Clinical characteristics and dynamic evaluation of hematoma morphology in patients with aspirin-related intracerebral hemorrhage

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Abstract. – OBJECTIVE: With the increasing awareness of thrombotic disease prevention and treatment, as well as advancements in cardiovascular valve replacement and cardiovascular disease resection surgeries, patients undergoing these procedures require antithrombotic medications. This work aimed to explore the dynamic changes in hematoma morphology and volume in aspirin-related intracerebral hemorrhage (ARICH).

PATIENTS AND METHODS: 43 cases with ARICH were selected as the experimental group and 40 cases of non-antithrombotic drug-related cerebral hemorrhage (non-ATT-ICH) were enrolled in the control group. General information about the two study groups was collected, and the initial laboratory test indices upon admission for each patient were recorded. Hematoma volumes were recorded within 6 hours, 24±3 hours, 72 hours, and 7 days after the onset of the disease. Volume changes were observed, and the absorption rates of the hematoma at 1 day, 3 days, and 7 days after onset were calculated.

RESULTS: In the baseline data, the baseline hematoma volume of the experimental group (19.37±3.21) was slightly higher than that of the control group (15.73±2.78), showing a statistically significant difference (p<0.05). In terms of hematoma morphology and location, the hematoma morphology irregularity of the experimental group compared with the control group was 67% vs. 40%. In terms of hematoma growth and expansion, patients with ARICH had a larger volume of hematoma growth within 1 to 3 days of onset. At 3 d and 7 d, the experimental group’s absorption rate was higher than the control group, and the experimental group’s hematoma absorption rate was faster than the control group. The experimental group’s hematoma morphology was mostly irregular, as can be seen (67%). If the hematoma volume increased from 1 d to 3 d after the onset of the disease, the hematoma volume of the patients in the experimental group was larger. The hematoma absorption rate of the experimental group was faster than that of the control group from 72 h to 7 d.

CONCLUSIONS: The morphology of ARICH hematoma was mainly irregular (67%). In ARICH patients, if the hematoma volume rose within 1-3 days of initiation, the hematoma volume increased even more. Compared with non-ATT-ICH, ARICH had a faster rate of hematoma absorption at 3-7 d.

Key Words: Aspirin, Intracerebral hemorrhage, Clinical features, Hematoma morphology, Dynamic changes of hematoma.

Introduction

Intracerebral hemorrhage (ICH) is caused by various factors, with hypertension and atherosclerosis being the most common triggers. Other causes include congenital cerebral vascular malformations or aneurysms, blood disorders, traumatic brain injury, anticoagulation, or thrombolytic therapy, and cerebral amyloid angiopathy. Currently, cerebrovascular diseases rank as the second leading cause of human mortality, with ischemic diseases accounting for 80% and hemorrhagic diseases accounting for 15%. A small portion of cases remains of unknown etiology, with disability rates rising to the fourth position. In China, cerebrovascular disease is the second leading cause of death among urban residents and the third leading cause among rural populations. Nearly half of these cases are attributed to spontaneous hypertensive intracerebral hemorrhage. However, with the increasing incidence of ischemic stroke and growing awareness of thrombotic disease prevention and treatment, as well as the performance of cardiac valve replacement and cardiovascular disease resection surgeries, these
patients often require antithrombotic medications such as antiplatelet therapy, anticoagulants, and thrombolytic agents to prevent and treat thrombotic disorders. Regardless of the specific antithrombotic treatment used, ICH remains one of the most dangerous complications. Antithrombotic drug-related cerebral hemorrhage (ATT-ICH) accounts for approximately 12-20% of all cases of cerebral hemorrhage, with oral antithrombotic drug-related cerebral hemorrhage (OAT-ICH) having an annual incidence rate as high as 9-13%, resulting in a 6.7-11.0% increased risk compared to other types of cerebral hemorrhage, and a mortality rate exceeding 50% with a poorer prognosis than other types of ICH.

In recent years, there has been a comprehensive understanding of the use of antiplatelet aggregating drugs. Medications such as Dipyridamole, Clopidogrel, and Aspirin, which have inhibitory effects on platelet aggregation, are widely used to control the exacerbation of acute ischemic stroke or prevent the occurrence of acute ischemic stroke and cardiovascular diseases. Among them, Aspirin (Asp) is the most commonly used oral medication for controlling platelet aggregation. Its role in the prevention and treatment of cardiovascular and cerebrovascular diseases has been widely recognized worldwide and is commonly used as a secondary preventive measure in most hospitals in China. Many patients with intracerebral hemorrhage have a history of starting Aspirin or other antiplatelet inhibitors prior to the occurrence of the disease. Literature studies have shown that patients with a history of intracerebral hemorrhage have a lower incidence of re-bleeding after taking Aspirin, while the incidence of re-bleeding significantly increases in patients with intracerebral hemorrhage after taking Aspirin, allowing surgeons to prioritize consideration of postoperative timing. A study has indicated that the risk of hemorrhagic stroke due to low-dose Aspirin is 0.3%, while the risk increases to 1.1% with high-dose Asp. The work also found that although taking Asp alone does not increase the in-hospital mortality rate of patients with intracerebral hemorrhage, the in-hospital mortality rate significantly increases with dual antiplatelet therapy.

The presence of Computed Tomography (CT) evidence of hematoma expansion in ICH is considered a gold standard for assessing significant brain bleeding. Different CT features of the head indicate varying risks and prognoses for patients with ICH. Existing research has also demonstrated that irregular hematomas are more prone to expansion than regular hematomas. Researchers have pointed out that, similar to regular residual hematomas, irregular hematomas are associated with a poorer prognosis, which is correlated with the degree of hematoma expansion. The mortality rate within 30 days for irregular-shaped hematomas is approximately 26.7%, significantly higher than the 6.6% for regular-shaped hematomas. Investigations have also shown that the incidence of hematoma expansion is nearly twice as high in patients with irregular-shaped hematomas compared to those with regular-shaped hematomas. Additionally, patients presenting with altered consciousness upon admission have a higher likelihood of experiencing hematoma expansion. As consciousness levels decrease and the Glasgow Coma Scale (GCS) score decreases, the brain damage caused by cerebral hemorrhage becomes more severe, leading to a higher risk of seizures, vomiting, agitation, increased blood pressure, and hematoma enlargement. Since the active bleeding time in ICH patients is transient, with bleeding tending to stabilize after six hours, patients who are admitted earlier have a shorter interval for the identification of hematoma expansion during CT examinations.

Once ICH occurs, it leads to irreversible damage to brain tissue, and the morphology and volume changes of the hematoma determine the severity of the damage. Generally, based on the morphology of the hematoma, it can be categorized as regular or irregular, and the volume changes of the hematoma vary according to its morphology and the time of occurrence. Currently, there is a considerable amount of research focusing on the morphology and volume changes of spontaneous intracerebral hemorrhage. However, irregular-shaped hematomas have a higher rate of hematoma expansion compared to regular round-shaped hematomas. Furthermore, hematomas with irregular shapes and separated components have the highest rate of hematoma expansion. According to research, changes in hematoma volume have also been observed. Due to an increase in bleeding volume, the rate of hematoma absorption slows down, but the absorption rate gradually increases on the first, third, and seventh days. As the time since bleeding increases, the absorption rate of the hematoma also gradually improves. However, different volumes of hematomas have varying absorption rates. Generally, hematomas with a volume between 10-30 mL exhibit faster absorption compared to hematomas with a volume lower than 10 mL or greater than 30 mL.
However, no comprehensive study of hematoma form features and hematoma volume dynamic changes has been conducted in ARICH, and the impact of antithrombotic medications on hematoma shape characteristics and volume fluctuations in cerebral hemorrhage is still unknown. Therefore, a controlled study of 43 patients with ARICH and 40 patients with non-ATTICH will be used in this paper to explore the dynamic changes in hematoma shape, hematoma absorption, and hematoma growth in ARICH.

Patients and Methods

Research Objects

318 patients with cerebral hemorrhage admitted to the Neurology Department, The Fourth Affiliated Hospital of Nanjing Medical University, from May 2020 to February 2022 were continuously collected in this work. The experiment had been approved by the Medical Ethics Committee of The Fourth Affiliated Hospital of Nanjing Medical University, and the patients and their families understood the research content and methods and agreed to sign the corresponding informed consent (Table I).

According to the above inclusion and exclusion criteria, 83 patients finally met the requirements of this work; the experimental group included 43 patients with ATT-ICH, and the control group consisted of 40 non-ATT-ICH patients.

Table I. Inclusion and exclusion criteria of research objects.

<table>
<thead>
<tr>
<th>No.</th>
<th>Inclusion criteria</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>All patients were older than 18 years</td>
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<tr>
<td>2</td>
<td>Onset was within 6 hours</td>
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<td>3</td>
<td>Brain CT confirmed cerebral hemorrhage</td>
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<td>4</td>
<td>Aspirin was taken at least for six months before the onset of symptoms</td>
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<tr>
<td>5</td>
<td>Complete clinical and imaging data were available</td>
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<tr>
<td>6</td>
<td>The informed consent was signed</td>
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<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>1 Cerebral hemorrhage caused by other causes, such as trauma, brain tumor, and cerebrovascular malformation.</td>
</tr>
<tr>
<td>2 Age &lt;18 years old</td>
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<tr>
<td>3 Failed to sign the informed consents</td>
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<tr>
<td>4 Patients suffered from coagulation disorders and blood disorders</td>
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Observation Indicators

This work was a prospective registration study, so it collected the baseline clinical data of the research subjects, including gender, age, history of hypertension, smoking history, GCS at admission, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission.

The initial partial laboratory assay indices, including blood platelet count (BPC), activated partial thromboplastin time (APTT), international normalized ratio (INR), and prothrombin time (PT), were recorded for each patient upon admission for treatment.

Based on its shape, the hematoma is classified into five types (Type I to Type V) as illustrated in Figure 1. Types I and II are considered regular, while Types III to V are categorized as irregular.

The locations of the hemorrhage include cerebral lobe ICH (frontal lobe, temporal lobe, parietal lobe, occipital lobe, cerebellum), basal ganglia ICH, thalamic ICH, brainstem ICH, and cerebellar ICH.

The hematoma volume (cm³), 72 h hematoma volume (cm³), and 7 d hematoma volume (cm³) of each patient were recorded within 6 h (i.e., baseline hematoma volume), 24±3 h, and 72 h hematoma volume (cm³) after the onset of each patient. The volume change was observed. If the hematoma absorption was found, the hematoma absorption rate at 1 d, 3 d, and 7 d from the onset was calculated according to the hematoma volume. Hematoma absorption is the ratio of the baseline hematoma volume and the difference of the hematoma volume at 1 d, 3 d, and 7 d. Whether there was hematoma growth within 24±3 h and 72 h was observed. If hematoma growth was found, the hematoma growth volume (cm³) was calculated. The hematoma growth volume is the difference between the 1 d or 3 d hematoma volume and the baseline hematoma volume. In addition, whether there was hematoma expansion within 24±3 h and 72 h was observed. Judgment criteria for hematoma expansion were given as follows: according to Brott’s criteria, two consecutive CT hematoma volumes were compared, and the hematoma volume increased by more than 33% compared with the previous one.

Blood volume scanning method: a Siemens 64-slice spiral CT machine (Munich, Germany) was used. The patient was placed in a supine position with the Orbitomeatal Line (OML) as the baseline for conventional axial horizontal scanning. The scanning parameters were as follows: slice thickness of 10 mm, voltage of 120 kV, and current of 250 mA.
Hematoma volume was measured as follows. After scanning the head, the image was transferred to the Picture Archiving and Communication System (PACS) image center and made into a CD in DICOM format. The hematoma volume estimated by the Tada equation was calculated as follows:

\[ V = A \times B \times C \times \frac{\pi}{6} \]

In the above equation, A was the plane long axis of the largest area of the head CT hematoma, B referred to the short axis length of the largest area of the hematoma (required to be perpendicular to A), and C represented the number of scan layers of the hematoma. Given the possibility of reduced blood loss in subsequent layers of the hematoma, it is assumed that the total blood loss in each layer is 0.75 times that of the first layer. Therefore, assign a weight of 1 to the first layer and a weight of 0.5 to any layer whose blood loss is between 25% and 75% of the first layer. Any layer whose blood loss is less than 25% of the first layer is not counted in the calculation. Hematoma volume does not include blood flow to ventricles or ventricles. The value was assumed to be lower than 0.25, this layer was not counted. The hematoma volume did not include blood flow into the ventricle or the sylvian cistern. Definition of hematoma margin: CT value of hematoma in the acute phase of cerebral hemorrhage was 60-80 HU, and the boundary was clear and easy to distinguish and measure. The edges of the hypodense zone around the hematoma absorption period were indistinct and measured at the border with CT values >40 HU.

**Results**

**Comparison of Clinical Data of Patients**

The clinical data of 43 ARICH patients and 40 non-ATT-ICH patients were compared. There were no significant differences in gender, age, hypertension history, smoking history, GCS score at admission, SBP, and DBP at admission, BPC, INR, APTT, PT, and other coagulation indexes on first admission between the two groups of patients. The baseline hematoma volume of the experimental group (19.37±3.21) was slightly higher than that of the control group (15.73±2.78), and the difference was statistically significant \((p<0.05)\). The specific results are shown in Figure 2.

**Comparison of Hematoma Morphology and Hematoma Location**

On the hematoma morphology, the comparison between the experimental group and the control group of hematoma morphology irregularity was 67% vs. 40%, which was statistically significant \((p<0.05)\). It was shown that, compared with the control group, the hematoma morphology of the experimental group was mainly irregular. In the basal ganglia, thalamus, cerebral lobe, cerebellum, and brainstem, there was no significant difference in hematoma placement between the experimental and control groups, as shown in Figure 3.
Hematoma morphology in aspirin-related intracerebral hemorrhage

Comparison of Hematoma Growth and Hematoma Expansion

As shown in Figure 4, there were 9 cases of hematoma volume growth in the experimental group and 12 cases of hematoma volume growth in the control group. The changes in hematoma volume and hematoma growth volume at 24±3 h and 72 h were compared between the two groups. In terms of hematoma volume, there was a statistically evident difference between the experimental group (41.26±16.82) and the control group (14.85±9.76) patients with hematoma growth at 24±3 h (\(p<0.01\)). There was a statistically great difference between the experimental group (34.55±11.31) and the control group (14.16±11.94) in patients with hematoma growth at 72 hours (\(p<0.01\)). It was shown that the patients in the experimental group would have a larger growth volume if hematoma growth occurred within 24±3 h to 72 h from the onset. The proportion of hematoma expansion in the experimental group and the control group at 24±3 h was 33.6% and 50.0%, respectively, showing a statistically notable difference (\(p>0.05\)).

Comparison of Hematoma Absorption

As shown in Figure 5, the number of patients in the experimental group was 20 with hematoma absorption, and that in the non-ATT-ICH group was 21. The rates of hematoma absorption were compared between the two groups of patients with hematoma absorption, and the results in both groups followed a normal distribution. The independent sample \(t\)-test results showed that the hematoma absorption rate of the experimental group (11%) and the control group (7%) had no statistical significance at 1 d onset (\(p>0.05\)).
was a statistically significant difference in the hematoma absorption rate between the experimental group (31%) and the control group (23%) at 3 days ($p<0.05$). At 7 d, the hematoma absorption rate of the experimental group (67%) and the control group (51%) was significantly different ($p<0.01$).

It indicated that there was no statistical difference in the hematoma absorption rate between the two groups on the 1st day of onset, but there was a statistical difference in the hematoma absorption rate on the 3rd and 7th day of onset. The patients in the experimental group had higher absorption rates than those in the control group at 3 d and 7 d, indicating that ARICH was faster than non-ATT-ICH hematoma absorption at 3 d and 7 d.

**Discussion**

**ARICH and Coagulation**

Both domestic and international researchers have conducted partial coagulation function tests on ICH patients within 6 hours of onset. They found that coagulation parameters (PT, INR, APTT, and TT) in Aspirin-related ICH patients were significantly higher compared to the group not taking aspirin. Additionally, the platelet count in aspirin-related ICH patients was significantly lower than in the group not taking aspirin. These findings indicate that the use of Aspirin leads to a significant increase in blood coagulation dysfunction during the severe phase of ICH, resulting in a unique risk factor associated with increased incidence and distinct prognostic factors. These factors are considered directly related to the clinical changes in acute ICH. Mortality in ARICH was significantly positively correlated with the INR. Studies have shown that when the INR>2.5, the risk of ICH is significantly increased. This study was the first to examine several coagulation-related measures in individuals with Aspirin-related ICH with those without. The baseline hematoma volume of the experimental group (19.37±3.21) was slightly higher than that of the control group (15.73±2.78), and the difference was statistically evident ($p<0.05$). There was no statistical significance in INR, APTT, and PT ($p>0.05$), which
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were different from the results of relevant literature. This could be due to the fact that some individuals in our study show pathological abnormalities in platelet count and coagulation function indicators for the first time. Because the number of examples collected in this work is quite modest, the sample size for verification research must be increased.

**ARICH with Hematoma Morphology and Hematoma Location**

The shape and location of the hematoma in patients with ICH are also one of the most important contents to be investigated after admission. The changes in hematoma in different states and in different parts are also different. Currently, the hematoma morphology of spontaneous ICH is extensively studied. According to the shape of the hematoma, some studies categorized it as follows: (1) the hematoma is round with smooth edges; (2) small nodules appear on the border of the hematoma with an irregular shape, and the incidence of irregularly shaped hematoma expansion is much greater than that of spherical hematoma. A multifactorial study showed that irregular hematoma shape was the only influencing factor for hematoma expansion. Research has also shown a direct association between irregular shapes and fatality/severe disability. However, there is still a lack of more relevant research results for ATT-ICH. In this work, the differences between ARICH and non-ATT-ICH-related forms of hematoma were explored. The results showed that 67% of ARICH patients had irregular hematoma morphology, and 40% of non-ATT-ICH patients had irregular hematoma morphology \( p < 0.05 \). This indicates that irregular hematoma is the main cause of Aspirin-related ICH. Hematoma sites in patients with ARICH were compared with those in patients with non-ATT-ICH. There was no significant difference in the location of ARICH hematoma in the basal ganglia, thalamus, lobe, cerebellum, and brainstem. A limitation of this work was that only Aspirin patients were collected in this work among the patients who used antiplatelet aggregation drugs. This work only compared the difference in hematoma shape between Aspirin-related ICH patients and non-ATT-ICH patients and did not investigate the relationship between hematoma shape and hematoma volume, the degree of inconsistency in hematoma density, and prognosis. If the association between irregular local hematomas and the degree of hematoma expansion was further investigated, expansion was still required when comparing mean blood loss with antiplatelet agents.

**ARICH and Hematoma Absorption**

The consistency of hematoma volume changes is the most important factor in determining clinical outcomes after ICH. After ICH, the hematoma volume fluctuates over time, which is a dynamic process. In most patients, the hematoma volume fluctuates with time. Much research has been done on the mechanism of hematoma absorption. Some experiments have shown that after intracerebral hemorrhage, the diameter of erythrocytes in blood clots decreases over time, accompanied by the accumulation of membrane attack complexes and a decrease in hemoglobin levels. Membrane attack complexes and human erythrocyte phagocytosis promote hematoma clearance after intracerebral hemorrhage. ICH can also result in a massive reduction of the hematoma and hypodensity around the hematoma in the absence of any effective bleeding and affecting the normal life activity of the surrounding brain. Szollosi, on the other hand, claimed that the lysis of blood clots and the phagocytosis of glial cells and macrophages, as well as the proliferation of the skin surface around the hematoma and the co-stimulation of phagocytes, are all important aspects of the hematoma process. Glial cell phagocytosis is common around hematoma, and the volume of hematoma is large. Although there are many cells on the surface of the surrounding skin, the surrounding brain tissue has a relatively strong ability to squeeze, and the local circulation conditions are poor, which is unfavorable for the absorption of the hematoma. Smaller hematomas occupy less space, which is conducive to the formation of new skin surfaces and the accumulation of phagocytosed bacteria, and the absorption rate of residual hematomas is also relatively fast. Therefore, the elimination time of bulky hematomas is also longer, which is different from the absorption rate of hematomas. However, there is much debate regarding the relationship between the amount of bleeding and the rate of hematoma absorption. In earlier studies, it was generally believed that the larger the residual hematoma, the faster the absorption rate, and the hematoma volume was linearly related to the absorption rate of the hematoma expansion. According to several scientific investigations, the hematoma volume has a direct impact on hematoma absorption, implying that hematoma absorption circumstances with a big hematoma volume are bad. The chronic hematoma will continue to disrupt substance metabolism, leading to inflammation of surrounding brain tissue, increased in-
tracranial pressure, decreased blood supply to the brain, cerebral ischemia, and potentially death. Studies have also demonstrated that the larger the hematoma volume, the faster the absorption rate, and the smaller the volume, the slower the absorption rate. These reports are all studies on hematoma's mechanism and absorption rate in spontaneous intracerebral hemorrhage. Currently, there are no studies of hematoma absorption in ARICH patients. Therefore, this work performed preliminary statistics on the hematoma absorption of ARICH with a small sample. It was shown that ARICH was faster than non-ATT-ICH hematoma absorption at 3 d and 7 d. However, its pathogenesis is still unclear, and an expansion of the sample size is needed to confirm the results of this work. Whether the mechanism of hematoma absorption in aspirin-related cerebral hemorrhage is related to the effect of aspirin on the phagocytosis of glial cells and macrophages and the proliferation of capillaries around hematoma can be further discussed. Another possibility is that it has to do with some anti-platelet aggregation during the breakdown of blood clots. The third possibility is related to cerebral edema in patients with cerebral hemorrhage within 3 days of onset, which may affect the measurement error.

**ARICH and Hematoma Growth**

After ICH, although the hematoma volume decreases with time in most patients, there are still a few patients who experience an increase in the hematoma volume during the acute phase of the cerebral hemorrhage. When the hematoma volume grows to a certain volume, it becomes a hematoma expansion, that is when the hematoma volume exceeds 12.5 mL or the volume exceeds 33%. The size of the hematoma is linked to the patient’s clinical prognosis, and there has been some dispute concerning the role of hematoma expansion in aspirin-related intracerebral hemorrhage. Regular Aspirin usage before the onset of ICH was found to be an independent predictor of death in a study, with a three-month mortality rate of 43.2% in the Aspirin group, indicating that regular Aspirin use before the onset of ICH was strongly linked with hematoma enlargement. One study included 253 patients with ICH, of whom 17 were taking Aspirin, and 15.4% developed hematoma expansion. The results of this work suggested that the prognosis of ICH was related to a large hematoma, independent of the use of antiplatelet drugs. Some scholars have studied the pathogenesis of intracranial hemorrhage and divided it into three stages: vessel wall fragility, vessel wall rupture, and hemorrhage expansion; and through research, it has been proved that antithrombotic treatment only affects the third step, not the first and second steps. The results of this work showed that in terms of hematoma volume, there was a statistically significant difference between the experimental group (41.26±16.82) and the control group (14.85±9.76) who developed hematoma growth at 24±3 h (p<0.01). There was a statistically significant difference between the experimental group (34.55±11.31) and the control group (14.16±11.94) in patients with hematoma growth at 72 hours (p<0.01). It was shown that patients with ARICH would have a larger growth volume if hematoma growth occurred within 24±3 h to 72 h of onset. The proportion of hematoma expansion in the experimental group and the control group at 24±3 h was 33.6% and 50.0%, respectively, and the difference was not statistically evident (p=0.05). According to the findings, there was no statistical difference in hematoma expansion between ARICH and non-ATT-ICH patients. This study’s sample size was relatively small, therefore, there could be inaccuracies. More long-term experimental samples are needed for additional verification.

**Conclusions**

The morphology of ARICH hematoma was mainly irregular (67%). In ARICH patients, if the hematoma volume rose within 1-3 days of initiation, the hematoma volume increased even more. However, ARICH has not yet conducted a comprehensive study on the dynamic changes of hematoma morphology and volume, and the influence of antithrombotic drugs on the morphological characteristics and volume fluctuations of hematoma in cerebral hemorrhage is still unclear. Compared with non-ATT-ICH, ARICH had a faster rate of hematoma absorption at 3-7 d.

**Ethics Approval**

The experiment had been approved by the Medical Ethics Committee of The Fourth Affiliated Hospital of Nanjing Medical University (acceptance number: NMU202002156347).

**Informed Consent**

The patients and their families understood the research content and methods and agreed to sign the corresponding informed consent.
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Not received.

Authors’ Contributions
Lirong Xu and Yan Zhao conducted patient information collection and quality control. Lirong Xu coordinated the work. Wei Huang edited and reviewed the article. Lirong Xu and Wei Huang conducted a statistical sample analysis.

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Data Availability
The data used to support the findings of this study are included in the article.

Conflicts of Interest
The authors declare that there are no conflicts of interest.

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