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ORIGINAL RESEARCH

The Impact of Needle-Directed Thrombolysis in Thrombosed Arteriovenous Fistulas on Angioplasty Efficacy and the Prognostic Factors Associated with Success

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Purpose: Urokinase thrombolysis is a feasible method for salvage of thrombosed arteriovenous fistulas (AVFs). The impact of optimizing thrombolysis outcomes on improving the efficacy of subsequent angioplasty remains unclear. This study is aimed to investigate the impact of thrombolysis outcomes and to identify the prognostic factors of thrombolysis.

Patients and Methods: The patients were divided into a complete lysis (CL) group of 336 treatments, an incomplete lysis (IL) group of 83 treatments, and a lysis failure (LF) group of 206 treatments. The efficacy data of the subsequent angioplasty and the patency before the next intervention were compared. Demographics, fistula characteristics, and baseline serum parameters were compared to screen for prognostic factors of thrombolysis outcomes.

Results: As the degree of thrombolytic therapy decreased, the complication rate significantly increased (CL, 14.6%; IL, 21.7%; LF, 30.6%; trend $P < 0.001$), whereas the clinical success rate of angioplasty decreased (CL, 97.0%; IL, 94.0%; LF, 82.3%; trend $P < 0.001$). However, no difference was noted in the patency interval before the next intervention among the three groups (log-rank $P = 0.562$). Elbow AVF and hemoglobin < 115 g/L were risk factors of poor lysis outcomes. The complete lysis rate of patients with both factors was 24.2%, whereas the rates of patients with one or neither factor were significantly higher (all > 50% and $P = 0.001$).

Conclusion: Complete thrombolysis is beneficial for improving the efficacy of recanalization procedures for thrombosed AVFs. Non-elbow AVFs and hemoglobin ≥115 g/L are predictors of an increased complete lysis rate.

Keywords: arteriovenous fistula, indwelling needle, prognostic factor, thrombolysis

Introduction

Arteriovenous fistula (AVF) is the preferred form of hemodialysis access for patients with end-stage renal disease (ESRD).[1] Most hemodialysis patients experience fistula dysfunction due to stenosis or occlusion of vessels. A meta-analysis revealed that the primary AVF patency rates were 60% at 1 year and 51% at 2 years.[2] Thrombolysis is a minimally invasive method for treating thrombosed hemodialysis access. The technical success rate of access recanalization varies from 73%- 98%, and similar patency rates can be achieved as those of thrombectomy.[3–6]

Pharmacomechanical thrombolysis and catheter-directed thrombolysis sometimes require the use of specialized recirculation devices and catheters.[6,7] However, it is difficult to manage in areas with limited medical resources. We propose an indwelling needle-delivered thrombolysis method, a cost-saving approach, to treat thrombosed dialysis access.[8] For patients without contraindications for thrombolysis, indwelling needle-delivered urokinase thrombolysis

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combined with percutaneous angioplasty (PTA) has been the preferred treatment in our center to treat thrombosis in fistulas and grafts. In this study, we further investigated the impact of thrombolysis outcomes on the results of AVF recanalization, as well as the predictive factors for thrombolysis outcomes.

Materials and Methods

Ethical Statement

The study was approved by the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University (approval NO. 2024-140-01) and was conducted in accordance with the Declaration of Helsinki. The committee waived the requirement for patient consent to review their medical records, as this behavior would not cause potential harm. All medical records were anonymized during the extraction process to protect patient data confidentiality.

Study Population

This was a retrospective observational study conducted on hemodialysis patients undergoing thrombosed AVF treatment at the Department of Nephrology. The patients were restricted to those treated with indwelling needle-delivered urokinase thrombolysis followed by PTA in our center from 1 June 2017 to 30 April 2022. The end of follow-up was 30 November 2023. The exclusion criteria were as follows: 1) patients under 18 years of age and 2) patients who were unable to complete thrombolytic therapy due to puncture failure. This study ultimately included 625 thrombolysis treatments received by 523 patients. Three groups were generated on the basis of thrombolysis outcomes: the complete lysis (CL) group (N=336), the incomplete lysis (IL) group (N=83), and the lysis failure (LF) group (N=206). The definitions of thrombolysis outcomes were previously described [8]. Briefly, CL refers to the state where the thrombus has lysed enough to allow fully restored blood flow; IL refers to the state where the thrombus has loosened and blood flow has been partially restored; otherwise, no relief of thrombus or blood flow is considered LF.

Treatment Procedures

Indwelling needle-delivered thrombolysis, surgical thrombectomy, and PTA were all performed under ultrasound guidance. Thrombolysis was performed first.[8] A 20-G indwelling needle was retrogradely pierced in the vessel and slowly pushed to within 0.5 cm of the starting position of the thrombus. Each dose of urokinase (3×10^5 units; Wuhan Humanwell Pharmaceutical Co. Ltd., Wuhan, China) diluted in 20 mL of saline was administered at a rate of 10 mL/h. Low-molecular-weight heparin (4000 units) was administered subcutaneously at the same time. During the period of thrombolysis, the patients were checked every half hour for thrombolysis progress and possible complications. Each patient received up to 4 doses of urokinase (2 doses per day for 2 days, with an interval of more than 6 hours), even if the thrombus failed to lyse. The patients would no longer receive further thrombolytic therapy if CL was achieved in the previous therapy or if thrombolysis-related complications occurred.

For patients in the LF group, thrombectomy via a Fogarty balloon catheter was performed to remove residual clots before PTA. For patients in the IL group, the thrombus had been lysed into a liquid-like state and thus could be removed by PTA without thrombectomy. PTA was then performed in every patient to relieve the underlying culprit stenosis. When palpable local thrill was felt and residual stenosis was < 30%, canalization treatment of thrombosed AVFs was considered technically successful.

Exposure Variables and Outcomes

The data involved in this study were collected from the electronic records in the hospital information system, including demographics (age and sex), basic disease information (diabetes, coronary heart disease, and smoking status), fistula characteristics (AVF type, anastomosis type, AVF location, AVF age), prethrombolysis serum biochemical parameters (hemostasis, hemogram, calcium, phosphorus, parathyroid hormone, and liver function), thrombolysis treatment details (lesion site, occlusion time, urokinase dosage, complications), operation time of PTA, and duration of patency after canalization.

The impact of thrombolysis outcomes on the therapeutic effect of AVF canalization was evaluated through the incidence of thrombolysis-related complications, the time of recanalization (PTA with/without thrombectomy), the clinical success rate of recanalization, and the patency interval before the next intervention. The clinical success of canalization was defined as the successful salvage of fistula occlusion and at least one adequate hemodialysis session (dialysis blood flow ≥ 300 mL/min) afterwards. Because some patients undergo multiple episodes of treatment to maintain fistula function, traditional outcomes, such as primary and secondary patency rates, are not very suitable for the setting of this study. Therefore, we adopted an indicator similar to primary patency, which was the patency interval before the next intervention. This indicator was defined as the duration from the current intervention to the next intervention (recanalization, recreation, or switch to other types of access) due to subsequent thrombosis or stenosis of the current fistula.

Statistical Analysis

GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA) and SPSS software version 22.0 (IBM, Armonk, NY, USA) were used for all the statistical analyses. The results of continuous variables are presented as medians with interquartile ranges (IQRs) or means with standard deviations on the basis of whether they followed a normal distribution. For comparisons of continuous variables with a normal distribution, an unpaired *t* test for two groups and one-way analysis of variance (ANOVA) for three groups were used. For comparisons of continuous variables with nonnormal distributions, the Mann–Whitney *U*-test for two groups and the Kruskal–Wallis *H*-test for three groups were used. Categorical variables are presented as frequency counts with percentages. For comparisons of categorical variables, the chi-square test was used except when the expected frequency of any cell was less than 5; then, Fisher's exact test was used. The patency interval before the next intervention was analyzed via Kaplan–Meier analysis with the Log rank test and Cox regression analysis. Logistic regression analysis was used to evaluate the impact of potential predictors of complete thrombolysis. Hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) were provided in the relevant analyses.

Results

The Impact of Thrombolysis Outcomes on the Treatment of Thrombosed AVFs

A total of 625 thrombolysis procedures were performed on 523 ESRD patients. The main causes of ESRD are glomerulonephritis (45.7%), diabetic nephropathy (18.4%), hypertensive nephropathy (16.1%), and polycystic kidney disease (5.16%). The baseline demographics, AVF information, and occlusion information are summarized in Table 1. There was a significant difference in the distribution of AVF locations among the CL, IL, and LF groups ($P = 0.021$). The proportion of elbow AVFs was lower, and the proportion of wrist AVFs was greater in the CL group.

Complications occurred in 130 thrombolytic procedures, with the majority being bleeding at the puncture site (58 out of 130) and local swelling of the infusion arm (39 out of 130), in addition to subcutaneous bruising, cyanosis of the fingers, blood oozing from the indwelling needle, and gingival bleeding. Local swelling and subcutaneous bruising did not require additional treatment and spontaneously resolved after treatment. Mild bleeding, such as bleeding at the puncture site and blood oozing from the indwelling needle, was stopped by manual compression. Thrombolytic therapy was discontinued for patients with finger cyanosis and gingival bleeding. The complications did not cause serious consequences. The complication rates were 14.6% in the CL group, 21.7% in the IL group, and 30.6% in the LF group. Moreover, clinical success of PTA was achieved in 571 recanalization procedures, with clinical success rates of 97% in the CL group, 94.0% in the IL group, and 82.3% in the LF group. The chi-square test for trend revealed that as the thrombolytic effect deteriorated, the incidence of complications during thrombolytic therapy significantly increased, whereas the clinical success rate of PTA significantly decreased (both $P < 0.001$; Table 2).

The recanalization procedure time was 30 (IQR: 22, 45) min for the CL group, 43.5 (IQR: 30, 58.25) min for the IL group, and 45 (IQR: 30, 65) min for the LF group. The procedure time was significantly shorter in the CL group (both $P < 0.001$ vs the IL group and LF group), whereas the difference was not obvious between the IL and LF groups ($P > 0.999$; Figure 1). The results are expected since these groups followed different protocols.

Table 1 Comparisons of Baseline Characteristics Among the Groups of Complete Lysis (CL), Incomplete Lysis (IL), and Lysis Failure (LF)

Variables	CL N=336	IL N=83	LF N=206	*P*
Male, n (%)	183 (54.5)	54 (65.1)	106 (51.5)	0.107
Age, years	56 (48, 68)	57 (51, 68)	56 (48, 66)	0.297
Age, n (%)				0.540
<60 years	189 (56.3)	44 (53.0)	123 (59.7)	
≥60 years	147 (43.8)	39 (47.0)	83 (40.3)	
Diabetes, n (%)	61 (21.8)	11 (15.7)	44 (25.4)	0.249
CHD, n (%)	20 (7.1)	4 (5.7)[a]	9 (5.2)	0.694
Smoking, n (%)	81 (28.9)	18 (25.7)	56 (32.4)	0.548
Anastomosis type, n (%)				0.858
End-to-side	248 (73.8)	64 (77.1)	151 (73.3)	
Other	88 (26.2)	19 (22.9)	55 (26.7)	
AVF type, n (%)				0.789
Radiocephalic	328 (97.6)	82 (98.8)	203 (98.5)	
Non-radiocephalic	8 (2.4)	1 (1.2)[a]	3 (1.5)[a]	
AVF location, n (%)				0.021
Elbow	22 (6.5)	16 (19.3)	23 (11.2)	
Wrist	251 (74.7)	53 (63.9)	139 (67.5)	
Forearm	56 (16.7)	12 (14.5)	41 (19.9)	
Snuff-box	7 (2.1)	2 (2.4)[a]	3 (1.5)[a]	
AVF age, days	1091 (547, 1646)	1334 (762, 1854)	1112 (547, 1835)	0.069
Lesion site, n (%)				0.301
Anastomosis	196 (58.3)	43 (51.8)	106 (51.5)	
Vein	40 (11.9)	16 (19.3)	31 (15.0)	
Artery	100 (29.8)	24 (28.9)	69 (33.5)	
Occlusion time, days	3 (2, 5)	3 (3, 5)	3 (2, 5)	0.499

Note: [a]The expected frequency of the cell was < 5.
Abbreviations: CHD, coronary heart disease; AVF, arteriovenous fistula.

Table 2 The Complication Rate of Thrombolysis and Clinical Success Rate of Angioplasty in the Groups of Complete Lysis (CL), Incomplete Lysis (IL), and Lysis Failure (LF)

Variables N (%)	CL N=336	IL N=83	LF N=206	$X2$ for trend	*P*
Complications	49 (14.6)	18 (21.7)	63 (30.6)	19.85	<0.001
Clinical success	326 (97.0)	78 (94.0)	167 (82.3)	35.44	<0.001

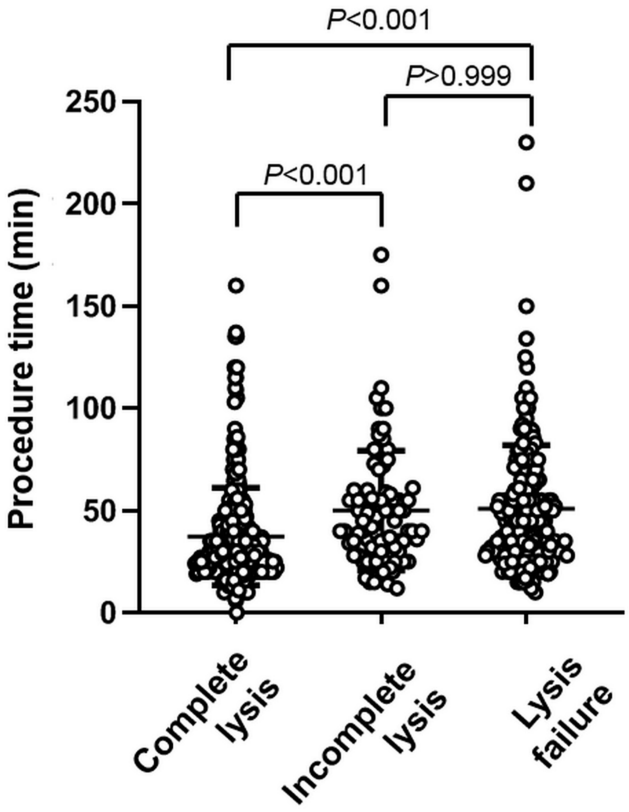

Figure 1 Recanalization procedure time for thrombosed AVFs after thrombolysis. For the complete lysis and incomplete lysis groups, the procedure time refers to the balloon angioplasty time. For the lysis failure group, the procedure time refers to the thrombectomy and balloon angioplasty time.

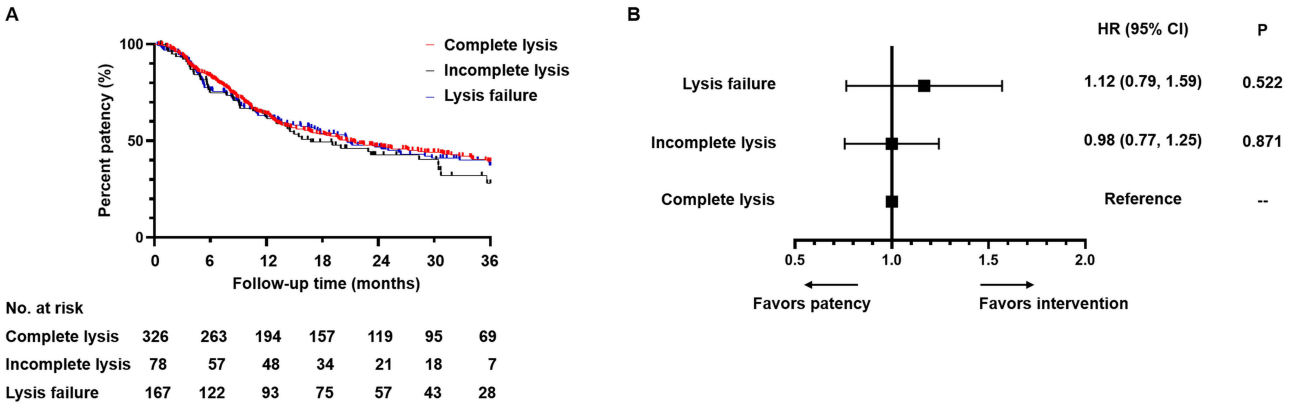

Figure 2 The impact of thrombolytic outcomes on the patency interval before the next intervention. (**A**) Kaplan–Meier survival curves of the patency interval in different groups. (**B**) Cox regression analysis showing the hazard ratios (HRs) with 95% confidence intervals (CIs) of different groups.

For patients whose fistulas were successfully recanalized, the subsequent patency was analyzed. The survival curve of the patency interval before the next intervention is shown in Figure 2A. The proportions of patency at 12, 24, and 36 months were 62.75%, 47.10%, and 39.43%, respectively, for the CL group; 62.89%, 42.69%, and 28.02%, respectively, for the IL group; and 62.31%, 46.77%, and 37.28%, respectively, for the LF group. The Log rank test showed that the patency curves were similar among the three groups ($P = 0.562$). The trends in the proportions of patency over time were further compared via Cox regression analysis (Figure 2B). Compared with those of the CL group, the HRs of reintervention in the IL group and the LF group were 0.98

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(95% CI: 0.77–1.25) and 1.12 (95% CI: 0.79–1.59), respectively, with no significant difference (P = 0.871 and 0.522, respectively).

Predictors of Complete Thrombolysis

We further investigated the predictive factors for complete thrombolysis. Table 1 shows that AVF location was a factor related to thrombolytic results. Comparisons of the biochemical parameters are shown in Supplementary Table 1. With respect to the absolute levels of these biochemical parameters, no significant differences were detected among the CL, IL, and LF groups (all $P > 0.05$). On the basis of the normal reference values in clinical practice (Supplementary Table 2), the biochemical parameters were transformed into categorical variables (lower, reference, and higher) and compared again (Supplementary Table 3). Thrombin time and hemoglobin were found to be related to thrombolysis outcomes. Although we combined some categories to meet the requirements of statistical analysis, there were still some cells with expected values less than 5. Therefore, we needed to further merge the two thrombolysis outcome groups. The distribution patterns of AVF location, thrombin time, and hemoglobin were similar in the IL and LF groups (Supplementary Figure 1), and the sample sizes of both groups were smaller than those of the CL group. Therefore, the IL and LF groups were merged and compared with the CL group (Table 3).

AVF location, thrombin time, and hemoglobin were the factors associated with significant differences among the three groups (P = 0.023, 0.002, and 0.004, respectively). The impact of AVF location on thrombolysis outcomes was related mainly to the difference in the ratio of the elbow and the wrist (Supplementary Table 4), so the categories of AVF location were merged into the elbow group and non-elbow group. Logistic regression analysis revealed that elbow AVF and hemoglobin < 115 g/L were two independent risk factors for incomplete thrombolysis/thrombolysis failure. Non-elbow AVF (OR: 0.45, 95% CI: 0.26–0.81, P = 0.007) and higher hemoglobin levels (OR: 0.637, 95% CI: 0.457–0.887, P = 0.008) were beneficial for reducing the risk of adverse thrombolysis outcomes (Table 4). Patients with both elbow AVFs and lower hemoglobin levels had the lowest complete thrombolysis rate of 24.2%, whereas patients with both non-elbow AVFs and higher hemoglobin levels had the highest complete thrombolysis rate of 60.5% (OR of adverse thrombolysis outcomes: 0.21, 95% CI: 0.09–0.48, $P < 0.001$). The complete thrombolysis rate was 52.2% for the patients with elbow AVFs and higher hemoglobin levels and 51.2% for the patients with non-elbow AVFs and lower hemoglobin levels. Compared with patients with both risk factors, patients with one or neither risk factor had a significantly higher complete thrombolysis rate ($\chi 2$ = 17.33, $P < 0.001$) and a lower OR of incomplete thrombolysis/thrombolysis failure (Figure 3).

Stratified Analyses of the Impact of Thrombolysis Outcomes

No difference was detected in the PTA duration between the elbow AVF and non-elbow AVF groups (35 [IQR: 29, 70] vs 35 [IQR: 25, 52.75], P = 0.081) or between the low hemoglobin and high hemoglobin groups (35 [IQR: 25, 53] vs 35 [IQR: 25, 55], P = 0.210). Logistic analyses revealed that AVF location was also associated with the clinical success rate of PTA (Supplementary Table 5), indicating that AVF location is a confounding factor. Therefore, a stratified analysis of the impact of thrombolysis outcomes on the clinical success rate of PTA was performed (Table 5). The overall success rate of PTA in the elbow AVF subgroup was lower than that in the non-elbow AVF subgroup. The correlation between the degree of thrombolysis and the clinical success rate of PTA was significant in the non-elbow AVF subgroup ($P <$ 0.001) but not in the elbow AVF subgroup (P = 0.274). After adjustment for AVF location, the clinical success rate was significantly lower in the IL and LF groups than in the CL group (OR: 0.189, 95% CI: 0.09–0.38, $P < 0.001$). The stratified OR was 0.61 in the elbow AVF subgroup (95% CI: 0.14–2.59, P = 0.502) and 0.14 in the non-elbow subgroup (95% CI: 0.06–0.31, $P < 0.001$).

Discussion

Indwelling needle-delivered thrombolysis is an economical, easy-to-implement, bedside-operated procedure with acceptable treatment results. The merits of our method have been described in detail in a previous study.[8] In routine clinical practice, thrombi that cannot be lysed via thrombolysis methods are removed via thrombectomy. Perhaps due to such dual treatment choices, previous studies have focused mostly on comparing thrombolysis with thrombectomy,[3–6] and the

Table 3 Comparisons of Baseline Characteristics and Serum Parameters Among the Groups of Complete Lysis (CL) and Incomplete Lysis (IL)/Lysis Failure (LF)

Variables	**CL N=336**	**IL/LF N=289**	***P***
Male, n (%)	183 (54.5)	160 (55.4)	0.822
Age, years	56 (48, 68)	56 (49, 67)	0.618
Age, n (%)			0.699
<60	189 (56.3)	167 (57.8)	
≥60	147 (43.8)	122 (42.2)	
Diabetes, n (%)	61 (21.8)	55 (22.6)	0.816
CHD, n (%)	20 (7.1)	13 (5.3)	0.400
Smoking, n (%)	81 (28.9)	74 (30.5)	0.703
Anastomosis type, n (%)			0.868
End-to-side	248 (73.8)	215 (74.4)	
Other	88 (26.2)	74 (25.6)	
AVF type, n (%)			0.365
Radiocephalic	328 (97.6)	285 (98.6)	
Non-radiocephalic	8 (2.4)	4 (1.4)	
AVF location, n (%)			0.023
Elbow	22 (6.5)	39 (13.5)	
Wrist	251 (74.7)	192 (66.4)	
Forearm	56 (16.7)	53 (18.3)	
Snuff-box	7 (2.1)	5 (1.7)	
AVF age, days	1091 (547, 1646)	1146 (583, 1844)	0.183
Lesion site, n (%)			0.157
Anastomosis	196 (58.3)	149 (51.6)	
Vein	40 (11.9)	47 (16.3)	
Artery	100 (29.8)	93 (32.2)	
Occlusion time, days	3 (2, 5)	3 (2, 5)	0.367
Prothrombin time, n (%)			0.938
Ref & lower (≤12s)[a]	224 (69.8)	192 (70.1)	
Higher (>12s)	97 (30.2)	82 (29.9)	
PTR, n (%)			0.685
Ref & lower (≤1.14)[a]	309 (96.3)	261 (95.6)	
Higher (>1.14)	12 (3.7)	12 (4.4)	

(*Continued*)

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Table 3 (Continued).

Variables	CL N=336	IL/LF N=289	*P*
INR, n (%)			0.857
Ref & lower (≤1.2)[a]	312 (97.2)	266 (97.4)	
Higher >1.2	9 (2.8)	7 (2.6)	
Prothrombin activity, n (%)			0.841
Ref & higher (≥75%)[a]	307 (95.6)	262 (96.0)	
Lower (<75%)	14 (4.4)	11 (4.0)	
APTT, n (%)			0.313
Ref (24.8–33.8s)	234 (72.9)	213 (78.0)	
Higher (>33.8s)	28 (8.7)	17 (6.2)	
Lower (<24.8s)	59 (18.4)	43 (15.8)	
Thrombin time, n (%)			0.002[b]
Ref & lower (≤21s)[a]	311 (96.9)	272 (100)	
Higher (>21s)	10 (3.1)	0 (0)	
Fibrinogen, n (%)			0.354
Ref & lower (≤3.5 g/L)[a]	185 (57.6)	147 (53.8)	
Higher (>3.5 g/L)	136 (42.4)	126 (46.2)	
D-dimer, n (%)L			0.087
Ref (≤0.55 mg/L)	89 (27.9)	59 (21.8)	
Higher (>0.55 mg/L)	230 (72.1)	212 (78.2)	
FDP, n (%)			0.621
Ref (≤5.0 μg/mL)	290 (90.9)	244 (89.7)	
Higher (>5.0 μg/mL)	29 (9.1)	28 (10.3)	
White blood cell, n (%)			0.704
Ref & higher (≥3.5×10^9/L)[a]	303 (96.8)	255 (96.2)	
Lower (<3.5×10^9/L)	10 (3.2)	10 (3.8)	
Red blood cell, n (%)			0.057
Ref & higher (≥3.8×10^{12}/L)[a]	180 (57.1)	131 (49.2)	
Lower (<3.8×10^{12}/L)	135 (42.9)	135 (50.8)	
Hemoglobin, n (%)			0.004
Ref & higher (≥115 g/L)[a]	182 (57.8)	122 (45.9)	
Lower (<115 g/L)	133 (42.2)	144 (54.1)	

(*Continued*)

Table 3 (Continued).

Variables	CL N=336	IL/LF N=289	*P*
Platelet, n (%)			0.096
Ref & higher (≥101×10^9/L)[a]	293 (93.0)	237 (89.1)	
Lower (<101×10^9/L)	22 (7.0)	29 (10.9)	
Calcium, n (%)			0.696
Ref (2.1–2.55 mM)	190 (59.9)	155 (58.1)	
Higher (>2.55 mM)	31 (9.8)	23 (8.6)	
Lower (<2.1 mM)	96 (30.3)	89 (33.3)	
Phosphorus, n (%)			0.550
Ref & lower (≤1.45 mM)[a]	62 (19.7)	47 (17.7)	
Higher (>1.45 mM)	253 (80.3)	218 (82.3)	
Parathyroid hormone, n (%)			0.072
Ref & lower (≤88 pg/L)[a]	45 (15.8)	25 (10.5)	
Higher (>88 pg/L)	239 (84.2)	214 (89.5)	
Total protein, n (%)			0.515
Ref (63–82 g/L)	235 (80.2)	214 (81.7)	
Higher (>82 g/L)	23 (7.8)	24 (9.2)	
Lower (<63 g/L)	35 (11.9)	24 (9.2)	
Albumin, n (%)			0.465
Ref & higher (≥35 g/L)[a]	268 (91.5)	244 (93.1)	
Lower (<35 g/L)	25 (8.5)	18 (6.9)	

Notes: [a]Two classes were combined because the sample size of one class was too small (expected frequency < 5). [b]P value was calculated using Fisher exact test.

Abbreviations: CHD, coronary heart disease; AVF, arteriovenous fistula; PT, prothrombin time; PTR, prothrombin time ratio; INR, international normalized ratio; PTA, prothrombin activity; APTT, activated partial thromboplastin time; FDP, fibrinogen degradation products; WBC, white blood cell; RBC, red blood cell; PTH, parathyroid hormone.

impact of thrombolysis outcomes on subsequent access recanalization remains unclear. Our study suggests that complete thrombolysis is beneficial for improving the efficacy of PTA. Non-elbow AVFs and hemoglobin ≥ 115 g/L are predictors of an increased complete lysis rate.

The overall clinical success rate of PTA was 91.4% in this study. Notably, the CL group also had the highest success rate among all the groups, although the patency interval of successfully salvaged AVFs did not differ regardless of the thrombolytic outcomes. Even in the IL group, the clinical success rate of PTA was still higher than that in the LF group. Our view is that only when access is successfully canalized will the subsequent maintenance and repair work be meaningful. Improving thrombolysis outcomes is beneficial for increasing the clinical success rate of recanalization, thus further prolonging the lifespan of access and saving vascular resources. Our opinion is in accordance with Letachowicz et al that preserving functional vascular access options rather than primary patency should be the priority in terms of maximizing patient survival.[9]

Table 4 Logistic Regression Analysis of the Effect of Selected Factors on Thrombolysis Outcomes

	B	SE	Wald	*P*	OR	95% CI for OR	
						Lower	Upper
Univariate							
AVF location							
Elbow					1.00		
Non-elbow	0.80	0.28	8.19	0.004	0.45	0.26	0.78
Thrombin time							
≤21s					1.00		
>21s	−21.07	12710	0	>0.999	0	0	
Hemoglobin							
<115 g/L					1.00		
≥115 g/L	−0.48	0.17	8.17	0.004	0.619	0.446	0.860
Multivariate							
AVF location							
Elbow					1.00		
Non-elbow	−0.79	0.29	7.20	0.007	0.45	0.26	0.81
Hemoglobin							
<115 g/L					1.00		
≥115 g/L	−0.45	0.17	7.13	0.008	0.637	0.457	0.887

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval.

In this study, the non-elbow location was composed of the distal positions for AVF creation. Although several guidelines recommend the adoption of stepwise vascular attempts from distal to proximal when creating AVFs,[1,10] a large shift from lower- to upper-arm AVFs has occurred in the United States.[11] The main motivation for this change is the

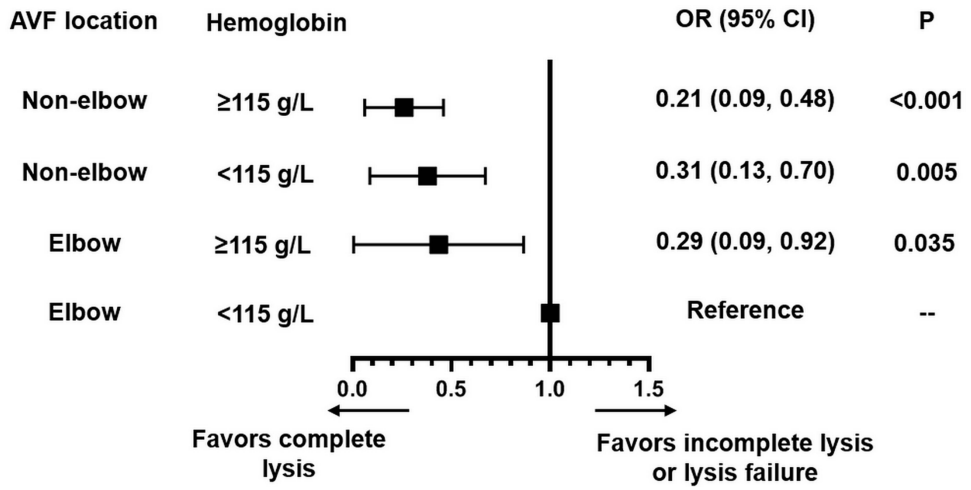

Figure 3 The impact of arteriovenous fistula (AVF) location and hemoglobin level on thrombolysis outcomes.
Abbreviations: OR, odds ratio; CI, confidence interval.

Table 5 Stratified Analysis of the Effect of Thrombolysis Outcomes on the Clinical Success Rate of Angioplasty

Variables N (%)	Complete lysis	Incomplete lysis	Lysis Failure	X2 for Trend	P
Elbow AVF	19 (86.4)	14 (87.5)	17 (73.9)	1.196	0.274
Non-elbow AVF	307 (97.8)	64 (95.5)	150 (82.0)	39.41	<0.001

observation of a higher maturation rate of upper-arm AVFs with smaller disparities in sex and age.[12–14] Although thrombolysis results were the main exposure factor in this study, we still performed a univariate Cox regression analysis of predictors of the patency interval before the next intervention (Supplementary Figure 2). Elbow AVFs were also related to a shorter patency interval. On the basis of our findings, we raised concerns about this lower- to upper-arm shift. Upper-arm AVF may be related to more frequent episodes of reintervention or even access replacement, and the resulting enormous economic burden and exhaustion of vascular resources are likely to threaten the long-term survival of patients. Therefore, if patients have a considerable life expectancy, careful lifetime planning and priority use of lower-arm sites for AVF creation may be a more cautious and responsible decision.

Anemia management in hemodialysis patients has reached a consensus because the hemoglobin concentration is strongly correlated with morbidity and mortality risk.[15,16] Although a target hemoglobin range of 110–113 g/L is recommended for renal anemia management,[16–18] a single value of 115 g/L was used in this study for the sake of statistical requirements, which is also the cutoff value for anemia diagnosis in clinical practice. A receiver-operating characteristic analysis of the effect of hemoglobin on thrombolysis outcomes was also performed (Supplementary Figure 3). The results indicated that 115.5 g/L was the optimal cutoff value yielding the largest Youden index (sensitivity = 56.2% and specificity = 56.0%). Therefore, the grouping value of 115 g/L was relatively reasonable. The results revealed that hemoglobin was a predictor of thrombolysis results. A high hemoglobin level was also found to be related to a longer patency interval before the next intervention (Supplementary Figure 2). Although anemia is a known risk factor for cerebral venous thrombosis,[19,20] its relationship with AVF patency has not been fully studied or clearly revealed. An article reported that the incidence of AVF failure was higher in patients with hemoglobin < 100 g/L, but did not differ in the subgroups with hemoglobin ≥ 100 g/L.[21] An association between a high red blood cell distribution width (also a marker of anemia) and reduced AVF patency was also reported in two articles.[22,23] Taken together, controlling anemia and maintaining a certain level of hemoglobin may be beneficial for AVF patency. In this study, the association between the hemoglobin level and AVF patency was relatively weak (P <0.05 but 95% CI of HR including 1, Supplementary Figure 2). This result may also be influenced by other unstudied factors. Unlike the AVF location, hemoglobin levels change, making it even more difficult to assess the impact on patency. The role of anemia in evaluating the patency of vascular access needs further investigation.

Currently, we adopted a urokinase dose of 3×10^5 units, mainly considering its ability to effectively lyse thrombi without a significant risk of serious complications. The complications we encountered were mild, easily manageable, and acceptable for us. The complication rates vary across studies, which may be related not only to dosage but also to the administration method. With the help of several new techniques such as the pulse-spray technique,[5] it is possible to reduce the total urokinase dose while increasing the local drug concentration, thereby reducing the occurrence of complications. However, catheter-directed thrombolysis is more expensive, and indwelling needle-directed thrombolysis is more affordable for our patients. Similarly, some studies have considered economic factors and used clinical scalp needles and spinal needles for direct intravascular thrombolysis.[24,25] Indwelling needles have several advantages over other needles. First, indwelling needles are flexible, so they can reduce the chance of scratching or puncturing the patient's vessels. Second, indwelling needles are widely used with sufficient supply and easy access.

Indwelling needle-delivered thrombolysis is more suitable for superficial thrombosis than for deep vein thrombosis, so the results of this study may not be repeated on other occasions. Moreover, this was a retrospective study with its

natural design limitations. For example, some interesting parameters (blood lipids and cholesterol) were too severely missing to be analyzed. Other factors clearly related to thrombosis, such as antiphospholipid antibody,[26] were not analyzed because they are not routine test items. To include as many samples as possible, both initial and old AVFs were included. Some patients have undergone several episodes of intervention before and after, and the intervention methods are not limited to thrombolysis; thus, the possible interference effects of other intervention methods cannot be estimated. The primary and secondary patency rates in the traditional sense cannot be analyzed either. Follow-up studies with initial AVFs and strictly assigned intervention methods may be necessary to evaluate the true efficacy of indwelling needle-delivered thrombolysis and the importance of complete lysis. A total of 76 patients received multiple treatments, accounting for 14.5% of all patients. These patients may pose selection bias and affect the analysis results, which is another limitation.

Conclusion

Indwelling needle-delivered thrombolysis is a feasible method for the treatment of thrombosed AVFs. During the thrombolysis procedure, a greater degree of lysis can improve the clinical success rate of PTA and is associated with a lower incidence of thrombolysis-related complications. However, it does not affect the patency interval from recanalization to the next intervention. Non-elbow AVF location and hemoglobin ≥ 115 g/L are predictive factors for achieving complete thrombolysis.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Z Wan, Y Zhou, and Q Lyu designed the study. Y Zhou, Q Lyu, Q Lai, X Gao, X Zhang and L Chen collected and checked the data. Y Zhou, Q Lyu, and Z Wan analyzed the data. Z Wan and Y Zhou interpreted the results. Z Wan and Y Zhou wrote the draft, and all authors revised and critically reviewed the article. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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