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# Research Progress on the Composition of Cerebral Arterial Thrombus in Acute Ischemic Stroke

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**Abstract:** Acute cerebral infarction, with a high incidence, disability, and recurrence rate, has brought a huge social burden to China and other countries. Understanding the pathological characteristics of cerebral thrombus can help in the selection of individualized treatment plans, thereby improving the good prognosis rate and reducing the recurrence rate of cerebral infarction patients. This article reviews the composition and imaging characteristics of cerebral thrombus, the relationship between cerebral thrombus composition and cerebral vascular recanalization therapy, the correlation between cerebral thrombus composition and the etiology of cerebral infarction, and the dynamic evolution of cerebral thrombus, to provide a more theoretical basis for the treatment of acute ischemic stroke.

**Keywords:** Acute cerebral infarction; Thrombectomy; Cerebral artery thrombus; Pathology

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## 1. Introduction

The number of patients with stroke in China ranks first in the world, and it is the number one killer threatening the lives of Chinese people. Among them, ischemic stroke accounts for about 80% of the stroke incidence, and the incidence rate has been increasing in recent years [1]. Timely and effective recanalization therapy for acute ischemic stroke can significantly improve the symptoms and prognosis of patients [2]. Intravenous thrombolysis and cerebral arterial endovascular therapy stand out as the most effective recanalization treatments currently available. However, while intravenous thrombolysis shows an effective reperfusion rate of less than 50% and an improvement rate of only about 30%, cerebral arterial endovascular therapy boasts an effective recanalization rate of over 80% [3]. Despite this success, the proportion of patients with a favorable prognosis remains below 50% [4]. The effectiveness of recanalization therapy can be influenced by several factors, such as the patient's underlying disease and the duration of treatment. However, the histological characteristics of the thrombus undoubtedly play a crucial role, significantly impacting the effectiveness of both intravenous thrombolysis and intravascular treatments [5]. This article reviews the relevant research on cerebral thrombus in patients with acute cerebral infarction in recent years, aiming to be helpful for the clinical diagnosis and treatment of ischemic stroke.

## 2. The composition and internal structure of cerebral thrombus

Based on numerous clinical trials on the removal of thrombus during endovascular treatment of intracranial arterial occlusion, people have gained more and more understanding of the components and internal structure of cerebral thrombi.

### 2.1. Components of thrombus

A typical cerebral thrombus is composed of red blood cells, fibrin, platelets, white blood cells, von Hemophilia factor (vWF), and neutrophil extracellular traps (NETs) [5–7]. In addition, some rare noncellular components can also be found in thrombus, such as vascular intimal tissue, pathogenic bacteria, or calcified components.

#### 2.1.1. Red blood cells, fibrin, platelets, and white blood cells

Red blood cells, fibrin, and platelets are the three components with the highest relative content in thrombus, and they all have various forms in thrombus. Among them, red blood cells can be divided into double concave disc-shaped red blood cells, double concave intermediate red blood cells, polyhedral intermediate red blood cells, polyhedral red blood cells, smooth surface convex red blood cells, and spiny red blood cells. Fibrin can be divided into bundle-like fibrin, fibrous-like fibrin, sponge-like fibrin, and fragmented fibrin. Platelets can also be divided into ordinary platelets and activated spherical platelets [8]. In contrast, the proportion of white blood cells in thrombus is relatively small with a mostly diffuse manner distribution, often coexisting with fibrin. Its content is negatively correlated with the content of red blood cells, and there are significant changes in the content of different kinds of thrombus [8–9]. Currently, thrombus classification primarily relies on Hematoxylin and Eosin (H&E) and Martius Scarlet Blue (MSB) staining methods. These methods semi-quantitatively measure the proportion of the first three main components in the thrombus [10]. Thrombus can be divided into red thrombus rich in red blood cells, white thrombus rich in fibrin/platelets, and mixed thrombus [11].

#### 2.1.2. Other components

NETs and vWF: NETs are secreted by neutrophils and are mainly composed of collagen, histone, and DNA. They participate in the formation of thrombus by interacting with platelets, red blood cells, vWF, and so on, and antagonize thrombolytic drugs by stabilizing the thrombus and promoting coagulation [12–15]. Mature thrombus has a higher content of NETs compared to fresh thrombus [16]. vWF is a large polymeric plasma protein synthesized by megakaryocyte and endothelial cells, which plays an important role in platelet adhesion [17–18]. It is often co-located with platelets in thrombus, so platelet-rich thrombus is also found to be rich in vWF content. NETs and vWF are negatively correlated with red blood cell content [19–20].

Vascular wall components, infectious embolus, calcified embolus: In rare cases, vascular intima, subintimal tissue, and other vascular wall components can be found in the removed thrombus, indicating that there may be more operations or relatively remote thrombus removal sites during the thrombus removal process [21– 22]. Infection is an important factor of AIS, especially for infective endocarditis [23]. The complicated cerebral embolism in this patient is likely to be an infectious embolus. Pathogenic bacteria are also found in the thrombus of a few patients without signs of infection before surgery, which emphasizes the necessity of conducting microbial analysis of the thrombus [24]. Sometimes, calcified components are found in blood clots, indicating a high possibility of arterial origin [25]. A relatively small proportion of cerebral embolism is found to be calcified embolus, and it should be noted that the effectiveness of thrombectomy treatment for this type of embolism is relatively poor [26].

### 2.2. The internal structure of thrombus

The heterogeneity of cerebral thrombosis is not only related to the content and morphology of different components within it but also to the spatial relative positions of various components in the thrombus. By histological and immunofluorescence, Pir et al. found that different thrombi are composed of different proportions of red blood cell-rich and platelet-rich regions [27]. The structure of the red blood cells-rich region is simple, consisting of dense red blood cells, thin fibrin grids, and a small number of white blood cells. The structure of platelet-rich regions is relatively complex, consisting of platelet polymers, thick and tightly arranged fibrin, and vWF merging together, containing a large number of white blood cells and NETs. These two regions are distributed in a layered or staggered manner, with white blood cells and NETs mainly distributed at the interface of the two regions and in regions rich in platelets. By electron microscopy, Meglio et al. found that the vast majority of thrombi have a distinct shell structure [6]. The outer shell is composed of high-density fibrin and platelets, while the inner core is composed of relatively loose red blood cells and sparse fibrin. The heterogeneity of thrombus is mainly because of the change of the inner core. They also verified that thrombus coat formation resistant to thrombolytic drugs is mediated by repeated in vitro experiments.

## 3. Cerebral thrombus composition and imaging examination

Although the study and observation of thrombus removed by endovascular treatment are more direct, it may cause damage to the original structure of the thrombus and loss of some components during surgical procedures or pathological analysis, thereby affecting the evaluation of the original volume, and content of various components, and physical properties of the thrombus [28]. Hence, the ideal strategy is to determine or roughly understand the composition of cerebral thrombus or embolism in situ through auxiliary examinations before intervention, which can guide clinical physicians to develop more accurate treatment methods. At present, scholars have applied bioelectrical impedance technology and nanotechnology to study the histological characteristics of in situ thrombus [29–31]. In addition, an artificial neural network classifier developed based on the features of thromboradiomics can also perform better prediction before surgery [32]. However, for most centers, skull CT and MRI, as common imaging examinations, are still the simplest and easiest ways to observe the thrombus in situ in vessel occlusion under living conditions. They can have some understanding of the composition and morphology of the thrombus before treatment, which is helpful to provide some information for the development of treatment strategies.

### 3.1. CT and composition of cerebral thrombus

#### 3.1.1. Thrombus density and components

The high-density artery sign (HAS) displayed on conventional CT scans is significantly associated with a thrombus rich in red blood cells, as well as better recanalization and good thrombolysis response [33–37]. The occluded large intracranial arteries are associated with thrombus rich in fibrin/platelets and are less sensitive to intravenous thrombolysis and thrombectomy [10, 36]. Intracranial arterial high density (HU value > 130) suggests that it may be a calcified embolus causing cerebral vascular occlusion [38]. Through proteomic analysis of thrombus, it is found that HAS-positive thrombus is rich in actin and other protein components related to the development of atherosclerosis, which further indicates that the possibility of LAA origin is high, while HAS-negative thrombus contains a large number of complement proteins, fibrin stabilized coagulation factor XIII, and so on, which indicates that the possibility of thrombus being cardiogenic is high [39].

#### 3.1.2. Thrombus permeability and composition

The permeability of a thrombus refers to the degree to which blood can pass through the thrombus structure and is quantitatively measured by both NCCT and single-phase CTA for thrombus attenuation [40]. Thrombosis with high permeability is rich in red blood cells, and high thrombus permeability is a good predictive factor for AIS recanalization treatment, which is associated with good functional prognosis and better clinical outcomes after intravenous thrombolysis with rt-PA [41]. However, Berdit et al. found a strong correlation between the higher permeability of thrombus, lower levels of red blood cells, and higher levels of fibrin/platelets [42]. Therefore, a large sample size of a prospective cohort study is still needed to explore the correlation between the permeability of thrombus and the pathology and clinical prognosis of thrombus.

### 3.2. MRI and composition of cerebral thrombus

The low signal observed on the GRE sequence of MRI imaging that spreads outward around cerebral thrombosis is called a magnetic susceptibility vessel sign (SVS). This special imaging sign is common in thrombus rich in red blood cells, and the absence of SVS often indicates a thrombus rich in fibrin [43–44]. However, there is currently no clear conclusion regarding the correlation between SVS and stroke etiology and its prognostic value for recanalization therapy. In addition to this typical imaging sign, the application of high-resolution magnetic resonance vascular wall imaging can evaluate the anatomical characteristics and thrombus burden of occluded vessels before surgery, and also assist in identifying the cause of arterial occlusion, such as carotid artery dissection, which is beneficial for the selection of surgical instruments and thrombectomy plans [45].

## 4. Composition of cerebral thrombus and cerebral vascular recanalization therapy

### 4.1. Composition of cerebral thrombus and intravenous thrombolysis

The composition of the thrombus has a certain impact on the thrombolytic effect of alteplase. A thrombus rich in red blood cells is more sensitive to thrombolysis than a thrombus rich in platelets [44]. The content and spatial arrangement of various components in different thrombi can also affect the effectiveness of intravenous thrombolysis. The area rich in red blood cells in the thrombus is easily dissolved by rt-PA due to the thin arrangement of fibrin, while the area rich in platelets has a dense arrangement of fibrin and contains a large amount of vWF and extracellular DNA that are resistant to thrombolytic drugs, making them less likely to be dissolved by rt-PA. There are significant differences in the proportion and arrangement of these two regions in different thrombi, which in turn leads to different thrombolytic reactivity [5]. Observation of thrombolytic-resistant clots by scanning electron microscopy reveals a dense shell structure consisting of fibrin, vWF, and aggregated platelets, which renders the thrombus difficult to dissolve [6]. Further studies using scanning electron microscopy and transmission electron microscopy have shown that thrombolytic-resistant thrombus contains a large number of compressed deformed red blood cells, and the surface fibrin is more densely arranged [46]. In addition, higher levels of NETs in thrombus are associated with resistance to thrombolytic drugs, possibly due to the formation of scaffold-like structures by NETs [15]. Special attention should be paid to the thrombolysis of patients with purulent embolism secondary to infective endocarditis because the direct infiltration of septic substances on the vessel wall and the arteritis and infected aneurysms mediated by it will cause an increased risk of hemorrhagic transformation [47].

In vitro thrombolysis with alteplase combined with deoxyribonuclease 1 (DNAse1) was performed on the thrombus taken out by intravascular treatment, and obvious effects were observed [16]. As a protease that can lyse and regulate vWF activity, animal experiments showed that ADAMTS13 could be dissolved in the thrombus rich in vWF [20]. Therefore, composite thrombolytic drugs targeting fibrin and non-fibrin components in thrombus may significantly improve the effectiveness of thrombolysis in the future, but the combination of multiple drugs may bring greater risks so more research is needed to improve safety [48].

## 4.2. Composition of cerebral thrombus and cerebral artery thrombectomy

The composition of the thrombus may have a significant impact on the difficulty and effectiveness of arterial thrombectomy. A systematic evaluation study in 2016 focused on multiple studies on the composition of cerebral thrombus after thrombectomy from 2005 to 2015 and found that the composition of thrombus was not related to the recanalization rate of cerebral artery thrombectomy [37]. Subsequent studies found a positive correlation between the content of red blood cells in the thrombus and the results of thrombectomy [33, 49]. Compared to thrombus rich in fibrin/platelets, thrombus rich in red blood cells have shorter thrombectomy times, less frequency of thrombectomy and secondary embolism, and better vascular recanalization effects and clinical outcomes [50–53]. Compared to previous semi-quantitative analyses of the proportion of various main components in thrombus, a recent study prepared thrombus into homogenates and quantitatively measured the specific content of red blood cells, platelets, and white blood cells. It was found that platelet content was positively correlated with the number of thrombectomy operations and thrombectomy time [54].

The different compositions of thrombus can lead to differences in their physical properties, which in turn affects the effectiveness of thrombectomy [55]. In vitro experiments have found that an increase in the content of red blood cells in thrombus increased their viscosity and elasticity, and the friction coefficient of thrombus rich in fibrin/platelets was significantly higher than that of thrombus rich in red blood cells [56–57]. However, a recent in vitro study of a small sample of thrombus removed from patients with acute cerebral infarction found that the stiffness of the thrombus increased with the increase of fibrin/platelet content [58]. However, compared with fibrin-rich thrombus, red blood cell-rich thrombus is more deformable and less frictional, making this thrombus easier to dislodge [59]. The suction catheter can only be in contact with the proximal surface of the thrombus, while the grid of the stent retrieval can be embedded in the overall thrombus to generate greater grasping force and reduce the risk of thrombus escape, resulting in a thrombus rich in red blood cells. The one-pass probability is higher than that of aspiration thrombectomy [60–61].

The content of other components in the thrombus also has a certain correlation with the results of arterial thrombectomy. Studies have confirmed that higher levels of white blood cells in thrombus are associated with lower recanalization rates and poorer clinical outcomes [9]. The content of NETs in the thrombus was found to increase the number of times of thrombus removal, prolong the time of thrombus removal, and was negatively correlated with the recanalization rate [15, 62]. The increase of vWF content in the thrombus was also found to be associated with poorer recanalization results [19]. In addition, the presence of blood vessel wall components in the thrombus is associated with a lower recanalization rate, and the time and frequency of thrombus removal for infected thrombus-containing bacteria are both longer but have no significant impact on clinical outcomes and prognosis [21, 24]. A recent study found a correlation between higher levels of S100b1 in thrombus and the occurrence of cerebral hemorrhage after thrombectomy [63].

## 5. Correlation between the composition of cerebral thrombus and etiology of cerebral infarction

TOAST classification is currently the most commonly used method to classify the etiology of cerebral infarction. Its significance lies in that it can guide clinicians to carry out more appropriate secondary preventive treatment for patients and effectively reduce the recurrence rate. Therefore, many scholars try to explore the correlation between the composition of cerebral thrombus and the etiology of cerebral infarction, to better guide clinical treatment.

### 5.1. Red blood cells, fibrin/platelets, and etiological classification

In 2006, Marder conducted the first histological study on thrombus in patients with acute cerebral infarction and found that there was no significant difference between the main components of cardiogenic thrombus and arterial thrombus [64]. However, this result may be affected by the low efficiency of the thrombectomy device used at the time and lack of credibility. A study from Japan in 2008 analyzed the source of cerebral thrombus through autopsy of patients with cerebral infarction and found that arterial thrombus was rich in platelets and platelets, and cardiogenic thrombus was rich in red blood cells [65]. This conclusion is also unreliable because the composition of this thrombus may be influenced by post-mortem hemodynamic changes. Subsequently, a series of studies both domestically and internationally have found that cardiogenic thrombosis contains higher levels of fibrin/platelets and lower levels of red blood cells, while arterial thrombosis contains higher levels of red blood cells [7, 42, 50, 53, 66–69]. At the same time, many studies have drawn different conclusions on the relationship between the main composition of thrombus and the classification of cerebral infarction etiology. These studies have found that cardiogenic thrombus is rich in red blood cells, while non-cardiogenic thrombus is rich in fibrin/platelets [33, 37, 43, 70-72]. A systematic review and meta-analysis only found that the content of fibrin was higher in cardiogenic and cryptogenic thrombus than in arterial thrombosis, while there was no significant difference in the content of red blood cells, platelets, and white blood cells in thrombus of different causes [73]. However, a systematic review and meta-analysis only found that the content of fibrin in cardiogenic and cryptogenic thrombus was higher than that in arterial thrombus, while the content of red blood cells, platelets, and white blood cells in thrombus of different etiologies was not significantly different [73]. However, some recent studies have found that there is no significant difference in the main components of cardiogenic thrombus and large artery atherosclerotic thrombus [74–75]. Therefore, there is no consistent conclusion on the relationship between the etiological types of cerebral infarction and the proportion of main components in cerebral thrombus.

It is worth noting that strokes of unknown etiology account for approximately 25% of ischemic strokes [76]. In most studies, it was found that the thrombus components had similar histological features and clinical prognosis to those of cardiogenic thrombus [7, 66, 68]. Recently, Kauw et al. used cardiac CTA to examine 370 patients with acute ischemic stroke and found that 6% of non-atrial fibrillation patients had left atrial appendage thrombus, and these patients would probably be classified as unknown etiology stroke in most medical centers [77]. Therefore, cerebral embolism of unknown etiology may partly come from left atrial appendage thrombus in non-atrial fibrillation patients.

### 5.2. Other components and etiological classification

Maekawa et al. studied the recovered thrombus and found that there was no significant difference in the leukocyte content in thrombus from different sources [50]. However, some studies have also found that higher levels of leukocytes are associated with cardiogenic thrombus [9, 78]. Therefore, there is no consistent conclusion about the correlation between the white blood cell content in thrombus and the etiology of cerebral infarction. Similarly, no correlation was found between the proportion of neutrophils in thrombus and TOAST classification in patients with acute cerebral infarction, and the relationship between the content of NETs and vWF in thrombus and TOAST classification was also uncertain [15, 20, 23].

Considering that the inflammatory response plays an important role in the development of aortic atherosclerosis, through the study of inflammatory cells and inflammatory mediators in thrombus, it was found that the contents of CD3+T cells and IL-1β in aortic atherosclerotic thrombus were significantly higher for cardiogenic thrombus and thrombus of unknown etiology [79–80]. However, there are still few studies on the relationship between the content of inflammatory mediators in thrombus and the etiology, so more research is still needed to confirm.

## 6. The dynamic evolution of cerebral thrombus

This study emphasizes the importance of time in ultra-early cerebral infarction intravenous thrombolytic therapy, mainly on the basis that ischemic brain tissue will evolve into irreparable necrotic brain tissue over time [81–82]. However, after cerebral infarction, in addition to ischemic brain tissue, the thrombus itself also changes dynamically [83]. The stiffness and coefficient of friction of fresh thrombus are low; the thrombus has good permeability, is highly sensitive to thrombolytic drugs, and is easy to take out. As time goes by, there are more and more fibrin deposits and more extensive fibrin and red blood cells. Cross-linking promotes more maturity and stability of thrombus, and the content of NETs in mature thrombus is relatively higher, and the possibility of thrombus being lysed and removed gradually decreases [84–87]. For patients receiving intravenous thrombolysis, the earlier the application of rt-PA, the greater the possibility of benefit [88]. Similarly, there is a significant correlation between the time interval from onset to recanalization of cerebral artery thrombectomy patients and clinical results. With the extension of the time interval, the effectiveness of patients with cerebral artery thrombectomy in comparison with the drug control-only group gradually decreases, and the effective reperfusion rate decreases with the extension of the time from medical treatment to femoral artery puncture (DPT) [89–90]. Kim et al. used thin CT scans of middle cerebral artery thrombus in patients with thrombolysis and found that the degree of thrombus dissolution and density gradually decreased with the prolongation of OTT (onset to treatment) [91]. Studies of the high-density sign of early middle cerebral arteries decreased over time, suggesting that the relative proportion of red blood cells in the thrombus gradually decreased over time [92]. With the development of thrombus, the content of fibrin will also increase in the further deposition of the original thrombus [93]. Other studies found that the content of white blood cells, fibrin, citrulline histone, and vWF in patients whose time from onset to femoral artery puncture was within 4 to 8 hours was significantly higher than that in patients whose time from onset to femoral artery puncture was within 4 hours [94]. Recent studies both domestically and internationally have found that the content of fibrin, platelets, and white blood cells in an old thrombus is higher than that in a fresh thrombus [95–96]. The above studies all suggest the dynamic evolution of cerebral artery thrombus. The change of thrombus in the time dimension may have a certain impact on the correlation between the histological characteristics of cerebral thrombus and imaging findings and the correlation with the etiology of cerebral infarction, which needs further research to confirm.

## 7. Conclusion

In summary, through the study of thrombus in patients with acute cerebral infarction, it can be found that the histological characteristics of thrombus have a certain influence on the sensitivity of intravenous thrombolysis, the difficulty of arterial thrombus removal, and the imaging characteristics of thrombus. The composition of the drug is dynamically changing, which will help the development of new thrombolytic drugs and thrombectomy devices and the improvement of stroke treatment procedures. However, there is no consistent conclusion on the correlation between thrombus components and the etiology of cerebral infarction. New research methods on thrombus using proteomics or new biomarkers may be used to clarify different sources of thrombus for effective secondary prevention in patients. In addition, actively exploring new inspection methods that can analyze intracranial cerebral artery thrombus in patients before treatment will have great guiding significance for the selection of treatment strategies.

## Disclosure statement

The authors declare no conflict of interest.

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