Peripheral blood occludin level as a biomarker for preoperative cerebral edema in patients with brain tumors

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Abstract

Objective

Cerebral edema is a common complication of brain tumors in the perioperative period. However, there is currently no reliable and convenient method to evaluate the extent of brain edema. The objective of this study is to explore the ability of serum occludin level to predict the extent of perioperative brain edema and outcome in patients with brain tumors.

Methods

This prospective study enrolled 55 patients with brain tumors and 24 healthy controls from Sanbo Brain Hospital from June 2019 through November 2019. Serum occludin level was measured preoperatively and on postoperative day 1. Peritumoral edema was assessed preoperatively using magnetic resonance imaging. Pericavity brain edema on postoperative day 1 was evaluated using computed tomography.

Results

Compared with healthy controls, serum occludin level was higher in patients with brain tumors both preoperatively and postoperatively ($P < 0.001$). Serum occludin level was significantly positively correlated with the extent of brain edema preoperatively ($r = 0.78$, $P < 0.001$) and postoperatively ($r = 0.59$, $P < 0.001$). At an optimal cutoff of 3.015 ng/mL, preoperative serum occludin level discriminated between mild and severe preoperative brain edema with a sensitivity of 90.48% and a specificity of 84.62%. At an optimal cutoff value of 3.033 ng/mL, postoperative serum occludin level distinguished between mild and severe postoperative brain edema with a sensitivity of 97.30% and a specificity of 55.56%.

Conclusions

Serum occludin level is associated with cerebral edema and could potentially be used as a biomarker for perioperative cerebral edema.

Introduction

Damage to the blood–brain barrier (BBB) in patients with brain tumors can cause cerebral edema or hemorrhage. Brain edema, as a major factor that governs clinical management, is responsible for clinical symptoms including neurological deficit and intracranial hypertension. The severity of perioperative brain edema and the occurrence of postoperative hemorrhage in patients with brain tumors are directly related to prognosis and risk of death[1]. Computed tomography (CT) and magnetic resonance imaging (MRI) can be used to indirectly evaluate the extent of brain edema and hemorrhage in patients with brain tumors. However, these imaging techniques are inconvenient and time-consuming and thus cannot be used to screen for rapid deteriorations in the postoperative condition of a patient in the intensive care unit. Therefore, it is vital that a reliable biomarker be identified that reflects the extent of cerebral edema and

risk of cerebral hemorrhage in the perioperative period, as this will facilitate the prevention of, or timely intervention for, cerebral edema or hemorrhage after surgery for craniocerebral tumors.

The expressions of several proteins in brain tissue, including N-cadherin, β-catenin, aquaporin-4, delta-like protein-4, matrix metallopeptidase (MMP)-9, and vascular endothelial growth factor, are associated with the occurrence of peritumoral brain edema (PTBE)[2–5]. However, few studies have examined the relationships between serum proteins and PTBE.

Tight junction proteins such as claudin-5 and occludin are key structural components of the BBB[6,7]. Occludin and claudin-5 form tight junction protein structures that seal the gap between the endothelial cells of the BBB and thus are responsible for maintaining the integrity of the BBB[8]. Since occludin expression alone does not result in tight junction formation[9], it is likely that claudin-5 forms the primary structure of the tight junction, with occludin acting as an additional supporting structure[10]. This may make occludin vulnerable to release into the bloodstream following damage to the BBB. PTBE formation is widely accepted to be vasogenic brain edema due to the damage of the BBB. There is some evidence that decreased expressions of occludin and claudin-5 in brain tissue are related to PTBE[11,12], suggesting that brain edema can arise if occludin and claudin-5 are lost from the BBB. Our recent studies have confirmed that degraded tight junction protein fragments are released into the blood and that their levels in the blood are closely related to the degree of BBB damage after cerebral ischemia[13,14]. This suggests that occludin could potentially be used as a biomarker to evaluate damage to the BBB. However, no previous investigations have reported whether occludin is degraded and released into the bloodstream because of damage to the BBB by a brain tumor or brain surgery.

It is widely recognized that patients with brain tumors can exhibit damage to their BBB both before and after surgery. Therefore, we hypothesized that the level of occludin in peripheral blood might serve as a biomarker for cerebral edema due to BBB damage in patients with brain tumors. To the best of our knowledge, there are no previous studies describing the association between the level of occludin in peripheral blood and the extent of PTBE or postoperative pericavity edema in patients with brain tumors. Therefore, the aim of the present study was to investigate the relationships between serum occludin level and the extent of PTBE before surgery and the extent of pericavity brain edema after surgery in patients with brain tumors.

Materials And Methods

Study design and participants

This prospective study enrolled consecutive patients with brain tumors scheduled for surgery at the Department of Neurosurgery of Sanbo Brain Hospital at Capital Medical University between June 1st, 2019 and November 1st, 2019. A control group of healthy individuals was also enrolled at the physical examination center of Sanbo Brain Hospital during the same period. The inclusion criteria for patients with brain tumors were as follows: (1) primary brain tumor confirmed by imaging investigations such as

CT and MRI, (2) met the indications for surgical treatment and scheduled to undergo surgery, (3) aged 18–80 years old, (4) had not received radiotherapy or chemotherapy before surgery, and (5) provided informed consent for inclusion in the study. The exclusion criteria were other diseases that might lead to the destruction of tight junction proteins between vascular endothelial cells, including: (1) severe hepatorenal disease, (2) severe gastrointestinal system disease, (3) peripheral vascular disease, and (4) autoimmune disease. The members of the healthy control group were randomly selected from individuals undergoing routine physical examinations at Sanbo Brain Hospital. Patients with craniopharyngioma or hypophysoma were treated at a dose of 250 mg methylprednisolone, and the other brain tumor patients received 5 mL/kg 20% mannitol intravenously for 3 days after operation. The study was approved by the Ethics Committee of Sanbo Brain Hospital, and all patients provided informed written consent for inclusion in the study.

Measurement of serum occludin level

Peripheral venous blood samples (4 mL) were obtained from patients with brain tumors at admission (i.e., preoperatively) and approximately 24 hours (range, 20–28 hours) after surgery. Blood samples from healthy subjects were taken during their visit to the physical examination center. Serum (100 μL) was separated from each blood sample, and the level of occludin in the serum was measured using a commercially available enzyme-linked immunosorbent assay kit for human samples (USCN, Wuhan, China).

Measurement of PTBE before surgery

PTBE was evaluated by 1.5T MRI (Achieva 1.5T; Philips, Amsterdam, Netherlands) before surgery (**Figure 1A, B**). The imaging sequences used in this study included axial T2-weighted sequences, fluid-attenuated inversion recovery (FLAIR) sequences, and axial and coronal T1-weighted spin-echo sequences before and after intravenous injection of contrast agent (gadopentetate dimeglumine; 0.1 mg/kg body weight). All images were analyzed digitally using picture archiving and communication system workstations. Enhanced T1-weighted images were used to determine the tumor boundary, and these maps were then compared with the respective T2-weighted images or FLAIR sequence. The extent of PTBE was determined by measuring the vertical distance from the outer edge of the maximal edema zone to the tumor boundary. PTBE was graded according to the Steinhoff classification[15] as follows: 0, no edema; I, PTBE limited to 2 cm; II, PTBE limited to half of the hemisphere; and III, PTBE extending to more than half of the hemisphere. For the analysis, mild edema was defined as Steinhoff grade 0 or I, and severe edema was defined as Steinhoff grade II or III. Determination of the Steinhoff grade was made independently by two clinicians who were deputy directors of imaging and had more than five years of work experience; any disagreements were resolved by discussion.

Measurement of pericavity edema after surgery

Pericavity brain edema was evaluated by CT (Brilliance 64, Philips) at approximately 24 hours (range, 20–28 hours) after surgery (**Figure 1C, D**). The extent of pericavity edema was measured as the vertical

distance from the outer edge of the maximal edema zone to the cavity boundary after surgery. Evaluation of the extent of edema was the same as that for PTBE (see above).

Measurement of neurological function and related complications

To further analyze the relationships between serum occludin level and neurological function and related complications, the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) were administered at admission and at approximately 24 hours (range, 20–28 hours) after surgery. In addition, information regarding the occurrence of intracranial hemorrhage was collected at approximately 24 hours (range, 20–28 hours) after surgery[16].

Statistical analysis

The data were analyzed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). All continuous data were confirmed to be normally distributed and thus are presented as the mean ± standard deviation (SD). One-way analysis of variance was used to compare serum occludin levels between groups. NIHSS and GCS scores were compared between groups using Student's t-test. Categorical data are presented as *n* (%) and were compared between groups using the chi-squared test or Fisher's exact test. The relationship between serum occludin level and the extent of the brain edema (vertical distance from the outer edge of the maximal edema zone to the tumor/cavity boundary) was assessed by calculating Pearson's correlation coefficient (*r*). Receiver operating characteristic (ROC) curve analysis with calculation of the area under the curve (AUC) was used to evaluate the ability of serum occludin level to distinguish between mild and severe edema. The optical cutoff for serum occludin level was established by calculating the Youden index, and sensitivity and specificity values were determined. Statistical significance was defined as a two-tailed *P*-value < 0.05.

Results

Baseline clinical characteristics of the study participants

A total of 55 patients with brain tumors and 24 healthy volunteers were enrolled in this study. The group of patients with brain tumors and the control group of healthy volunteers exhibited no significant differences in mean age (47.42 ± 15.72 years vs. 40.63 ± 14.42 years) or gender (56.4% female vs. 51.2% female; **Table 1**). Additional clinical data for the patients with brain tumors are shown in **Table 1**.

Comparison of serum occludin levels in patients with brain tumors and healthy volunteers

There was no significant difference between preoperative and postoperative serum occludin levels in patients with brain tumors. However, both levels were significantly higher in patients with brain tumors than they were in healthy individuals (**Figure 2**). These results suggest that brain tumors may induce damage to the BBB, leading to the release of occludin into the bloodstream.

Analysis of the relationship between preoperative serum occludin level and the extent of preoperative PTBE and tumor diameter

Pearson correlation analysis revealed that preoperative serum occludin level was significantly positively correlated with the extent of preoperative PTBE as measured by the vertical distance from the outer edge of the maximal edema zone to the tumor boundary ($r = 0.78$, $P < 0.0001$; **Figure 3A**). Preoperative serum occludin level was also significantly correlated with the extent of preoperative PTBE as measured by the Steinhoff classification ($P < 0.05$ for all pairwise comparisons; **Figure 3B**). However, preoperative serum occludin level was not significantly correlated with the diameter of the tumor ($r = 0.222$; $P = 0.103$; **Figure 3C**).

ROC curve analysis of the ability of preoperative serum occludin level to predict the severity of preoperative PTBE

ROC curve analysis indicated that preoperative serum occludin level had an excellent ability to distinguish between mild and severe PTBE, with an AUC value of 0.9002 (95% confidence interval, 0.8069–0.9934; $P < 0.0001$; **Figure 3D**). At an optimal cutoff value of 3.015 ng/mL for preoperative serum occludin level, the sensitivity was 90.48% and the specificity was 84.62%. These results suggest that preoperative serum occludin level could potentially be used to reflect the extent of PTBE before surgery.

Analysis of the relationship between postoperative serum occludin level and the extent of pericavity edema and tumor diameter

Pearson correlation analysis indicated that postoperative serum occludin level was significantly positively correlated with the extent of postoperative pericavity edema as measured by the vertical distance from the outer edge of the maximal edema zone to the cavity boundary ($r = 0.590$, $P < 0.0001$; **Figure 4A**). Similarly, postoperative serum occludin level was significantly related to the extent of postoperative pericavity edema as measured by the Steinhoff classification ($P < 0.05$ for all pairwise comparisons; **Figure 4B)**. Postoperative serum occludin level was not significantly correlated with tumor diameter ($r = 0.104$, $P = 0.449$; **Figure 4C**).

ROC curve analysis of the ability of postoperative serum occludin level to predict the severity of postoperative pericavity edema

ROC curve analysis demonstrated that postoperative serum occludin level had a good ability to discriminate between mild and severe pericavity edema, with an AUC value of 0.7763 (95% confidence interval, 0.6267–0.9258; $P < 0.0001$; **Figure 4D**). At an optimal cutoff value of 3.033 ng/mL for postoperative serum occludin level, the sensitivity was 97.30% and the specificity was 55.56%.

Relationship between preoperative serum occludin level and clinical outcomes

To examine whether preoperative serum occludin level might be related to clinical outcomes, patients were divided into two groups according to the optimal cutoff value for preoperative occludin level (3.015

ng/mL). Compared with patients with a preoperative serum occludin level <3.015 ng/mL, those with an occludin level ≥3.015 ng/mL had significantly higher NIHSS scores at admission (3.60 ± 0.48 vs. 2.31± 0.42; *P* < 0.001; **Figure 5A**) and a significantly higher incidence of severe PTBE at admission (65.3% vs. 15.2%; *P* < 0.001; **Figure 5B**), but both groups had similar GCS scores at admission (14.47 ± 1.60 vs. 14.85 ± 0.70; *P* = 0.219; **Figure 5A**) and a similar incidence of intracranial hemorrhage at 1 day after surgery (20.0% vs. 20.0%; *P* = 1.000; **Figure 5B**).

Relationship between postoperative serum occludin level and clinical outcomes

The relationship between postoperative serum occludin level and clinical outcomes was also assessed. Compared with patients with a postoperative serum occludin level <3.033 ng/mL (the optimal cutoff value), those with an occludin level ≥3.033 ng/mL had a significantly higher incidence of severe pericavity edema at 1 day after surgery (90.9% vs. 18.2%; *P* < 0.001), but both groups had similar NIHSS scores (6.82 ± 6.64 vs. 4.52 ± 6.66; *P* = 0.306), GCS scores (13.55 ± 2.07 vs. 14.09 ± 1.09; *P* = 0.407), and incidence of intracranial hemorrhage (27.3% vs. 18.2%; *P* = 0.800) at 1 day after surgery (**Figure 5C, D**).

Discussion

The present report demonstrates that patients with brain tumors exhibit perioperative changes in the serum level of occludin, a protein that contributes to the structure and function of the BBB. Importantly, this study revealed a relationship between the serum level of occludin and the severity of brain edema in patients with brain tumors. Previous investigations have confirmed that PBTE is vascular edema caused by damage to the BBB[17–19]. Occludin is an important component of the tight junctions that constitute the BBB. Previous animal experiments have reported that cerebral ischemia results in the activation of MMP-2 and MMP-9 in brain tissue, leading to the degradation of occludin and the destruction of the BBB[20,21]. The present study found that serum occludin level was higher in patients with brain tumors as compared with healthy controls, suggesting that tumor-induced damage to the BBB during the perioperative period may lead to the loss of occludin from the BBB. Furthermore, we demonstrated that serum occludin level correlated well with the extent of brain edema and could be used to predict the severity of perioperative brain edema in patients with brain tumors.

We found that serum occludin level was significantly higher in patients with brain tumors, both before and after surgery, than in healthy individuals. These results suggest that damage to the BBB occurs in patients with brain tumors, leading to the release of degraded occludin fragments into the blood and thus an increase in the serum level of occludin. Notably, the patients included in this study had a broad range of tumor types located in different parts of the brain, suggesting that damage to the BBB and the degradation and release of occludin may be a common consequence of many different types of brain tumors, irrespective of the mechanism by which the BBB is damaged. Therefore, our study has identified a novel circulating biomarker that may be beneficial for the detection and/or monitoring of BBB damage during the perioperative period in patients with brain tumors. Future studies will need to establish whether

the performance of serum occludin level as a clinical biomarker varies between different pathological types of tumors.

Interestingly, we found a positive correlation between peritumoral or pericavity brain edema and serum occludin level, with a higher occludin level associated with more severe brain edema. Notably, serum occludin level was related only to the extent of brain edema and not to the size of the tumor. Vascular brain edema is a well-recognized feature of BBB damage, which likely leads to the release of degraded occludin. Previous studies have shown that PTBE is associated with a low content of occludin in the tumor[22,23], but it has not been clarified whether the low content of occludin in the BBB of patients with brain tumors is mainly due to the degradation or low expression of occludin. Our observation of an elevated level of serum occludin suggests that a low content of occludin within a tumor may, at least in part, be due to the degradation of occludin rather than down-regulated expression. Further studies are needed to clarify the mechanisms underlying BBB damage and changes in occludin in brain tumors.

Depending on the type of brain tumor, the development of brain edema can involve a variety of factors including glioma cells, vascular endothelial cells, neuroglial cells, microglial cells[24,25], and cyclooxygenase-2[26]. Our study found that serum occludin level correlated well with the grade of brain edema, suggesting that damage to occludin in the BBB may be a common molecular mechanism underlying the development of brain edema in patients with brain tumors. Some studies of glioma have shown that MMP expression or activation is related to the down-regulation of occludin in the BBB, which leads to destruction of the BBB[27,28]. It is possible that MMP activation may be a major mechanism by which degradation of occludin and damage to the BBB occurs in patients with brain tumors. However, further research is needed to clarify the relevant molecular mechanisms in humans.

This study utilized ROC curve analysis to evaluate the ability of preoperative and postoperative serum occludin levels to distinguish between mild and severe edema. Preoperative and postoperative serum occludin levels showed excellent (AUC value of 0.9002) and good (AUC value of 0.7763) discriminatory ability, respectively. At an optimal cutoff value of 3.015 ng/mL, preoperative serum occludin level discriminated between mild and severe preoperative brain edema with a high sensitivity (90.48%) and a specificity (84.62%). At an optimal cutoff value of 3.033 ng/mL, postoperative serum occludin level also distinguished between mild and severe postoperative brain edema with a high sensitivity (97.30%), although the specificity was somewhat lower (55.56%). Taken together, the findings of the ROC curve analysis suggest that serum occludin level has the potential to be a novel biomarker for perioperative brain edema in patients with brain tumors.

Brain edema may be an important factor affecting the neurological function of patients with brain tumors. This study found that patients with high serum occludin levels before surgery also had a higher preoperative NIHSS score, which may be related to more severe damage to the BBB. However, although the group of patients with elevated serum occludin levels after surgery had more severe brain edema, their postoperative NIHSS score did not differ from that of patients with lower occludin levels. This apparent discrepancy may be due to the neurological functions of these patients being more affected by

other surgery-related factors. We also found no difference in the incidence of postoperative cerebral hemorrhage between patients with high and low preoperative or postoperative levels of occludin. This latter finding suggests that postoperative acute cerebral hemorrhage may be primarily related to surgical factors (such as damage to micro-vessels or incomplete hemostasis) rather than BBB injury.

This study has some limitations. First, the sample size was not large, and an extensive range of tumor pathological types was included. Further large-scale clinical studies are needed to validate our results and to perform subgroup analyses based on different brain tumor types. Second, we did not perform long-term follow-up to evaluate the prognosis of the patients and explore whether outcomes were related to serum occludin level.

Conclusion

Perioperative serum occludin level is associated with the severity of peritumoral/pericavity edema in patients with brain tumors. Serum occludin level could potentially be used as a biomarker for perioperative cerebral edema in patients with brain tumors. Further large-scale clinical studies are needed to validate our results and perform subgroup analyses based on different brain tumor types.

Declarations

Data availability

The results of our study supporting the findings are included within this paper. In order to protect patient privacy, the personal data supporting the findings of this study are restricted by the Ethics Committee of Sanbo Brain Hospital, Capital Medical University. Data are available to researchers who meet the criteria for access to confidential data from the corresponding author.

Competing interests

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Ethics approval and consent to participate

I confirm that I have read the Editorial Policy pages. This study was conducted with approval from the Ethics Committee of our hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

All participants signed a document of informed consent.

Authors' contributions

SSH and CJL conceived the idea and conceptualised the study. SSH and ZCY collected the data. CJL and LT analysed the data. SSH, ZXY and SYX drafted the manuscript, then WBG, ZY and LWL reviewed the manuscript. All authors read and approved the final draft.

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Tables

TABLE 1. **Baseline clinical characteristics of the study participants**

Characteristic	Patients with brain tumors (*n* = 55)	Healthy volunteers (*n* = 24)	*P*
Age (years)	47.42 ± 15.72	40.63 ± 14.42	0.074
Female	31 (56.4%)	13 (51.2%)	0.857
Tumor location			
Frontal lobe	15 (27.3%)	N/A	N/A
Temporal lobe	14 (25.5%)	N/A	N/A
Occipital lobe	6 (10.9%)	N/A	N/A
Parietal lobe	3 (5.5%)	N/A	N/A
Sella region	6 (10.9%)	N/A	N/A
Cerebellum	4 (7.3%)	N/A	N/A
Brain stem	5 (9.1%)	N/A	N/A
Basal ganglia	2 (3.6%)	N/A	N/A
Tumor pathology			
Glioma	22 (40.0%)	N/A	N/A
Meningioma	12 (21.8%)	N/A	N/A
Neurilemmoma	7 (12.7%)	N/A	N/A
Hypophysoma	4 (7.3%)	N/A	N/A
Hemangioma	4 (7.3%)	N/A	N/A
Germinoma	2 (3.6%)	N/A	N/A
Craniopharyngioma	2 (3.6%)	N/A	N/A
Chordoma	1 (1.8%)	N/A	N/A
Cholesteatoma	1 (1.8%)	N/A	N/A

Data are presented as mean ± standard deviation or *n* (%). N/A: not applicable.

Figures

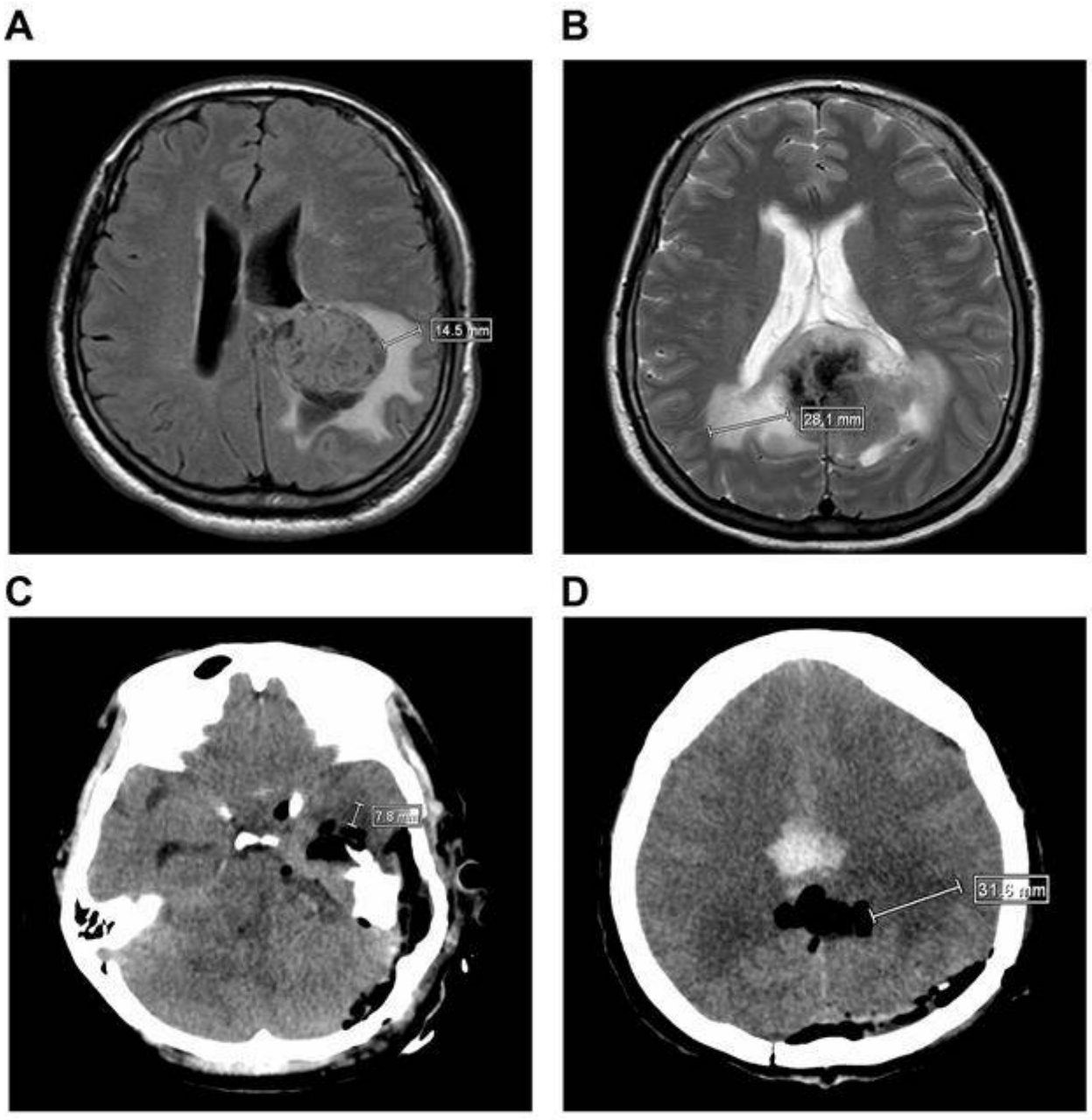

Figure 1

Evaluation of PTBE and pericavity brain edema by MRI and computed CT, respectively. (A) MRI scan showing mild PTBE before surgery. (B) MRI scan showing severe PTBE before surgery. (C) CT scan showing mild brain edema around the cavity after surgery. (D) CT scan showing severe brain edema around the cavity after surgery.

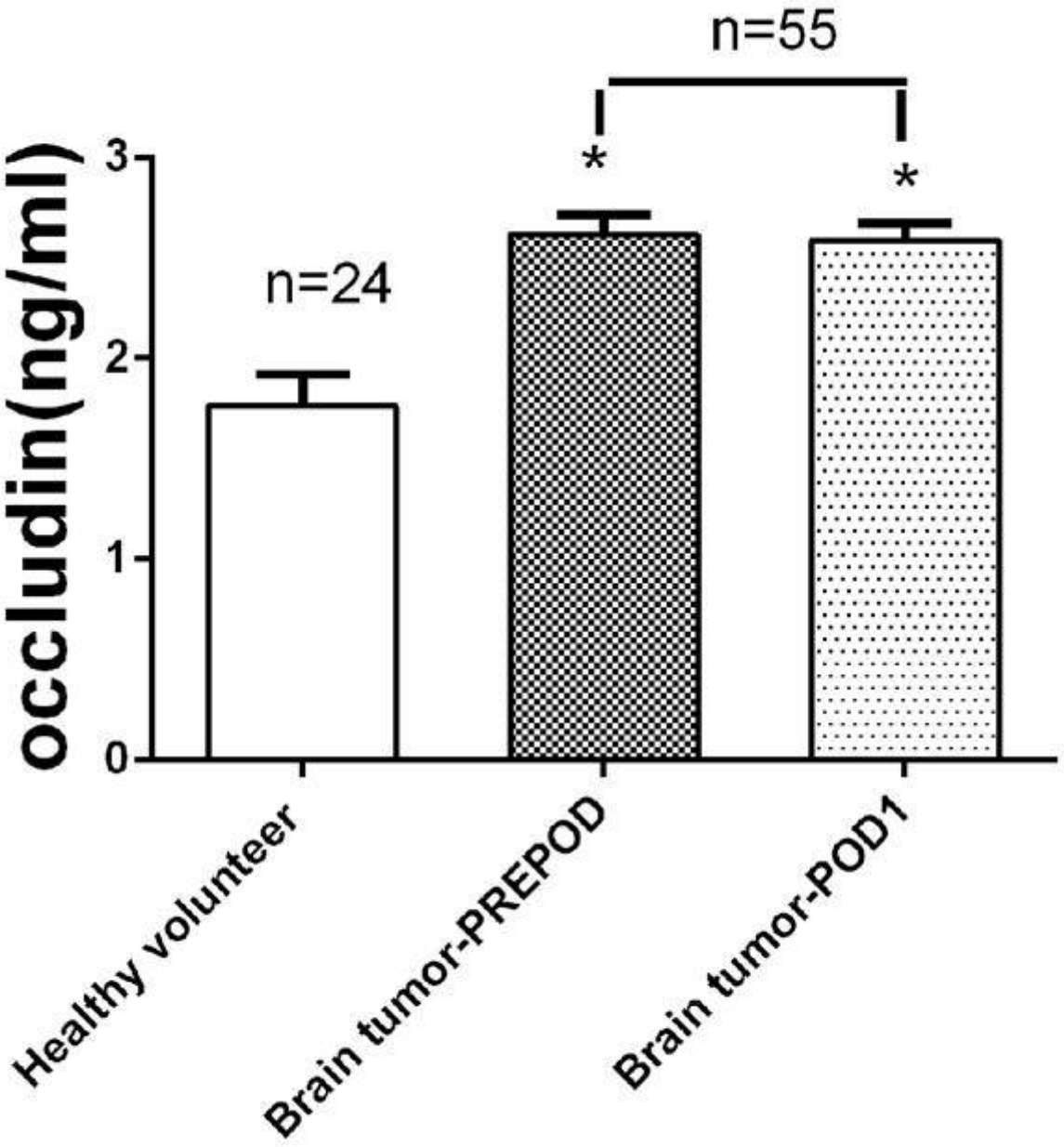

Figure 2

Comparison of serum occludin levels between patients with brain tumors and healthy volunteers. Compared with healthy volunteers (n = 24), serum occludin levels in patients with brain tumors (n = 55) were significantly higher both before surgery (Brain tumor-PREPOD) and 1 day after surgery (Brain tumor-POD1). Data are expressed as the mean ± SD. * $P < 0.05$ versus the healthy volunteer group.

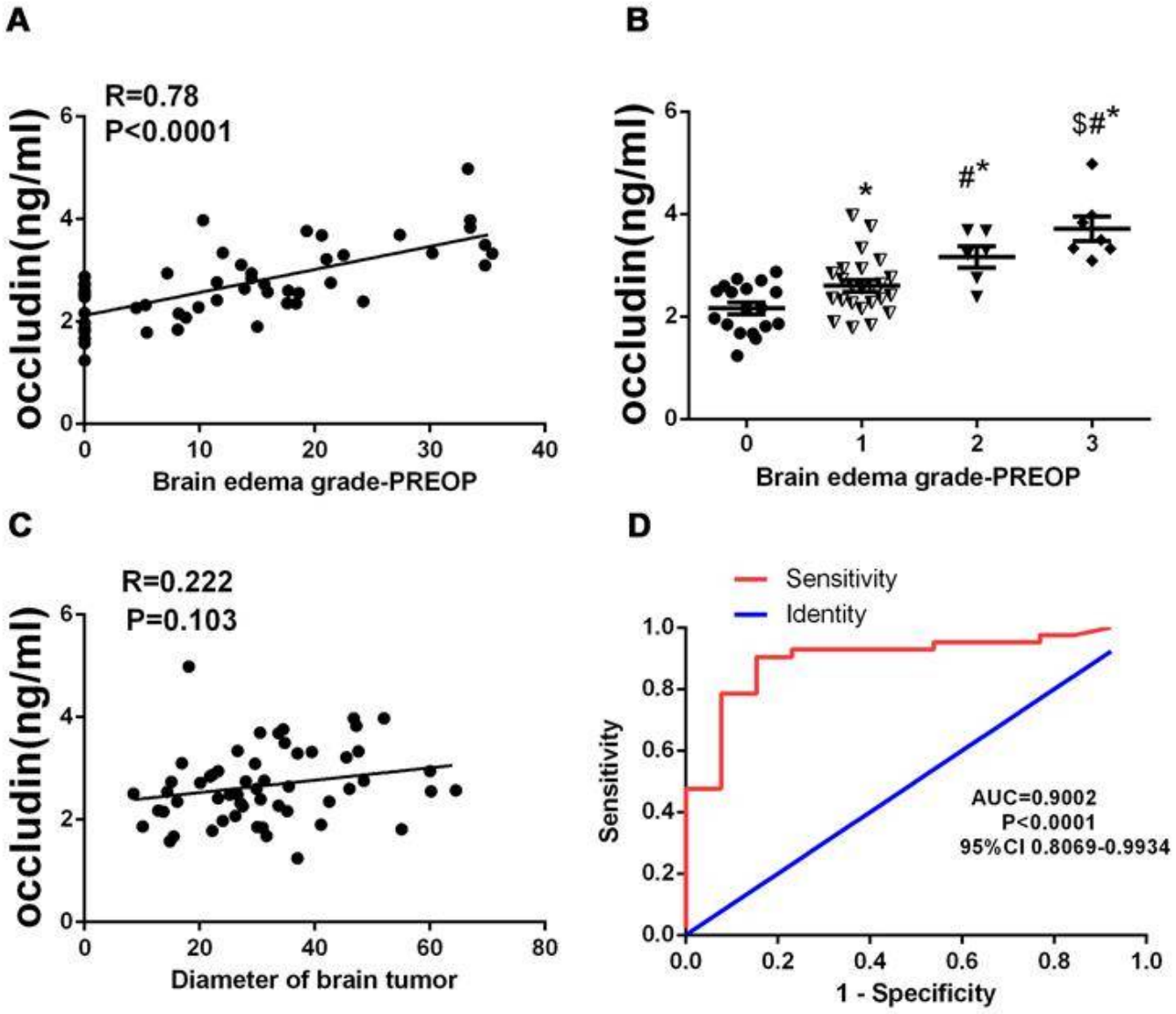

Figure 3

The relationship between preoperative serum occludin level and PTBE before surgery. (A) Pearson correlation analysis showing that preoperative serum occludin level was significantly positively correlated with the extent of preoperative PTBE as measured by the vertical distance from the outer edge of the maximal edema zone to the tumor boundary (n = 55). (B) Preoperative serum occludin levels for the various Steinhoff grades of PTBE. Data are presented as the mean ± SD (grade 0, n = 18; grade I, n = 24; grade II, n = 6; grade III, n = 7). * P < 0.05 vs. grade 0; # P < 0.05 vs. grade I; $ P < 0.05 versus grade II. (C) Pearson correlation analysis showing that preoperative serum occludin level was not significantly correlated with tumor diameter. (D) ROC curve for the ability of serum occludin level to distinguish between mild and severe PTBE.

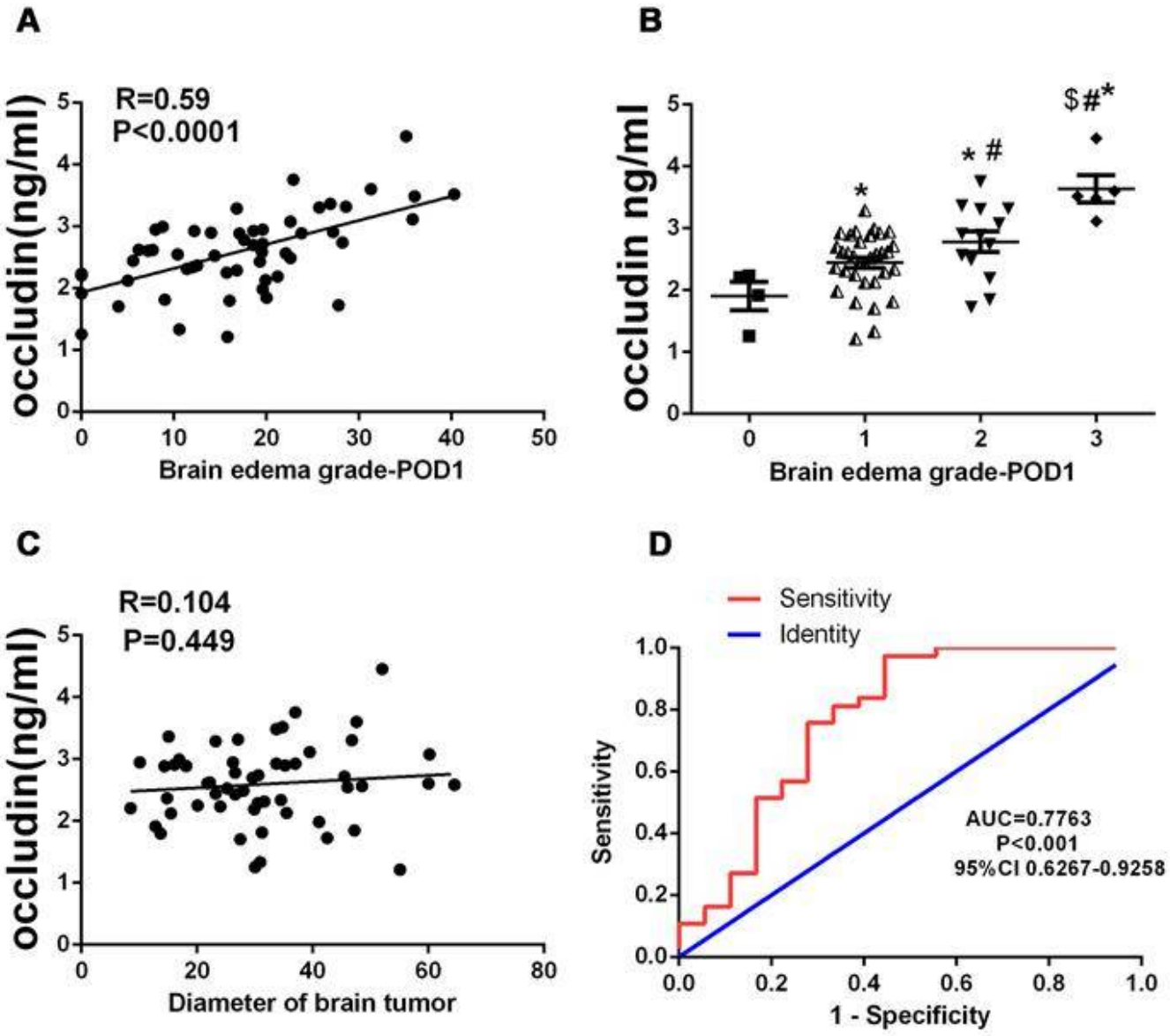

Figure 4

The relationship between postoperative serum occludin level and pericavity brain edema after surgery. (A) Pearson correlation analysis indicating that postoperative serum occludin level was significantly positively correlated with the extent of postoperative pericavity edema as measured by the vertical distance from the outer edge of the maximal edema zone to the cavity boundary (n = 55). (B) Postoperative serum occludin levels for the various Steinhoff grades of pericavity edema. Data are presented as the mean ± SD (grade 0, n = 4; grade I, n = 33; grade II, n = 13 ; grade III, n = 5). * P < 0.05 vs. grade 0; # P < 0.05 vs. grade I; $ P < 0.05 versus grade II. (C) Pearson correlation analysis indicating that postoperative serum occludin level was not significantly correlated with tumor diameter. (D) ROC curve for the ability of postoperative serum occludin level to distinguish between mild and severe pericavity edema.

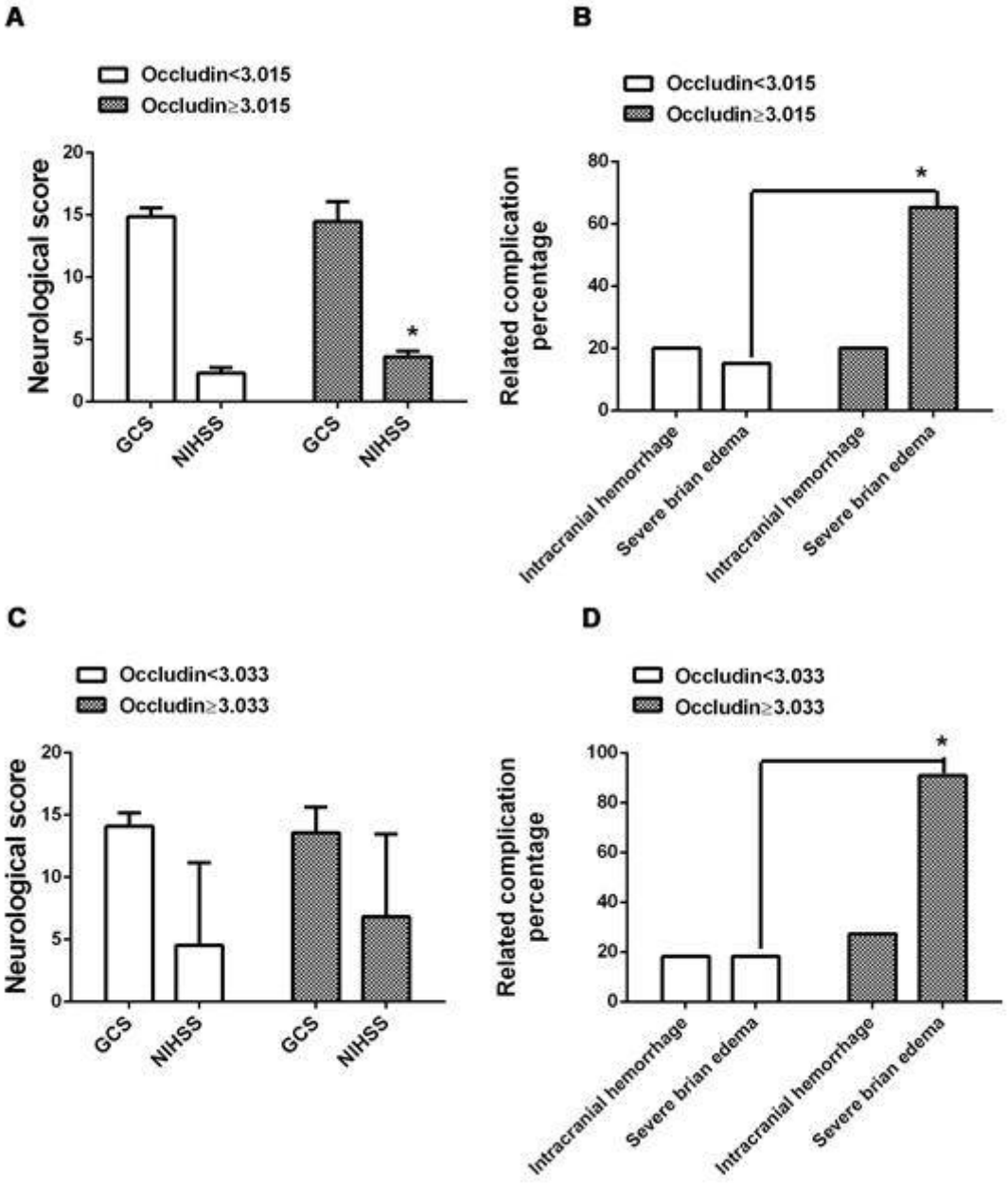

Figure 5

The relationship between serum occludin level and clinical outcomes in patients with brain tumors. (A) Comparison of NIHSS and GCS scores at admission between patients with a preoperative occludin level <3.015 ng/mL (n = 40) and those with a preoperative occludin level ≥3.015 ng/mL (n = 15). (B) Comparison of the incidences of preoperative severe brain edema and intracranial hemorrhage between patients with a preoperative occludin level <3.015 ng/mL (n = 40) and those with a preoperative occludin level ≥3.015 ng/mL (n = 15). (C) Comparison of NIHSS and GCS scores at 1 day after surgery between patients with a postoperative occludin level <3.033 ng/mL (n = 44) and those with a postoperative occludin level ≥3.033 ng/mL (n = 11). (D) Comparison of the incidences of postoperative severe brain

edema and intracranial hemorrhage between patients with a postoperative occludin level <3.033 ng/mL (n = 44) and those with a postoperative occludin level ≥3.033 ng/mL (n = 11).