, et al. **Correlational study of peritumoral brain edema, histological grades and the expression of Ki-67 in gliomas.** *Journal of International Oncology* 2015;42:165–68
22. Lin ZX. **Glioma-related edema: new insight into molecular mechanisms and their clinical implications.** *Chin J Cancer* 2013;32:49–52 CrossRef Medline
23. Tamiya T, Ono Y, Matsumoto K, et al. **Peritumoral brain edema in intracranial meningiomas: effects of radiological and histological factors.** *Neurosurgery* 2001;49:1046–51 CrossRef Medline
24. Zhu L, Qi X-H, Kang Q-F, et al. **The correlation of tumor volume, peritumoral edema with cerebral glioma histologic grade.** *Chinese J Magn Reson Imaging* 2015;6:656–62
25. Baris MM, Celik AO, Gezer NS, et al. **Role of mass effect, tumor volume and peritumoral edema volume in the differential diagnosis of primary brain tumor and metastasis.** *Clin Neurol Neurosurg* 2016;148:67–71 CrossRef Medline