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Research article

Thrombectomy versus combined thrombolysis and thrombectomy in patients with large vessel occlusion and chronic kidney disease

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ABSTRACT

Background: Whether intravenous thrombolysis (IVT) should be bridged before mechanical thrombectomy (MT) remains uncertain in patients with large vessel occlusion (LVO) and chronic kidney disease (CKD).

Methods: This research systematically enrolled every patient with both acute ischemic stroke (AIS) and CKD who received MT and fulfilled the criteria for IVT from January 2015 to December 2022. According to whether they underwent IVT, the patients were categorized into two cohorts: MT and combined IVT + MT. A binary logistic regression model was used to adjust for potential confounders, and propensity score matching analysis was used to assess the efficacy and safety of IVT in AIS patients with CKD who underwent MT.

Results: A total number of 406 patients were ultimately included in this study, with 236 patients in the MT group and 170 in the combined group. After PSM, there were 170 patients in the MT group and 170 in the combined group, and the clinical characteristics between the two groups were well balanced. The MT + IVT group had better long-term functional outcomes than the MT group (35.9% versus 21.2%, $P = 0.003$) and more modified thrombolysis in cerebral infarction (mTICI) (2b-3) (94.1% versus 87.6%, P = 0.038), while no significant difference was found regarding symptomatic intracranial hemorrhage (sICH). In line with the results observed in the in the postmatched population, the logistic regression revealed that patients in the IVT + MT group demonstrated superior clinical outcomes (adjusted OR 0.440 [95% CI (0.267–0.726)], P = 0.001) in the prematched population.

Conclusion: For LVO patients with CKD and indications for IVT, IVT bridging MT improves their prognosis compared with direct MT.

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1. Introduction

Abbreviations

MT	Mechanical thrombectomy
LVO	Large-vessel occlusion
IVT	Intravenous thrombolysis
AIS	Acute ischemic stroke
CKD	Chronic kidney disease
ICH	Intracranial hemorrhage
GFR	Glomerular filtration rate
AF	Atrial fibrillation
TIA	Transient ischemic attack
NIHSS	National Institutes of Health Stroke Scale
DNT	Door-to-needle time
DTP	Door-to-puncture time
mTICI	Modified Thrombolysis in Cerebral Infarction
sICH	Symptomatic intracranial hemorrhage;
mRS	Modified Rankin Scale
IQR	Interquartile range
PSM	Propensity score matching

Mechanical thrombectomy (MT), a standard treatment for stroke patients with large-vessel occlusion (LVO), has been widely used in the clinic [1–3]. However, the role of intravenous thrombolysis (IVT) before and during MT remains uncertain in patients with ischemic stroke. Strokes caused by LVO tend to benefit less from IVT, particularly in patients with tandem lesions, proximal occlusion, cardioembolic stroke, or a high clot burden [4–6]. Certain research indicates that IVT may might contribute to the thrombus's softening, potentially diminishing the procedure duration and the required number of passes for successful recanalization [7]. The DIRECT-MT trial established that performing MT without prior IVT was comparable, and not inferior, to the combination of IVT followed by MT in terms of functional outcomes for patients with acute LVO [8]. Another real-world matching study also confirmed this conclusion [9]. However, whether this conclusion is applicable to LVO patients with chronic kidney disease (CKD) has not been reported.

Approximately 20%–35% of acute ischemic stroke (AIS) patients have CKD [10]. Although these patients can benefit from MT [11,12], CKD patients notably have a relatively poor prognosis and a higher risk of intracranial hemorrhage (ICH) after MT [12–16]. In addition, some studies have observed that AIS patients with CKD have a higher risk of ICH after IVT [17,18]. Therefore, IVT before MT in these patients may not only be unhelpful but also cause damage. Regarding the high incidence of CKD among AIS patients, whether IVT should be bridged before MT should be investigated.

2. Methods

2.1. Study population

Data were obtained from the prospectively collected stroke registry of Jingjiang People's Hospital and Shaoxing Second Hospital. This study systematically encompassed all AIS patients and CKD who underwent MT and fulfilled the criteria for IVT between January 2015 and December 2022. According to whether they received rt-PA, the patients were categorized into two cohorts: MT and combined IVT + MT.

The inclusion criteria were patients who (1) met the current criteria for AIS [19,20], (2) underwent MT, (3) fulfilled the criteria for CKD, (4) were admitted within 4.5-h, and (5) had indications for IVT [19,20]. The decision on whether the patient underwent IVT was collaboratively made by the patient's caregivers and the physician. This study received approval from the medical ethics committees of both Jingjiang People's Hospital and Shaoxing Second Hospital. The treatment plan was completely communicated during hospitalization, and written informed consent was obtained from either the patient or their caregiver.

2.2. Renal function

Serum creatinine levels were evaluated upon admission. CKD is classified into 5 stages according to the glomerular filtration rate (GFR) [21]. Stage 1: GFR (greater than 90 ml/min/1.73 m^2), stage 2: Mild reduction in GFR (60–89 ml/min/1.73 m^2), stage 3a: Moderate reduction in GFR (45–59 ml/min/1.73 m^2), stage 3b: Moderate reduction in GFR (30–44 ml/min/1.73 m^2), stage 4: Severe reduction in GFR (15–29 ml/min/1.73 m^2) and stage 5: Renal failure (GFR less than 15 ml/min/1.73 m^2). Patients with a consistently GFR below 60 mL/min/1.73 m^2 are likely to exhibit clinical manifestations due to the ongoing decline in kidney function. For this

study, we included individuals with AIS who had stage 3–5 disease.

2.3. Data collection and outcome measures

We prospectively gathered all initial characteristics, encompassing demographic details (age and sex), historical medical information (drinking habits, smoking history, diabetes, hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation (AF), stroke, and transient ischemic attack (TIA), laboratory test results (GFR), and National Institutes of Health Stroke Scale (NIHSS) score. We also collected workflow intervals, including onset-to-door time, door-to-needle time (DNT), door-to-puncture time (DTP) and puncture-to-reperfusion time.

Radiological and clinical outcomes in this study comprised successful reperfusion (defined as a modified thrombolysis in cerebral infarction (mTICI) score of 2b or 3 [22]), symptomatic intracranial hemorrhage (sICH) within 24 h based on the Heidelberg Bleeding Classification [23], and the 3-month modified Rankin Scale (mRS) score. A favorable long-term functional outcome was specified as a 3-month mRS score ranging from 0 to 2.

2.4. Statistical analysis

Statistical analyses were conducted using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). The Wilcoxon test was employed for the analysis of continuous or ordinal variables with their description presented as the median [interquartile range (IQR)]. Fisher's exact test was applied for categorical variables, which are described as numbers (percentages). A P *value* < 0.05 was deemed indicative of statistical significance. Subsequently, to enhance the comparability between the two groups, propensity score matching (PSM) was conducted at a 1:1 ratio using the nearest-neighbor matching method without replacement within a caliper of 0.05. This process aimed to match IVT + MT patients with MT-alone patients. In the same manner, the comparison between the two groups was performed in the postmatched population. We conducted a subgroup analysis based on CKD grade to identify the prognosis of MT and IVT + MT at different levels of renal function in the postmatched population. Moreover, to verify the PSM results, we employed a binary logistic

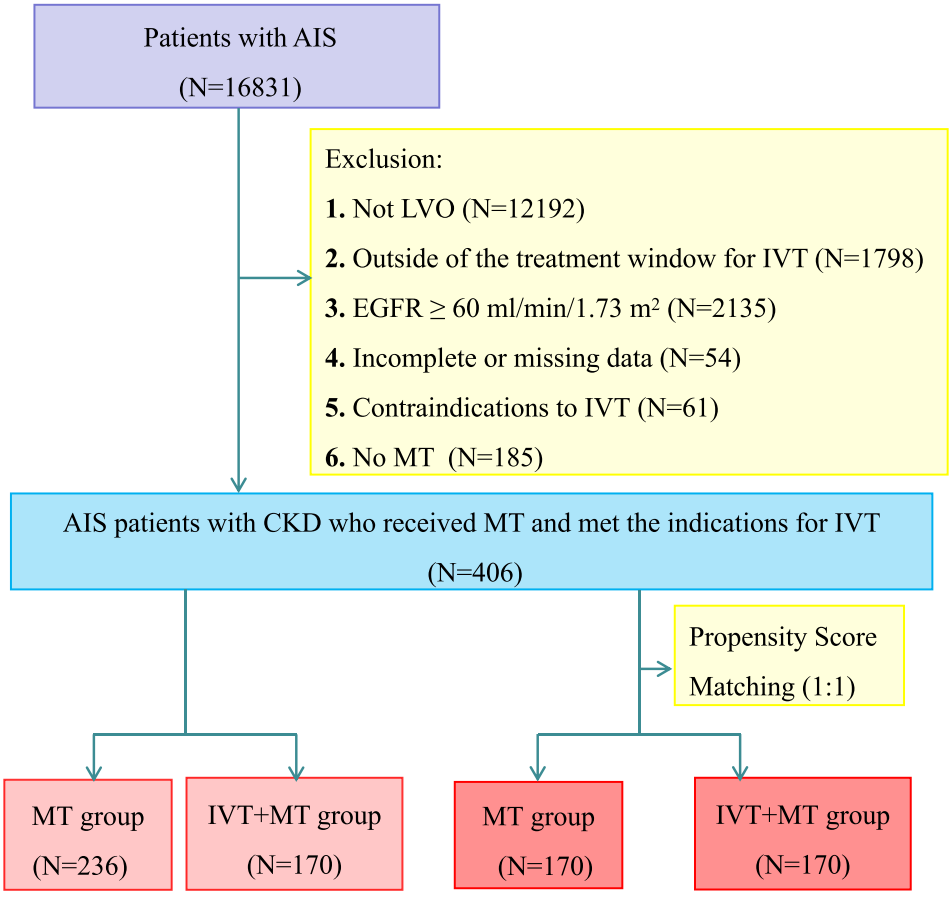

Fig. 1. Flowchart of the patient selection.
AIS: acute ischemic stroke; LVO: large vessel occlusion; IVT: intravenous thrombolysis; eGFR: estimated glomerular filtration; MT: mechanical thrombectomy; and CKD: chronic kidney disease.

regression model, adjusting for potential confounders, to compare the outcome indicators between the groups before PSM.

3. Results

A combined total of 16831 patients with AIS were admitted to the two stroke centers from January 2015 to December 2022. Among them, 12192 individuals did not have LVO, 1798 patients fell outside the 4.5-h window for IVT, 2135 patients had eGFR ≥60 ml/min/1.73 m^2, 54 patients had incomplete data, 61 patients had contraindications to IVT, and 185 patients did not undergo MT. Ultimately, 406 patients were included in this study, with 236 patients in the MT group and 170 in the combined group. After PSM, 170 patients in the MT group and 170 in the combined group were identified (Fig. 1).

3.1. Demographic and clinical characteristics

The baseline characteristics of the two groups are shown in Table 1. Before PSM, the IVT + MT group had a longer median DTP (119 vs. 109, P < 0.001) than the MT group. After PSM, the clinical characteristics between the two groups were effectively balanced.

3.2. Clinical outcomes

Among the postmatched patients, the numbers of patients with TICI (2b-3) were 160 (94.1%) in the IVT + MT group and 149 (87.6%) in the MT group (P = 0.038); 27 (15.9%) patients in the IVT + MT group developed sICH; and 14.0% of patients in the MT group developed sICH ($P = 0.595$). The IVT + MT group exhibited better long-term functional outcomes than the MT group (35.9% versus 21.2%, $P = 0.003$). The distribution of 3-month mRS scores was also significantly different between the two groups (Table 2).

Table 3 shows the clinical outcomes of patients with different levels of renal function treated with MT and IVT + MT in the postmatched population. The proportion of patients with eGFR (45–59) who chose IVT + MT was higher than that of patients with eGFR (<45). In the eGFR (45–59) population, 39.8% of patients in the IVT + MT group achieved a favorable outcome, whereas the MT group had a favorable outcome rate of only 22.2%. However, no statistically significant difference was observed in the use of IVT + MT for eGFR (<45) in achieving favorable outcomes. The IVT + MT group with eGFR (45–59) had a better prognosis than the MT group (P = 0.009) compared to the eGFR (<45) population (P = 0.167). The IVT + MT group did not have increased bleeding in the eGFR (45–59) population or eGFR (<45) population.

3.3. Risk factors associated with poor outcome at 90 days

In alignment with the findings in the postmatched population, subsequent to adjusted analyses in the prematched population, it was observed that patients in the IVT + MT group demonstrated improved clinical outcomes (adjusted OR 0.440 [95% CI

Table 1
Demographic and clinical characteristics of the two groups (median, IQR/cases, %).

	Before PSM			After PSM		
	MT group (n = 236)	IVT + MT group (n = 170)	*P*	MT group (n = 170)	IVT + MT group (n = 170)	*P*
Demographic						
Male (case, %)	128(54.2)	96(56.5)	0.655	99(58.2)	96(56.5)	0.742
Age/year	80(74–84)	80(73–84)	0.526	80(74–84)	80(73–84)	0.681
Past medical history						
Drinking status (case, %)	50(21.2)	35(20.6)	0.884	37(21.8)	35(20.6)	0.791
Smoking status (case, %)	60(25.4)	50(29.4)	0.372	50(29.4)	50(29.4)	>0.999
Hypertension (case, %)	179(75.8)	126(74.1)	0.691	130(76.5)	126(74.1)	0.615
Diabetes (case, %)	53(22.5)	32(18.8)	0.375	31(18.2)	32(18.8)	0.889
Hyperlipidemia (case, %)	33(14)	24(14.1)	0.969	26(15.3)	24(14.1)	0.759
CHD (case, %)	65(27.5)	35(20.6)	0.109	36(21.2)	35(20.6)	0.894
AF(case, %)	129(54.7)	89(52.4)	0.645	87(51.2)	89(52.4)	0.828
TIA (case, %)	5(2.1)	4(2.4)	>0.999	4(2.4)	4(2.4)	>0.999
Stroke (case, %)	61(25.8)	38(22.4)	0.419	38(22.4)	38(22.4)	>0.999
Laboratory examination						
GFR (ml/min/1.73m^2)	45(37–54)	48(37–53)	0.439	46.4(37–54)	48(37–53)	0.944
Admission NIHSS score	17(12–22)	16(12–20)	0.086	16(11–19)	16(12–20)	0.986
Workflow intervals						
Onset-to-door time (min)	116(77–162)	111(71–167)	0.401	116(64–160)	111(71–167)	0.962
Door-to-needle time (min)		43(29–60)			43(29–60)	
Door-to-puncture time (min)	109(74–130)	119(85–150)	<0.001	117(87–143)	119(85–150)	0.358
Puncture-to-reperfusion time (min)	88(68–123)	88(70–106)	0.136	87(68–120)	88(70–106)	0.648

PSM: propensity score matching; MT: mechanical thrombectomy; IVT: intravenous thrombolysis; CHD: coronary heart disease; AF: arterial fibrillation; TIA: transient ischemic attack; GFR: glomerular filtration; and NIHSS: National Institutes of Health Stroke Scale.

Table 2
Clinical outcomes of patients treated with MT and IVT + MT.

	Before PSM			After PSM		
	MT group (n = 236)	IVT + MT group (n = 170)	*P*	MT group (n = 170)	IVT + MT group (n = 170)	*P*
mTICI (2b-3)	208(88.1)	160(94.1)	0.041	149(87.6)	160(94.1)	0.038
sICH	36(15.3)	27(15.9)	0.863	33(19.4)	27(15.9)	0.595
Good outcome (mRS 0–2)	44(18.6)	61(35.9)	<0.001	36(21.2)	61(35.9)	0.003
3m-mRS distribution			<0.001			<0.001
0	8(3.4)	18(10.6)		7(4.1)	18(10.6)	
1	32(13.6)	16(9.4)		26(15.3)	16(9.4)	
2	4(1.7)	27(15.9)		3(1.8)	27(15.9)	
3	16(6.8)	7(4.1)		8(4.7)	7(4.1)	
4	44(18.6)	23(13.5)		29(17.1)	23(13.5)	
5	64(27.1)	34(20.0)		46(27.1)	34(20.0)	
6	68(28.8)	45(26.5)		51(30.0)	45(26.5)	

PSM: propensity score matching; MT: mechanical thrombectomy; IVT: intravenous thrombolysis; mTICI: modified thrombolysis in cerebral infarction; sICH: symptomatic intracerebral hemorrhage; and mRS: modified Rankin Scale.

Table 3
Clinical outcomes of patients with different levels of renal function treated with MT and IVT + MT in the postmatched population.

	eGFR (45–59)			eGFR (<45)		
	MT group (n = 90)	IVT + MT group (n = 103)	*P*	MT group (n = 80)	IVT + MT group (n = 67)	*P*
mTICI (2b-3)	82(91.1)	97(94.2)	0.413	67(83.8)	63(94)	0.052
sICH	19(21.1)	20(19.4)	0.770	14(17.5)	7(10.4)	0.224
Good outcome (mRS 0–2)	20(22.2)	41(39.8)	0.009	16(20.0)	20(29.9)	0.167
3m-mRS distribution			<0.001			0.002
0	7(7.8)	8(7.8)		0(0)	10(14.9)	
1	13(14.4)	12(11.7)		13(16.3)	4(6.0)	
2	0(0)	21(20.4)		3(3.8)	6(9.0)	
3	3(3.3)	7(6.8)		5(6.3)	0(0)	
4	16(17.8)	12(11.7)		13(16.3)	11(16.4)	
5	27(30.0)	18(17.5)		19(23.8)	16(23.9)	
6	24(26.7)	25(24.3)		27(33.8)	20(29.9)	

eGFR: estimated glomerular filtration; MT: mechanical thrombectomy; IVT: intravenous thrombolysis; mTICI: modified thrombolysis in cerebral infarction; sICH: symptomatic intracerebral hemorrhage; and mRS: modified Rankin Scale.

Table 4
Risk factors associated with poor outcome at 90 days.

	Good outcome (n = 105)	Poor outcome (n = 301)	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
IVT	61(58.1)	109(36.2)	0.409(0.260–0.644)	<0.001	0.440(0.267–0.726)	0.001
Age	76(70–81)	81(76–85)	1.070(1.042–1.098)	<0.001	1.076(1.041–1.112)	<0.001
Female	46(43.8)	136(45.2)	1.057(0.676–1.654)	0.808		
Drinking status	15(14.3)	70(23.3)	1.818(0.989–3.341)	0.054	3.382(1.629–7.022)	0.001
Smoking status	26(24.8)	84(27.9)	1.176(0.706–1.958)	0.533		
Hypertension	85(81.0)	220(73.1)	0.639(0.369–1.107)	0.110		
Diabetes	16(15.2)	69(22.9)	1.654(0.911–3.003)	0.098	1.884(0.974–3.645)	0.060
Hyperlipidemia	14(13.3)	43(14.3)	1.083(0.566–2.073)	0.809		
CHD	31(29.5)	69(22.9)	0.710(0.431–1.168)	0.178		
AF	56(53.3)	162(53.8)	1.020(0.653–1.592)	0.931		
TIA	1(1.0)	8(2.7)	2.840(0.351–22.978)	0.328		
Stroke	30(28.6)	69(22.9)	0.744(0.450–1.228)	0.247		
mTICI(2b-3)	96(91.4)	272(90.4)	0.879(0.402–1.924)	0.748		
Admission NIHSS score	13(6.5–17)	17(13–23)	1.106(1.069–1.144)	<0.001	1.088(1.050–1.127)	<0.001
GFR	50(39–53)	46(36–53)	0.978(0.956–1.000)	0.054	1.010(0.983–1.038)	0.476
Onset-to-door time	100(51–165)	113(76–162)	1.003(0.999–1.006)	0.165		

IVT: intravenous thrombolysis; CHD: coronary heart disease; AF: arterial fibrillation; TIA: transient ischemic attack; GFR: glomerular filtration; mTICI: modified Thrombolysis in Cerebral Infarction; NIHSS: National Institutes of Health Stroke Scale; and GFR: glomerular filtration.

(0.267–0.726)], P = 0.001). In the logistic regression analysis, older age, drinking history, and higher NIHSS score at admission were independent risk factors for a worse outcome (Table 4).

4. Discussion

Our study confirmed that for LVO patients with CKD and indications for IVT, IVT combined with MT may improve their prognosis compared with direct MT. This is the first study to investigate whether bridging IVT should be performed before MT in LVO patients with CKD. A previous study observed noninferiority of direct MT to IVT bridging MT in LVO patients [8,24–27], but our study suggests that patients with CKD should not forego IVT before MT.

CKD affects 8%–16% of the population worldwide [28–30]. These patients are at higher risk for stroke and have a worse prognosis after stroke than individuals with normal kidney function [31,32]. Furthermore, a meta-analysis demonstrated that moderate-to-severe CKD is linked to elevated increased risks of ICH and poorer functional outcomes in patients with AIS undergoing IVT [17]. Furthermore, patients with CKD are prone to a higher risk of bleeding and a worse prognosis after MT [12–16]. Current studies have focused more on the poor prognosis caused by CKD in AIS patients after IVT or MT, but few studies have paid attention to the benefits of IVT/MT for CKD patients. Since these patients are at risk for a poor prognosis, we speculate that forgoing IVT before MT may reduce bleeding risk and improve outcomes, but this conclusion is a dramatic reversal from our previous assumptions. We speculate that the benefit from IVT bridging MT may be associated with hypercoagulability in CKD patients [33,34].

The clearance of alteplase is mediated primarily by the liver. An animal study using a rat model of bilateral nephrectomy showed that the pharmacokinetics and half-life of alteplase were not altered [35]; therefore, alteplase is considered safe for patients with impaired renal function. Studies have observed that patients with chronic renal insufficiency have a faster coagulation rate and increased clot strength in comparison to those with normal renal function, suggesting that patients with renal insufficiency are in a relatively hypercoagulable state [36]. In addition, renal impairment induces changes in hemostatic systems that can lead to a pro-thrombotic state [36,37]. CKD has a tendency to attenuate the reperfusion impact of IVT because of impaired release of endogenous tissue plasminogen activator. Additionally, it elevates levels of lipoprotein(a) and plasminogen activator inhibitor-1, further hindering plasminogen activation [38]. Furthermore, CKD contributes to increased endothelial dysfunction, resulting in arterial media stiffness, intimal plaque atherosclerosis, and vascular calcification [39,40], which increases the probability of vessel reocclusion after MT. Therefore, we speculate that the effect of IVT is more pronounced in CKD patients with a hypercoagulable state and a higher risk of thrombosis. After MT, patients who underwent IVT may have a reduced reocclusion rate due to the poorer intimal conditions of CKD patients. The above speculation based on the characteristics of CKD patients may explain the advantages of IVT bridging MT, but further research is needed to confirm this speculation.

In this study, LVO patients with CKD had a good prognosis (mRS 0–2) rate of 18.6%, which was lower than that of patients who underwent IVT bridging MT (35.9%). Compared with the good prognosis rate of 44.2% vs. 43% observed in the Chinese multicenter study conducted by Xu Tong et al. [9], LVO patients with CKD had a worse prognosis. This may be a secondary consequence of CKD by combining common traditional vascular risk factors, such as oxidative stress, chronic inflammation, cerebral hypoperfusion, mineral bone disease, anemia and systemic disease, combined with renal insufficiency [29,39,41]. However, these factors conversely highlight the benefits of IVT. The results of the subgroup analysis show that the IVT + MT group with eGFR (45–59) had a better prognosis than the MT group compared to the eGFR (<45) population. It is essential to note that the bridging group still exhibited a trend toward more favorable outcomes. In the study by Xu Tong et al., the incidence of sICH in MT patients was 7.6% [9], and we observed that the incidence of sICH in MT patients with CKD was 15.5%, confirming that CKD increases the risk of bleeding. However, our study grouping, matching analysis and subgroup analysis did not find that IVT increased the risk of bleeding after MT in CKD patients, which further confirmed that bleeding and poor prognosis were caused by vascular risk factors caused by CKD rather than IVT.

There are some limitations of our study. First, although this study included prospectively collected data and although all enrolled patients had LVO and met the criteria for IVT within 4.5 h of symptom onset, it was not a randomized study, and even with adjustment and matching, it is possible that potential confounders may not have been completely eliminated. Second, this analysis excluded patients who achieved recanalization or recovery after IVT and did not undergo MT. Third, in this study, renal function was assessed solely at the time of admission, but the definition of stages 3–5 CKD requires a persistent eGFR <60 mL/min/1.73 m^2 for 3 months.

5. Conclusion

Our study found that in LVO patients with CKD and indications for IVT, IVT bridging MT improves the prognosis of patients compared with direct MT.

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Ethics approval and consent to participate

This study was reviewed and approved by the medical ethics committees of Jingjiang People's Hospital and Shaoxing Second

Hospital, with approval numbers 2022-KY-109-01 and 2022LC00091, respectively. The comprehensive treatment plan was thoroughly communicated during hospitalization, and written informed consent was secured from either the patient or their caregiver.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Jiali Niu: Writing – review & editing, Writing – original draft, Software, Methodology, Data curation, Conceptualization. **Kaixia Chen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Jian Wu:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Data curation, Conceptualization. **Li Ma:** Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Guangyu Zhao:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Yunlong Ding:** Writing – review & editing, Visualization, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yunlong Ding reports financial support was provided by Taizhou Municipal Science and Technology Bureau (CN). Yunlong Ding reports financial support was provided by Research Fund of Jingjiang People's Hospital.

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