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INTRAVENOUS RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR IN ACUTE ISCHEMIC STROKE: FACTORS AFFECTING CLINICAL OUTCOMES

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ABSTRACT

Stroke is one of the leading causes of disability and death worldwide. Thrombolytic therapy using intravenous recombinant tissue plasminogen activator (rt-PA) is the recommended treatment. However, functional outcomes vary due to various factors. Objective: The aim of this study was to analyze the factors affecting clinical outcomes of acute ischemic stroke patients treated with intravenous rt-PA. Method: This research was a retrospective study with a total sample of 52 acute ischemic stroke patients who received intravenous rt-PA therapy. The research variable data were collected from medical records, then statistically analyzed and correlated with patient clinical outcomes. Data from medical records were collected based on inclusion and exclusion criteria, then statistically analyzed using STATA 13. Univariate analysis is presented in a list of categories according to the research variables determined by percentage (standard error). Bivariate analysis was tested using simple logistic regression and multivariate analysis using multiple logistic regression. Results: The results of this study showed that patient clinical outcomes are not significantly impacted by risk factors (age, gender, prior stroke history, comorbidities), COVID-19 vaccination, onset and severity of stroke, HCTS onset, dosage, or onset therapy. The side effects of intravenous rt-PA have a significant impact on patient clinical outcomes, including therapy response and discharge condition (p = 0.008, p < 0.05, and p = 0.012, OR 34.073 (95% CI 2.165 - 536.147)), but do not affect the length of hospital stay. Conclusions: In considering the other factors, the study indicates that patients experiencing adverse effects from intravenous rt-PA have worse clinical outcomes.

Keywords: acute ischemic stroke; clinical outcome; intravenous rt-PA

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INTRODUCTION

Stroke remains one of the most prevalent diseases causing morbidity and mortality in Indonesia. The Basic Health Research data from 2018 shows that 1 in 100 people in Indonesia suffer from a stroke (BPPK, 2019). Based on data from the World Health Organization (WHO) in 2019, there were 132 deaths per 100,000 people in Indonesia due to stroke ((WHO, 2019). Ischemic strokes account for 70% of all stroke incidents, while the remaining are hemorrhagic and subarachnoid strokes (Benyamin et al., 2019). Acute ischemic stroke is characterized by the sudden loss of blood flow to a specific area of the brain, resulting in the loss of neurological function. This is caused by thrombosis or embolism that blocks the cerebral blood vessels supplying certain areas of the brain (Phipps & Cronin, 2020).

The treatment of acute ischemic stroke involves a multidisciplinary approach that previously always included critical care consultant specialists. Before 1990, the treatment options for acute ischemic stroke were limited to symptomatic management, secondary prevention, and rehabilitation. After that, a revolutionary discovery occurred with the approval of intravenous recombinant tissue plasminogen activator (rt-PA) by the Federal Drug Administration (FDA)

as a therapy for acute ischemic stroke in 1995 (NIDN, 1995). Since then, there has been significant progress in the treatments available to reduce the effects of acute ischemic stroke. When applied to the right patients, intravenous thrombolysis with rt-PA has been proven to improve outcomes in acute ischemic stroke by removing the blockage and restoring blood flow to the affected area of the brain. Intravenous rt-PA has become one of the main therapies for acute ischemic stroke with an onset of less than 4.5 hours and can provide good outcomes for stroke patients who meet the inclusion criteria (Derraz et al., 2023; Xu et al., 2021; Cooray et al., 2021). Although proven effective, the use of intravenous thrombolysis is not without the risk of side effects. The potential for serious side effects, especially intracerebral hemorrhage, poses significant challenges for its implementation (Luo et al, 2016; Frey et al., 2020; Yu et al., 2021). Therefore, it is important to consider the benefits and risks of intravenous thrombolysis side effects in clinical decision-making. The aim of this study was to analyze the factors affecting clinical outcomes of acute ischemic stroke patients treated with intravenous rt-PA.

METHOD

This study is a cross-sectional retrospective study examining patients with acute ischemic stroke who receiving intravenous rt-PA at Central General Hospital of Soeradji Tirtonegoro from April 2022 to October 2024. The sample size was calculated using total sampling and purposive sampling, with inclusion criteria being those with a 4.5-hour onset and receiving intravenous thrombolytic therapy. Exclusion criteria included those who left against medical advice, did not receive thrombolysis due to medical reasons, and did not have any malignancies, autoimmune diseases, or blood disorders. Secondary data was collected from medical records, including demographic data and the research variables. The factors assessed in this study were age, gender, prior stroke history, comorbidities (hypertension, diabetes mellitus, dyslipidemia, heart disease, and chronic kidney disease), COVID-19 vaccination, onset and severity of stroke, onset of Head Computed Tomography Scan (HCTS), and intravenous rt-PA therapy (onset, dosage, side effects). Clinical outcomes were assessed based on therapy response (changes in National Institutes of Health Stroke Scale (NIHSS) scores before and after therapy), length of hospital stay, and patient condition at discharge. Data analysis was carried out using STATA 13 for statistical analysis, including univariate, bivariate, and multivariate analyses. with logistic regression. Univariate analysis is presented in a list of categories according to the research variables determined by percentage (standard error). Bivariate analysis was tested using simple logistic regression and multivariate analysis using multiple logistic regression. The research has passed ethical review by the Health Research Ethics Committee of 'Aisyiyah University Surakarta (No. 227/VIII/AUEC/2024).

RESULT

In this study, 55 subjects of acute ischemic stroke patients who were recommended for intravenous thrombolysis were collected for total sampling. However, the number of samples that met the inclusion and exclusion criteria was 52 samples. Three samples were eliminated because the patient had an autoimmune condition (Systemic Lupus Erythematosus/SLE), intra-arterially administered thrombolysis, and were not given intravenous rt-PA due to the medication was unavailable. Following the collection of the 52 samples, a patient registry was made based on the variable or sub-variable criteria required for the research's analysis.

The characteristics of the respondents in this study are distributed as follows (Table 1): majority are male (57.69%), over 60 (57.69%), have no history of stroke (63.46%), have comorbid HT (88.46%), have no DM (71.15%), have no dyslipidemia (53.85%), have no heart disease (82.69%), and have no chronic kidney disease (100%). A total of 80.77% of the respondents evaluated have received a COVID-19 vaccination, with the third dosage being the largest number (42.31%). The onset of stroke mostly occurred between 1-3 hours (55.77%) with a moderate stroke severity level (65.28%). The response time for HCTS mostly met the

standard (< 30 minutes), which is 69.23%. However, the onset of intravenous rt-PA therapy administration is still mostly below standard (> 60 minutes), at 90.38%. Alteplase is the only type of regimen used with varying therapeutic doses, where the majority use 0.9 mg/kgBW (55.77%) with an incidence of side effects around 25%. Acute ischemic stroke patients who received intravenous rt-PA mostly showed an improvement in therapy response (86.54%) with a length of hospital stay around 0-7 days (69.23%) and were discharged in a living condition (86.54%). The study surveyed 57.69% of respondents, primarily male and over 60, with no stroke history, comorbidities, or chronic kidney disease. As many as 80.77% of respondents received COVID-19 vaccinations. Stroke onset was 1–3 hours, with moderate severity. Response time for HCTS met the standard, but intravenous rt-PA therapy onset was below standard. Alteplase was the only regimen used, with varying doses and side effects. Acute ischemic stroke patients showed improvement in therapy response.

Table 1. Respondent characteristics (n= 52)

	naracteristics (n= 52)	0/
Respondent characteristics	f	%
Age (years)		1.00
< 40	1	1.92
40-60	21	40.39
> 60	30	57.69
Gender		
Male	30	57.69
Female	22	42.31
Prior Stroke History		
Yes	19	36.54
No	33	63.46
Comorbidities		
Hypertension (HT)		
Yes	46	88.46
No	6	11.54
Diabetes Mellitus (DM)		
Yes	15	28.85
No	37	71.15
Dyslipidemia		
Yes	24	46.15
No	28	53.85
Heart Disease		
Yes	9	17.31
No	43	82.69
Chronic Kidney Disease		
Yes	0	0
No	52	100
COVID-19 Vaccination		
Yes	42	80.77
Dose 1	4	7.69
Dose 2	16	30.77
Dose 3	22	42.31
No	7	13.46
N/A (No Data)	3	5.77
Onset of Stroke (Hours)	-	
< 1	15	28.85
1-3	29	55.77
> 3-4.5	8	15.38
Severity of Stroke (NIHSS)		15.50
Mild (<5)	2	3.85
Moderate (5-15)	34	65.38
Severe (16-20)	11	21.15
Very Severe (> 20)	5	9.62
Onset of HCTS (minutes)	<i>J</i>	7.02
≤ 30	36	69.23
> 30	16	30.77
· JU	10	30.77

Respondent characteristics	f	%
Intravenous rt-PA Therapy		
Regimen of rt-PA		
Alteplase	52	100
Non Alteplase	0	0
Onset of Therapy (minutes)		
≤ 60	5	9.62
> 60	47	90.38
Dosage of rt-PA		
0.6 mg/kgBB	23	44.32
0.9 mg/kgBB	29	55.77
Side Effect of rt-PA		
Yes	13	25
No	39	75
Clinical Outcome		
Therapy Response (NIHSS)		
Improvement	45	86.54
Deterioration	7	13.46
Length of Hospital Stay (days)		
0-7	36	69.23
> 7	16	30.77
Discharge Condition		
Recover (Alive)	45	86.54
Dead	7	13.46

Table 2.
Bivariate Logistic Regression Analysis of Factors Influencing Respondents' Clinical Outcomes

Variables/ Subvariables	P-value (Therapy	P-value (Length of	P-value
	Response)	Hospital Stay)	(Discharge
			Condition)
Age (years)	0.141	0.546	0.141
Gender	0.435	0.099	0.435
Prior Stroke History	0.640	0.183	0.640
Comorbidities			
• HT	0.807	0.438	0.807
• DM	0.376	0.799	0.376
 Dyslipidemia 	0.851	0.156	0.851
 Heart Disease 	0.821	0.855	0.821
 Chronic Kidney Disease 	=	=	-
COVID-19 Vaccination	0.613	0.140	0.613
COVID-19 Vaccination Dose	0.811	0.192	0.811
Onset of Stroke	0.234	0.595	0.234
Severity of Stroke	0.062	0.088	0.062
Onset of HCTS	0.329	0.960	0.329
Regimen of rt-PA	-	-	-
Onset of Therapy	-	-	-
Dosage of rt-PA	0.378	0.963	0.378
Side Effect of rt-PA	0.008	0.490	0.008

Based on bivariate analysis, Table 2 shows that only rt-PA side effects have a significant impact on patient clinical outcomes, specifically therapy response (p = 0.008, p < 0.05) and discharge condition (p = 0.008, p < 0.05). However, the length of hospital stay was not substantially impacted by the side effects of rt-PA. The variables comorbid chronic kidney disease (CKD), regimen of rt-PA, and onset of therapy could not be analyzed due to the lack of data variability. Multiple logistic regression is used in multivariate analysis to determine which variables have a significant impact on patient clinical outcomes. A significance level of 5% is applied in the decision-making criteria; a p-value of less than 0.05 can be considered significantly influential. The largest Odds Ratio (OR) is used to identify the variable with the greatest influence. A variable must have p < 0.25 in the bivariate analysis using simple logistic regression in order to be included in the multivariate analysis.

Table 3.

Multivariate Logistic Regression Analysis of Factors Influencing Therapy Response

Variables/ Subvariables	Odds Ratio	P-value	95% CI
Age (years)	12.085	0.084	0.715-204.277
Onset of Stroke	2.052	0.402	0.382-11.013
Severity of Stroke	4.895	0.053	0.983-24.377
Side Effect of rt-PA	34.073	0.012	2.165-536. 147

Table 4.

Multivariate Logistic Regression Analysis of Factors Influencing Length of Hospital Stay

Variables/ Subvariables	Odds Ratio	P-value	95% CI
Gender	0.168	0.045	0.029-0.964
Prior Stroke History	2.168	0.355	0.421-11.165
Dyslipidemia	0.502	0.368	0.112-2.246
COVID-19 Vaccination	7.483	0.236	0.269-
			208.223
COVID-19 Vaccination Dose	0.927	0.903	0.271-3.163
Severity of Stroke	1.827	0.232	0.680-4.9031

Table 5.

Multivariate Logistic Regression Analysis of Factors Influencing Discharge Condition

Variables/ Subvariables	Odds Ratio	P-value	95% CI
Age (years)	12.085	0.084	0.715-204.277
Onset of Stroke	2.052	0.402	0.382-11.013
Severity of Stroke	4.895	0.053	0.983-24.377
Side Effect of rt-PA	34.073	0.012	2.165-536. 147

The results of the multivariate analysis above (Tables 3 and 5) show that only the side effects of rt-PA have a significant impact on therapy response and discharge condition, with p = 0.012 (p < 0.05), OR 34.073 (95% CI 2.165 – 536.147). Table 4 shows that the only factor influencing the length of hospital stay is gender, with p = 0.045 (p < 0.05). The results of the bivariate analysis, which indicated that the gender variable had no effect on the length of hospital stay when considered alone, differ from those of this multivariate analysis. When considering the variables of previous stroke history, dyslipidemia, vaccination history, and COVID-19 vaccine doses, it turns out that gender can affect the length of hospital stay. Women are less likely to stay in treatment for longer than seven days.

DISCUSSION

Demographics of Respondents

According to the study's characteristics of acute ischemic stroke patients, the majority of cases (57.69%) happened in those over 60, with an average age of 61.54 years. Similar results were found in the study by Alnaami et al. (2021), which found that 45.7% of stroke patients were between the ages of 60 to 80, and the average age of ischemic stroke patients was 62.6 ± 17 years. Another study revealed that the majority of ischemic stroke patients were in the 61-75 age range, with 52 individuals (56.5%) and an average age of 62 (Marja, 2024). This indicates that the risk of ischemic stroke increases in direct proportion to age. The underlying cause of this is the aging process, which leads to a decrease in the homeostasis function of the brain blood vessels and a reduction in endothelial elasticity due to the thickening of the tunica intima, resulting in atherosclerosis, thereby reducing blood flow to the brain (Mongkau et al., 2022; Marja, 2024) While age had no effect on the clinical outcomes of patients in this study, previous research has demonstrated that a one-year increase in age significantly increases the mortality rate. Along with the higher death rate, the study also shown that in patients with acute ischemic stroke and COVID-19, growing older is strongly linked to worse functional clinical outcomes (Dmytriw et al, 2021).

The results of this study show that the characteristics of patients with acute ischemic stroke are more prevalent in males (57.69%) compared to females (42.31%). Similar findings were also found in a study conducted in Saudi Arabia, where the majority of acute ischemic stroke patients were Saudi citizens (91.5% had less than a university degree, and 6.4% smoked), and the prevalence was higher among men (62.6%) than women (37.4%) (Alnaami et al., 2021). Similar proportions are seen in other research, where men outnumber women (56.2%) (Alawneh et al., 2022). The study show that acute ischemic stroke occurs more frequently in men due to their lifestyle, which includes higher rates of smoking and alcohol consumption, thereby increasing the risk and severity of stroke. Men are generally twice as likely to suffer a stroke in early adulthood compared to women, while the incidence of stroke is higher in men, averaging 25-30% during productive age (Alnaami et al., 2021; Maharani, 2021). However, other studies show that the distribution of patients with ischemic stroke is higher in females (50.51%), especially in atherothrombotic stroke (58.6%) and lacunar stroke (66.7%), whereas in thromboembolic stroke, the proportion of females (33.3%) is lower compared to males (66.7%). Based on the results of a meta-analysis study by Poorthuis et al. (2017), women are at a higher risk of stroke due to hormonal risk factors and pregnancy complications (such as preeclampsia). The hormone estrogen in women plays a role in increasing high-density lipoprotein (HDL) and decreasing low-density lipoprotein (LDL), thereby preventing atherosclerosis. However, in the menopausal condition, there is no protection against the process of atherosclerosis, so the risk of ischemic stroke increases in elderly women (Poorthuis et al., 2017; Maharani et al., 2021).

In this study, only 36.54% of respondents had a prior stroke history, with 95.45% being ischemic/infarction strokes and 4.55% being ICH. The results of this study indicate that there is no influence of a previous stroke history on the clinical outcomes of patients. However, based on the study by Qin et al. (2020), patients with a history of stroke have a higher risk of recurrence and mortality compared to patients without a history of stroke within 6-12 months during hospitalization, although significant differences were only found in the mortality rate within 3 months after adjusting for various risk factors. On the other hand, in the follow-up phase, patients without a history of stroke had a higher risk of recurrence and mortality at 12 months compared to patients with a history of stroke at 3 months.

Factors Influencing Respondents' Clinical Outcomes

Intravenous rt-PA thrombolysis has been widely acknowledged for its safety and effectiveness in treating acute ischemic stroke, and national guidelines in numerous nations recommend its use. Clinical results after rt-PA thrombolysis differed from patient to patient. Since the factors influencing clinical outcomes are still poorly understood, it was predicted that this retrospective analysis of 52 patients treated with thrombolysis would identify some of the factors that may affect the clinical outcome of thrombolytic therapy. This would help physicians better screen patients for thrombolytic therapy, maximize the effectiveness of rt-PA thrombolysis, and provide clinical evidence for prognosis prediction in patients receiving thrombolysis.

Side Effect of Intravenous rt-PA in Acute Ischemic Stroke Clinical Outcome

Overall, the study's findings show that only the intravenous rt-PA side effects significantly affect patient clinical outcomes among the 17 variables and sub-variables analyzed. Intravenous rt-PA side effects were found to have a significant impact on the therapy response and the patient's discharge condition in both bivariate (p = 0.008, p < 0.05) and multivariate analyses (p = 0.012, p < 0.05). The side effects of intravenous rt-PA are a variable that strongly influences the clinical outcomes of patients with acute ischemic stroke, with an OR of 34.073 (95% CI 2.165 – 536.147), both in terms of therapeutic response and the patient's

discharge condition. In comparison to patients who do not have side effects, the value shows that patients who experience side effects of intravenous thrombolysis have a 34 times increased risk of deterioration and mortality. Twenty-five percent of participants in this trial experienced intravenous rt-PA side effects of any variety. However, 53.85% of patients who experienced side effects from intravenous rt-PA had a worsening condition and death. The following side effects from intravenous thrombolysis were observed in this study: gum bleeding (30.77%), bradycardia (15.38%), decreased consciousness (15.38%), gastrointestinal bleeding (7.69%), urethral bleeding (7.69%), intracerebral hemorrhage (ICH) (7.69%), intraventricular hemorrhage (IVH) (7.69%), and severe headache (7.69%). The cause of the decreased consciousness in this study has not yet been evaluated whether it was due to intracerebral hemorrhage or other causes because the patient did not have a repeat HCTS.

Several studies have shown that intravenous rt-PA administration also causes significant side effects, although it has been proven to improve survival rates and functional independence in acute ischemic stroke. The main side effects include symptomatic intracranial hemorrhage (sICH), orolingual angioedema, acute hypotension, and systemic bleeding. In clinical trials, sICH occurred in 6.4% of patients, whereas in real-world clinical practice, this figure ranges from 0% to 5.9%. Orolingual angioedema, although rare, can be fatal if not treated promptly (Jauch et al., 2010). Other studies have shown that rt-PA therapy can cause various types of complications, including bleeding (intracerebral and systemic hemorrhage), reperfusion injury with edema, angioedema, seizures, and neurotoxicity in the brain. Ineffective thrombolysis can also cause reocclusion and secondary embolization (Balami et al., 2013). These complications can be life-threatening in animal studies and serious in clinical settings, resulting in prolonged stays, increased medical treatment, hospital stays, and delayed rehabilitation (Balami et al., 2013; Dong et al., 2016).

Mechanism of Intravenous rt-PA Side Effect

In this study, all respondents used alteplase, where for acute ischemic stroke, intravenous thrombolysis with alteplase is the standard medical intervention. Alteplase is the recombinant form of tissue plasminogen activator (t-PA), which is found naturally in the endothelium and other vascular cells. Plasminogen is converted to plasmin by alteplase, which cleaves the arginine-valine bond at positions 560 and 561. Plasmin, an active protease, breaks down the thrombus into fibrin degradation products (FDP), which dissolves the blood clot. Lysine side chains bind fibrin monomers together to create a thrombus (Warach et al., 2020; Katta et al., 2025). The mechanism of the side effect is related to the fibrinolytic properties of rt-PA, which can cause damage to the brain blood vessels. Additionally, rt-PA can increase the production of matrix metalloproteinase-3 (MMP-3) through the LRP/NF-κB pathway in endothelial cells, which contributes to an increased risk of intracranial hemorrhage (Liu et al., 2022). Rt-PA causes neurotoxicity by cleaving the N-methyl-D-aspartate (NMDA) NR1 subunit, which increases excitatory toxicity and dangerous calcium excess. Rt-PA can either directly or indirectly stimulate a large amount of ROS, which releases iron and thrombin from blood clots and raises the expression of 4-HNE in blood vessels inside the cerebral infarct. Moreover, it has been demonstrated that Rt-PA causes acute direct cytotoxicity in blood vessels and aids in the breakdown of the microvascular basal lamina (Liu et al., 2022). Additionally, rt-PA can increase the production of reactive oxygen species (ROS) and damage the basal layer of the microvasculature, contributing to cerebral edema and bleeding (Katta et al., 2025).

Other studies have shown that rt-PA increased mortality rate probably through disrupting BBB, aggravating brain edema and inducing intracerebral hemorrhage. Preventing or minimizing these complications can be achieved through adherence to treatment guidelines and early detection. The clinical impact of these side effects can include prolonged treatment in the intensive care unit, increased medical care needs, extended hospital stays, delayed

rehabilitation, and increased morbidity and mortality (Dong et al., 2016; Katta et al., 2025). Therefore, it is important to understand the potential side effects and to monitor and manage them appropriately to minimize the negative impact on patients with acute ischemic stroke.

Influence of Gender in Acute Ischemic Stroke Clinical Outcome

In addition to the side effects of intravenous rt-PA, interesting results show a significant influence of gender on the clinical outcomes of patients with acute ischemic stroke, specifically the length of hospital stay (LOS) in multivariate analysis (p = 0.045 (p < 0.05), OR 0.168 (95% CI 0.029-0.964)). In the bivariate analysis, gender did not have a significant impact on patient clinical outcomes, but when considering other variables (prior stroke history, dyslipidemia, vaccination, and dose of COVID-19), gender can affect the length of stay. The female gender is less likely to have a length of stay longer than 7 days compared to males. The research results show that 40% of male respondents have a LOS > 7 days, whereas only 18.18% of female respondents have a LOS > 7 days. Thus, it can be concluded that men are at a higher risk of having a longer length of stay compared to women. This is likely because women (22.72%) have a lower proportion of adverse events compared to men (26.67%), although not significantly different.

Other studies have also shown gender differences in the clinical outcomes of patients with acute ischemic stroke who received intravenous thrombolysis. The study showed that there are gender differences in risk factors, stroke etiology, and treatment timelines for patients with acute ischemic stroke treated with rt-PA. However, both genders showed similar improvements in neurological and functional outcomes. Both sexes have different predictors of poor outcome and mortality: bleeding for females, DM and longer door-to-needle time for males (Khedr et al., 2024). On the other side, based on research using data from the Asian Acute Stroke Registries, women have a worse prognosis compared to men after receiving rt-PA therapy for acute ischemic stroke, which worsens with age, marked by increased stroke severity, incidence of atrial fibrillation, and cardioembolic stroke in those over 70 years old (Wang et al., 2020). A stroke registry-based study in Sweden with a total of 2245 patients also showed that women had a higher severity of stroke compared to men. However, regarding the 3-month functional outcome, males benefited more from thrombolysis, whereas females benefited more from thrombectomy. Additionally, women more frequently experience reinfarction compared to men (Mavridis et al., 2024).

The reason for the difference in stroke outcomes between males and females is not well understood. One possible explanation is that females have higher levels of plasminogen activator inhibitor-1 (PAI-1) at the time of stroke, which could potentially inhibit tPA administered for thrombolysis and decrease thrombolytic potential (Kain et al., 2001; Mavridis et al., 2024). Another possibility is the cardioprotective and neuroprotective effects of estrogen, which may lower PAI-1 levels and increase fibrinolytic potential. Estradiol also exerts a neuroprotective effect after a cerebral infarction. Additionally, estradiol reference values for postmenopausal females are lower than those of males, potentially exposing them to worse outcomes (Mavridis et al., 2024). Naturally, our study has several limitations: (1) it is a retrospective study; (2) it only collected a small number of cases from a small region; (3) a relatively small sample size may have affected the statistical power and generalizability of the findings. So, it is possible that there may be other factors that could influence the outcome of acute ischemic stroke treated with intravenous rt-PA thrombolysis. To address this limitation, future studies should use cohorts with larger samples and better collect more comprehensive clinical outcome factors.

CONCLUSION

It can be concluded that the side effects of thrombolysis have a significant impact on the clinical outcomes of patients, such as therapy response and discharge condition, but do not affect the length of hospital stay. This study shows that patients with acute ischemic stroke who experience thrombolysis side effects have a higher risk of condition deterioration up to death compared to patients without thrombolysis side effects. Interestingly, when considering other factors, gender has a significant impact on the length of hospital stay, with men being at higher risk of having a longer treatment duration compared to women.

REFERENCES

- Alawneh KZ, Qawasmeh MA, Raffee LA, Al-Mistarehi AH (2022). Ischemic stroke demographics, clinical features and scales and their correlations: an exploratory study from Jordan. Future Sci OA, 2022 Aug;8(7):FSO809. Available from: http://dx.doi.org/10.2144/fsoa-2022-0017.
- Alnaami I, Alhazzani A, Alburaidi I, Alkhayri M, Dibssan H, Alqahtani MS, et al. (2021). Demographic characteristics and types of stroke in Southwestern Saudi Arabia, and the potential demand of neuro endovascular specialists. Neurosciences (Riyadh), 2021 Jan; 26(1):62–8. Available from: http://dx.doi.org/10.17712/nsj.2021.1.20200104.
- Badan Penelitian dan Pengembangan Kesehatan (BPPK) (2019). Laporan Nasional RISKESDAS 2018. Jakarta: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan (LPB) Kementerian Kesehatan Republik Indonesia. [cited 2025 May 07]. Available from: https://repository.badankebijakan.kemkes.go.id/id/eprint/3514/1/Laporan%20Riskesdas% 202018%20Nasional.pdf.
- Balami JS, Sutherland BA, Buchan AM. (2013). Complications associated with recombinant tissue plasminogen activator therapy for acute ischaemic stroke. CNS Neurol Disord Drug Targets. 2013 Mar;12(2):155-69. doi: 10.2174/18715273112119990050. PMID: 23394532.
- Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. (2019). Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation, Mar 5;139(10):e56–528. Available from: http://dx.doi.org/10.1161/CIR.00000000000000659.
- Cooray C, Karlinski M, Kobayashi A, Ringleb P, Kõrv J, Macleod MJ, et al. (2021). Safety and early outcomes after intravenous thrombolysis in acute ischemic stroke patients with prestroke disability. Int J Stroke, 2021 Aug;16(6):710–8. Available from: http://dx.doi.org/10.1177/1747493020954605.
- Derraz I, Moulin S, Gory B, Kyheng M, Arquizan C, Costalat V, et al. (2023). Endovascular thrombectomy outcomes with and without intravenous thrombolysis for large ischemic cores identified with CT or MRI. Radiology, 2023 Oct;309(1):e230440. Available from: http://dx.doi.org/10.1148/radiol.230440.
- Diedler J, Ahmed N, Sykora M, Uyttenboogaart M, Overgaard K, Luijckx GJ, et al. (2010). Safety of intravenous thrombolysis for acute ischemic stroke in patients receiving antiplatelet therapy at stroke onset. Stroke, 2010 Feb;41(2):288–94. Available from: http://dx.doi.org/10.1161/STROKEAHA.109.559724.

- Dmytriw AA, Dibas M, Schirmer CM, Settecase F, Heran MKS, Efendizade A, et al. (2021). Age and Acute Ischemic Stroke Outcome in North American Patients With COVID-19. J Am Heart Assoc, 2021 Jul 20; 10(14):e021046. Available from: http://dx.doi.org/10.1161/JAHA.121.021046.
- Dong MX, Hu QC, Shen P, Pan JX, Wei YD, Liu YY, Ren YF, Liang ZH, Wang HY, Zhao LB, Xie P. (2016). Recombinant Tissue Plasminogen Activator Induces Neurological Side Effects Independent on Thrombolysis in Mechanical Animal Models of Focal Cerebral Infarction: A Systematic Review and Meta-Analysis. PLoS One. 2016 Jul 7;11(7):e0158848. doi: 10.1371/journal.pone.0158848. PMID: 27387385; PMCID: PMC4936748.
- Frey BM, Boutitie F, Cheng B, Cho TH, Ebinger M, Endres M, Fiebach JB, Fiehler J, Ford I, Galinovic I, Königsberg A, Puig J, Roy P, Wouters A, Magnus T, Thijs V, Lemmens R, Muir KW, Nighoghossian N, Pedraza S, Simonsen CZ, Gerloff C, Thomalla G; WAKE-UP investigators (2020). Safety and efficacy of intravenous thrombolysis in stroke patients on prior antiplatelet therapy in the WAKE-UP trial. Neurol Res Pract. 2020 Nov 20:2:40. doi: 10.1186/s42466-020-00087-9. PMID: 33324940; PMCID: PMC7678217.
- Gebara OC, Mittleman MA, Sutherland P, et al. (1995). Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. Circulation. 91(7): 1952-1958.
- Huang YH, Zhuo ST, Chen YF, Li MM, Lin YY, Yang ML, Chen ZJ, et al. (2013). Factors influencing clinical outcomes of acute ischemic stroke treated with intravenous recombinant tissue plasminogen activator. Chinese Medical Journal 126(24):p 4685-4690, December 20, 2013. DOI: 10.3760/cma.j.issn.0366-6999.20132354.
- Jauch EC, Cucchiara B, Adeoye O, Meurer W, Brice J, Chan YF, Gentile N, and Hazinski MF. (2010). 2010 American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation, Volume 122, Issue 18_suppl_3, 2 November 2010; Pages S818-S828. https://doi.org/10.1161/CIRCULATIONAHA.110.971044.
- Katta A., Jillella T. (2025). Tissue Plasminogen Activator in Stroke: A Review on Medical Management of Stroke and Mechanism of Action of TPA, Contraindications, Time Sensitivity, Journal of Clinical Cardiology and Cardiology Research, BioRes Scientia Publishers. 4(1):1-6. DOI: 10.59657/2837-4673.brs.25.042.
- Khedr EM, Abo-Elfetoh N, Hasan AM, et al. (2024). The impact of sex differences on stroke risk factors and 3-month outcomes in patients receiving thrombolytic therapy for acute ischemic stroke. Egypt J Neurol Psychiatry Neurosurg 60:126. https://doi.org/10.1186/s41983-024-00900-1.
- Liu C, Xie J, Sun S, Li H, Li T, et al. (2022). Hemorrhagic Transformation After Tissue Plasminogen Activator Treatment in Acute Ischemic Stroke. Cell Mol Neurobiol. 42(3):621-646.
- Luo S, Zhuang M, Zeng W, Tao J (2016). Intravenous Thrombolysis for Acute Ischemic Stroke in Patients Receiving Antiplatelet Therapy: A Systematic Review and Meta-analysis of 19 Studies. J Am Heart Assoc. 2016 May 20;5(5):e003242. doi: 10.1161/JAHA.116.003242. PMID: 27207999; PMCID: PMC4889195.

- Maharani T, Juli C, Hermawan A (2021). Karakteristik luaran klinis neurologis pasien stroke iskemik berdasarkan NIHSS. J Kedokt Syiah Kuala, 2021 Dec 23;21(3). Available from: https://jurnal.usk.ac.id/JKS/article/view/20646.
- Marja FA (2024). Gambaran karakteristik pasien penyakit stroke di ruang rawat inap rumah sakit umum daerah cut meutia aceh utara tahun 2021 dan 2022. Aceh: Fakultas Kedokteran Universitas Malikussaleh Lhokseumawe. Available from: https://rama.unimal.ac.id/id/eprint/714/5/Full-Text.pdf.
- Mavridis A, Reinholdsson M, Sunnerhagen KS, Abzhandadze T. (2024). Predictors of functional outcome after stroke: Sex differences in older individuals. J Am Geriatr Soc. 2024; 72(7): 2100-2110. doi:10.1111/jgs.18963.
- Mongkau L, Langi FLFG, Kalesaran AFC (2022). Studi ekologi prevalensi diabetes melitus dengan stroke di Indonesia. Prepotif: Jurnal Kesehatan Masyarakat, 2022 Jun 25; 6(2):1156–62. Available from: http://journal.universitaspahlawan.ac.id/index.php/prepotif/article/view/4027
- National Institute of Neurological Disorders (NIND) and Stroke rt-PA Stroke Study Group Massachusetts Medical Society. (1995). Tissue plasminogen activator for acute ischemic stroke. N Engl J Med, 333(24):1581–7. Available from: http://dx.doi.org/10.1056/NEJM199512143332401.
- Phipps MS, Cronin CA (2020). Management of acute ischemic stroke. BMJ, 2020 Feb 13;368:16983. Available from: http://dx.doi.org/10.1136/bmj.16983.
- Poorthuis MHF, Algra AM, Algra A, Kappelle LJ, Klijn CJM (2017). Female- and male-specific risk factors for stroke: A systematic review and meta-analysis. JAMA Neurol, 2017 Jan 1;74(1):75–81. Available from: http://dx.doi.org/10.1001/jamaneurol.2016.3482.
- Qin H, Wang P, Zhang R, Yu M, Zhang G, Liu G, Wang Y. (2020). Stroke history is an independent risk factor for poor prognosis in ischemic stroke patients: Results from a large nationwide stroke registry. Curr Neurovasc Res. 2020;17(4):487-494. doi: 10.2174/1567202617666200817141837. PMID: 32807054; PMCID: PMC8493791. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8493791/.
- Wang X, Carcel C, Wang R, et al. (2020). Worse prognosis in women, compared with men, after thrombolysis: An individual patient data pooling study of Asian acute stroke registries. International Journal of Stroke. 2020;16(7):784-791. doi:10.1177/1747493020938307.
- Warach SJ, Dula AN, Milling TJ Jr. (2020). Tenecteplase Thrombolysis for Acute Ischemic Stroke. Stroke. 51(11):3440-3451.
- World Health Organization (2019). Health data overview for the Republic of Indonesia [Internet]. [cited 2024 Jul 22]. Available from: https://data.who.int/countries/360.
- Xu M, Guo J, Tao X, Zeng K (2021). The Efficacy and safety of intravenous thrombolysis in older chinese patients with acute ischemic stroke. Neurol India, 2021 Jan-Feb;69(1):91–6. Available from: http://dx.doi.org/10.4103/0028-3886.310086.
- Yang SH, Shi J, Day AL, Simpkins JW. (2000). Estradiol exerts neuroprotective effects when administered after ischemic insult. Stroke 31(3): 745-750; discussion 9–50, 750.

Yu Y, Zhang FL, Qu YM, Zhang P, Zhou HW, Luo Y, et al. (2021). Intracranial calcification is predictive for hemorrhagic transformation and prognosis after intravenous thrombolysis in non-cardioembolic stroke patients. J Atheroscler Thromb, 2021 Apr 1;28(4):356–64. Available from: http://dx.doi.org/10.5551/jat.55889.