Thrombus Signal on T1-Weighted Black-Blood MR Predicts Outcomes of Catheter-Directed Thrombolysis in Acute Deep Vein Thrombosis

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Abstract

Objectives Catheter-directed thrombolysis (CDT) is an effective therapy for acute deep vein thrombosis (DVT). However, predicting the CDT outcomes remains elusive. We hypothesized that the thrombus signal on T1-weighted black-blood magnetic resonance (MR) can provide insight into CDT outcomes in acute DVT patients.

Methods A total of 117 patients with acute iliofemoral DVT were enrolled for T1-weighted black-blood MR before CDT in this prospective study. Based on the signal contrast between thrombus and adjacent muscle, patients were categorized into the iso-intense thrombus (Iso-IT), hyper-intense thrombus (Hyper-IT), and mixed iso-/hyper-intense thrombi (Mixed-IT) groups. Immediate treatment outcome (i.e., vein patency) and long-term treatment outcome (i.e., the incidence rate of postthrombotic syndrome) were accessed by the same expert. Histological analysis and iron quantification were performed on thrombus samples to characterize the content of fibrin, collagen, and the ratio of Fe^{3+} to total iron.

Results Compared to Mixed-IT and Hyper-IT groups, the Iso-IT group had the best lytic effect ($90.5 \pm 1.6\%$ vs. $78.4 \pm 2.6\%$ vs. $46.5 \pm 3.3\%$, $p < 0.001$), lowest bleeding ratio (0.0 vs. 11.8 vs. 13.3, $p < 0.001$), and the lowest incidence rate of postthrombotic syndrome on 24 months (3.6 vs. 18.4 vs. 63.4%, $p < 0.001$) following CDT. The Iso-IT group had a significantly lower ratio of Fe^{3+} to total iron ($93.1 \pm 3.2\%$ vs. $97.2 \pm 2.1\%$,

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- deep vein thrombosis
- magnetic resonance imaging
- thrombolytic treatment
- postthrombotic syndrome

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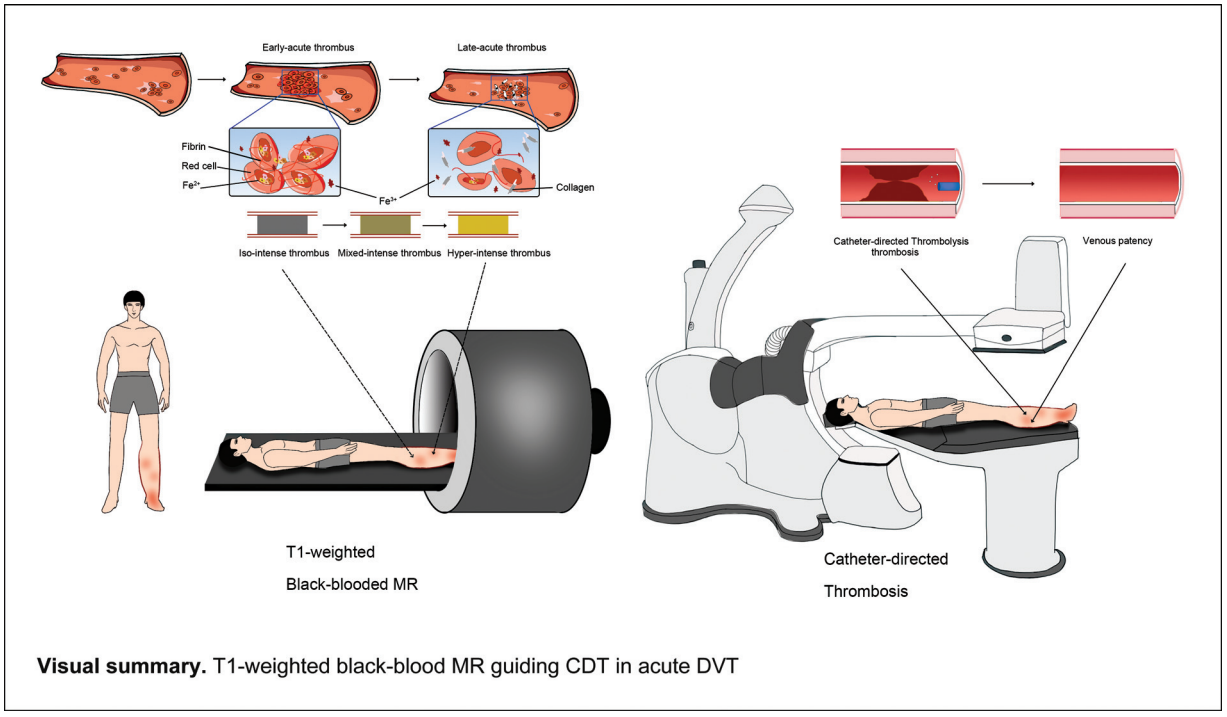

Visual summary. T1-weighted black-blood MR guiding CDT in acute DVT

$p = 0.034$) and a higher content of fibrin ($12.5 \pm 5.3\%$ vs. $4.76 \pm 3.18\%$, $p = 0.023$) than Hyper-IT.

Conclusion Thrombus signal characteristics on T1-weighted black-blood MR is associated with CDT outcomes and possesses potential to serve as a noninvasive approach to guide treatment decision making in acute DVT patients.

Key Points

- Thrombus signal on T1-weighted black-blood MR is associated with lytic therapeutic outcome in acute DVT patients.
- Presence of iso-intense thrombus revealed by T1-weighted black-blood MRI is associated with successful thrombolysis, low bleeding ratio, and low incidence of the postthrombotic syndrome.
- T1-weighted thrombus signal characteristics may serve as a noninvasive imaging marker to predict CDT treatment outcomes and therefore guide treatment decision making in acute DVT patients.

Introduction

Deep vein thrombosis (DVT) is a serious condition that occurs blood clots in deep veins of the leg, leading to venous obstruction and adversely impacting venous return.[1] DVT may precede a potentially life-threatening complication—pulmonary embolism (PE)—and lead to postthrombotic syndrome (PTS).[2] Previous studies demonstrate that PTS develops in 20 to 50% of DVT patients within 2 years after standard treatment.[2–4]

Thrombolytic therapy is reasonable to consider for patients with acute DVT involving the iliac and common femoral veins (higher risk of more severe PTS) or extensive DVT.[5] The American Society of Hematology 2020 guideline panel (Recommendation 8) suggests using catheter-directed thrombolysis (CDT) over systemic thrombolysis,[5] because CDT is effective at restoring venous patency, relieving symptoms, maintaining venous valve function, and reducing the risk of PE.[6] CDT is particularly useful in preventing PTS development and is more effective than anticoagulation alone.[7] However, a recent clinical trial as well as several meta-analysis studies demonstrated that the incidence of bleeding events is higher in CDT than in the anticoagulation therapy alone, leading to the concerns of patient selection and the cost-effectiveness in choosing this invasive procedure.[8,9] A question is if we can find subsets of patients with

proximal DVT that still benefit from more aggressive therapy upfront. Meanwhile, an approach to predicting CDT outcomes, such as immediate thrombolysis success, low bleeding rate, and PTS, would be valuable for guiding both treatment decision and post-CDT patient care.

T1-weighted magnetic resonance (MR) imaging (MRI) can be used to accurately locate, characterize, and follow up the thrombus involved in DVT.[10–12] The change in concentration of methemoglobin during the progression of DVT results in time-varying thrombus signals on T1-weighted MRI.[13,14] This is because methemoglobin has strong paramagnetic effects and causes a shortening of the T1 relaxation time. Based on this observation, T1-weighted MRI has been used to differentiate acutely recurrent thrombosis from residual chronic one.[15,16] The lysis of thrombus was also evaluated successfully using T1 relaxation time mapping in a murine model.[13] However, whether the thrombus signal on T1-weighted MRI is predictive of CDT outcomes remains unknown.

In this study, we conducted a prospective study to investigate the association between the thrombus signal on prethrombolysis T1-weighted MRI and thrombolysis outcomes in acute DVT patients receiving CDT treatment.

Materials and Methods

Study Population

This prospective single-center study was approved by the local ethics committee (approval numbers: K20150030 and H20170024); written informed consent was obtained from all patients. Patients with a clinical diagnosis of acute iliofemoral DVT ($\leq$14 days of symptom onset) were consecutively enrolled between September 2015 and June 2021. The patients' inclusion criteria were (1) age 18 to 75 years; (2) onset of symptoms within the past 14 days; (3) ultrasound-verified DVT localized in the upper half of the thigh, the common iliac vein, or the combined iliofemoral segment; (4) being planned to receive CDT treatments. Exclusion criteria were (1) any treatment before MR examination; (2) contraindications to thrombolytic treatment, including bleeding diathesis; (3) severe anemia (hemoglobin $<$80 g/L); (4) thrombocytopenia (platelets $<80 \times 10^9$/L); (5) severe renal failure (estimated creatinine clearance $<$30 mL/min); (6) history of subarachnoid or intracerebral bleeding; (7) disease with life expectancy less than 24 months; (8) drug misuse or mental disease that could interfere with treatment and follow-up; (9) contraindications to MR. All the clinical information of the venous lesions would be analyzed in demographics, such as age, gender, weight, May–Thurner syndrome, coexisted malignancy, hip prosthesis, etc.

MR Study

MR examinations were performed on a 1.5-Tesla scanner (MAGNETOM Avanto, Siemens Healthcare) within 24 hours prior to CDT. All patients were scanned in a supine position using a combination of a 6-channel body coil, an 8-channel peripheral vascular coil, and an integrated spine array coil. A previously developed T1-weighted MR black-blood thrombus imaging (BTI) technique was used for data acquisition without a contrast agent.[17] This technique builds on a variable-flip-angle three-dimensional turbo spin-echo sequence with a delay alternating with nutation for tailored excitation (DANTE) module, which can effectively suppress venous blood signals and directly visualize the thrombus within dark venous lumen. Three-station MR scans were performed to cover entire lower limbs. Scan parameters for BTI were: oblique coronal orientation, TR/TE = 650/11 ms, field of view = 352×352 mm^2, spatial resolution = $1.4 \times 1.4 \times 1.4$ mm^3 reconstructed to $0.7 \times 0.7 \times 0.7$ mm^3, number of slices = 208–256, bandwidth = 698 Hz/pixel, parallel imaging (GRAPPA) acceleration factor = 2, DANTE radio-frequency (RF) pulse train length = 125, interpulse duration = 1.0 ms, and RF pulse flip angle = 15°. The scan time of the three-station BTI scans was 10 to 15 minutes.

MR Image Analysis

All MR images were loaded onto a workstation (Leonardo, Siemens AG) for image review and analysis. To evaluate whether thrombus signal characteristics were associated with different treatment outcomes, all images were reviewed to determine the presence of iso-intense thrombus (Iso-IT) or hyper-intense thrombus (Hyper-IT) of each lower limb by two independent and experienced radiologists. Specifically, the thrombus was defined as Iso-IT if the thrombus signal intensity is comparable to the adjacent muscle, and the thrombus was defined as Hyper-IT if the thrombus signal intensity is obviously higher than the adjacent muscle. Each patient was then assigned to the Iso-IT, Hyper-IT, or Mixed-IT group (both Iso-IT and Hyper-IT were observed) by the two experienced radiologists. Disagreements were later resolved by mutual consensus.

To quantitatively analyze the differences in thrombus volume and thrombus signal intensity among the Iso-IT, Hyper-IT, and Mixed-IT groups, the thrombus was automatically segmented by in-house software. The segmented results from each patient were then adjusted and confirmed by the consensus of two radiologists using a medical image segmentation tool (ITK-SNAP, open-source software, www.itksnap.org/pmwiki/pmwiki.php) before quantitative analysis. Due to the use of parallel imaging for accelerating data acquisition, the relative signal contrast, instead of contrast-to-noise ratio, between the thrombus and adjacent muscle was used to quantify thrombus signal differences and was calculated as $SI_{thrombus}/SI_{muscle}$, where $SI_{thrombus}$ and SI_{muscle} were the mean signal intensities of the thrombus and the muscle, respectively.

Treatments for the Patients

The procedures of CDT after MR examination were performed on the patients according to existing guidelines.[18–20]

Venous access for CDT was obtained in the ipsilateral popliteal vein with an 8F catheter sheath (Cook Medical). Approximately 20 mL iodinated contrast agent (ioversol, H20113430) was manually injected through the 8F vascular sheath to obtain an ascending venogram. An inferior vena cava filter was placed just below the renal vein through the femoral vein on the symptomless side before CDT to prevent the occurrence of PE. A 5F multi-side hole intravenous

infusion catheter (Cook Medical) was then placed inside the thrombus and the thrombolytic agent (Urokinase, H20113006, Biochemical Pharmaceutical) was administered directly into the thrombus using a micropump device. Heparin (J20150059, Sanofi China) was administered contemporaneously at a speed of 0.3×10^5 U/24 h via the infusion catheter. Venography was repeated during thrombolysis to evaluate progress based on clinical observation and laboratory monitoring according to the existing guidelines.[18] None of the patients had received balloon angioplasty or stenting.

Activated partial thromboplastin time was monitored twice daily to adjust the heparin dose with a target of 60 to 80 seconds. The blood coagulation function was closely monitored during the thrombolysis procedure (fibrinogen >1 g/L). Thrombolytic therapy was terminated when there was at least 90% thrombus removal with the restoration of flow or when a major complication occurred. When minor bleeding complications related to CDT still appeared in spite of the dosage of thrombolytic drug reduced, the thrombolytic treatment would be terminated. Venography was repeated every day after thrombolytic therapy. Postprocedural anticoagulation using warfarin sodium with a target international normalized ratio of 2.0 to 3.0 was administered for a minimum total duration of 3 months.

Immediate Procedural Outcome Post-CDT Treatment

The total units of urokinase infused and thrombolysis duration were recorded. The thrombolysis ratio was used to estimate venous vessel patency for the patients according to the method of Porter and Moneta.[21] Specifically, venograms acquired before and after thrombolysis were reviewed and scored for each segment. The venous system of each lower limb was divided into seven segments, including the inferior vena cava, the common iliac vein, the external iliac vein, the common femoral vein, the proximal portion of the femoral vein, the distal portion of the femoral vein, and the popliteal vein. A thrombus score was determined for each segment based on a 4-point scale[21]: 0 = patent with no residual thrombus, 1 = partial occlusion (<50%), 2 = partial occlusion (>50%), and 3 = complete occlusion. The total scores pre- and post-lysis were then calculated by adding the seven venous segments' scores. The thrombolysis ratio was calculated as (Total thrombus scores pre lysis – Total thrombus scores post lysis)/Total thrombus scores pre lysis × 100%. All images were assessed by two independent and experienced radiologists. Disagreements were resolved by mutual consensus.

Histology Analysis and Iron Quantification

Because the thrombus signal intensity on T1-weighted MR and treatment effect of thrombolysis are related to the thrombus composition, especially the contents of Fe^{3+} and fibrin,[13] histological analysis and iron quantification were performed. In order to avoid possible analytical bias due to the Iso-IT and Hyper-IT coexisted in the patients within the Mixed-IT group, 6 patients within the Iso-IT group and 6 patients within the Hyper-IT group were selected randomly to extract the pure Iso-IT or Hyper-IT for 6 repeated analyses. The samples were obtained during CDT using the 8F introducer catheter under the guidance of digital subtraction angiography. We referred to the thrombus signal and location shown by MR images during thrombus extraction and inserted the catheter into the corresponding position to extract the thrombus manually. Only the solid clots extracted from the patients with Iso-IT or Hyper-IT were used for histological analysis and iron quantification. The clots were placed in 10% formalin for 24 hours before being embedded in paraffin. Each 5-µm paraffin section was stained using hematoxylin and Martius Scarlet Blue (MSB) for red blood cell, fibrin, and collagen content.[13] Digital images of stained sections were captured and processed using image analysis software (Image Pro-plus 7, Media Cybernetics) with the percentage area of thrombus containing each stain calculated.

Inductively coupled mass spectroscopy (PE 200 LC system linked to PerkinElmer Sciex Elan 6100 DRC, PerkinElmer) was performed on the thrombus samples for total iron concentration quantification.[13] Thrombus was digested in 70% nitric acid at 37°C overnight, followed by dilution with deionized water for inductively coupled mass spectroscopy analysis. A chromogen that forms a blue-colored complex with Fe^{2+} reagents in this kit was used to convert any Fe^{3+} within the sample to Fe^{2+}, allowing the assessment of total iron concentration measured by mass spectrometry. The ratio of Fe^{3+} content to total iron content within the processed thrombi was then calculated as (Fe^{3+}/Total Fe = 1 – Fe^{2+}/Total Fe).

Clinical Follow-Up after Treatment

Clinical follow-up at 6, 12, and 24 months after initial treatment were performed by a surgeon and vascular physiologist. PTS was diagnosed with the Villalta score, which accounts for the severity of both subjective symptoms and physical signs of PTS,[22] as a primary treatment outcome if the score was 5 or more or if a venous ulcer was present.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS 17.0, Chicago, Illinois, United States) software. The Shapiro–Wilk test was used to test the normality of the continuous variables prior to analysis. Continuous variables were presented as mean ± standard deviation, and discrete variables were presented as median with interquartile range. The interobserver agreement in categorizing patients into Iso-IT, Mixed-IT, and Hyper-IT groups was evaluated by Cohen's kappa coefficient. A two-sample unpaired *t*-test or the Mann–Whitney test was used to compare continuous variables. A Chi-square test was used for comparison of proportions of categorical variables. A stepwise logistic regression model was used to determine the independent factors to predict the incidence of PTS at 6, 12, and 24 months. $p < 0.05$ indicated statistical significance.

Results

There were 117 patients with a clinical diagnosis of acute iliofemoral DVT (≤14 days of symptom onset). In total, 14 of 117 patients were excluded; 5 patients had history of intracerebral bleeding, 2 patients received treatment before

Table 1 Patient characteristics in each group

Characteristics	Iso-IT group ($N = 37$)	Mixed-IT group ($N = 51$)	Hyper-IT group ($N = 15$)
Age, mean ± SD (y)	53.6 ± 2.5	58.2 ± 2.6	62.8 ± 3.3
Females, *n* (%)	26 (70.3)	29 (56.9)	6 (40.0)
Weight, mean ± SD (kg)	57.4 ± 8.5	56.2 ± 10.6	59.5 ± 8.7
Duration of symptoms, mean ± SD (d)	5.5 ± 0.5	8.8 ± 0.6	10.1 ± 1.0
Left-side DVT, *n* (%)	30 (81.1)	38 (74.5)	11 (73.3)
Previous PE or DVT, *n* (%)	5 (13.5)	6 (11.7)	3 (20.0)
Cancer, *n* (%)	1 (2.7)	3 (5.8)	2 (13.3)
May–Thurner syndrome, *n* (%)	11 (29.7)	16 (31.4)	4 (26.7)
Hip prosthesis, *n* (%)	0	1 (1.9)	0
Major surgery, *n* (%)	1 (2.7)	2 (3.9)	1 (6.6)
Trauma, *n* (%)	3 (8.1)	5 (9.8)	1 (6.6)
Childbirth, *n* (%)	1 (2.7)	2 (3.9)	1 (6.6)
Relative signal contrast	1.19 ± 0.01	1.45 ± 0.03	1.75 ± 0.06
Thrombus volume (mL)	48.6 ± 4.4	46.0 ± 3.2	26.3 ± 3.2

Note: DVT, deep vein thrombosis; Hyper-IT, hyper-intense thrombus; Iso-IT, iso-intense thrombus; Mixed-IT, mixed iso-/hyper-intense thrombus; PE, pulmonary embolism; SD, standard deviation.

MRI, and 7 patients refused to do CDT. A total of 103 patients with acute DVT completed the MR examinations. The average time interval between MR and symptom onset was 7.6 ± 4.1 days. A total of 103 patients received CDT within 24 hours after MR. Seventy-seven of them completed 2 years of follow-up. None of the patients received CDT or other endovascular therapy after the initial treatment. Baseline patient characteristics are listed in ►**Table 1**.

Patient Categorization Based on T1-Weighted MR Signal of the Thrombus

Venous thrombosis was identified on MR images of all patients. Based on the thrombus signal contrast, 37 out of 103 (35.9%) patients presented with Iso-IT, 15 (14.6%) patients presented with Hyper-IT, and 51 (49.5%) patients presented with Mixed-IT (►**Fig. 1**). Representative images of patients with Iso-IT, Hyper-IT, and Mixed-IT are shown

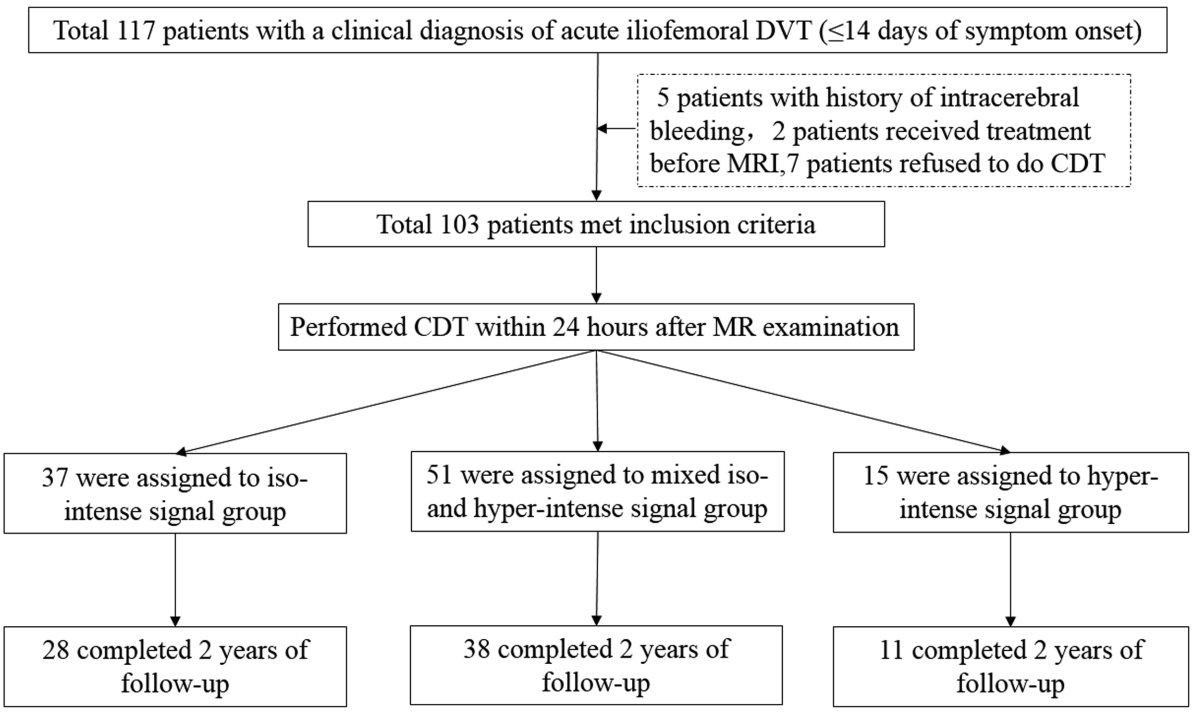

Fig. 1 Flow chart illustrating patient recruitment and analysis.

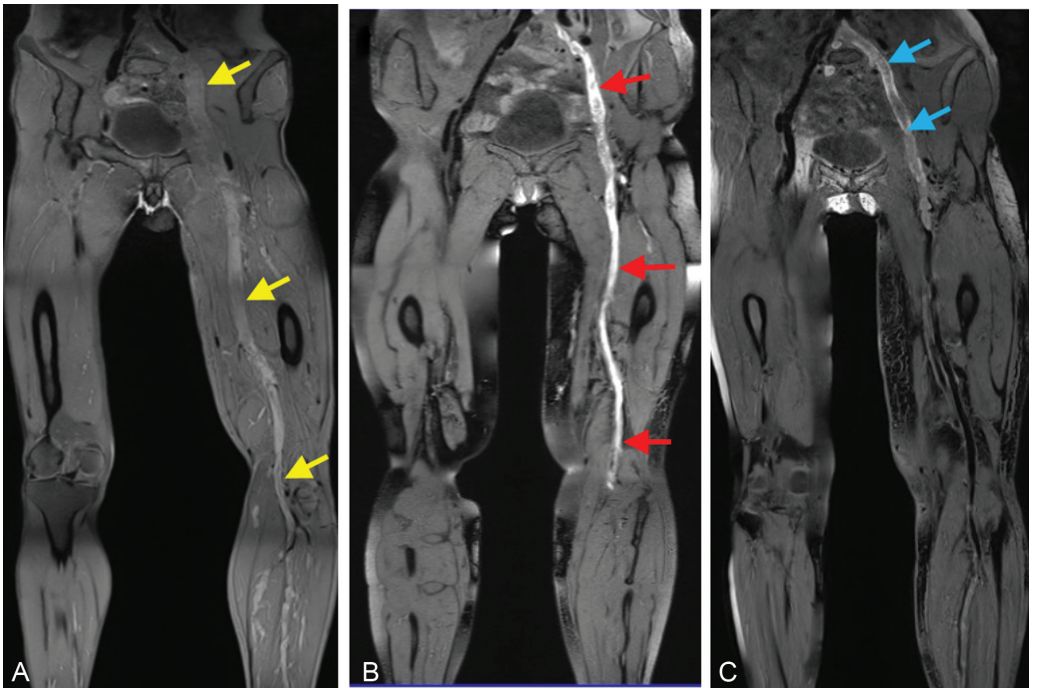

Fig. 2 Thrombi in acute DVT patients present in (**A**) iso-, (**B**) hyper-, and (**C**) mixed iso-/hyper-intense signals on noncontrast T1-weighted black-blood MR images. *Yellow arrows* denote the iso-intense thrombi with comparable signal intensity to the adjacent muscle. *Red arrows* denote the hyper-intense thrombi with higher signal intensity than the adjacent muscle. *Blue arrows* denote the mixed iso-/hyper-intense thrombi compared to the adjacent muscle. DVT, deep vein thrombosis; MR, magnetic resonance.

in ►**Fig. 2**. Excellent agreement in categorizing the patients into Iso-IT, Hyper-IT, and Mixed-IT groups was achieved by the two radiologists (kappa test: k value = 0.937, $p < 0.001$). Nine patients presented with Iso-IT, 13 patients presented with Mixed-IT, 4 patients presented with Hyper-IT were lost to follow-up. These patients were excluded from the per-protocol analysis. The rates of follow-up patients were similar in all groups, it showed no significant differences among the three groups.

The average duration of symptoms was 5.5 ± 0.5 days in Iso-IT, 8.8 ± 0.6 days in Mixed-IT, and 10.1 ± 1.0 days in Hyper-IT groups, respectively. Their thrombus' relative signal contrast was 1.19 ± 0.01, 1.45 ± 0.03, and 1.75 ± 0.06, respectively. The average thrombus volume in the Hyper-IT group (26.3 ± 3.2 mL) was smallest compared to those in the Iso-IT (48.6 ± 4.4 mL) and Mixed-IT (46.0 ± 3.2 mL) groups. Other characteristics were not significantly different except sex among the three groups in ►**Table 1**.

Differential Immediate Treatment Outcomes among the Three Patient Groups

Detailed information of thrombolysis is shown in ►**Table 2**. Less amount of urokinase was administered in patients with Iso-IT (23.7 ± 7.5 million units) than in those with Mixed-IT (29.5 ± 8.9 million unit, $p = 0.001$) and Hyper-IT (31.2 ± 11.6 million units, $p = 0.016$). No significant difference in the duration of urokinase administration ($p = 0.60$) was found among the three groups.

The Iso-IT group (90.5 ± 1.6%) had significantly higher thrombolysis ratio than the Mixed-IT (78.4 ± 2.6%, $p < 0.001$) or Hyper-IT (46.5 ± 3.3%, $p < 0.001$) groups. ►**Fig. 3** demonstrates the immediate thrombolytic outcomes of patients

Table 2 Thrombolysis in patients given CDT

Thrombolysis	Iso-IT group ($N = 37$)	Mixed-IT group ($N = 51$)	Hyper-IT group ($N = 15$)
Thrombus score pre-lysis, mean ± SD	13.4 ± 0.6	14.0 ± 0.6	9.3 ± 1.1
Thrombus score post-lysis, mean ± SD	1.4 ± 0.2	2.8 ± 0.4	4.7 ± 0.6
Thrombolysis ratio, mean ± SD (%)	90.5 ± 1.6	78.4 ± 2.6	46.5 ± 3.3
Units of urokinase infused, mean ± SD (million units)	23.7 ± 7.5	28.6 ± 9.4	28.8 ± 12.3
Duration of urokinase administration (d)	5.5 ± 1.1	5.8 ± 1.9	6.4 ± 2.1
Thrombolysis duration, mean ± SD (d)	3.3 ± 0.2	3.6 ± 0.2	3.6 ± 0.3
Bleeding, *n* (%)	0 (0.0%)	6 (11.8%)	2 (13.3%)

Abbreviations: CDT, catheter-directed thrombolysis; SD, standard deviation.

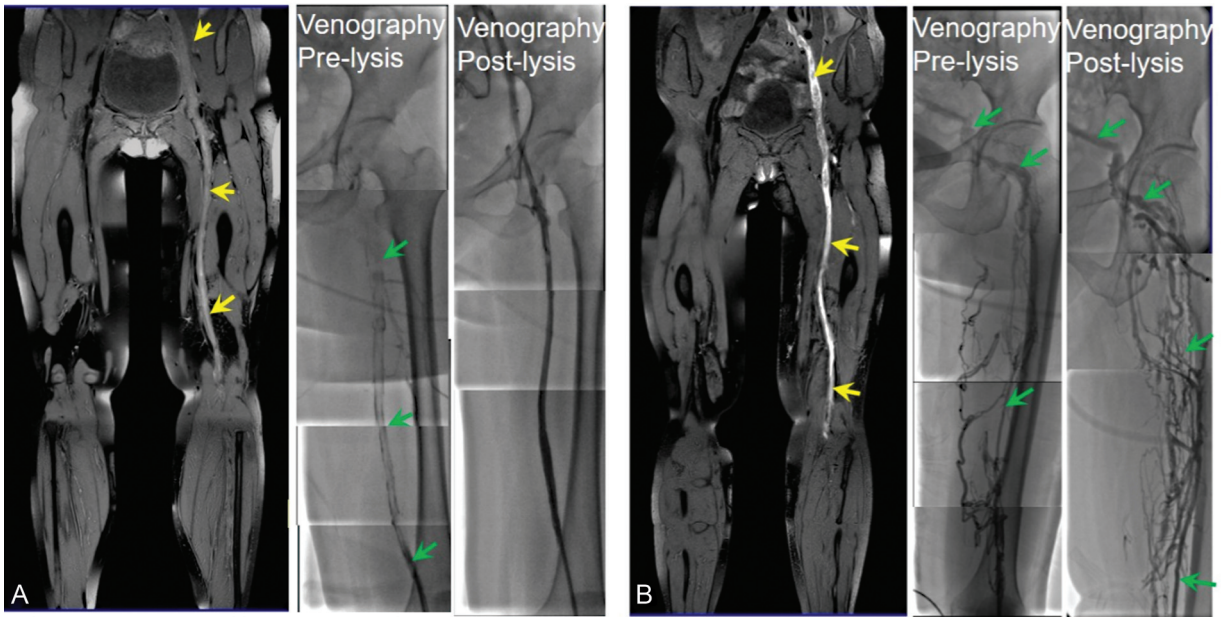

Fig. 3 Representativecases with different immediate thrombolysis outcomes. The thrombi with iso-intense signals on T1-weighted black-blood MR images are successfully dissolved (**A**), as indicated by pre-/post-lysis venography, whereas those with hyper-intense signals are not (**B**). *Arrows* denote the thrombi.

presenting with Iso-IT and Hyper-IT, respectively. Categorization into the Iso-IT group was a strong predictor for successful lysis (►**Fig. 4**). The thrombolysis ratio was dependent on the relative signal contrast between the thrombus and adjacent muscle ($R = 0.528, p < 0.001$) but independent on the duration of symptom ($p = 0.623$) or the duration of thrombolysis ($p = 0.142$). The inter-reader agreement for the thrombolysis ratio was excellent (kappa test: k value = 0.863, $p < 0.001$).

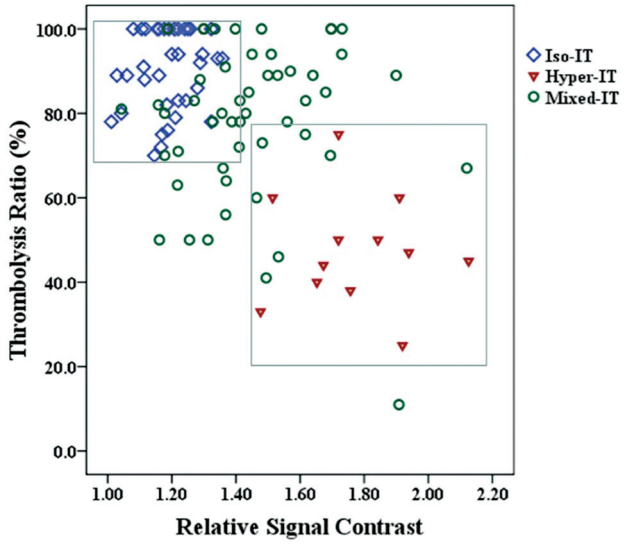

Fig. 4 Patients with Iso-IT could be a good predictor for successful lysis. All patients with Iso-IT were lysed successfully, part of the patients with Mixed-IT and most of the patients with Hyper-IT were not well lysed. Note that the thrombolysis ratio was calculated as (total thrombus scores pre lysis – total thrombus scores post lysis)/total thrombus scores pre lysis × 100% and the relative contrast ratio is the relative contrast calculated as $SI_{thrombus}/SI_{muscle}$, where $SI_{thrombus}$ and SI_{muscle} were the mean signal intensities of the thrombus and the muscle, respectively. Hyper-IT, hyper-intense thrombus; Iso-IT, iso-intense thrombus; Mixed-IT, mixed iso-/hyper-intense thrombus.

Eight bleeding complications related to CDT were reported. Two were classified as major and six as clinically relevant. The major bleeding events included one hematuria and one inguinal puncture-site hematoma. There were no deaths, PEs, or cerebral hemorrhage related to CDT. Six patients had small access-site hematoma related to CDT. There were no bleeding complications in the patients with Iso-IT during the same period. Bleeding occurred in 6 (11.8%) in the Mixed-IT group and in 2 (13.3%) patients in the Hyper-IT group ($p < 0.001$).

Differential Fibrin and Fe^{3+} Content among the Three Patient Groups

Representative histological sections from patients with Iso-IT and Hyper-IT are shown in ►**Fig. 5a**. Variable fibrin (red color), collagen (blue color), and red blood cell (yellow color) content were found in thrombi. Based on the semi-quantitative analysis, the percentage of thrombus area stained as fibrin in Iso-IT was higher than that in Hyper-IT (►**Fig. 5b**). However, the percentage of thrombus area stained as collagen in Iso-IT was smaller than that in Hyper-IT (►**Fig. 5b**). Results from mass spectrometry-based iron quantification are shown in ►**Fig. 6**. The ratio of Fe^{3+} to the total iron in Iso-IT was significantly lower than that in Hyper-IT ($p = 0.034$).

Differential Incidence Rates of PTS among the Three Patient Groups

Short- and long-term primary clinical outcomes of patients are summarized in ►**Table 3**. Patients with Iso-IT had significantly lower incidence rates of PTS at 6, 12, and 24 months,

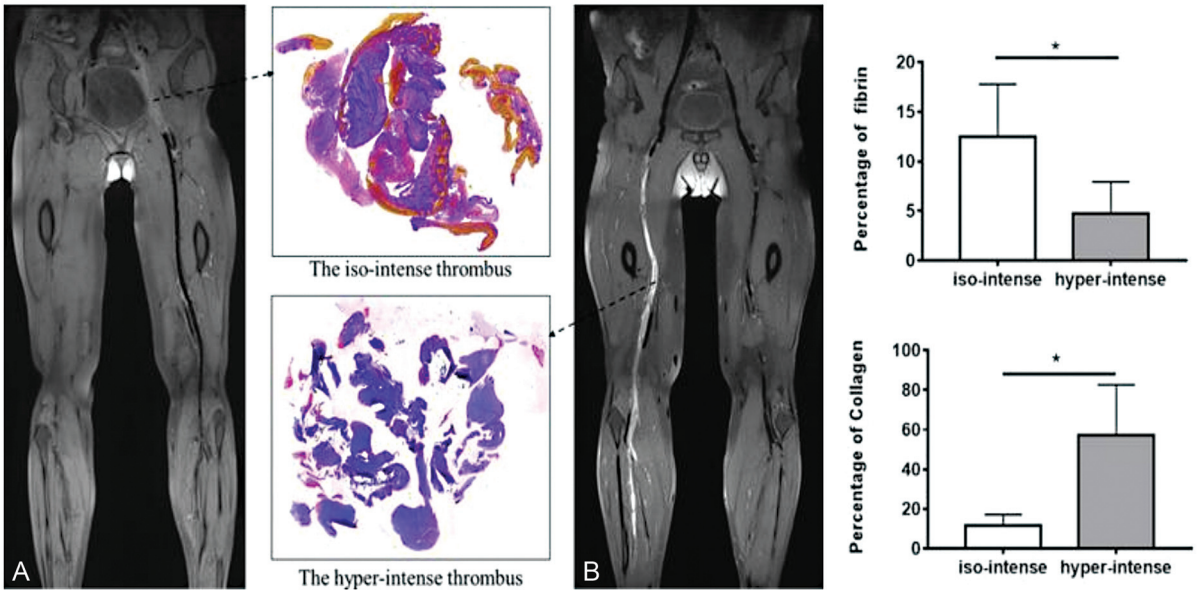

Fig. 5 T1-weighted MR signal characteristic of thrombus is associated with histological vein thrombus content stained by Martius Scarlet Blue (MSB). (**A**) The area of fibrin (*red color*) in the iso-intense signal thrombus was larger than that in hyper-intense signal thrombus. (**B**) The iso-intense thrombus had significantly greater fibrin ($p = 0.023$) but lower collagen ($p = 0.006$) content than the hyper-intense thrombus. MR, magnetic resonance.

respectively. For instance, at 24-month follow-up, the patients with Iso-IT had significantly lower incidence rate (3.6%) of PTS than the patients with Mixed-IT (18.4%, $p < 0.001$) and the patients with Hyper-IT (63.4%, $p < 0.001$).

Discussion

In this study, the T1-weighted signal contrast of thrombus relative to the surrounding muscle was found to be associated with the outcomes of CDT treatment in acute DVT patients. Patients with Iso-IT had the best CDT treatment outcomes, whereas those with Hyper-IT had the worst.

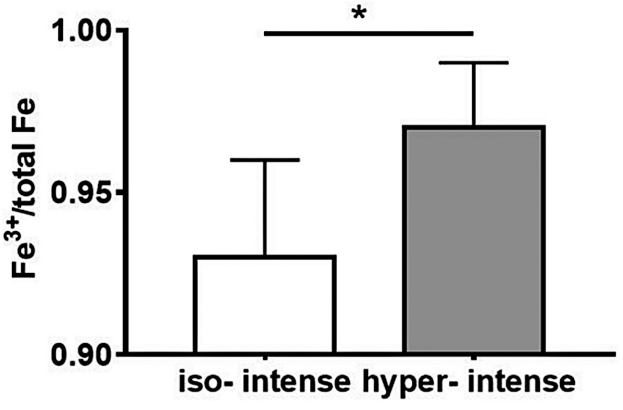

Fig. 6 T1-weighted MR signal characteristic of thrombus is dependent on the ratio of Fe^{3+} to the total iron. The iso-intense thrombus had significantly lower Fe^{3+}/total Fe than the hyper-intense thrombus ($p = 0.034$). MR, magnetic resonance.

It has been reported that iron, gradually brought into the thrombus by fibrin-trapped red blood cells, is oxidized through inducible nitric oxide synthase. This results in the accumulation of paramagnetic Fe^{3+} that can shorten the T1 relaxation time of the thrombus.[13] Thus, the T1 relaxation time of the thrombus in the acute phase gradually becomes shorter, and the thrombus appears brighter on T1-weighted MR images. Iron quantification in this work showed that the ratio of Fe^{3+} to total iron was higher in Hyper-IT than in Iso-IT (►**Fig. 6**). We also found that the average duration of symptoms in the patients with Iso-IT (5.5 ± 0.5 days) was significantly shorter than those of the patients with Mixed-IT (8.8 ± 0.6 days) and Hyper-IT (10.1 ± 1.0 days). These findings suggest that Iso-IT may be at an earlier stage than Hyper-IT in acute DVT patients. Of note, the thrombolysis ratio has little correlation with duration of symptoms (**Supplementary Material**, available in the online version). Therefore, an objective method such as MR technique to identify thrombi most suitable to lysis would improve the care of patients presenting with thrombosis.

The content of fibrin in the thrombus changes as the thrombus progresses. It is interesting that a higher content of fibrin was observed in the murine thrombus with short T1 relaxation time (i.e., Hyper-IT) by Saha et al.[13] In contrast, this study has demonstrated a higher content of fibrin in the human thrombus with an iso-intense signal (►**Fig. 5B**). Because the urokinase and other thrombolytic drugs' target is fibrin, it follows that the lysis effect was more pronounced for Iso-IT. Patients with Iso-IT had a significantly higher thrombolysis ratio despite the significantly lower dose of urokinase. Our results are consistent with a clinical study on human cerebral venous thrombosis by Yang et al, in which Iso-IT was more easily lysed than Hyper-IT.[14] In addition, a previous study

Table 3 Short-term and long-term primary outcomes of patients with iso- and hyper-intense thrombus under CDT

Characteristics	Iso-IT group ($N = 28$)	Mixed-IT group ($N = 38$)	Hyper-IT group ($N = 11$)
Villalta scores at 6 months			
0–4	28	34	7
5–9	0	4	4
10–14	0	0	0
≥15	0	0	0
PTS at 6 months	*0 (0.0%)*	*4 (10.5%)*	*4 (36.4%)*
Villalta scores at 12 months			
0–4	27	32	7
5–9	1	6	4
10–14	0	0	0
≥15	0	0	0
PTS at 12 months	*1 (3.6%)*	*6 (15.8%)*	*2 (36.4%)*
Villalta scores at 24 months			
0–4	27	31	4
5–9	1	7	7
10–14	0	0	0
≥15	0	0	0
PTS at 24 months	*1 (3.6%)*	*7 (18.4%)*	*7 (63.4%)*

Abbreviation: CDT, catheter-directed thrombolysis.
Note: PTS indicates postthrombotic syndrome, defined as a Villalta score of 5 points or higher.

reported that early initiation of lytic therapy can result in better thrombolysis of DVT.[23] Different findings between murine study and human studies might be due to differences between human and mice, which could involve in different thrombotic components, drug resistance, and autolysis systems.

CDT plays an important role on treating acute DVT because early venous recanalization helps to protect valve functions and to prevent PTS development.[24] As the patients with Iso-IT were lysed successfully, the incidence rate of PTS in Iso-IT group was found significantly lower than those in Mixed and Hyper-IT groups at 6-, 12-, and 24-month follow-ups. Of note, there were fewer patients with severe PTS in each group, but the vast majority of patients with PTS were in the "mild" category (5–9 scores). Our study found that the incidence of PTS was as high as 63.4% in "acute thrombosis" patients with Hyper-IT, so PTS rates in our study were not too low compared to randomized trials on this topic. Due to the low incidence of PTS in patients with Iso-IT and Mixed-IT, it illustrated the revolutionary significance of this technology. The reason may be due to our standardized treatment, smaller clot size in the iliofemoral segment,[25] and better patient compliance. With the increase of patients and the extension of follow-up time, the number of patients may increase in severe PTS incidence.

Bleeding is the main complication of CDT due to the use of fibrinolytic drugs and venous catheter placement. When fibrinolytic drugs cannot dissolve excessive collagen in the DVT patient with Hyper-IT, the "excess" fibrinolytic drugs consuming the limited fibrinogen in the body may cause the other tissues bleeding. Eight bleeding events were reported in this study, including six patients in the Mixed-IT group and two patients in the Hyper-IT group. Of note, none of the patients in the Iso-IT group had bleeding. Hematuria, inguinal puncture-site hematoma, and subcutaneous hemorrhage events in Mixed-IT or Hyper-IT group showed that the incidence of bleeding events still was high in CDT. The previous research reported that there were higher bleeding events in CDT than in the anticoagulation therapy alone. Our research suggested that incidence of bleeding events in CDT should be reduced when the thrombus presents an isointense signal.

To the best of our knowledge, this work is the first attempt to quantify the contents of Fe^{3+}, fibrin, and collagen in the venous thrombus obtained from patients in vivo. The thrombi were extracted from acute DVT patients in Iso-IT and Hyper-IT groups based on the guidance of T1-weighted MRI. A lower ratio of Fe^{3+} to the total iron and a lower percentage of collagen but a higher percentage of fibrin were found in Iso-IT than Hyper-IT. These quantification results can explain the reasons behind the observed thrombus signal intensities and the thrombolysis outcomes. Of note, the Iso-IT group has the best thrombolysis and lowest incidence rates of both PTS development and bleeding complication. Thus, T1-weighted thrombus signal characteristics may serve as a noninvasive imaging marker that can be used to predict good immediate and long-term CDT treatment outcomes.

Study Limitations

First, the per-protocol analysis was used for data analysis instead of intention-to-treat analysis. We note, however, that ►**Table 1** indicates no significant differences among the three groups. Thus, the per-protocol analysis appears to have been reasonable and appropriate. Our results also should be verified in a large randomized controlled trial and a multicenter core laboratory in the near future. Second, we simply divided the patients into Iso-IT, Mixed-IT, and Hyper-IT groups. Other grouping methods might be applied but it would be much more complicated. An automatic approach for this can be based on machine leaning, which can explore more signal characteristics automatically on T1-weighted black-blood MR images in future. Third, although acute DVT patients have been recruited strictly according to the clinical guideline, the accuracy of the onset of the first episode of DVT is difficult since DVT may be asymptomatic. However, this study is focused on predicting outcomes of CDT in acute DVT patients. We show that T1-weighted black-blood MRI based on thrombus signal has potential to identify thrombi most suitable for lysis regardless of thrombus progression in acute patients. Fourth, we found that patients with Iso-IT have better response to CDT than the patients with Hyper-IT and Mixed-IT. However, it remains unclear that if the patients with Iso-IT are less likely to need CDT, because there is no control group for comparison at present. Our investigation will be continued to verify this in the future.

Conclusion

A T1-weighted signal of thrombus from acute DVT patients is related to the fibrin content and oxidative state of iron during the progression of DVT development. Compared to the patients in Mixed-IT and Hyper-IT groups categorized based on T1-weighted thrombus signal characteristics, the patients in the Iso-IT group have much better treatment outcomes in terms of higher average thrombolysis ratio and lower incidence rates of both PTS development and bleeding complication. Our findings strongly suggest the potential of using T1-weighted black-blood MRI to predict CDT treatment outcomes and therefore guide treatment decision making and postprocedural patient care.

What is known about this topic?

- Thrombus signal on T1-weighted black-blood MR is associated with lytic therapeutic outcome in acute DVT patients.
- T1-weighted thrombus signal characteristics may serve as a noninvasive imaging marker to predict CDT treatment outcomes and therefore guide treatment decision-making in acute DVT patients.
- Presence of iso-intense thrombus revealed by T1-weighted black-blood MRI is associated with successful thrombolysis, low bleeding ratio, and low incidence of the postthrombotic syndrome.

What does this paper add?

This is the first clinical study showing that the thrombus MRI signal is associated with lytic therapeutic outcomes in acute DVT patients.
A total of 103 patients near the onset of their acute DVT were correlated with the outcomes of CDT at different time points.

Clinical Trial Registration
URL: http://www.chictr.org.cn.

Unique identifier
ChiCTR1900023986.

Data Availability Statement
The datasets analyzed for the current study are available from the corresponding author on request.

Ethics Approval and Consent to Participate
This study was approved by both institutional review boards of Guangzhou Panyu Central Hospital (K20150030 and H20170024). Besides, consent informs were obtained from all participants.

Authors' Contribution
C.H. and G.X. designed the research; C.H., X.H, Y.X., Y.Y., and Y.S. performed the research; C.H., G.X., X.H., Y.X., and H.C. analyzed and interpreted data; C.H., X.H., Y.X., G.X., Z. F., R.D, R.K.R., and D.L. wrote the manuscript, and all authors approved the final version of the manuscript.

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Conflict of Interest
None declared.

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