Original Article

Correlation analysis between TSP2, MMP-9 and perihematoma edema, as well as the short-term prognosis of patients with hypertensive intracerebral hemorrhage

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Background: To analyze the correlation between thrombospondin-2 (TSP2), matrix metalloproteinase (MMP)-9, and perihematomal edema, as well as the short-term prognosis of patients with hypertensive intracerebral hemorrhage.

Methods: The clinical data of 114 patients with hypertensive intracerebral hemorrhage admitted to our hospital from January 2018 to February 2020 were collected and divided into groups according to the levels of TSP2 and MMP-9. We compared edema indexes in patients with different levels of TSP2 and MMP-9, and analyzed the correlation between TSP2, MMP-9 and relative edema volume index (REI), edema change index (AEI). We also assessed the TSP2 and MMP-9 levels in patients with different prognoses, and analyzed the predictive value of TSP2 and MMP-9 for poor prognosis of patients.

Results: (I) There was no difference in the REI and AEI values between the low and high TSP2 groups at admission and 24 h after admission ($P>0.05$), while the REI and AEI values of the high TSP2 group at 5 and 15 d after admission were significantly lower than those of the low TSP2 group ($P<0.05$); (II) the REI and AEI values of patients with different MMP-9 levels were not different between admission and 24 h after admission ($P>0.05$), while the REI and AEI values of the high MMP-9 group were significantly higher than those of the low MMP-9 group at 5 and 15 d after admission ($P<0.05$); (III) Pearson correlation analysis showed that MMP-9 was positively correlated with REI and AEI, while TSP2 was negatively correlated ($P<0.05$); (IV) among 114 patients, 39 had poor prognosis, 75 had good prognosis The MMP-9 levels of patients with a poor prognosis were significantly higher than those of patients with a good prognosis, and the TSP2 level was the opposite ($P<0.05$); (V) receiver operating characteristic (ROC) curve showed that the sensitivity, specificity and the area under the curve (AUC) of the TSP2 + MMP-9 combination in the diagnosis of hypertensive cerebral hemorrhage were significantly higher than when TSP2 and MMP-9 were tested separately ($P<0.05$).

Conclusions: In patients with hypertensive intracerebral hemorrhage, TSP2 is negatively correlated with edema around the hematoma, while MMP-9 is positively correlated.

Keywords: Hypertensive cerebral hemorrhage; thrombospondin-2 (TSP2); matrix metalloproteinase-9 (MMP-9); edema around the hematoma; short-term prognosis

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Introduction

Due to the long-term effects of hypertension and cerebral arteriosclerosis, patients with hypertensive cerebral hemorrhage may have pathological changes in the small cerebral arteries. For these patients, blood pressure is not controlled over a long period of time, and intracranial vascular rupture and bleeding can be caused by excessive blood fluctuations. The disease progresses rapidly with high morbidity and mortality (1). Hypertension, age and dyslipidemia are risk factors for hypertensive cerebral hemorrhage. The factors leading to a poor prognosis in hypertensive intracerebral hemorrhage include primary mechanical injury, secondary mechanical bleeding, inflammatory response, and secondary brain edema. Among these factors, brain edema is the key factor for the secondary injury of patients, which can lead to intracranial hypertension, affect the nervous system and brain tissue, and is an important factor leading to poor prognosis and death of cerebral hemorrhage. Previous studies have found that the coefficient of variation of arterial pressure and average artery can affect the risk factors of perihematoma edema in patients with hypertensive intracerebral hemorrhage (2). Paying attention to the prevention of related risk factors in clinical practice is of positive significance to improve the prognosis of patients. Studies have found that matrix metalloproteinase (MMP) may be involved in the formation and progress of brain edema as well as a variety of molecular interactions (3). MMP-9 is one of the members of the MMP family; it has a degradation effect on the vascular basement membrane of the body and can promote the migration of neutrophils, thereby aggravating local inflammation and ultimately damaging the cerebrovascular barrier and further triggering brain edema (4). Studies have also reported that thrombospondin (TSP) can regulate the expression of MMP, indicating that TSP has a certain relationship with cerebral vascular barrier structural damage (5). Based on this, this paper compares the edema around hematoma in patients with different levels of TSP2 and MMP-9, and analyzes the correlation between TSP2, MMP-9 and edema around hematoma, as well as the short-term prognosis. We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2553).

Methods

General information

The clinical data of 114 patients with hypertensive cerebral hemorrhage admitted to our hospital from January 2018 to February 2020 were collected, including 63 males and 51 females, aged 38–76 years, with an average age of 51.26±3.29 years. The inclusion criteria were as follows: (I) patients diagnosed according to the national cerebrovascular disease academic conference diagnostic criteria (6); (II) all cases were diagnosed by CT or MRI; (III) cases where the subtentorial hemorrhage did not enter the ventricle; (IV) patients aged ≥18 years; and (V) all patients underwent surgical treatment. The exclusion criteria were as follows: (I) patients combined with liver cell injury, malignant tumor, nephrotic syndrome, tuberculosis, and other diseases; (II) incidence at admission >48 h; (III) cases involving cerebral hemorrhage secondary to other systemic diseases; and (IV) patients who had used anticoagulant drugs prior to admission. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Sichuan Provincial People's Hospital [Lunshen (Research) No. 419, 2020]. Individual consent for this retrospective analysis was waived.

Study methods

Grouping

A total of 114 patients were subjected to intravenous blood sampling (4 mL) within 24 h after admission, and the serum was separated after centrifugation. TSP2 and MMP-9 were detected by enzyme-linked immunosorbent assay (ELISA). The kits were provided by Wuhan Boster Company (Hubei), and the operation was carried out in strict accordance with the manufacturer's instructions. The patients were divided into groups according to the levels of TSP2 and MMP-9 [low TSP2 group (≤106 ng/mL, 41 cases), high TSP2 group (>106 ng/mL, 73 cases); low MMP-9 group (≤66 μg/mL, 46 cases), and high MMP-9 group (>66 μg/mL, 68 cases)] (7).

Edema measurement method

All patients were examined by CT at 24 h, 3 d, and 7 d after admission. The volume of cerebral hematoma and its

Table 1 Comparison of edema indexes in patients with different levels of TSP2 ($\bar{x}$±s)

Group	Case number	REI				AEI		
		On admission	24 h	5 d	15 d	24 h	5 d	15 d
Low TSP2 group	41	1.04±0.10	1.11±0.15	2.78±0.37	2.54±0.51	0.30±0.17	1.82±0.18	0.96±0.37
High TSP2 group	73	1.02±0.12	1.09±0.16	1.65±0.21	1.08±0.17	0.32±0.15	0.44±0.16	0.41±0.17
t	–	0.904	0.654	20.832	22.406	0.650	42.235	10.849
P	–	0.367	0.513	<0.001	<0.001	0.516	<0.001	<0.001

TSP2, thrombospondin-2; REI, relative edema volume index; AEI, edema change index.

surrounding edema were detected, and secondary cerebral infarction was excluded. The changes of the cerebral hematoma and its surrounding edema were dynamically detected. The hematoma and edema were calculated using the Careteam RIS & PACS imaging system (Version 11.0) (Neusoft, Shenyang) for CT quantification, and the hematoma volume (Vh), total specific lesion volume (Vt), and absolute edema volume [(Vp) = Vt – Vh] were measured. Vp – Vh (measured at initial admission) = relative edema volume index (REI), [Vp (4d, 15d after onset) – Vp (at admission)]/Vh (measured at initial admission) = edema change index (AEI).

Follow-up

From the first day after the end of treatment, a 6-month follow-up was conducted to understand the prognosis of patients by outpatient follow-up or telephone. The Modified Rankin Scale (MRS) was used to evaluate the prognosis of neurological function in patients: MRS >3 indicated poor prognosis, while MRS ≤3 signified a good prognosis.

Observation indicators

(I) The edema indexes of patients with different levels of TSP2 and MMP-9 were compared;
(II) The correlation between TSP2, MMP-9 and edema degree was analyzed;
(III) The levels of TSP2 and MMP-9 in patients with different prognoses were compared;
(IV) The predictive value of TSP2 and MMP-9 for poor prognosis of patients was analyzed.

Statistical analysis

SPSS20.0 software (SPSS, Chicago, USA) was used for statistical analysis of the data in this study. The measurement data were described by mean ± standard deviation ($\bar{x}$±s), as well as the *t*-test and variance test among multiple groups. The pass rate or constituent ratio of count data was expressed, and the χ^2 test was used. Pearson's test was used to analyze the correlation between TSP2, MMP-9 and the edema degree index. A ROC curve was drawn to analyze the predictive value of TSP2 and MMP-9 for poor prognosis of patients, and the area under the curve (AUC) was calculated. P<0.05 indicated that the difference was statistically significant.

Results

Comparison of edema indexes in patients with different levels of TSP2 and MMP-9

Comparison of edema index in patients with different levels of TSP2

There was no significant difference in the REI value between the low and high TSP2 groups at admission and 24 h after admission (P>0.05). The REI value of the high TSP2 group at 5 and 15 d after admission was significantly lower than that of the low TSP2 group (P<0.05). The AEI value of the high TSP2 group at 5 and 15 d after admission was significantly lower than that of the low TSP2 group (P<0.05), as shown in *Table 1*.

Comparison of edema indexes in patients with different levels of MMP-9

There was no significant difference in the REI value between the low and high MMP-9 groups at admission and 24 h after admission (P>0.05). The REI value of the high MMP-9 group at 5 and 15 d after admission was significantly higher than that of the low MMP-9 group (P<0.05). The AEI of the high MMP-9 group at 5 and 15 d after admission was significantly higher than that of the low

Table 2 Comparison of edema indexes of MMP-9 patients at different levels ($\bar{x}$±s)

Group	Case number	REI				AEI		
		On admission	24 h	5 d	15 d	24 h	5 d	15 d
Low MMP-9 group	46	1.10±0.21	1.12±0.17	1.57±0.31	1.44±0.31	0.26±0.11	1.08±0.19	0.87±0.21
High MMP-9 group	68	1.09±0.12	1.14±0.11	2.41±0.21	2.93±0.74	0.28±0.10	1.67±0.11	1.94±0.61
t	–	0.322	0.763	17.259	12.897	1.006	20.959	11.433
P	–	0.747	0.447	<0.001	<0.001	0.316	<0.001	<0.001

MMP-9, matrix metalloproteinase-9; REI, relative edema volume index; AEI, edema change index.

Table 3 Correlation analysis between TSP2, MMP-9 and edema index

Factor	REI		AEI	
	r	P	r	P
TSP2	–0.297	0.024	–0.398	0.012
MMP-9	0.748	<0.001	0.695	<0.001

TSP2, thrombospondin-2; MMP-9, matrix metalloproteinase-9; REI, relative edema volume index; AEI, edema change index.

Table 4 Comparison of TSP2 and MMP-9 levels in patients with different prognoses ($\bar{x}$±s)

Group	Case number	TSP2 (ng/ mL)	MMP-9 (μg/mL)
Good prognosis	75	187.84±10.17	52.26±7.41
Poor prognosis	39	95.26±6.54	213.15±10.64
t	–	51.521	94.299
P	–	<0.001	<0.001

TSP2, thrombospondin-2; MMP-9, matrix metalloproteinase-9.

MMP-9 group (P<0.05), as shown in *Table 2*.

Correlation analysis between TSP2, MMP-9 and edema index

Pearson correlation analysis showed that MMP-9 was positively correlated with REI and AEI, and TSP2 was negatively correlated with REI and AEI (P<0.05), as shown in *Table 3*.

Comparison of TSP2 and MMP-9 levels in patients with different prognosis

Among the 114 included patients, 39 had poor prognosis, and 75 had good prognosis. The MMP-9 levels in patients with poor prognosis were significantly higher than those in patients with good prognosis, and the TSP2 levels were lower than those in patients with good prognosis. The difference between groups was statistically significant (P<0.05), as shown in *Table 4*, *Figures 1-4*.

Predictive value of TSP2 and MMP-9 for poor prognosis of patients

According to the ROC curve, the sensitivity and specificity of TSP2 + MMP-9 in the diagnosis of hypertensive cerebral hemorrhage were 84.50% and 78.90%, respectively. The AUC =0.803 (95% CI: 0.704–0.901), which was significantly higher than that of TSP2 and MMP-9 alone (P<0.05), as shown in *Table 5* and *Figure 5*.

Discussion

The internal and surgical treatment of hypertensive cerebral

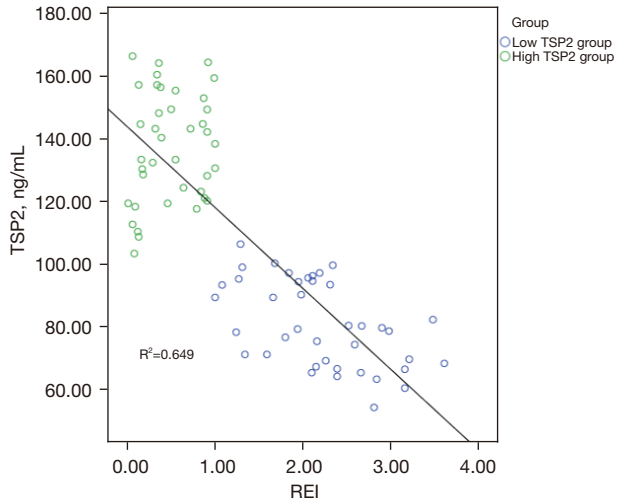

Figure 1 Correlation between TSP2 and edema index REI. TSP2, thrombospondin-2; REI, relative edema volume index.

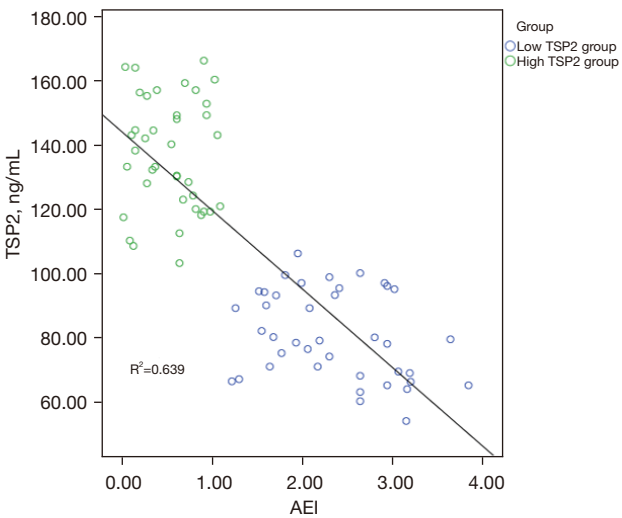

Figure 2 Correlation between TSP2 and edema index AEI. TSP2, thrombospondin-2; AEI, edema change index.

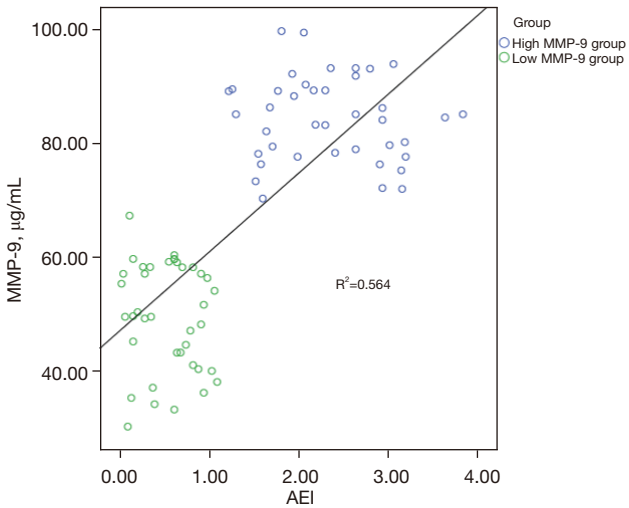

Figure 3 Correlation between MMP-9 and edema index AEI. MMP-9, matrix metalloproteinase-9; AEI, edema change index.

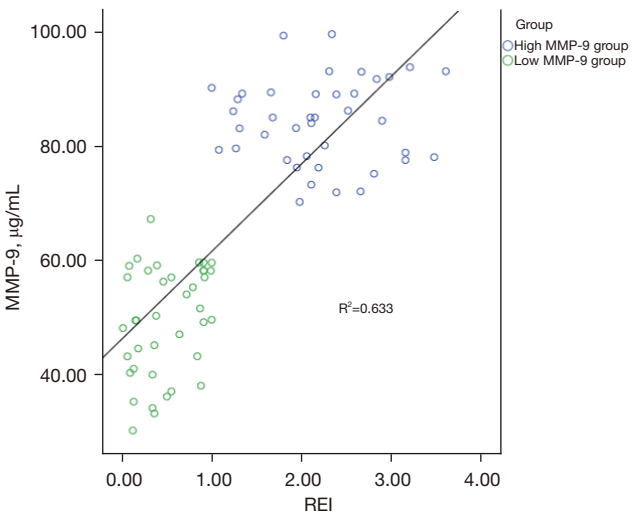

Figure 4 Correlation between MMP-9 and edema index REI. MMP-9, matrix metalloproteinase-9; REI, relative edema volume index.

Table 5 Predictive value of TSP2 and MMP-9 on poor prognosis of patients

Predictor	AUC	95% CI	Sensitivity	Specificity
TSP2	0.693	0.576–0.811	0.698	0.681
MMP-9	0.762	0.655–0.868	0.734	0.675
TSP2 + MMP-9	0.803	0.704–0.901	0.845	0.789

AUC, area under the curve; TSP2, thrombospondin-2; MMP-9, matrix metalloproteinase-9.

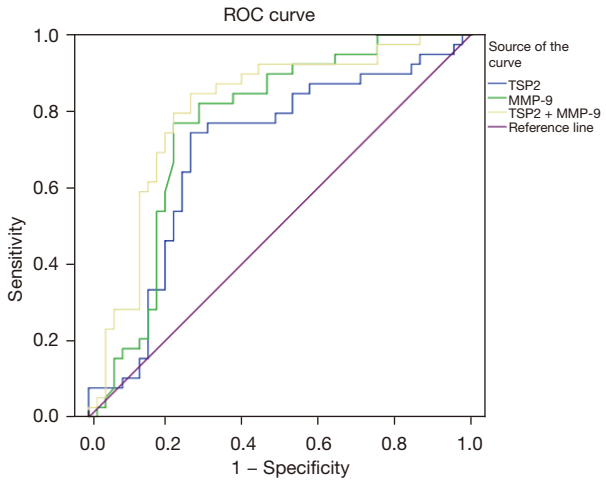

Figure 5 ROC curve of TSP2 and MMP-9 in predicting poor prognosis of patients. ROC, receiver operating characteristic; TSP2, thrombospondin-2; MMP-9, matrix metalloproteinase-9.

hemorrhage has made great progress, and early minimally invasive surgery and drug combination therapy can achieve satisfactory therapeutic effect. However, cerebral hemorrhage itself and the effect of intracerebral hematoma occupancy after cerebral hemorrhage can cause brain tissue damage, which is an important pathological factor leading to poor prognosis of patients. An effective strategy to reduce the mortality of patients would involve clarifying the cerebral hemorrhage situation, timely removal of the hematoma, reducing brain tissue damage, and preventing secondary cerebral hemorrhage (8).

MMP is a zinc-dependent protease secreted by astrocytes and endothelial cells, and MMP-9 is an important functional subtype. The main role of MMP-9 is the degradation of extracellular matrix components (9). Under normal conditions, the expression level of MMP-9 in blood and brain tissue is low. Once the body has tumor, inflammation, and other pathological conditions, the level of MMP-9 is significantly increased. It has been shown that the expression of MMP-9 in the brain tissue of patients with cerebral hemorrhage is up-regulated; hydrolyzed laminin, collagen fibers, and other causes of cell tight junctions and extracellular matrix molecules are destroyed, the permeability of cerebral vascular barrier is increased, and the occurrence of cerebral edema is promoted (10,11). Mouchtouris *et al.* (12) found that the MMP-9 levels of hypertensive cerebral hemorrhage patients with neurological symptoms within 24 hours were significantly increased, and were positively correlated to the degree of edema around the hematoma as well as to patients with consciousness disturbance. In this study, it was observed that the 5 and 15 d REI and AEI values in the low MMP-9 group were significantly lower than those in the high MMP-9 group after admission, and were positively correlated with the edema indexes REI and AEI. These results are consistent with the findings of previous studies (13).

TSP is a family of glycoproteins that are highly related to the structure and function of the body, and exhibit regulatory properties. TSP is secreted by platelets and inner-screening cells when activated in a high blood glucose environment. The stimulation of neurons and glial cells to a certain extent can lead to a large number of TSP secretions, and TSP2 is an important member of the TSP family (14,15). Previous studies have reported that the role of TSP is closely related to the expression level of MMP (16,17). Studies have also found that TSP1 can inhibit MMP-9, thereby controlling tumor angiogenesis (18). Gürpınar *et al.* (19) demonstrated that TSP2 gene expression in colorectal cancer cells can reduce the expression of MMP-9 and MMP-2. Huang *et al.* (20) analyzed the correlation between TSP, hematoma, and peripheral edema in patients with cerebral hemorrhage. They found that the level of TSP2 increased within 3–5 days after onset, which may be related to the inhibition of MMP, the protection of the blood-brain barrier, the promotion of hematoma regression, the improvement of secondary cerebral edema, and the reduction of neurological impairment.

In this study, the REI and AEI values of high TSP2 patients were lower than those of low TSP2 patients at 5 and 15 d after admission, and were negatively correlated with perihematoma edema, which was consistent with the aforementioned findings. However, the research on the expression and regulation of MMP regulated by TSP has not been perfect, and requires further exploration. According to the analysis of different prognoses, the MMP-9 levels of patients with a poor prognosis were significantly higher than those of patients with a good prognosis, while the TSP2 levels of these patients were lower than those of patients with a good prognosis. The ROC curve showed that the combination of TSP2 and MMP-9 had a high value in evaluating the prognosis of patients, suggesting that in the course of treatment, the detection of TSP2 and MMP-9 levels in patients can be used as an effective indicator for clinical prognosis.

In conclusion, TSP2 is negatively correlated with perihematoma edema in patients with hypertensive

intracerebral hemorrhage, and MMP-9 is positively correlated. Both of these can provide new ideas for the diagnosis and prognosis of secondary edema in patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2553). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Sichuan Provincial People's Hospital [Lunshen (Research) No.419, 2020]. Individual consent for this retrospective analysis was waived.

References

1. Liu J, Li Q, Ren J, et al. Association of Sex with Serum Potassium, Sodium, and Calcium Disorders after Hypertensive Intracerebral Hemorrhage. World Neurosurg 2020;141:e367-e373.
2. Hu S, Ma Q, Li B, et al. Association of Hypothyroidism with Hypertensive Intracerebral Hemorrhage: A Case-Control Study. World Neurosurg 2020;134:e8-e11.
3. Shao X, Wang Q, Shen J, et al. Comparative Study of Micro-Bone Window and Conventional Bone Window Microsurgery for Hypertensive Intracerebral Hemorrhage. J Craniofac Surg 2020;31:1030-3.
4. Yang Q, Zhuang X, Peng F, et al. Relationship of plasma matrix metalloproteinase-9 and hematoma expansion in acute hypertensive cerebral hemorrhage. Int J Neurosci 2016;126:213-8.
5. Xia L, Han Q, Ni XY, et al. Different Techniques of Minimally Invasive Craniopuncture for the Treatment of Hypertensive Intracerebral Hemorrhage. World Neurosurg 2019;126:e888-e894.
6. Hawkes MA, Rabinstein AA. Acute Hypertensive Response in Patients With Acute Intracerebral Hemorrhage: A Narrative Review. Neurology 2021;97:316-29.
7. Tsai HH, Chen SJ, Tsai LK, et al. Long-Term Vascular Outcomes in Patients With Mixed Location Intracerebral Hemorrhage and Microbleeds. Neurology 2021;96:e995-e1004.
8. Xu S, Du B, Shan A, et al. The risk factors for the postoperative pulmonary infection in patients with hypertensive cerebral hemorrhage: A retrospective analysis. Medicine (Baltimore) 2020;99:e23544.
9. You S, Zheng D, Delcourt C, et al. Determinants of Early Versus Delayed Neurological Deterioration in Intracerebral Hemorrhage. Stroke 2019;50:1409-14.
10. Esfandiari G, Biranvand AS, Poursaleh A, et al. Effect of a Peptide Construct on Differentiated Macrophage MMP-2 and MMP-9 Levels of Varicose Patients. Curr Pharm Des 2019;25:4303-9.
11. Pasi M, Charidimou A, Boulouis G, et al. Cerebral small vessel disease in patients with spontaneous cerebellar hemorrhage. J Neurol 2019;266:625-30.
12. Mouchtouris N, Saiegh FA, Chalouhi N, et al. Low diagnostic yield in follow-up MR imaging in patients with spontaneous intracerebral hemorrhage with a negative initial MRI. Neuroradiology 2021;63:1009-12.
13. Eslami V, Tahsili-Fahadan P, Rivera-Lara L, et al. Influence of Intracerebral Hemorrhage Location on Outcomes in Patients With Severe Intraventricular Hemorrhage. Stroke 2019;50:1688-95.
14. Vila V, Martínez-Sales V, Almenar L, et al. Inflammation, endothelial dysfunction and angiogenesis markers in chronic heart failure patients. Int J Cardiol

2008;130:276-7.
15. Chuck C, Kalagara R, Abrantes T, et al. Abstract P455: Time to Blood Pressure Control and Association With Outcomes in Intracerebral Hemorrhage. Stroke 2021;52:85-6.
16. Gong W, Zhang S, Li X, et al. Dexmedetomidine is superior to midazolam for sedation and cerebral protection in postoperative hypertensive intracerebral hemorrhage patients: a retrospective study. J Int Med Res 2020;48:300060520957554.
17. Tsai HH, Pasi M, Tsai LK, et al. Superficial Cerebellar Microbleeds and Cerebral Amyloid Angiopathy: A Magnetic Resonance Imaging/Positron Emission Tomography Study. Stroke 2020;51:202-8.
18. Sun G, Li X, Chen X, et al. Comparison of keyhole endoscopy and craniotomy for the treatment of patients with hypertensive cerebral hemorrhage. Medicine (Baltimore) 2019;98:e14123.
19. Gürpınar T, Kosova F, Kurt FO, et al. Effect of geldanamycin on the expression of the matrix molecules and angiogenetic factors in a gastric cancer cell line. Biotech Histochem 2021;96:111-6.
20. Huang X, Lan Y, Li E, et al. Diagnostic values of MMP-7, MMP-9, MMP-11, TIMP-1, TIMP-2, CEA, and CA19-9 in patients with colorectal cancer. J Int Med Res 2021;49:3000605211012570.

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