

The expression of MMP-7 in serum and aneurysm tissues of patients with abdominal aortic aneurysm associated with hypertension and the clinical efficacy of endovascular exclusion

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Abstract. – **OBJECTIVE:** To investigate the expression of matrix metalloproteinase-7 (MMP-7) in abdominal aortic aneurysm (AAA) with hypertension, and the clinical efficacy of endovascular exclusion.

PATIENTS AND METHODS: Seventy-two cases of AAA with hypertension were retrospectively analyzed. Patients were divided into the observation group (34 cases) and control group (38 cases). The control group was treated by AAA incision with artificial vascular replacement, while the observation group was treated by endovascular graft exclusion. Over the same period, 72 age- and sex-matched healthy adults and 72 patients with hypertension were selected. MMP-7 expression in patients with hypertension, aneurysm associated with hypertension, and healthy controls were measured by ELISA and immunohistochemical staining.

RESULTS: ELISA showed that serum MMP-7 levels of patients with an aneurysm were significantly higher than those of patients with simple hypertension and healthy controls ($p < 0.05$). The operative time, blood loss, and blood transfusion in the observation group were significantly lower than those in the control group ($p < 0.05$). At the 1-month follow-up, the prevalence of pulmonary infection, incision infection, lower limb thrombosis, and lower limb weakness in the observation group were significantly lower than in the control group ($p < 0.05$). The quality of life scores in the observation group after 1 and 3 months was significantly higher than those in the control group ($p < 0.05$). Immunohistochemistry showed that the expression of MMP-7 in aneurysm tissue was significantly higher than in normal tissue. The expression of MMP-7 in the two groups was significantly decreased compared with before surgery ($p < 0.05$).

CONCLUSIONS: The detection of MMP-7 expression in hypertensive patients is an early marker of the occurrence of AAA. The use of en-

dovascular exclusion for the treatment of AAA with hypertension is minimally invasive and safe. Furthermore, postoperative vital signs of patients are stable, and the quality of life is improved.

Key Words:

Abdominal aortic aneurysm, Hypertension, Endovascular exclusion, Artificial blood vessel replacement, MMP-7.

Introduction

An aortic aneurysm is a relatively rare clinical problem. Primary abdominal aortic aneurysm accounts for only 2% of all incidences, and although this incidence is low, the prognosis is poor and the mortality rate is high^{1,2}. The disease is characterized by expansion of the artery by over 50% of the normal diameter; abdominal aortic diameter > 3 cm is considered an abdominal aortic aneurysm (AAA)^{3,4}. Epidemiological studies showed that hypertension is the main risk factor for AAA, and the peak age of occurrence is about 65 years old. Hypertension occurs mostly in older people. Because the mortality rate of AAA associated with hypertension is 90% or more, it requires surgical treatment, and the disease has surgical indications⁵. In the 1990s, a minimally invasive surgical treatment for AAA with hypertension was developed, and it remains a standard operation. However, it causes trauma to patients, there are severe complications of the heart and lung, and postoperative recovery is relatively slow. With improvements in surgical technique, and the development of anesthesia and perioperative treatment, endovascular

aneurysm repair (EVAR) has been widely used. Some studies⁶⁻⁸ show that mortality and morbidity from endovascular treatment are lower than that of open surgery. Compared with open surgery, endovascular treatment has advantages. However, some scholars believe that traditional surgery is applicable to all AAAs of the renal artery associated with hypertension. Also, endovascular surgery is restricted by the anatomical characteristics of the aneurysm neck, iliac artery angles, aneurysm neck plaque, severe calcification, and important branch arteries⁹.

Matrix metalloproteinase-7 (MMP-7) is a key enzyme involved in the regulation of extracellular matrix (ECM) decomposition. The co-factor of MMP-7 is Zn^{2+} , and type IV collagen and gelatin are its main substrates in the ECM. It is believed that MMP-7 can promote the occurrence of aneurysms by degrading the ECM of the aorta^{10,11}.

In this study, we investigated the expression of MMP-7 in patients with AAA associated with hypertension. Also, we evaluated the clinical effects of endovascular exclusion for the treatment of AAA associated with hypertension.

Patients and Methods

Patients

From February 2013 to January 2015, 72 cases of AAA associated with hypertension, 72 patients with hypertension, and 72 healthy controls were selected in our hospital.

Inclusion criteria of AAA with hypertension: patients met the diagnostic criteria for AAA associated with hypertension; the package of the palpable abdominal pulse could be felt; aneurysm of < 5 cm; informed consent of the patient was obtained.

Exclusion criteria: severe liver or kidney disease; mental illness; pregnant women; age < 20 years old or > 80 years old.

Inclusion criteria of simple hypertension: according to the 1999 World Health Organization diagnostic criteria, measured systolic pressure > 140 mmHg or diastolic blood pressure > 90 mmHg at least twice, or currently taking antihypertensive drugs.

The group made up of patients affected by aneurysm associated with hypertension was divided into two subgroups: the observation group (38 cases) and the control group (34 cases). The differences in sex, age, tumor size, smoking status, alcohol consumption, systolic blood pressure, diastolic blood pressure, and other indicators between

the two groups were not statistically significant ($p > 0.05$) (Table I).

Surgical Methods

Control group: incisions of AAAs were made combined with artificial blood vessel replacement. After general anesthesia, the open layer was separated from the soft tissue layer-by-layer, the peritoneum was cut open, and the AAA was exposed. The proximal and distal ends of the abdominal aneurysm and the distal end of the tumor were occluded. The anterior wall of the aortic aneurysm was opened, and the lumbar artery and inferior mesenteric artery were ligated. Next, suitable artificial blood vessels were transplanted to restore blood flow after anastomosis. The artificial blood vessel was wrapped by the aneurysm wall, and the abdominal incision was closed after examination.

Observation group: endovascular exclusion was used. Local anesthesia was performed in the operating room with an angiographic device. A bilateral inguinal region oblique incision with the length of about 5 cm was made, and the bilateral femoral artery was exposed. Abdominal aortic angiography with a Seldinger puncture catheter was performed to determine the feasibility of endovascular repair of the AAA. In the appropriate position of the abdominal aorta, the stent was inserted in the right position of the abdominal aorta with a suitable film-coated stent. The film-coated stent was released, so that the anchor area was close to adherence. The blood circulation of the abdominal aorta was observed after the release of the coated stent, and the incision of the bilateral femoral artery was repaired.

Observational Indexes

Perioperative indexes: the operative time, intraoperative blood loss, blood transfusion volume, and total hospital costs were observed between the two groups. Criteria for success of endovascular exclusion: AAA was completely isolated and was without rupture, and the stent was in the patency of blood flow. The successful standard of incision of the AAA and artificial vascular replacement: abdominal aorta was in the patency of blood flow, and blood flow within artificial blood vessels was without artificial vascular infection.

Complications: patients were observed for complications 1 month after surgery, including pulmonary infection, wound infection, lower limb thrombosis, and lower extremity weakness.

Quality of life: all patients were analyzed with the SF-36 simplified scale of quality of life survey

Table I. Comparison of basic parameters of patients.

Index	Observation group (n=34)	Control group (n=38)	Simple hypertension group (n=72)	Healthy control (n=72)	χ^2 or t	p
Sex (male/female)	20/14	11/7	28/24	31/21	0.064	>0.05
Age	63.23±2.89	63.19±3.19	62.44±3.28	63.47±4.38	0.078	>0.05
Tumor diameter	5.56±1.09	5.58±1.11	-	-	0.034	>0.05
Smoking	38 (72.9%)	12 (66.7%)	26 (50.0%)	21 (40.4%)	0.043	>0.05
Alcohol consumption	21 (61.8%)	10 (55.6%)	24 (46.2%)	20 (38.5%)	0.067	>0.05
Systolic pressure	159.33±11.98	160.09±12.78	161.3±38.5	112.4±13.3	20.119	<0.05
Diastolic pressure	97.19±9.23	97.56±8.91	93.4±20.3	71.2±10.7	19.098	<0.05

Table II. Comparison of perioperative indexes ($\bar{x} \pm s$).

Index	Observation group (n=34)	Control group (n=38)	t	p
Operative time (min)	146.34±10.34	210.98±15.39	6.988	<0.05
Intraoperative blood loss (ml)	50.56±11.98	1000.89±150.32	12.983	<0.05
Blood transfusion volume (ml)	100.98±12.11	800.38±387.38	8.397	<0.05
Total hospitalization expenses (RMB)	138023±1593.98	38453.20±1932.78	11.867	<0.05

Table III. Comparison of postoperative complications between the two groups (n).

Index	Observation group (n=34)	Control group (n=38)	χ^2	p
Pulmonary infection	0	3	7.113	<0.05
Incision infection	1	4		
Thrombosis of lower limb	0	3		
Lower limb weakness	1	3		
Total	2 (3.3%)	12 (20.0%)		

1 and 3 months after surgery. Total scores were calculated. Higher scores implied higher quality of life.

Statistical Analysis

SPSS15.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data analysis. Numerical data are presented as $\bar{x} \pm s$. The independent samples t -test was used for comparisons between groups. Categorical data are presented as cases or ratio, and the χ^2 -test was used for comparisons. $p < 0.05$ was considered statistically significant.

Results

Comparison of Perioperative Indexes

After observation, all operations were considered to have been successful. The operative time, intraoperative blood loss, and blood transfusion volume in the observation group were significantly lower than those in the control group, while the

total cost of hospitalization was significantly higher than in the control group ($p < 0.05$) (Table II).

Comparison of Postoperative Complications

At the 1-month follow-up, the total prevalence of pulmonary infection, incision infection, lower limb thrombosis, and lower limb weakness in the observation group was significantly lower than in the control group ($p < 0.05$) (Table III).

Comparison of Quality of Life

After the investigation, the quality of life scores in the observation group after 1 and 3 months was significantly higher than those in the control group ($p < 0.05$) (Table IV).

Case Analysis

Assessment of the aorta by computed tomography (CT) was performed before and after surgery. Figure 1 shows the imaging data of endovascular exclusion for the treatment of AAA with



Figure 1. Imaging data of the treatment of abdominal aortic aneurysm with hypertension by endovascular exclusion. *A*, Pre-operative computed tomography (CT) shows the first interlayer rupture location, and the neck was measured; *B*, Seven days after surgery, the position and shape of the stent were good; *C*, One month after surgery, the position and shape of the stent were good, and no internal leakage formed; *D*, Two months after surgery, the diameter of the aorta was increased, and the aorta was not in flexion; *E* and *F*, After 3 months, there was no internal leakage or new hair dissection.

hypertension. Figure 2 shows the imaging data of AAA and artificial blood vessel replacement in the treatment of AAA with hypertension. CT

showed that the stent was in good condition and no internal leakage formed, thereby explaining the success of the surgery.

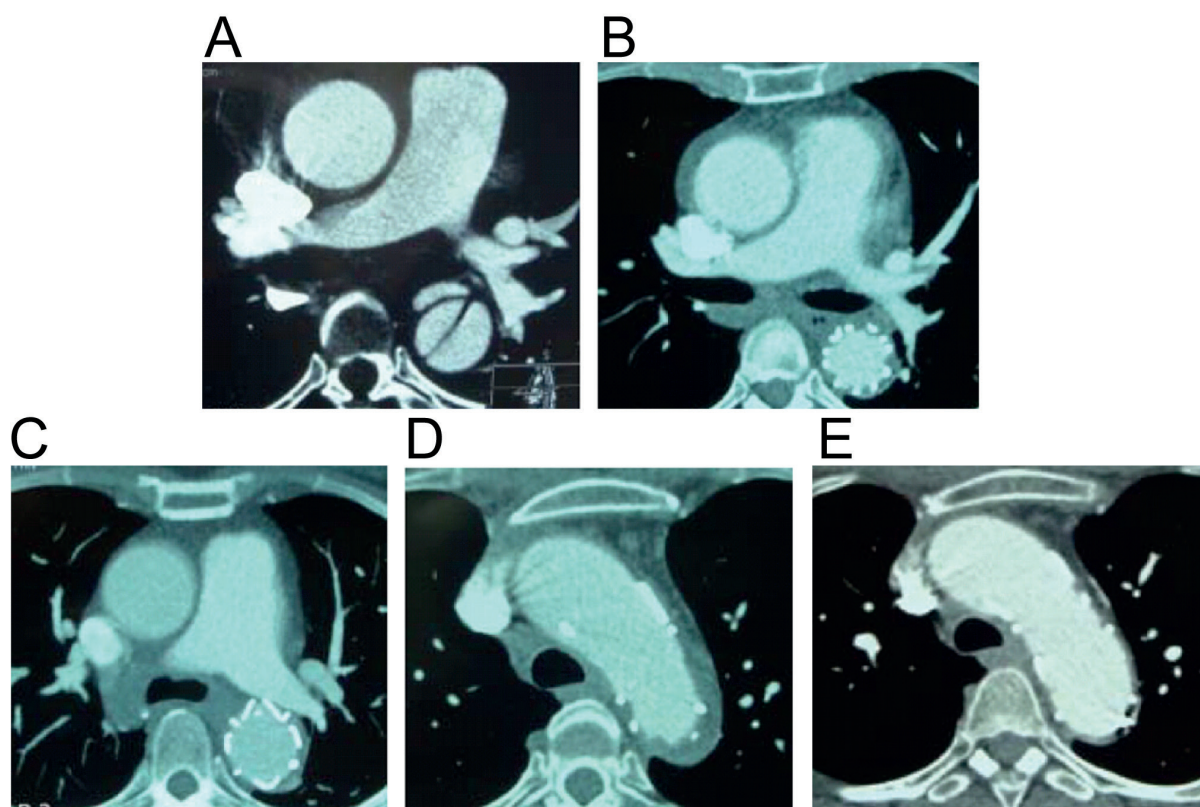


Figure 2. Imaging of abdominal aortic aneurysm with artificial blood vessel replacement in the treatment of abdominal aortic aneurysm with hypertension. **A**, Preoperative CT. Thoracic descending aorta and aortic dissection; **B**, Seven days after surgery, the aortic wall was found to have a change of exudation, and the range was limited; **C**, One month after surgery, the thoracic descending aorta was enlarged; **D**, After 2 months, the stent was in good condition, and no internal leakage formed; **E**, After 3 months, the stent was in good condition, and the exudation change had disappeared.

Table IV. Comparison of the quality of life scores (points, $\bar{x} \pm s$) between two groups.

Index	Observation group (n=34)	Control group (n=38)	<i>t</i>	<i>p</i>
1 month after surgery	80.98 $\pm$ 3.71	67.82 $\pm$ 4.11	12.081	<0.05
3 months after surgery	88.89 $\pm$ 4.21	73.29 $\pm$ 4.98	13.992	<0.05

Expression of Serum MMP-7 in Patients and Healthy Controls

To study the serum levels of MMP-7 in AAA, we evaluated 72 cases of hypertension and 72 healthy controls (adult patients undergoing health examination) in the medical examination center of our hospital over the same period. Patients were matched for age, sex, and body mass index (BMI). After measuring serum MMP-7 in each group, it was found that MMP-7 in the peripheral blood of AAA patients with hypertension was significantly higher than in patients with simple hypertension and healthy controls. The differences were statistically significant ($p < 0.05$) (Table V and Figure 3).

MMP-7 Expression is Increased in Abdominal Aortic Aneurysms

To further explore the expression of MMP-7 in the aneurysm tissue of AAA patients with hypertension, we performed H&E staining, elastic fiber staining, and immunohistochemical staining of MMP-7 on tissue sections collected from patients during the operation. MMP-7 was significantly increased in patients with AAA, which was significantly higher than in adjacent normal tissue ($p < 0.05$) (Figure 4).

Discussion

AAA with high blood pressure is a severe disease of the aorta that can seriously threaten the life

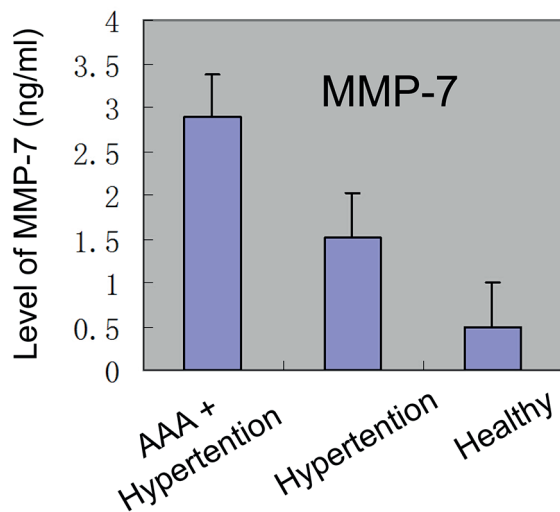


Figure 3. The levels of MMP-7 in peripheral blood from abdominal aortic aneurysm patients with hypertension were significantly higher than those of patients with simple hypertension and healthy controls ($p<0.05$).

of the patient. If it is allowed to progress, it will eventually lead to the necrosis of the tumor body. Therefore, it requires early intervention. Although current surgical and anesthetic techniques continue to improve, the treatment of AAAs remains a difficult problem faced by clinicians¹⁰.

Regarding surgical treatment, because of open AAA and artificial vascular replacement with large trauma and increased complications, there are many shortcomings to current clinical applications¹¹. The technique of endovascular graft exclusion for AAA involves inserting an appropriate stent graft into the abdominal aorta through the femoral artery under dynamic imaging monitoring. The stent is made to cover the AAA at the proximal and distal aneurysms; because of endovascular exclusion of the AAA wall and blood flow, coated stents are in the blood circulation to achieve the goal of maintaining patency of the abdominal aorta¹². According to perioperative in-

dications, surgery in all patients in this study was successful. The operative time, blood loss, and blood transfusion volume of patients in the observation group were significantly lower than those of the control group, while the total cost of hospitalization was significantly higher than that of the control group ($p<0.05$). This shows that endovascular surgery can significantly reduce perioperative bleeding and blood transfusion volume, and shorten hospitalization time. Therefore, the effect on the circulatory system of patients was small, with small trauma to the body, and there was reduced risk of complications associated with transfusion. Similarly, the postoperative vital signs of patients in the observation group were more stable, and the whole body condition recovered faster, demonstrating the unique advantages of endovascular surgery. Although there is the shortcoming of increased cost, it is still worth being promoted clinically^{13,14}.

Patients were followed-up at 1 month. The total occurrence of pulmonary infection, wound infection, lower limb thrombosis, and lower extremity weakness in the observation group was significantly lower than in the control group ($p<0.05$). Patients in the observation group primarily had less trauma and shorter hospital stay, which helped reduce the occurrence of complications. It is necessary to shorten operative time as much as possible. In particular, shortening the time of blocking of the aorta can reduce the occurrence of infection. Aortic CT angiography or magnetic resonance angiography can display endovascular aortic lesions, and provide a reference for the initial surgical treatment and choice of diameter and length of support¹⁵. To prevent the stent from being displaced by high-velocity blood flow during the release process, low blood pressure should be controlled before releasing the stent. In the release of coated stents, it is recommended to promote the use of stent grafts whose distal end have better adaptability than the proximal end,

Table V. Expression of serum MMP-7 in patients and healthy control.

Group	Number of cases	Age	BMI (kg/m ²)	MAP (mmHg)	MMP-7 (ng/ml)
Abdominal aortic aneurysm associated with hypertension	72	62.1±12.6	21.7±1.5	113.2±13.8*▲	2.887*▲
Simple hypertension group	72	63.4±13.3	22.4±2.1	112.4±14.6*▲	1.52*▲
Healthy control	72	64.2±10.9	21.2±3.4	88.4±14.3	0.50
<i>t</i> value	-	0.33	0.37	12.8	0.35
<i>p</i> -value	-	0.72	0.42	0.03	0.003

Note: compared with healthy controls, * $p<0.01$; compared with healthy control group, ▲ $p<0.01$.

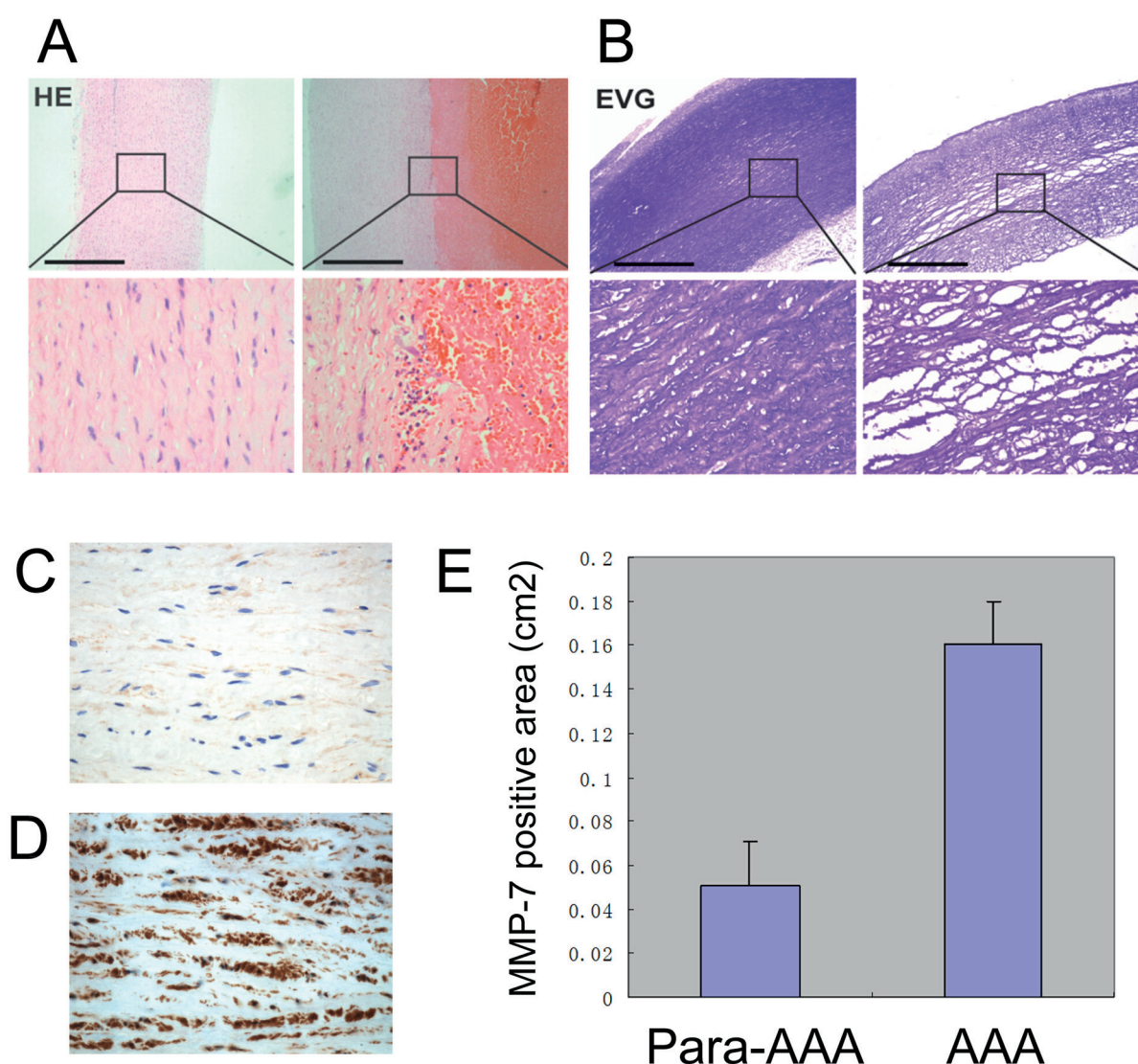


Figure 4. MMP-7 expression is increased in abdominal aortic aneurysm: **A-B**, H&E staining and elastic fiber staining showed blood invasion of the abdominal aortic wall and elastic fiber breakage in samples from patients; **C-E**, The positive area of MMP-7 staining in patients with abdominal aortic aneurysm with hypertension was significantly higher than that in adjacent normal tissues ($p < 0.05$).

and where the diameter of the distal end is less than that of the proximal end¹⁶.

In our study, we found that the use of endovascular exclusion for AAA achieved a good therapeutic effect. Operative time (min), intraoperative blood loss (ml), blood transfusion volume (ml), and total hospital costs (yuan) of patients were significantly lower than those of the control group. At the 1-month follow-up, the total incidence of pulmonary infection, incision infection, lower limb thrombosis, and lower limb weakness in the observation group was significantly lower

than in the control group ($p < 0.05$). The quality of life scores in the observation group after 1 and 3 months was significantly higher than those in the control group ($p < 0.05$). These results indicate that the therapeutic efficacy and cost of endovascular exclusion are significantly superior to those of treatment of aortic aneurysm by incision combined with artificial vascular replacement. We believe this is because of endovascular exclusion, compared with traditional open surgery, is a minimally invasive surgery without thoracotomy. Furthermore, it is associated with less trauma, decreased

intraoperative blood loss, which reduces coagulation disorders and post-traumatic inflammatory factor release caused by bleeding, and significantly improves the prognosis of patients. For older patients and patients with other cardiovascular and systemic diseases, the general state of patients in the perioperative period was significantly improved¹⁷.

The SF-36 scale is also referred to as a health survey. It is a common scale used to investigate the quality of life of patients that undergo surgery, mainly through the analysis of their psychological and physical health. It is used to evaluate the effects of surgery, and has been widely applied in the evaluation of the health status of patients^{17,18}. The quality of life scores of patients in the observation group after 1 and 3 months was significantly higher than those in the control group ($p < 0.05$).

MMPs are proteolytic enzymes that are dependent on the presence of zinc ions. They play an important role in the process of degradation of ECM components, in the regulation of many soluble factors in cells, and for the tissue reconstruction. Furthermore, MMPs are closely associated with the occurrence, invasion, and metastasis of tumors. Under normal physiological conditions, MMPs act synergistically with tissue inhibitors of metalloproteinases (TIMPs) and also regulate changes of ECM, to maintain the relative stability of the cell. MMPs dysfunction can accelerate the degradation of matrix barriers, or indirectly promote tumor growth, metastasis, and invasion, by releasing growth factors associated with the ECM. Therefore, MMPs have become an attractive target in cancer research and in the development of anti-tumor drugs¹⁸⁻²⁰. In our study, we found that serum MMP-7 was significantly increased in patients with AAA compared with those with hypertension and healthy controls. Also, immunohistochemistry showed that the expression of MMP-7 was significantly increased in aneurysm tissue. Elastic fiber staining showed that the structure of the abdominal aorta was loose, with blood invasion of the abdominal aortic wall, and elastic fiber breakage. We believe that in the occurrence of AAA, MMP-7 can loosen elastic fibers through the degradation of ECM. This is more likely to cause an aortic aneurysm in patients with perennial hypertension. MMP-7 released from local tissue damage can enter the circulation. Therefore, we suggest that in patients undergoing screening for hypertension, screening for MMP-7 has significance for the early diagnosis of AAA.

There are limitations to the present study. Firstly, because aortic aneurysms are not common, the number of included patients was limited. Secondly, the accuracy of the statistical data is likely to cause some error. Therefore, we did not include patients with thoracic aortic aneurysms. The aneurysm tissue of patients with AAA and the mechanism of increased expression of serum MMP-7 require further verification with animal experiments.

Conclusions

Given appropriate economic conditions, the use of endovascular exclusion for the treatment of AAA with hypertension is advantageous in that it is minimally invasive and safe. Also, the postoperative vital signs of patients are stable, and the quality of life is improved.

Acknowledgments

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Conflict of interest

The authors declare no conflicts of interest.

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