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The Prognostic Value of Serum ET-1, MCP-1, and Lactic Acid Levels in Patients with Ruptured Intracranial Aneurysm After Interventional Embolization

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ABSTRACT

AIM: To evaluate the prognostic value of serum endothelin-1 (ET-1), monocyte chemotactic protein-1 (MCP-1), and lactic acid (LA) levels in patients with ruptured intracranial aneurysm (IA) after interventional embolization.

MATERIAL and METHODS: Patients with ruptured IA were divided into mild, moderate, and severe groups according to Hunt-Hess grades, and the correlation between serum parameters and disease severity was analyzed. Multivariate logistic regression was employed to analyze the influence of serum ET-1, MCP-1, and LA levels on the prognosis of patients, and ROC curves were plotted to analyze the predictive value of these parameters.

RESULTS: There were 29 cases in the mild group (grade I), 49 cases in the moderate group (grade II-III), and 25 cases in the severe group (grade IV-V). In the severe group, serum ET-1, MCP-1, and LA were elevated compared to the moderate and mild groups, with the moderate group showing higher levels than the mild group. Serum ET-1, MCP-1, and LA levels were positively correlated with the severity of IA ($p<0.05$). The Hunt-Hess grade, Fisher grade, and serum ET-1, MCP-1, and LA levels in patients with poor prognosis were higher than those with good prognosis. Hunt-Hess grade IV-V, Fisher grade 3 to 4, ET-1 ≥ 41.78 pg/mL, MCP-1 ≥ 229.05 ng/L, and LA ≥ 7.13 mmol/L were risk factors affecting the prognosis of patients after interventional embolization. The AUC values of serum ET-1, MCP-1, and LA levels to evaluate the prognosis of patients were 0.772, 0.871, and 0.791, respectively.

CONCLUSION: Serum ET-1, MCP-1, and LA levels correlate with disease severity in patients with ruptured IA and have predictive values for the prognosis of patients after interventional embolization. They are risk factors for poor prognosis of patients after interventional embolization.

KEYWORDS: Intracranial aneurysms, Interventional embolization, Endothelin-1, Monocyte chemotactic protein-1, Lactic acid, Prognosis

INTRODUCTION

Intracranial aneurysm (IA), or intracranial aneurysms, are localized pathological dilatations on cerebral arteries, identified by weakened vessel walls (9). In individuals free from comorbidities, unruptured IA has a prevalence of about 3.2%, typically emerging at the mean age of 50 (22). Unruptured IA generally presents no symptoms and may remain hidden until a rupture happens. Upon rupture, it frequently results in aneurysmal subarachnoid hemorrhage (SAH) with potentially severe outcomes. The mortality rate for aneurysmal SAH continues to be about 30-40%, despite advances in neurosurgical intensive care (16), and close to half of the survivors encounter disabilities or persistent cognitive difficulties (3,4). The level of lactic acid (LA) in cerebrospinal fluid of patients with IA was increased (20). LA in cerebrospinal fluid is produced by anaer-

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obic glycolysis in neurons and neuroastrocytes. The pyruvate formed by glycolysis is reduced to LA under hypoxia conditions. The use of serum LA levels to predict postoperative outcomes of IA still requires more investigation. Endothelin-1 (ET-1) has a contractile effect on blood vessels (23). ET-1 is involved in vascular dysfunction associated with cardiovascular diseases, including arterial spasms after cerebral aneurysm rupture and hemorrhage, atherosclerosis, hypertension, and cardiac hypertrophy. Monocyte chemoattractant protein-1 (MCP-1) has a strong chemoattractant effect on monocyte macrophages, which can infiltrate the damaged brain parenchyma. As a result, MCP-1 present in the serum can indirectly signify the severity of brain tissue damage (7,14). Therefore, the purpose of this study was to explore the prognostic value of serum ET-1, MCP-1, and LA levels of patients with ruptured IA after interventional embolization.

MATERIAL and METHODS

Clinical Data

This was a prospective study that followed STROBE guidelines. The study was approved by The Affiliated Hospital of Guangdong Medical University (No.202105ZJ-3) ethics committee and informed consent was obtained from all patients. A total of 103 patients with ruptured IA with SAH were studied, including 62 males and 41 females. There were 58 patients aged ≥ 60 years and 45 patients aged < 60 years, 45 cases with hypertension, and 39 cases with diabetes. Hunt-Hess classification identified 29 cases of grade I, 49 cases of grade II- III, and 25 cases of grade IV-V. There were 50 cases with anterior communicating artery aneurysms, 24 cases with internal carotid aneurysms, 4 cases with middle cerebral aneurysms, 14 cases with posterior communicating aneurysms, and 11 cases with vertebrobasilar aneurysms.

Inclusion Criteria

1) Spontaneous SAH was diagnosed by computed tomography (CT) (25); 2) Patients met the diagnostic criteria for IA; 3) Patients had complete clinical data; 4) Patients underwent interventional embolization.

Exclusion Criteria

1) Patients had severe cardiac, liver, and renal dysfunction; 2) Patients did not undergo embolization or craniotomy; 3) Patients had multiple aneurysms; 4) Patients had incomplete clinical data.

Ethical Statement

The present study was approved by the Ethics Committee of The Affiliated Hospital of Guangdong Medical University (No.202105ZJ-3) and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Interventional embolization

The patients underwent a routine examination before surgery and femoral artery puncture using the Seldinger technique after general anesthesia. Angiography was conducted on both the vertebral and internal carotid arteries. Thompson and lateral photographs were taken, and oblique photographs at appropriate angles were selected. After being diagnosed, the catheter was replaced and patients were administered heparin. The microcatheter was guided into the aneurysm. Using coils, the aneurysm was embolized while keeping the artery open. The catheter was slowly withdrawn once it was confirmed that there was no contrast agent left in the aneurysm. The catheter sheath was removed 6 h after interventional embolization, and the femoral artery was compressed about 15 mm at about 1 cm above the puncture point. Once bleeding had ceased, a compression bandage was administered, and the lower limb of the puncture site was immobilized for 24 hours after the interventional embolization.

Serum ET-1, MCP-1 and LA levels

Fasting peripheral venous blood samples of 5 mL were taken from all patients before and one week after surgery, then centrifuged at 3000 rpm for 10 min. Serum ET-1 level was measured by radioimmunoassay with the detection kit (Beijing Purevalley Biotechnology Co., Ltd.). Serum MCP-1 level was detected by ELISA kits (R&D Company, USA). Serum LA level was detected by Abbott C8000 automatic biochemical analyzer.

Severity

According to Hunt-Hess classification (13), the patients were divided into the mild group (grade I, 29 cases), moderate group (grade II-III, 49 cases), and severe group (grade IV-V, 25 cases).

Outcome Measures

The prognosis was assessed using the Glasgow Outcome Scale (GOS) six months post-operation (12). The scoring system assigned 1 point for death, 2 points for a vegetative state with minimal responses, 3 points for clear consciousness accompanied by severe disability or inability to live independently, 4 points for mild disabilities capable of independent living and work, and 5 points for recovery with slight defects. In 35 cases, a score of 1 to 3 points was indicative of a poor prognosis, while in 68 cases, a score of 4 to 5 points indicated a good prognosis.

Statistical Analysis

All data were evaluated by SPSS 22.0 software. Enumeration data (%) were subjected to comparative analysis using χ^2 test, and measurement data (mean ± standard deviation) after normal tests were compared by *t*-test. Spearman test was applied to analyze the correlation between serum parameters and disease severity. Multivariate logistic regression was conducted to analyze the effects of serum ET-1, MCP-1, and LA levels on the prognosis of patients, and ROC curves were plotted to analyze the prognostic value of each index. P<0.05 emphasized a significant statistical difference.

RESULTS

Changes in preoperative and 1-week postoperative serum ET-1, MCP-1, and LA levels Serum ET-1, MCP-1, and LA levels decreased at 1 week postoperatively compared with preoperatively (p<0.05, Table I). Serum ET-1, MCP-1, and LA levels in patients with different severity

In the severe group, serum ET-1, MCP-1, and LA levels were elevated compared to the moderate and mild groups, with the moderate group showing higher levels than the mild group (p<0.05, Figure 1).

Correlation analysis

Serum ET-1, MCP-1, and LA levels were positively correlated with disease severity (p<0.05, Figure 2).

Univariate analysis of prognosis

The Hunt-Hess grade, Fisher grade, and serum ET-1, MCP-1, and LA levels were higher in patients with poor prognosis than those with good prognosis (p<0.05, Table II).

Multivariate analysis of prognosis

Hunt-Hess grade IV-V, Fisher grade 3-4, ET-1 ≥ 41.78 pg/ml, MCP-1 ≥ 229.05ng/L, LA ≥ 7.13 mmol/L were risk factors affecting the prognosis of patients after interventional embolization (p<0.05, Table III).

Evaluation value of serum ET-1, MCP-1, and LA levels for prognosis of patients

The AUC values of serum ET-1, MCP-1, and LA levels for the prognosis of patients were 0.772, 0.871, and 0.791, respectively (Table IV and Figure 3).

Table I: Serum ET-1, MCP-1 and Lactate Levels in Patients

Factors	Before operation	1 week after operation	t	p-value
ET-1 (pg/ml)	38.87 ± 13.50	30.12 ± 8.36	5.593	<0.001
MCP-1 (ng/L)	213.91 ± 44.40	175.45 ± 20.94	7.951	<0.001
Lactic acid (mmol/L)	6.64 ± 1.68	5.69 ± 2.03	3.659	<0.001

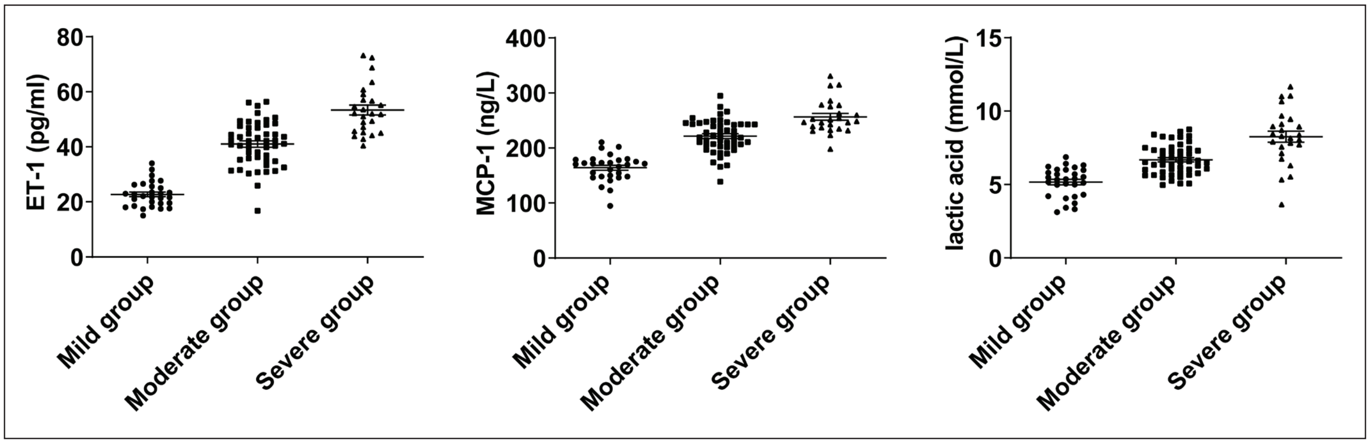

Figure 1: Serum ET-1, MCP-1, and LA levels in patients with different severity.

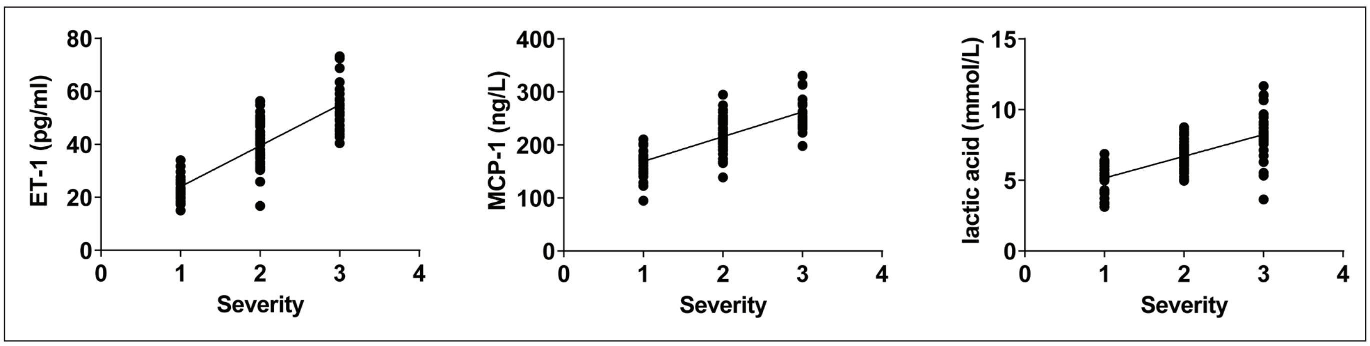

Figure 2: Correlation analysis of serum ET-1, MCP-1, LA levels and severity of disease.

Table II: Univariate Analysis of Prognosis After Interventional Embolization

Factors		Poor prognosis (n = 35)	Good prognosis (n = 68)	χ^2/t	p-value
Gender	Male	20	42	0.206	0.650
	Female	15	26		
Age (years)	≥ 60	19	39	0.088	0.766
	< 60	16	29		
Combined hypertension		15	30	0.015	0.903
Combined diabetes		13	26	0.012	0.914
Hunt-Hess grade	I	5	24	21.698	<0.001
	II-III	12	37		
	IV-V	18	7		
Location	Anterior communicating aneurysm	19	31	1.751	0.781
	Internal carotid aneurysm	8	16		
	Middle cerebral aneurysm	1	3		
	Posterior communicating aneurysm	5	9		
	Vertebrobasilar aneurysm	2	9		
Operation timing	Early stage	16	30	0.104	0.949
	Middle stage	2	5		
	Late stage	17	33		
Tumor diameter	< 15 mm	16	29	0.088	0.766
	≥ 15 mm	19	39		
Ratio of tumor length diameter to width	< 0.5	13	27	0.064	0.800
	≥ 0.5	22	41		
Fisher grade	1-2	12	42	6.996	0.008
	3-4	23	26		
ET-1 (pg/ml)		52.81 ± 10.37	30.08 ± 6.52	13.615	<0.001
MCP-1 (ng/L)		263.85 ± 42.21	189.52 ± 30.19	10.296	<0.001
Lactic acid (mmol/L)		8.72 ± 1.28	5.75 ± 1.03	12.742	<0.001

Table III: Multivariate Analysis of Prognosis After Interventional Embolization

Factors	β	SE	wald χ^2	OR	95%CI	p-value
Hunt-Hess grade	0.583	0.134	18.929	1.791	1.378~2.329	< 0.001
Fisher grade	0.819	0.257	10.156	2.268	1.371~3.754	0.002
ET-1	0.673	0.291	5.349	1.96	1.108~3.467	0.021
MCP-1	0.438	0.201	4.748	1.55	1.045~2.298	0.030
Lactic acid	0.749	0.228	10.792	2.115	1.353~3.306	0.001

Assignment: *Hunt-Hess grade (1 for grades IV to V, 0 for grades I to III); Fisher grade (1 for grades 3 to 4, 0 for grades 1 to 2); ET-1 (≥ 41.78 pg/ml was 1, < 41.78 pg/ml was 0); MCP-1 (≥ 229.05 ng/L was 1, < 229.05 ng/L was 0); Lactic acid (≥ 7.13 mmol/L was 1, < 7.13 mmol/L was 0).*

Table IV: Prognostic Value of Serum ET-1, MCP-1 and Lactate Levels in Patients

Factors	Cut-off value	AUC	SE	95%CI	p-value
ET-1	41.78 pg/ml	0.772	0.056	0.662~0.883	<0.05
MCP-1	229.05 ng/L	0.871	0.037	0.799~0.942	<0.05
Lactic acid	7.13 mmol/L	0.791	0.051	0.691~0.890	<0.05

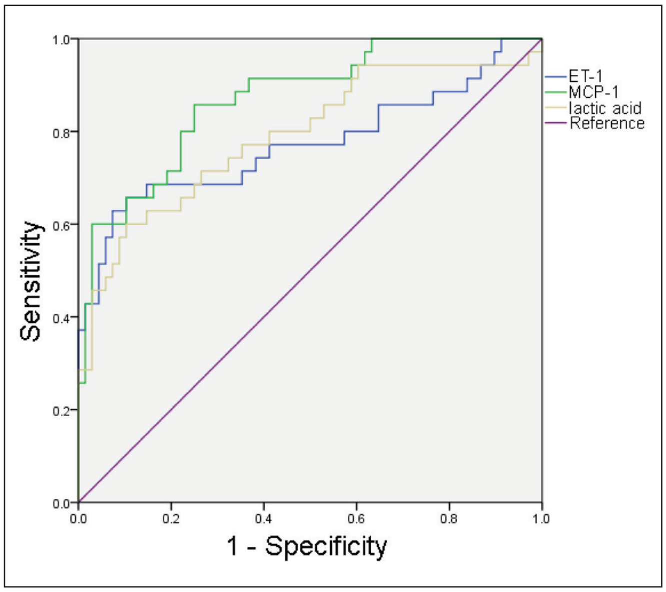

Figure 3: ROC curve of serum ET-1, MCP-1, and LA levels.

DISCUSSION

IA poses a significant public health challenge, impacting 3.2%-7.0% of adults (8). Aneurysm rupture and bleeding are major threats to IA, clinically manifested as severe subarachnoid hemorrhage, rapid onset, and severe headache. Patients might experience symptoms like projectile vomiting due to elevated intracranial pressure, and in severe instances, they may lose consciousness or fall into a coma. Surgical intervention is the mainstay of IA treatment, and DSA-guided aneurysm embolization has become the predominant treatment for most IA patients. MCP-1 acts as a chemotactic agent for mononuclear macrophages, being a specific inflammatory cytokine, and is expressed at low levels in healthy human brain tissue. In the event of brain tissue damage, macrophages and neurons release significant amounts of MCP-1, attracting mononuclear macrophages to infiltrate the brain parenchyma and contribute to brain injury. Therefore, MCP-1 level can indirectly reflect the severity of brain tissue injury (19,26). ET-1 is involved in vascular dysfunction related to cardiovascular diseases (1,4). As a potent vasoconstricting active substance released after blood vessel damage, ET-1 can stimulate the enhancement of platelet activity, aggravation of microcirculation disorders, vasospasm, and damage of neurons (21). It is currently believed that when brain activity is intensifies, the energy needed goes up, enhancing glycolysis and increasing LA production. LA can accumulate in traumatic brain injury as it is produced by glycolysis, especially when brain neurons are damaged (15,24). Hydrocephalus and intracerebral hemorrhage are related to the change in LA levels (5), suggesting that LA is related to the severity of cerebrovascular diseases. Further analysis showed that serum ET-1, MCP-1, and LA were positively correlated with the severity of patients' disease.

IA might rupture unexpectedly, resulting in subarachnoid hemorrhage, a swift increase in intracranial pressure, severe headache, and irritation of the meninges. IA treatment aims to stop blood flow in the diseased artery, prevent tumor rupture, and limit damage to the patient's normal functions (6). Endovascular interventional embolization is one of the main methods for IA, but some patients have poor prognosis after surgery (11). In this study, it was found that Hunt-Hess grade IV-V, Fisher grade 3-4, ET-1 ≥ 41.78 pg/mL, MCP-1 ≥ 229.05 ng/L, and LA ≥ 7.13 mmol/L were risk factors affecting the prognosis of patients after interventional embolization.

Even with a successful aneurysm surgery, patients can experience nerve function defects, and many postoperative complications may follow. Therefore, finding effective indicators to predict the prognosis of IA and formulating reasonable treatment plans have clinical values for postoperative outcomes of IA. Increased serum LA concentrations are largely attributed to tissue hypoxia and/or oxygen debt resulting from inadequate perfusion (10,18). Elevated serum LA is associated with the prognosis of patients with aneurysmal SAH (2,17). This study showed that the AUC values of serum ET-1, MCP-1, and LA levels in evaluating the prognosis of patients were 0.772, 0.871, and 0.791, respectively, all greater than 0.75, suggesting that all indexes have predictive values for the prognosis of patients.

CONCLUSION

In summary, serum ET-1, MCP-1, and LA levels correlate with disease severity in patients with ruptured IA and have predictive value for the prognosis of patients after interventional embolization. They are also risk factors for poor prognosis of patients after interventional rembolization. However, there are limitations to our study. The foremost issue is the small sample size, potentially leading to biased outcomes; second, this was a single-center study, and the findings may reflect only local characteristics. Therefore, we hope that a multicenter study with a larger sample size can be conducted in the future to validate these findings.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: HL

Data collection: HL, ZBL, QWY

Analysis and interpretation of results: TW, ZXH

Draft manuscript preparation: HL

Critical revision of the article: ZXH

All authors HL, ZBL, QWY, TW, ZXH) reviewed the results and approved the final version of the manuscript.

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