Research Progress of Oxidative Stress and MicroRNAs in the Prevention of Catheter-Related Thrombus Under Resistance Exercise

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Abstract
Central venous access devices (CVADs) have completely changed the care for patients who require long-term venous access. With the widespread use of CVADs, the incidence of catheter-related thrombus (CRT) has increased. Catheter-related thrombus is a common complication in patients who use CVADs and is mainly caused by endothelial injury, blood stasis, and hypercoagulability. In recent years, the correlations between oxidative stress (OS) and microRNA (miRNA) and CRT have become a hot topic in clinical research. When a catheter punctures the vessel wall, it causes OS damage to the vascular endothelial cells, leading to a series of CRT diseases. MicroRNAs can regulate the mechanism of thrombus and play an important role in the formation of anti-thrombus. Numerous studies have shown that resistance exercise can reduce the level of OS in vascular endothelial cells, inhibit vascular endothelial cell dysfunction, and maintain the stability of hemodynamics and biochemical state. In the current work, the recent studies on the effects of resistance exercise on OS and miRNA in vascular endothelial cells were reviewed.

Keywords
central venous catheter, resistance exercise, catheter-related thrombosis (CRT), oxidative stress, microRNAs (miRNAs)

Introduction
The central venous access device (CVAD), also known as the central venous catheter, is a small, soft, and hollow catheter whose tip is inserted percutaneously into a large vein near the heart.¹ Its advantages of long indwelling time and few puncture times promote its wide use in clinical practice to provide interventional treatment for acute and chronic diseases.²,³ With the widespread application of CVADs, a series of symptoms, such as catheter blockage and thrombosis, has continuously emerged.⁴ Catheter-related thrombosis (CRT) is one of the most common and most serious complications.⁵ Catheter-related thrombus is mainly caused by injury to endothelial cells and hemodynamic changes that promote the hypercoagulability of blood.⁶ The oxidative stress (OS) level of endothelial cells in the cardiovascular system regulates vascular physiology, and OS injury and vascular endothelial dysfunction can promote thrombosis.⁷ Thrombotic diseases involve multiple factors and systems. Studies on the molecular mechanism of thrombosis have shown that OS and microRNAs (miRNAs) play an important role in the pathological process of thrombotic diseases, such as atherosclerosis, myocardial infarction, and other arterial thrombotic diseases; and pulmonary embolism, deep vein thrombosis, and other venous thrombotic diseases.⁸ In recent years, resistance exercise has been widely used in clinical practice to prevent CRT, and exercise methods, such as ball clenching, grip clenching, and routine fist clenching, have been adopted to reduce the occurrence of CRT.⁹,¹⁰ The relationship between

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Resistance exercise and thrombus is currently a hot topic among many scholars. The current study reviews the relationship between resistance exercise and related markers and the signaling pathways of OS and miRNAs in CRT prevention.

**Epidemiological Characteristics of Peripherally Inserted Central Catheter-Associated Thrombus**

Peripherally inserted central catheters (PICCs) have become a conventional treatment for patients with cancer and blood diseases. Peripherally inserted central catheters are mainly used for antitumor drug infusion and adjuvant therapy, including blood transfusion. Catheter-related thrombus refers to the formation of blood clots on the inner wall of a vessel and the wall where the catheter is located; these blood clots result in the partial or complete blockage of the catheter with or without clinical symptoms after catheterization due to a direct injury to the vascular intima via puncture or the catheter itself and due to the patient’s own state. A prospective study of patients with cancer with PICCs revealed that 51.4% of the patients developed CRT according to ultrasonic examination; 45.6% of them were asymptomatic, and the incidence of symptomatic CRT was only 1% to 5%. Symptoms included swelling, pain or numbness in the limbs, erythema in the limbs, and venous dilatation. Severe cases can lead to recurrent deep vein thrombosis, postthrombotic syndrome, or pulmonary embolism. Catheter-related thrombus increases pain and the risk of death as it can lead to catheter dysfunction, central vein stenosis, and treatment interruption.

**Thrombus Formation and Treatment**

Thrombosis is a blood clot formed by red blood cells, white blood cells, fibrin, and platelets in the vein. Thrombosis formed in the axillary vein, the subclavian vein of the upper extremity, the vein at the confluent of the upper extremity deep vein, and the vein at the brachial vein is called upper extremity deep vein thrombosis (Table 1). Anticoagulant therapy is complex and often complicated by severe thrombocytopenia among patients with a high risk of bleeding. The systemic prophylactic use of anticoagulants can reduce or eliminate the high coagulation state of blood but will also lead to complications, such as bleeding and hematoma. Data from a randomized controlled trial and observational study do not support the routine use of fixed-dose warfarin to prevent thrombosis. In 2012, the International Institute of Thrombosis and Hemostasis and Thoracic Society Clinical Practice Guideline did not recommend the routine use of anticoagulants to prevent CRT in patients with cancer with CVADs. Warfarin has attracted attention in recent years in the treatment of CRT, but its safety and efficacy are unknown.

In clinical practice, the mechanism of CRT formation is believed to be mainly caused by puncture or the catheter itself (Figure 1). The 3 major factors of classical venous thrombosis are vascular intima injury, blood stasis, and high blood coagulation. Colwell et al pointed out that the difference between anticoagulant drugs and physical exercise in reducing the incidence of thrombus is not statistically different and that physical exercise can effectively prevent the complications of CRT. Resistance exercise not only improves vascular endothelial function and blood flow velocity but also inhibits the adverse effects of anticoagulants, such as warfarin and heparin, to prevent CRT formation.

**Resistance Exercise in Recent Years**

Resistance exercise, also known as resistance training or strength training, usually refers to the process through which the body overcomes resistance to achieve muscle growth and increase strength. Effective upper limb exercise can improve blood circulation and reduce the incidence of CRT. Early aerobic exercise and resistance exercise at the side of catheterization can increase blood flow velocity, muscle strength, endurance, the pressure load of the heart, and the blood perfusion under the endocardium; such effects result in the improved balance between the supply and demand of cardiovascular physiology and the body's ability to handle the pressure of cardiovascular activity. This can help to prevent thrombus formation and vascular complications.
Regular and moderate physical exercise is one of the most effective interventions to improve endothelial cell function. Souza et al demonstrated the positive exercise response in patients after catheterization. Resistance exercise is safe, noninvasive, straightforward to learn, economical for patients, and easy to popularize; such factors provide the basis for the clinical system management of the upper limb exercise of patients after catheterization.

Factors Influencing the Effects of Resistance Exercise on Vascular Endothelial Injury

Located on the lumen of the vessel wall, the vascular endothelium is a complete structure composed of a monolayer of endothelial cells. It is in direct contact with the blood stream and plays anticoagulant and anti-inflammatory roles by keeping the blood vessels unobstructed mainly through the secretion of a series of molecular substances, such as nitric oxide, thrombin A2, prostacyclin, and endothelin-1. When the vascular intima is damaged, endothelial cells can quickly cover and replenish the damaged endothelium. According to statistics, 70% of deep vein thrombosis in the upper limb is caused by catheters, accounting for 10% of all types of venous thrombosis. Regular and moderate physical exercise is one of the most effective interventions to improve endothelial cell function. Souza et al demonstrated the positive exercise response in the hearts of rats undergoing resistance training for 12 weeks; this result suggests that resistance exercise increases the thickness of the aortic wall. Regular exercise with moderate intensity can change the shear stress of the bloodstream, regulate antioxidant protection, inhibit endothelial inflammatory signaling pathways, and improve vascular endothelial function and morphology. Thus, this form of exercise plays a role in preventing venous thrombosis to some extent.

Factors Influencing the Effects of Resistance Exercise on Hemodynamics

The catheter tip is mainly placed in the inferior vena cava whose vascular diameter is relatively narrow and blood flow is relatively minimal and slow. It prolongs the contact time between the vascular endothelium and the stimulating liquid or chemotherapy drugs, increases the degree of damage to the vascular endothelium, and causes deep vein thrombosis. In addition to the vascular damage caused by catheter implantation, when blood flow is slowed down or irregular, the catheter through the narrow venous lumen can promote platelet aggregation to release serotonin, clotting factor, and other substances. When central venous catheterization itself causes blood stasis, the patient consciously reduces the exercise of the limb; hence, the blood flow slows down, and the risk of thrombosis increases. Studies have shown that intravascular catheter placement can decrease local blood flow velocity by approximately 60%. The sharp decrease in blood flow shear stress may directly induce OS damage to the vascular endothelial cells and promote CRT formation. At present, clinical researchers have reported that exercise intervention can prevent venous thrombosis. Several researchers subjected patients implanted with PICC to grip strength training. After the patients squeezed the elastic ball for 10 seconds, they were tired out and allowed to relax for 10 seconds; the maximum blood flow of the axillary vein was detected by ultrasound. In study by Ayse and colleagues, patients with PICC were required to exercise for 20 minutes a day for 5 days a week and to contract and relax the forearm muscles by gripping and relaxing a ball for 4 seconds to increase blood flow to the forearm.

Factors Influencing the Effects of Resistance Exercise on the Hypercoagulable State

Numerous studies have shown that venous thrombosis and its development originate in the venous sinuses or valves. The hypercoagulable microenvironment caused by the blood stasis and hypoxia in the valvular sinus results in the decreased expression of thromboregulatory protein and endothelial protein C receptor; thus, thrombus formation is promoted. The change in blood composition in a high coagulation state is the decisive factor for CRT formation, which is manifested by increased fibrin degradation products and platelets, hyperfibrinogenemia, and prothrombin prolongation. In the elderly, blood viscosity increases, and erythrocyte deformability is poor. With increasing age, the fibrinolytic activity decreases, and the antifibrinolytic activity increases, thereby increasing the possibility of thrombus formation. Vascular injury caused by catheter insertion, venous stasis caused by catheter indwelling, continuous movement of the catheter in the vein, platelet adhesion, and coagulation caused by the interaction of some tumor cells and their products with host cells, and the release of prothrombin kinase can promote high blood coagulation, which in turn results in occluded mural thrombus. Chemotherapy drugs are prone to antigen and antibody reactions in the blood vessels, which cause vascular endothelial injury and thrombin release. The feedback causes an increase in fibrinogen, thus aggravating the hypercoagulable state of the blood, which further causes vascular endothelial injury. Resistance exercise not only makes the muscle contract and squeezes the upper limb blood vessels but also promotes the venous blood flow of the catheter’s arm, improves fibrinolytic activity, and timely dissolves platelets and fibrinogen aggregation; under these conditions, the incidence of CRT is ultimately reduced.

Relationship Between the Molecules Associated With OS and Thrombus

Overview of Oxidation System

Oxidative stress was initially described as a pro-oxidant-antioxidant imbalance disorder that may lead to cell damage and
temporary or long-term reactive oxygen species (ROS) elevation, which disrupts cell metabolism and damages cell components. When a catheter punctures the vessel wall or is left in the vessel for a long time, the vascular endothelial cells become damaged, and their biological function is consequently affected. A series of defense reactions then occurs. Oxidative stress refers to the excessive production of ROS and reactive nitrogen species resulting from the harmful stimulation of the body and the imbalance between oxidation and antioxidants in the body; most of these reactions are negative. The OS damage of the vascular imbalance between oxidation and antioxidants in the body; most resulting from the harmful stimulation of the body and the excessive production of ROS and reactive nitrogen species damaged, and their biological function is consequently affected. In the cardiovascular system, ROS plays a role in the control of inflammation, proliferation, apoptosis, endothelial function, and angiogenesis. Reactive oxygen species is one of the important factors leading to thrombosis development. Aizawa et al showed that cellular ROS can promote the occurrence of thrombus and that the increase in ROS in endothelial cells is a major factor for endothelial dysfunction and the occurrence and development of cardiovascular diseases. Studies have shown that when intravascular blood flow is slowed down or blocked, endothelial cell OS damage is induced, and endothelial cell dysfunction may occur. Numerous animal studies have demonstrated that ROS overexpression has a pathogenic effect on atherosclerosis and thrombotic cerebral apoplexy, which has attracted considerable attention in many fields. When ROS increases, atherosclerosis, aging, and ischemia–reperfusion injury may occur.

A high ROS content can peroxidize the polyunsaturated fatty acids on the cell membrane, produce malondialdehyde (MDA), cause further tissue OS damage, and change the permeability of the cell membrane, and finally induce the rupture of the double-layer structure of the cell membrane. Malondialdehyde, an oxidase, is a product of lipid peroxide degradation that can cause the reaction of macromolecules to produce strong biological toxicity. Damage to the vascular endothelial cells can cause the lipid peroxidation of polyunsaturated fatty acids on the cell membrane and their degradation to MDA. In animal experiments of deep vein thrombosis in the upper limb, atherosclerosis, and myocardial infarction, the MDA content in the experimental group greatly increased. Malondialdehyde, as a transmitter of OS, plays an important role in thrombosis. Several studies found that the MDA content in the deep vein thrombosis group was significantly higher than that in the control group (2.49 vs 1.01 μM/L; P < .05); these studies also observed changes in deep vein thrombosis. Therefore, OS plays a key role in thrombosis.

**Effects of Antioxidant System on Thrombus**

The antioxidant system, which mainly includes enzyme and nonenzyme antioxidant systems, can effectively remove free radicals from living organisms to protect cells from OS damage. Oxidative stress damage is mainly related to ROS-mediated oxidases, such as superoxide dismutase (SOD), heme oxygenase (HO), and catalase. Nonenzymatic systems mainly consist of glutathione, vitamin E, vitamin C, and some trace elements. In the antioxidant system, SOD and HO-1, in particular, reduce ROS to achieve the effect of the vascular antioxidant system. Superoxide dismutase is an important antioxidant enzyme that scavenges reactive oxygen free radicals and serves as an important marker of intracellular OS. Superoxide dismutase is the main antioxidant in vascular endothelial cells that can remove lipid peroxides in the body, reduce peroxidation damage to cells, bind platelet/endothelial cell adhesion molecule 1 antibodies, and specifically bind to endothelial cells so as to play an antioxidant defense role in vascular endothelial cells. Villegas et al reported that according to the results of a large number of animal experiments, SOD can reduce hypoxia-induced pulmonary hypertension and pulmonary vascular remodeling. Bahnson et al inserted catheters into the external carotid artery of rats to establish a carotid injury model and found that SOD is involved in regulating OS and inhibiting the development of new intima.

Heme oxygenase is a speed-limiting enzyme in heme catalolism, and carbonic oxide in the human body is mainly produced via HO metabolism. Heme oxygenase has 3 types: oxygen stress induction (HO-1), enzyme composition (HO-2), and HO-3. Heme oxygenase 3 and HO-2 have homologous expressions in multiple organs. Heme oxygenase 1, a member of the HO protein family, is a common inducible enzyme in mammals that protects cells from OS damage by degrading pro-oxidizing heme to produce the antioxidant bilirubin. Heme oxygenase 1 is expressed in the vascular endothelial cells and smooth muscle cells and can inhibit vascular smooth muscle cell proliferation and migration from the middle layer of the artery to the intima; thus, it can protect damaged blood vessels. Studies have shown that HO-1 induction inhibits
arterial and venous thrombosis in animal models. Many studies have reported that the expression levels of HO-1 are related to the expression levels of atherosclerosis biopsy. The results indicate that increasing the expression of antioxidant enzymes and stress proteins could prevent the development of cardiovascular diseases.

Effects of Resistance Movement on Antioxidant Systems

Resistance training brings the redox reaction to a balanced state, thereby reducing metabolic and immune-related diseases. After resistance training, the increase in total SOD activity is inhibited because the adaptation of endogenous antioxidants produced by high levels of exogenous antioxidants in the skeletal muscle is inhibited. After short-term strenuous exercise and 24 hours recovery, antioxidants exert a blocking effect on SOD activity. Regular physical exercise plays an important role in improving vascular function. In studies related to the reduction of pro-inflammatory cytokines, statistically differences in the effects of 12 weeks physical exercise and high-triglyceride diet on HO-1 concentration in rat aorta ($P < .0001$), voluntary wheel movement restored the concentration and activity of HO enzymes in the aorta and heart. Exercise training preserves vascular endothelial function, but its underlying molecular mechanisms are unclear. Heme oxygenase 1 induced by training mainly exists in the vascular endodermis and perivascular layer. Oxidative stress is likely to participate in CRT formation; resistance exercise can regulate OS and affect CRT formation (Figure 2). However, the underlying downstream targets and related signaling pathways still need to be further explored.

Pathway of Resistance Exercise and Oxidative Stress-Mediated Thrombus

Oxidative stress can promote thrombotic diseases by activating the nuclear factor kappa-B (NF-κB) and the mitogen-activated protein kinase (MAPK) signaling pathways. Nuclear factor κB is a member of the transcription factor protein family that is widely found in cells in the form of various NF-κB complexes. When the cell is stimulated by a variety of extracellular motions, physical and biochemical interventions, and so on, the inhibitor of NF-κB kinase is activated, leading to the phosphorylation, ubiquitination, and degradation of the IκB protein and causing the release of NF-κB dimers. Dissociative NF-κB quickly shifts to the nucleus, combines with specific gene sequences, and induces the transcription of related genes; this series of events results in tissue damage and thus causes a variety of cardiovascular diseases. Onai et al. injected a novel IκB phosphorylation inhibitor to inhibit NF-κB in a rat myocardial infarction model and observed improvements in the ventricular remodeling and left ventricular diastolic function. Reactive oxygen species can activate the NF-κB signaling pathway to accelerate vascular endothelial cell apoptosis and increase the production of tissue factors and thrombogenic molecules to promote venous thrombosis. Tabasum et al. downregulated the NF-κB expression with Perizol to reduce OS and improve the outcome of thrombotic stroke. Therefore, many experts have proposed that inhibiting NF-κB and other signaling pathways can effectively control the state of OS, improve the antioxidant capacity of endothelial cells, and prevent the occurrence and development of thrombosis. Regulating reactive oxygen production induced by regular training can be adaptive against oxidase gene expression through the NF-κB pathway in the skeletal muscle. In other words, exercise training can improve the antioxidant system of the body and increase its resistance to OS. After resistance exercise training, the activation of the NF-κB signaling pathway leads to the phosphorylation of its inhibitor (IκB), leading to the release and binding of NF-κB from its position to the DNA; as such, the gene expressions of SOD, catalase, and other enzymes are stimulated, and antioxidant defense is strengthened. Therefore, resistance exercise training can stimulate the NF-κB signaling
pathway, leading to the expression of certain antioxidants. The body’s total antioxidant capacity is enhanced, thereby inhibiting the formation of CRT.

The MAPK signaling pathway is a serine/threonine kinase family activated by the phosphorylation of various extracellular or intracellular stimuli, such as growth factors, cytokines, and OS; it regulates cell proliferation, differentiation, and apoptosis. The increased phosphorylation of p38, JNK, and extracellular-regulated protein kinases (ERK) caused by ROS suggests that ROS-induced apoptosis may be mediated by regulating the MAPK signaling pathway. Yang determined that the platelet scavenger receptor CD36 promotes thrombosis by increasing MAPK extracellular signals to activate ERK5.

The mechanism of the downregulation of P38 MAPK and NF-κB signals by low-dose and low-oxygen mesenchymal stem cells can inhibit pulmonary embolism and thrombosis. After resistance exercise training, the supplementation of antioxidants can block the cell signaling pathways associated with muscle hypertrophy (MAPK and p70S6 kinase) without affecting the partial synthesis rate of muscle proteins. Evidence suggests that MAPK is activated by OS.

The activation of JNK is related to the regulation of cell proliferation, apoptosis, inflammation, and DNA repair. The elevated ROS in skeletal muscles caused by exercise may play an important role in exercise adaptation, and antioxidant supplementation inhibits JNK phosphorylation. We hypothesized that resistance movement could downregulate the P38 MAPK and NF-κB signaling pathways, induce ROS production, reduce OS damage, and improve vascular endothelial function.

Meanwhile, miRNAs and MDA produced by the peroxidation of polyunsaturated fatty acids caused by a high content of ROS can be used as indicators for the early diagnosis and prognosis assessment of venous thrombus. However, the study of OS and miRNAs in the context of deep vein thrombosis is still in the initial stage, and extensive research is needed to clarify their mechanisms of action.

Relation Between miRNAs and CRT Disease

MicroRNAs are a class of noncoding small RNA molecules with an endogenous length of about 22 nucleotides. They control gene expression mainly by degrading mRNAs by binding to the 3' UTR region of the target gene mRNA and/or inhibiting the translation control gene expression of the target gene at the transcriptional level. More than 500 human miRNAs have been identified so far. MicroRNAs are important gene adjusting factors in the body that participate in cell proliferation, migration, angiogenesis, insulin secretion, neural differentiation, and heart embryonic organization development process. Many studies have demonstrated that miRNAs play an important role and function in the development of and changes in diseases. Comprehensive research data prove that miRNAs are the targets of effective treatments for many diseases, such as tumor- and thrombosis-related diseases. Different miRNAs have different transport mechanisms and specific releases. They are surrounded by different extracellular vesicles that prevent RNA enzymes from degrading them. As an endothelium-specific miRNA, miR-126 is only expressed in endothelial cells. Therefore, miR-126 is considered as an important factor regulating angiogenesis and inflammation in clinical practice. Moreover, miR-126 directly regulates the adhesion of endothelial monocytes to target Vascular Cell Adhesion Molecule-1 to control vascular inflammation. Other miRNAs can combine with proteins to form complexes. For example, miR-92a can be transported after binding with lipid proteins. MicroRNAs can form complexes that are not degraded by RNA enzymes to some extent.

Currently, most studies on miRNAs focus on their effects on cancer, and their role in the cardiovascular system has been gradually confirmed. MicroRNAs released from cells can be stable in the circulation of peripheral blood and are highly sensitive and easy to detect. Therefore, many experts agree that miRNAs may be a new marker for the diagnosis of thrombotic diseases. Qin et al confirmed that miRNAs play a crucial role in deep vein thrombosis and that the detection of peripheral blood miRNAs may replace d-dimers as markers for the diagnosis of thrombotic diseases. Meng et al reported that miRNAs play an important role in thrombolytic recanalization and that the expression levels of miR-199a and miR-483 in patients with venous thrombosis were significantly changed relative to those in healthy controls. Further studies have confirmed the involvement of miR-199a and miR-483 in thrombolytic recanalization and angiogenesis. Moreover, miR-92a has been found to be highly expressed in human vascular endothelial cells. Studies have shown that plasma miR-92a mainly comes from Annexin V + / CD31 + microparticles (MPs) released by endothelial cells and platelets. Its main mechanism may be as follows. After vascular endothelial cells and platelets are activated during thrombosis, miR-92a is released in the form of MPs to inhibit angiogenesis. In summary, the catheter puncture injury of the vascular wall and long-term catheterization lead to the dysfunction of endothelial cells in patients and thereby causes a series of CRT diseases. MicroRNAs play an important role in the formation of antithrombotic agents and may become a new marker for the prevention of CRT. MicroRNAs may also be involved in the regulation of certain signaling pathways, such as miR-10a, which mediates thrombotic diseases by regulating the NF-κB pathway. In the endothelial cells mediated by OS, the expression of miR-200c is upregulated. Therefore, miRNAs may be involved in the occurrence and development of thrombotic diseases in different ways.

Regulation of miRNA by Resistance Exercise to Prevent CRT

A few studies have explored the hemodynamic effects of resistance exercise training on central venous catheters. As resistance exercise training may also affect the target genes of OS and cardiovascular autonomic function, the current research status of the correlation between miRNAs and CRT diseases should be further verified. The latest research results of our team have confirmed that miR-92a-3p and OS are related to venous
thrombosis. The expression levels of venous miR-92a-3p, HO-1, p38 MAPK, and NF-κB p65 mRNA in the CRT group were significantly upregulated, and miR-92a-3p was positively correlated with HO-1 ($r = 0.770$, $P = .015$). The relationship between specific signaling pathways that are activated during resistance exercise is changing considerably. After acute endurance exercise, the increased gene expressions of biogenic mechanisms and members of the output pathways of miRNAs have been observed in skeletal muscles. The studies on differential miRNA expression and the potential role of miRNAs in specific pathways have revealed that increased resistance exercise is associated with changes in circulating miRNA levels.

**Conclusion**

The implantation of central venous catheters leads to the OS injury of vascular endothelial cells. Moreover, miRNA-mediated endothelial cell apoptosis and vascular inflammation lead to thrombosis. These conditions lead to different degrees of thrombotic diseases involving multiple systems and organs, seriously endangering the life of patients. Resistance exercise is a popular strategy for promoting health and fitness because of its beneficial effects on the cardiovascular system. Early resistance exercise interventions can change blood flow velocity, reduce the occurrence of CRT, and thereby minimize related complications and improve cardiovascular function. At present, a few clinical studies have proved that OS and miRNA-related markers are closely related to thrombosis. Further studies are needed to provide a strong basis and direction for the prevention and treatment of CRT.

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