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Long-Term Efficacy of Ultrasound-Guided Percutaneous Transluminal Angioplasty for Arteriovenous Fistula Outflow Stenosis Caused by Venous Valve

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Keywords

Venous valve-related stenosis · Percutaneous transluminal angioplasty · Arteriovenous fistula · End-stage renal disease · Primary patency

Abstract

Introduction: Venous valve-related stenosis (VVRS) is an uncommon type of failure of arteriovenous fistula among patients with end-stage renal disease (ESRD). There is a paucity of data on the long-term efficacy of ultrasound-guided percutaneous transluminal angioplasty (PTA) for VVRS. ***Methods:*** ESRD patients who underwent PTA because of VVRS between January 2017 and December 2021 at the First Affiliated Hospital of Chongqing Medical University were enrolled. Patients were classified into three cohorts (cohort1, VVRS located within 3 cm of the vein adjacent to the anastomosis; cohort2, VVRS located over 3 cm away from the anastomosis; cohort3, multiple stenoses). The patency rates were assessed by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox analyses were performed to identify the risk factors. ***Results:*** A total of 292 patients were enrolled, including 125 (42.8%), 111 (38.0%), and 56 (19.2%) patients in cohort1, cohort2, and cohort3, respectively. The median follow-up was 34.8 months. The 6-month, 1-year, 2-year, and 3-year primary patency rates were 86.0%, 69.4%, 47.5%, and 35.3%, respectively. The secondary patency rates were 94.5%, 89.4%, 75.5%, and 65.3%, respectively. Cohort1 showed a relatively better primary patency compared to cohort2 and cohort3. The secondary patency rates were comparable in the three cohorts. Duration of dialysis and VVRS type were potential factors associated with primary patency. ***Conclusions:*** This study showed acceptable long-term primary and secondary patency rates after PTA for VVRS in ESRD patients, especially for those with VVRS located within 3 cm of the vein adjacent to the anastomosis.

Introduction

The number of patients with end-stage renal disease (ESRD) who require hemodialysis therapy continues to increase worldwide [1]. Maintenance of adequate hemodialysis can help improve the survival and quality of life of these patients. Arteriovenous fistula (AVF) is the

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preferred mode of vascular access in this population [2]. A patent vascular access is essential for routine dialysis. However, approximately 60% of dialysis patients experience access failure at 12 months, and venous stenosis or occlusion is the most common reason [3, 4].

Stenosis caused by intimal hyperplasia (IH) is the most common reason for the dysfunction of AVF, while venous valve-related stenosis (VVRS) is an uncommon cause [5, 6]. Patients with VVRS and patients with IH stenosis present with similar symptoms. Hence, an ultrasound examination is necessary for an accurate diagnosis of VVRS, which typically shows a thickened valve with membrane-like tissue located at the site of suspected stenosis [4].

The standard treatment methods for venous stenosis include percutaneous transluminal angioplasty (PTA) and surgical reconstruction. PTA offers the advantages of minimal invasiveness and repeatability. However, the clinical benefit of PTA for VVRS of AVF in ESRD patients has not been sufficiently studied. Most of the contemporary literature comprises studies with a small sample size or individual case reports. The aim of this study was to retrospectively assess the efficacy of PTA among this population and identify the associated prognostic factors.

Methods

Patients

ESRD patients, who underwent first PTA due to VVRS of AVF were enrolled in this study. The inclusion criteria were: (1) ESRD patients with mature AVF; (2) dysfunctional dialysis access because of VVRS, which was confirmed by ultrasound; (3) PTA was performed between January 2017 and December 2021. Patients who were lost to follow-up were excluded from the analysis. Patients with venous valve-related occlusion were not included in this study. This study was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University (K2023-211), and the informed consents of patients were waived because of the retrospective nature of the study.

Variables

Data pertaining to following variables were retrospectively collected: age, sex, body mass index, duration of dialysis, cause of ESRD, diabetes mellitus, coronary heart disease, smoking history, complication of PTA, AVF side (left or right arm), AVF location (wrist, snuffbox, forearm, or elbow), AVF type (radial-cephalic, ulnar-basilic, brachial-cephalic, ulnar-cephalic, or radial-basilic), and surgical technique of AVF (end to side, end to end, or side to side).

Patients were classified into three cohorts according to the types and numbers of VVRS. Patients with only one type I VVRS (defined as VVRS located within 3 cm of the vein adjacent to the anastomosis) were classified into cohort1. Patients with only one type II VVRS (defined as VVRS located in the vein and more than 3 cm away from the anastomosis) were classified into cohort2. Patients with multiple stenoses, which included at least one VVRS with/without other vein stenosis, were classified into cohort3.

Study Endpoints

The primary endpoint was postintervention primary patency, which was defined as the period of uninterrupted patency after intervention until the next intervention. The second endpoint was postintervention secondary patency, which was defined as the period from the PTA to the time when AVF was surgically declotted, revised, or abandoned. Follow-up data were obtained from the medical records or via telephonic contact with the patient. The last follow-up time was November 30, 2022.

Statistical Analysis

Continuous variables were described as mean ± standard deviation or median with interquartile range. Categorical variables were described as frequency (percentage). Patient characteristics were compared among the three cohorts. Continuous variables were compared by one-way ANOVA or Mann-Whitney U test, and the categorical variables were compared by Pearson's χ^2 test. The postintervention primary and secondary patency rates were assessed by the Kaplan-Meier method and the between-group differences were assessed using the log-rank test. Univariate Cox analysis was performed to identify the potential risk factors associated with primary patency. Then, factors associated with *p value <0.05* were selected for further multivariate Cox analysis. Two-tailed *p values <0.05* were considered indicative of statistical significance. All statistical analyses were performed using the R software (version 4.2.2; https://www.r-project.org/).

Results

Ultrasound Characteristic of the VVRS

Two representative cases of VVRS were selected. Panels A and B of Figure 1 pertain to case 1, which shows the thickened valve with membrane-like tissue (Fig. 1a), and an aliasing phenomenon (Fig. 1b). Panels C and D of Figure 1 pertain to case 2, which corresponds to the stenosis segment prior to and after PTA. As shown in Figure 1d, the diameter of the stenosis segment became normal after PTA. In addition, in case 1, the blood flow velocity decreased to normal, and the resistance index decreased from 0.66 to 0.55 (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/536309).

Patient Characteristics

A total of 328 patients with ESRD underwent PTA because of the VVRS of AVF during the study reference period. Of these, 36 patients were lost to follow-up. The remaining 292 patients were included in this study. Of these, 125 (42.8%), 111 (38.0%), and 56 (19.2%) patients

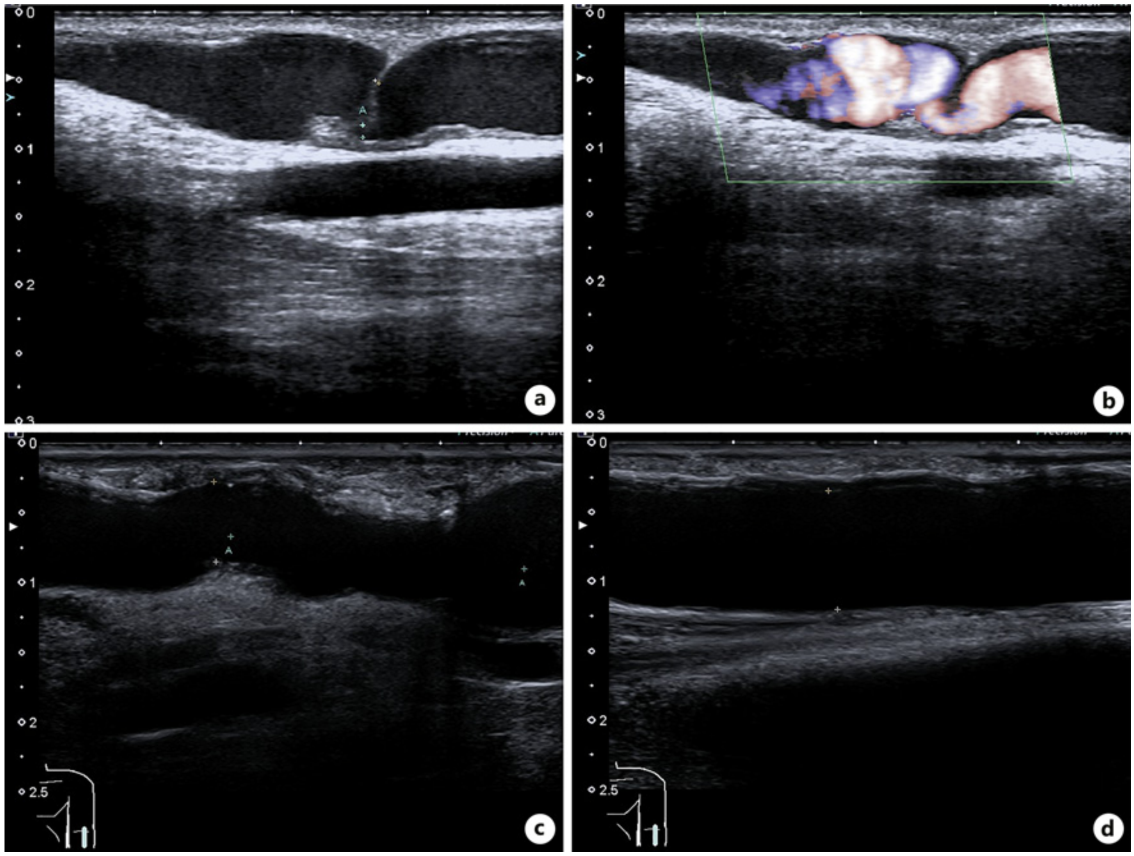

Fig. 1. Representative cases illustrating the ultrasound characteristics of the VVRS. **a** Thickened valve with membrane-like tissue. **b** the aliasing phenomenon in case 1. **c**, **d** show the stenosis segment prior to and after percutaneous transluminal angioplasty in case 2.

were classified into cohort1, cohort2 and cohort3, respectively. The baseline characteristics of all patients are summarized in Table 1. The median age of patients in this study was 57 years and the median duration of dialysis was 24.78 months. Male patients accounted for 56.8% of the total study population. The main causes of ESRD were nephritis (42.5%), diabetes (23.6%), and hypertension (14.0%). Approximately 29.5%, 10.6%, and 37.0% of patients had a history of diabetes mellitus, coronary heart disease, and smoking, respectively. A total of 230 (78.8%) patients had the AVF on the left arm and 240 (82.2%) patients had the AVF on the wrist. The most common AVF type was radial-cephalic (96.9%), and the most common surgical technique was end to side (90.1%). A total of 119 (40.8%) patients developed at least one PTA-induced complication, including venous rupture (36.3%), acute thrombosis (1.0%), hematoma (7.2%), and arterial dissection (0.3%).

A comparison of the baseline patient characteristics among the three cohorts is presented in online supplementary Table S1. Patients in cohort1 had a relatively shorter median duration of dialysis (17.97 vs. 27.43 vs. 26.84 months, $p = 0.086$). A higher proportion of male patients was found in cohort2 and cohort3, while in cohort1, the proportions of male patients and female patients were similar. There were no other significant differences between the three cohorts.

Primary and Secondary Patency Rates

All patients were followed up after PTA with a median follow-up of 34.8 months (interquartile range 31.1–39.7). For all patients, the 6-month, 1-year, 2-year, and 3-year primary patency rates were 86.0%, 69.4%, 47.5%, and 35.3%, respectively (Fig. 2a). The secondary patency rates were 94.5%, 89.4%, 75.5%, and 65.3%, respectively (Fig. 2b). Patients in cohort1 showed relatively better primary patency after PTA compared to patients in cohort2 and cohort3 (6 months: 84.8 vs. 88.3 vs. 83.9; 1 year: 71.9 vs. 70.2 vs. 62.3; 2 years: 51.8 vs. 47.2 vs. 39.0; 3 years: 43.8 vs. 35.4 vs. 12.4%; $p = 0.020$; Fig. 3a).

Table 1. Baseline patient characteristics

Variables	Total, *N* = 292 (%)
Age, years (median, IQR)	57 (49, 67)
Duration of dialysis, months (median, IQR)	24.78 (9.67, 52.53)
BMI (mean±SD)	22.47±3.41
Sex	
Male	166 (56.8)
Female	126 (43.2)
Cause of ESRD	
Diabetes	69 (23.6)
Hypertension	41 (14.0)
Glomerulonephritis	136 (46.6)
Nephritis	124 (42.5)
IgA nephropathy	8 (2.7)
Interstitial nephritis	3 (1.0)
Antineutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis	1 (0.3)
Others	46 (15.8)
Polycystic kidney disease	17 (5.8)
Obstructive nephropathy	14 (4.8)
Systemic lupus erythematosus	3 (1.0)
Gouty nephropathy	7 (2.4)
Vasculitis	1 (0.3)
Hepatitis B-related glomerulonephritis	2 (0.7)
Unknown	2 (0.7)
Diabetes mellitus	
Yes	86 (29.5)
No	206 (70.5)
Coronary heart disease	
Yes	31 (10.6)
No	261 (89.4)
Smoking history	
Yes	108 (37.0)
No	184 (63.0)
AVF side	
Left arm	230 (78.8)
Right arm	62 (21.2)
AVF location	
Wrist	240 (82.2)
Others	52 (17.8)
Snuffbox	22 (7.5)
Forearm	26 (8.9)
Elbow	4 (1.4)
AVF type	
Radial-cephalic	283 (96.9)
Others	9 (3.1)
Ulnar-basilic	4 (1.4)
Brachial-cephalic	3 (1.0)
Ulnar-cephalic	1 (0.3)
Radial-basilic	1 (0.3)
Surgical technique	
End to side	263 (90.1)
Others	29 (9.9)
End to end	28 (9.6)
Side to side	1 (0.3)
Complication of PTA	
Yes	119 (40.8)
No	173 (59.2)

IQR, interquartile range; BMI, body mass index; SD, standard deviation; ESRD, end-stage renal disease; AVF, arteriovenous fistula; PTA, percutaneous transluminal angioplasty.

However, there were no significant differences between the three cohorts with respect to secondary patency rates (6 months: 96.8 vs. 93.7 vs. 91.1; 1 year: 92.8 vs. 88.3 vs. 83.9; 2 years: 77.8 vs. 74.4 vs. 72.7; 3 years: 66.4 vs. 66.3 vs. 60.0%; $p = 0.640$; Fig. 3b).

Factors Associated with Primary Patency

To identify factors associated with primary patency, univariate and multivariate Cox analyses were performed. For continuous variables, i.e., age, duration of dialysis, and body mass index, the best cutoff values were calculated using the R package "survminer." The best cutoff for these three variables was 57 years, 27.83 months, and 21.63, respectively. On multivariate analysis, a longer duration of dialysis was a protective factor (>27.83 vs. ≤ 27.83 months: hazard ratio [HR] 0.71, 95% confidence interval [CI]: 0.52–0.97, $p = 0.028$) for better primary patency. Compared to patients in cohort1, the HR for cohort2 showed no statistical significance (1.19, 95% CI: 0.85–1.67, $p = 0.310$), while the HR for cohort3 indicated a risk factor (1.81, 95% CI: 1.21–2.72, $p = 0.004$). The details are summarized in Table 2.

Discussion

This study assessed the long-term efficacy of PTA for the treatment of VVRS of AVF in ESRD patients. Over a median follow-up of approximately 3 years, the primary and secondary patency rates in this population were acceptable, indicating the long-term efficacy of PTA for the treatment of VVRS. In a previous study, all 16 patients with VVRS who were treated with PTA showed normal access function at 6 months, suggesting effectiveness of PTA for the treatment of VVRS [6]. In addition to PTA, surgical reconstruction is also a common and effective treatment method for venous stenosis. Yao et al. enrolled 43 patients with VVRS who underwent surgical reconstruction after stenosis [4]. Over a mean follow-up of 22.5 months, the 2-year and 4-year primary patency rates were 92.2% and 79.0%, respectively. Compared to surgical reconstruction, endovascular techniques have the advantage of minimal invasiveness, minimal complications, and repeatability.

Though Yao et al. reported better results of surgical reconstruction compared to the results of PTA in the present study, their study was a retrospective analysis of a small number of patients. In addition, there may have been potential differences in baseline clinical features of patients. A randomized prospective study directly comparing the patency rates between endovascular treatment and surgical treatment may provide robust evidence of the superiority of one method over the other.

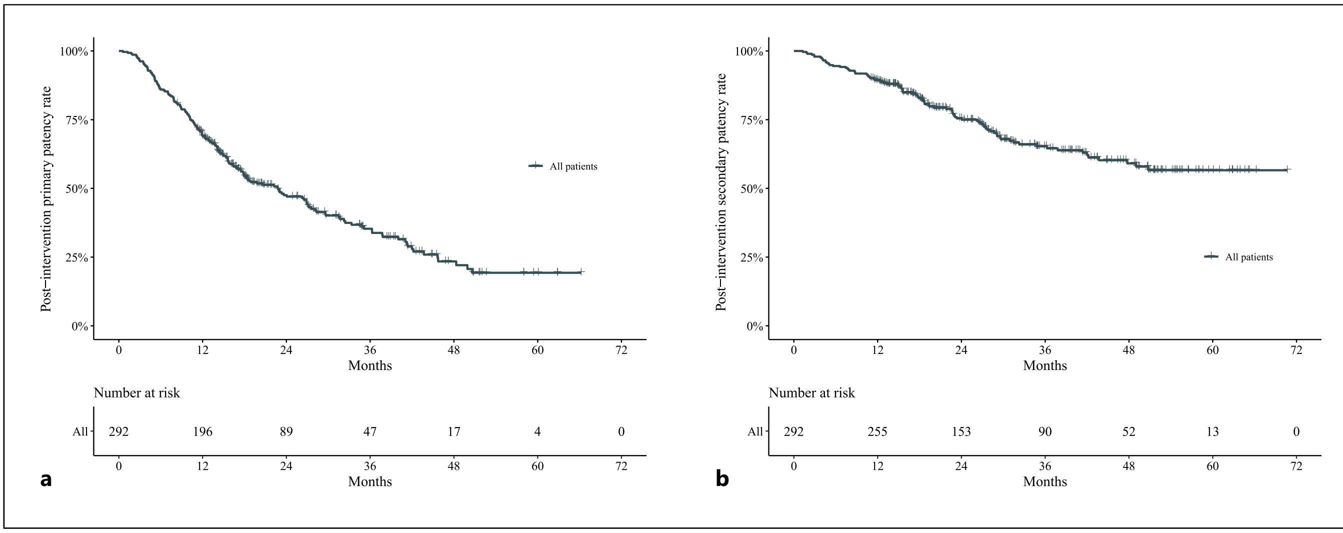

Fig. 2. Cumulative patency rates in the whole study population. **a** Primary patency rate. **b** Second patency rate.

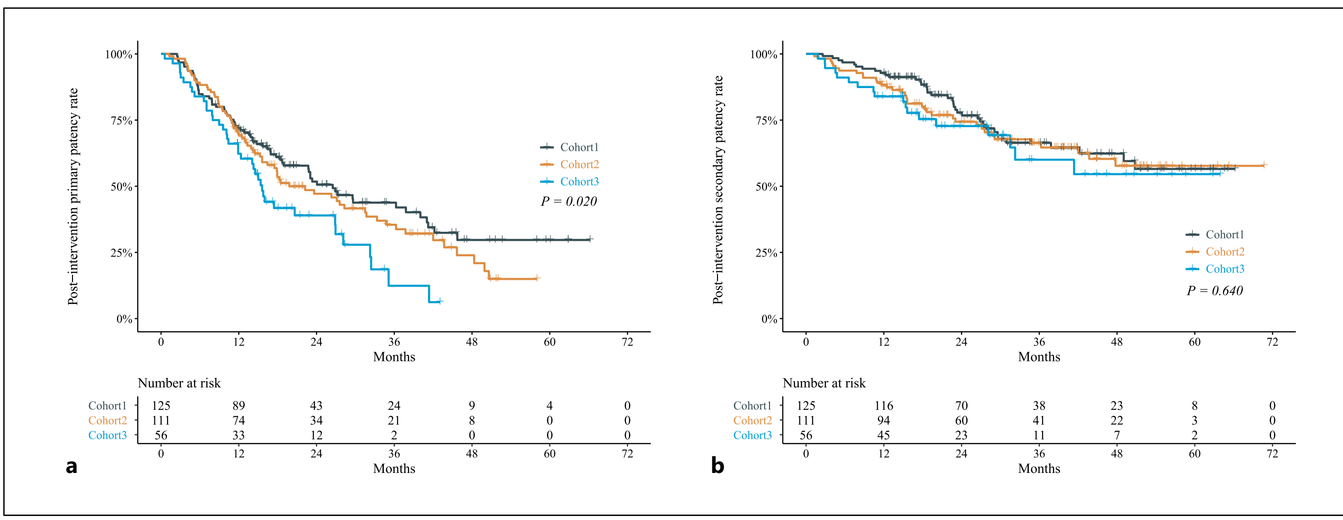

Fig. 3. Comparison of cumulative patency rates stratified by cohort. **a** Comparison of primary patency rate. **b** Comparison of second patency rate.

This study directly compared the primary patency rates among patients with different types of VVRS, and the primary patency rates varied across the different types of stenosis. Though the primary patency within the first year was similar between patients with type I VVRS and type II VVRS, but the curves separated after the first year (Fig. 3a), which demonstrated a relatively better long-term primary patency in patients with type I VVRS. In contrast, the primary patency of patients with multiple stenoses was the worst among the three cohorts. The three cohorts showed no significant difference in secondary patency rates.

In this study, the duration of dialysis was found to be independently associated with primary patency. Those with longer duration of dialysis would benefit more from PTA (HR 0.70, 95% CI: 0.51–0.96, p = *0.025).* A few previous studies have also supported our result, though the cut-off of duration of dialysis varied in each study [7–9]. However, in some studies, the duration of dialysis was not a key determinant of primary patency [10, 11]. Therefore, further research is warranted to better characterize the role of duration of dialysis in ESRD patients undergoing PTA and to elucidate the underlying mechanisms.

Table 2. Predictive factor associated with primary patency

Variable	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age				
≤57 years	Reference	–	Reference	–
>58 years	1.56 (1.17–2.13)	0.003	1.34 (0.97–1.85)	0.076
Sex				
Female	Reference	–		
Male	1.27 (0.94–1.72)	0.122		
Duration of dialysis				
≤27.83 months	Reference	–	Reference	–
>27.83 months	0.68 (0.50–0.92)	0.012	0.70 (0.51–0.96)	0.025
BMI				
≤21.63	Reference	–		
>21.63	0.88 (0.65–1.19)	0.408		
Cause of ESRD				
Diabetes	Reference	–		
Glomerulonephritis	0.94 (0.65–1.37)	0.752		
Hypertension	1.18 (0.73–1.92)	0.493		
Others	0.99 (0.63–1.58)	0.980		
Diabetes mellitus				
No	Reference	–		
Yes	0.98 (0.74–1.41)	0.893		
Coronary heart disease				
No	Reference	–	Reference	–
Yes	1.56 (1.02–2.38)	0.040	1.39 (0.88–2.17)	0.154
Smoking history				
No	Reference	–		
Yes	1.12 (0.82–1.51)	0.478		
Cohort				
Cohort1	Reference	–	Reference	–
Cohort2	1.21 (0.86–1.68)	0.274	1.19 (0.85–1.67)	0.310
Cohort3	1.76 (1.18–2.61)	0.006	1.81 (1.21–2.72)	0.004
AVF side				
Left	Reference	–		
Right	1.01 (0.71–1.45)	0.956		
AVF location				
Others	Reference	–		
Wrist	0.81 (0.56–1.18)	0.282		
AVF type				
Others	Reference	–		
Radial-cephalic	1.68 (0.62–4.53)	0.305		
Surgical technique				
End to side	Reference	–		
Others	1.07 (0.68–1.70)	0.763		
Complication of PTA				
No	Reference	–		
Yes	0.96 (0.71–1.30)	0.811		

HR, hazard ratio; CI, confidence interval; BMI, body mass index; ESRD, end-stage renal disease; AVF, arteriovenous fistula; PTA, percutaneous transluminal angioplasty.

Morphological patterns may also be a potential factor affecting AVF dysfunction after intervention. In the study by Suemitsu et al., compared to patients with IH stenosis, those with shrinking lumen stenosis were found to be at a higher risk of restenosis (HR 2.05, 95% CI: 1.25–3.36, $p = 0.005$), while those with VVRS were at a lower risk of restenosis (HR 0.19, 95% CI: 0.04–0.79, $p = 0.023$) [6]. Chen et al. [12] also demonstrated that the stenosis caused by IH had dismal primary patency compared to stenosis caused by other initial reasons. Compared to our previous study [13], which consisted of 96 patients who developed juxta-anastomotic stenosis or occlusion caused by IH, this study found a relatively better 6 months (86.0 vs. 77.4%), 1 year (69.4 vs. 53.6%), 2 years (47.5 vs. 37.0%), and 3 years (35.3 vs. 33.2%) primary patency rates. The above evidence suggests a negative impact of IH on primary patency.

According to a review, VVRS was the initial cause for patients with cephalic arch stenosis [14]. However, the incidence of VVRS was low. A study reported that approximately 10.1% of patients with AVF failure were caused by VVRS [6]. The incidence may be underestimated because of similar symptoms with IH stenosis, which could lead to a misclassification. But more cases with VVRS are likely to be identified owing to the more frequent use of preoperative ultrasound examination. Combining our results and those of previous studies, the main ultrasound finding is thickened valve with membrane-like tissue and an aliasing phenomenon localized in the VVRS site [5, 6]. The blood flow volume at the stenosis site is decreased, but the resistance index is increased [5]. The histological result suggested that, in some cases, part of the valve would develop hypertrophy, and the prominent venous valves would fuse together in the middle of the vein [15].

Some limitations of this study should be acknowledged. The histological characteristics of VVRS were not analyzed in this study, because all patients in this study received PTA instead of surgery. The histological characteristics may help illustrate the difference in primary patency rate. This may be addressed in further studies.

Conclusion

In this study, PTA of VVRS in patients with ESRD resulted in acceptable primary and secondary patency rates, suggesting the effectiveness of PTA treatment in this population. However, the patency rates varied across the three cohorts. A more robust randomized study with a larger sample size may help identify the subpopulation that is more likely to benefit from this approach.

Statement of Ethics

This study was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University (K2023-211), and the informed consents of patients were waived because of the retrospective nature of the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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The authors declare that no funding was received for the present study.

Author Contributions

Conception and design and administrative support: Ziming Wan; provision of study materials or patients: Bo Chen and Ling Chen; collection and assembly of data: Qiao Yang, Xuejing Gao, and Qiquan Lai, Bo Tu; data analysis and interpretation: Bo Chen, Bo Tu, and Ziming Wan; manuscript writing: all authors; final approval of the manuscript: all authors.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request. Further inquiries can be directed to the corresponding author.

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