INTRODUCTION

Acute ischemic stroke (AIS) is the most common type of stroke and the vital cause of death and disability in the world (Murray et al., 2012; Sousa et al., 2017). Among the treatment methods of AIS, intravenous thrombolysis is recognized as the best option (Hacke et al., 2008; Powers et al., 2018). As the most commonly used thrombolytic drug, recombinant tissue plasminogen activator (rt-PA) is...
considered to effectively improve the outcomes of AIS patients who are treated within 4.5 hr (Pan et al., 2014; Prabhakaran, Ruff, & Bernstein, 2015).

Although the outcomes of most AIS patients tend to be improved after intravenous thrombolytic therapy, there is still certain portion of patients experiencing early neurological deterioration (END). Unfortunately, no definition of END has been unified up to now. Most studies define END as ≥4-point increase in National Institutes of Health Stroke Scale (NIHSS) between admission and 24 hr (Chi & Chan, 2017; Ong, Wong, Wu, & Su, 2017; Seners et al., 2017; Yang et al., 2016). Besides, some different definitions of END have been put forward by researchers. For instance, END has been defined as ≥1-point increase in motor NIHSS or ≥2-point increase in total NIHSS (Choi et al., 2016; Nam et al., 2017), ≥2-point increase in NIHSS between admission and 24 hr (Kim et al., 2016), and ≥4-point increase in NIHSS within 48–72 hr (Weimar et al., 2005). Because of the different definitions of END, the rate of END occurring after thrombolytic therapy reported in studies varied greatly.

To date, studies have been conducted extensively on the rate of END occurring after thrombolytic therapy. However, the overall rate cannot be easily estimated from individual publication with limited cases. Therefore, a meta-analysis was conducted to evaluate the rate of END occurring after thrombolytic therapy.

2 | METHODS

2.1 | Searching strategy

A literature search from PubMed, EMBASE, and Cochrane Collaboration Database was conducted to identify the relevant studies up to June 2018. The following terms were used during the searching: (“early neurological deterioration” OR “END”) AND “thrombolysis” AND (“stroke” OR “cerebral infarction” OR “transient ischemic attack” OR “TIA”). No language or other restriction was used. Meanwhile, the references used in the eligible articles were also reviewed as sources to identify potential studies.

2.2 | Inclusion and exclusion criteria

The studies included in the meta-analysis had to meet the following criteria: (a) randomized trials or observational studies aiming at stroke or ischemic attack; (b) patients had received thrombolysis therapy; (c) sample size > 100; (d) providing the number of patients with END; and (e) having clear definition of END. In view of the fact that the definition of END is closely related to the rate of END, the definition of END was prespecified according to the most commonly used definition: ≥4-point increase in NIHSS between admission and 24 hr.

Studies were excluded when they were as follows: (a) reviews, letters, case reports, protocols, or animal studies; (b) studies involving other definitions of END; and (c) studies providing insufficient information needed in the meta-analysis.

2.3 | Data extraction

Information was extracted independently by two experienced investigators, and any discrepancy was resolved by the third investigator. The authors whose studies did not provide adequate information should be contacted. The following data were collected as follows: first author’s name, publication year, country, age, gender ratio, onset to treatment time (OTT), NIHSS at admission, thrombolytic drug type, thrombolytic drug dose, sample size, and the number of patients with END.

2.4 | Quality assessment

Agency for Healthcare Research and Quality (Rockville, 2004) was used to assess the quality of the included studies. The assessment scale included 11 items. If an item was answered “Yes,” it would get one point; no point with answer “NO” or “UNCLEAR.” A study was considered high quality with 8–11 points; moderate quality with 4–7; and low quality with 0–3.

2.5 | Statistical analysis

Data management and rate calculation of END were estimated by STATA 12 for Windows (Stata, College Station, TX, USA). Since meta-analysis of rate generally has a significant heterogeneity, random effects model was chosen. A chi-square test was used to examine heterogeneity between the included studies, and a p < 0.10 was considered statistically significant (Higgins, Thompson, Deeks, & Altman, 2003). To explore sources of heterogeneity, subgroup analyses were performed by continent (Asia, Europe or North America), OTT (≤120.0, 120.1–179.9 or 180.0–270.0 min), NIHSS at admission (≤4.0, 5.0–15.0, or 16.0–20.0), thrombolytic drug dose (0.6, 0.7, 0.8, 0.9 or 1.1 mg/kg), and study quality (high quality, moderate quality, or low quality). To evaluate the influence of each study on the pooled rate of END, sensitivity analysis was conducted. Publication bias was examined by using Begg’s correlation and Egger’s regression (Begg & Mazumdar, 1994; Egger, Davey, Schneider, & Minder, 1997). A p < 0.05 was considered to be statistically significant.

3 | RESULTS

3.1 | Searching results

According to our searching strategy, a total of 2,079 potential relevant studies were identified. Of these studies, 558 studies were from PubMed, 1,003 studies were from EMBASE, and 518 studies were from Cochrane Collaboration Database. Among these studies, 487 studies were excluded by reviewing titles. Then 1,552 studies were excluded by retrieving abstracts. Of the remains, 15 studies with insufficient information and 14 duplicate studies were removed. Finally, 11 studies met all the inclusion criteria. A flow diagram summarizing the whole process of selection procedures is shown in Figure 1.
3.2 | Characteristics of the eligible studies

Eleven studies with a total of 3,539 subjects, including 373 patients with END and 3,166 patients without END, met the inclusion and exclusion criteria. Of these studies, there were 4 studies from Asia (Chi & Chan, 2017; Mori et al., 2012; Ong et al., 2017; Yang et al., 2016), 6 studies from Europe (Fiorelli et al., 1999; Hansen, Christensen, Havsteen, Ovesen, & Christensen, 2018; Seners et al., 2014, 2017; Simonsen et al., 2016; Zinkstok et al., 2014), and 1 study from North America (Saqqur et al., 2007). The baseline characteristics of all the included studies were shown in Table 1. Four studies provided the type and dose of the thrombolytic drug (Fiorelli et al., 1999; Mori et al., 2012; Ong et al., 2017; Yang et al., 2016), and the remaining studies provided insufficient information of the thrombolytic drug (Chi & Chan, 2017; Hansen et al., 2018; Saqqur et al., 2007; Seners et al., 2014, 2017; Simonsen et al., 2016; Zinkstok et al., 2014) (Table 2).

3.3 | Quality assessment

The quality score of each study was presented in Table 1. There were 6 studies with high quality, 5 studies with moderate quality, and no study with low quality. The quality assessment showed reasonable study design and clear results. No study was excluded on grounds of quality.

3.4 | Pooled analysis

The rate of END occurring after thrombolytic therapy was calculated and ranged from 3.4% to 28.8% (Figure 2). The pooled rate of the 11 studies was about 11.0% (95% CI: 7.8%–14.3%). Substantial heterogeneity was found among the included studies ($p < 0.001$, $I^2 = 91.7\%$).

3.5 | Subgroup analysis

In the subgroup analysis, studies were categorized by continent, OTT, NIHSS at admission, thrombolytic drug dose, and study quality. The results of the subgroup analysis were showed in Table 3. In the subgroup analysis by continent, we found that the rate of END occurring after thrombolytic therapy in Europe was 7.6% (95% CI: 4.9%–10.3%), and in North America was 11.8% (95% CI: 8.5%–15.0%). However, the rate was higher in Asia (15.9%, 95% CI: 7.4%–24.5%). In the subgroup analysis by OTT, the rate of END occurring after thrombolytic therapy of the patients whose OTT ≤120.0 min,
from 120.1 to 179.9 min and from 180.0 to 270.0 min was 5.4% (95% CI: 1.2%–9.5%), 15.6% (95% CI: 9.6%–21.5%), and 18.5% (95% CI: 11.2%–25.8%), respectively. In the subgroup analysis by NIHSS at admission, the results showed that the rate of END occurring after thrombolytic therapy of the patients whose NIHSS at admission was from 5.0 to 15.0 was 10.1% (95% CI: 6.1%–14.2%), and the rate of the patients whose NIHSS at admission was from 16.0 to 20.0 was 14.3% (95% CI: 8.0%–20.6%). However, the rate was higher in the patients whose NIHSS at admission ≤4.0 (18.5%, 95% CI: 11.2%–25.8%). Besides, the results of the subgroup analysis also showed that END rates were not associated with rt-PA dose or study quality.

3.6 | Sensitivity analysis

The sensitivity analysis was performed to evaluate the influence of each individual study on the pooled rate by omitting every single study. The analysis results reflected that the results were statistically stable and reliable (Figure 3).

3.7 | Publication bias

Funnel plots showed slight asymmetry through visual inspection. However, Begg’s test did not indicate significant publication bias in the meta-analysis (Z = 1.25, p = 0.213).

4 | DISCUSSION

To our knowledge, the paper has been the first meta-analysis to evaluate the rate of END occurring after thrombolytic therapy. In the present study, 11 independent studies were included with a total of 3,539 subjects, comprised of 373 patients with END and 3,166 patients without END. The pooled analysis showed the rate of END occurring after thrombolytic therapy ranged from 3.4% to 28.8%, and the overall rate was about 11.0%. The results indicated that among one hundred patients who received thrombolytic therapy, eleven patients might experience END.

In the subgroup analysis by continent, the rate of END occurring after thrombolytic therapy was higher in Asia than in Europe and North America. One possible explanation for this result is the stroke pathophysiology in Asia differs from that in Europe and North America. In Asia, there are more arteriosclerotic large vessel stroke patients and large vessel occlusion patients who might have high NIHSS at baseline (Gorelick, Wong, Bae, & Pandey, 2008; Wong, 2006). In addition, the different programs for standard quality of care may also be responsible for this result. In the economically developed areas, the patients might receive better care quality than the patients in underdeveloped areas.

The "time is brain" concept has been introduced more than two decades which emphasizes the importance of time in treating acute stroke (Gomez, 1993). In our subgroup analysis by OTT, we found that the rate of END occurring after thrombolytic therapy was 5.4%, 15.6%, and 18.5% for the patients whose OTT ≤120.0 min,
Therefore, OTT might significantly affect the rate of END occurring after thrombolytic therapy, and the rate might increase with the increase of OTT. Pulvers and Watson (2017) reported that emergency medical pathways, stroke symptomatology, patient and bystander behavior, patient health characteristics, and stroke
treatment awareness might affect OTT, and reducing OTT might improve the stroke outcomes, which is consistent with our results.

National Institutes of Health Stroke Scale at admission is also a factor which has an important influence on the rate of END occurring after thrombolytic therapy. Some researchers suggested that NIHSS at admission in high level might increase the mortality and cause poor functional outcomes of patients receiving thrombolytic therapy (Kim et al., 2015; Lin, Chen, Hu, & Bai, 2018; Mazya et al., 2015). However,
our results in this meta-analysis did not conform to these conclusions. In the present subgroup analysis by NIHSS at admission, the rate of END occurring after thrombolytic therapy of the patients with NIHSS at admission ≤4.0 was highest among the three groups, which is inconsistent with most literatures. Two possible explanations for the phenomenon might be as follows. First, the study in which OTT is inconsistent with most literatures. Two possible explanations for one study was included in which NIHSS at admission was ≤4.0 (Yang et al., 2016), and OTT might have a greater impact on the rate of END than NIHSS at admission. Second, only one study was included in which NIHSS at admission was ≤4.0, so the results might be influenced by the inadequate sample size.

Some limitations of the meta-analysis should be addressed. First, similar to other meta-analyses of rate, high heterogeneity existed in the present study. Since there is no control group in the single arm studies, background difference in subjects cannot be well controlled and hardly be reduced by subgroup analysis, which often leads to great heterogeneity in the meta-analysis of rate. Second, because the most commonly used definition of END (≥4-point increase in NIHSS and hardly be reduced by subgroup analysis, which often leads to especially in the subgroup analysis. Therefore, studies with larger sample size are needed in the future. Finally, only publications were included in the present study, so we need more unpublished reports to expand our analysis. Despite the limitations, our meta-analysis significantly increased the statistical power based on substantial data from different studies. The sensitivity analysis and publication bias outcomes both reflected that our results were statistically stable and reliable.

In summary, the meta-analysis suggests that the rate of END occurring after thrombolytic therapy is about 11.0%. This finding may provide a scientific reference for researchers to evaluate the efficacy and safety of thrombolytic therapy. In order to reach a more definitive conclusion, a consistent definition of END is needed for future studies.

ACKNOWLEDGMENTS

We are really appreciative of all the participants in this study.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ORCID

Xiaowen Hou  
https://orcid.org/0000-0002-8490-9435

Huisheng Chen  
https://orcid.org/0000-0002-4408-7801

REFERENCES

Begg, C. B., & Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. Biometrics, 50(4), 1088–1101. https://doi.org/10.2307/2533446

Chi, M. S., & Chan, L. Y. (2017). Thrombolytic therapy in acute ischemic stroke in patients not fulfilling conventional criteria. Neurologist, 23(6), 219–226. https://doi.org/10.1097/NRL.0000000000000149

Choi, K. H., Park, M. S., Kim, J. T., Kim, H. S., Kim, J. H., Nam, T. S., ... Cho, K. H. (2016). Lipoic acid use and functional outcomes after thrombolysis in patients with acute ischemic stroke and diabetes. PLoS ONE, 11(9), e0163484. https://doi.org/10.1371/journal.pone.0163484

Egger, M., Davey, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. British Medical Journal, 315(7109), 629–634. https://doi.org/10.1136/bmj.315.7109.629

Fiorelli, M., Bastianello, S., von Kummer, R., del Zoppo, G. J., Larrue, V., Lesaffre, E., ... Boffa, L. (1999). Hemorrhagic transformation within 36 hours of a cerebral infarct: Relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke, 30(11), 2280–2284. https://doi.org/10.1161/01.STR.30.11.2280

Gomez, C. R. (1993). Editorial: Time is brain!. Journal of Stroke and Cerebrovascular Diseases, 3(1), 1–2.

Gorelick, P. B., Wong, K. S., Bae, H. J., & Pandey, D. K. (2008). Large artery intracranial occlusive disease: A large worldwide burden but a relatively neglected frontier. Stroke, 39(8), 2396–2399. https://doi.org/10.1161/STROKEAHA.107.505776

Hacke, W., Ringelstein, B. E., Bousser, M. G., Ford, G., Bath, P., Brainin, M., & Cordonnier, C. (2008). Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovascular Diseases, 25(5), 457–507. https://doi.org/10.1159/000131083

Hansen, C. K., Christiansen, A. H., Havsteen, I., Ovesen, C., & Christensen, H. (2018). Prevalence of early neurological deterioration after IV‐thrombolysis in acute ischaemic stroke patients—A hospital-based cohort study. Clinical Neurology and Neurosurgery, 171, 58–62. https://doi.org/10.1016/j.clineuro.2018.05.003

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. British Medical Journal, 327(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557

Kim, B. J., Park, J. M., Kang, K., Lee, S. J., Ko, Y., Kim, J. G., ... Bae, H. J. (2015). Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. Journal of Stroke, 17(1), 38–53. https://doi.org/10.5853/jos.2015.171.38

Kim, J. M., Moon, J., Ahn, S. W., Shin, H. W., Jung, K. H., & Park, K. Y. (2016). The etiologies of early neurological deterioration after thrombolysis and risk factors of ischemia progression. Journal of Stroke and Cerebrovascular Diseases, 25(2), 383–388. https://doi.org/10.1371/journal.pone.0163484

Lin, S. F., Chen, C. I., Hu, H. H., & Bai, C. H. (2018). Predicting functional outcomes of posterior circulation acute ischemic stroke in first 36 h of stroke onset. Journal of Neurology, 265(4), 926–932. https://doi.org/10.1007/s00415-018-8746-6

Mazya, M. V., Lees, K. R., Collas, D., Rand, V. M., Mikulik, R., Toni, D., & Ahmed, N. (2015). IV thrombolysis in very severe and severe ischemic stroke: Results from the SITS-ISTR registry. Neurology, 85(24), 2098–2106. https://doi.org/10.1212/WNL.0000000000002199

Mori, M., Naganuma, M., Okada, Y., Haseqawa, Y., Shiokawa, Y., Nakaqawara, J., ... Toyoda, K. (2012). Early neurological deterioration within 24 hours after intravenous rt-PA therapy for stroke patients: The stroke acute management with urgent risk factor assessment and improvement rt-PA registry. Cerebrovascular Diseases, 34(2), 140–146. https://doi.org/10.1159/000339759

Murray, C. J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., ... Lopez, A. D. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. The Lancet, 380(9859), 2197–2223. http://doi.org/10.1016/S0140-6736(12)61689-4
Nam, K. W., Kim, C. K., Kim, T. J., An, S. J., Oh, K., Ko, S. B., & Yoon, B. W. (2017). Intravenous thrombolysis in acute ischemic stroke with active cancer. BioMed Research International, 2017, 4635829. https://doi.org/10.1155/2017/4635829

Ong, C. T., Wong, Y. S., Wu, C. S., & Su, Y. H. (2017). Outcome of stroke patients receiving different doses of recombinant tissue plasminogen activator. Drug Design, Development and Therapy, 11, 1559–1566. https://doi.org/10.2147/DDDT.S133759

Pan, Y., Chen, Q., Zhao, X., Liao, X., Wang, C., Du, W., … Wang, Y. (2014). Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke in China. PloS ONE, 9(10), e110525. https://doi.org/10.1371/journal.pone.0110525

Powers, W. J., Rabinstein, A. A., Ackerson, T., Adeoye, O. M., Bambakidis, N. C., Becker, K., & Tirschwell, D. L. (2018). 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American heart association/American stroke association. Stroke, 49(3), e46–e110. https://doi.org/10.1161/STR.0000000000000172

Prabhakaran, S., Ruff, I., & Bernstein, R. A. (2015). Acute stroke intervention: A systematic review. JAMA, 313(14), 1451-1462. https://doi.org/10.1001/jama.2015.3058

Pulvers, J. N., & Watson, J. D. G. (2017). If time is brain where is the improvement in prehospital time after stroke? Frontiers in Neurology, 8, 617. https://doi.org/10.3389/fneur.2017.00617

Rockville (2004, September). Celiac disease: Agency for healthcare research and quality (US). 2004. (Evidence Reports/Technology Assessments, No.104) Appendix D. Quality Assessment Forms. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK35156

Saqqur, M., Molina, C. A., Salam, A., Siddiqui, M., Ribo, M., Uchino, K., … Alexandrov, A. V. (2007). Clinical deterioration after intravenous recombinant tissue plasminogen activator treatment: A multicenter transcranial Doppler study. Stroke, 38(1), 69-74. https://doi.org/10.1161/01.STR.0000251800.01964.86

Seners, P., Hurford, R., Tisserand, M., Turc, G., Legrand, L., Naggara, O., … Baron, J. C. (2017). Is unexplained early neurological deterioration after intravenous thrombolysis associated with thrombus extension? Stroke, 48(2), 348–352. https://doi.org/10.1161/STROKEAHA.116.015414

Seners, P., Turc, G., Tisserand, M., Legrand, L., Labeyrie, M. A., Calvet, D., … Baron, J. C. (2014). Unexplained early neurological deterioration after intravenous thrombolysis: Incidence, predictors, and associated factors. Stroke, 45(7), 2004–2009. https://doi.org/10.1161/STROKEAHA.114.005426

Simonsen, C. Z., Schmitz, M. L., Madsen, M. H., Mikkelsen, I. K., Chandra, R. V., Leslie-Mazwi, T., & Andersen, G. (2016). Early neurological deterioration after thrombolysis: Clinical and imaging predictors. International Journal of Stroke, 11(7), 776–782. https://doi.org/10.1177/1747493016650454

Souza, L. V. A., Paiva, L. D. S., Figueiredo, F. W. D. S., Almeida, T. C. D. C., Oliveira, F. R., & Adami, F. (2017). Trends in stroke-related mortality in the ABC region, Sao Paulo, Brazil: An ecological study between 1997 and 2012. The Open Cardiovascular Medicine Journal, 11, 111–119. https://doi.org/10.2174/1874192401711010111

Weimar, C., Mieck, T., Buchthal, J., Ehrenfeld, C. E., Schmid, E., & Diener, H. C. (2005). Neurologic worsening during the acute phase of ischemic stroke. Archives of Neurology, 62(3), 393–397. https://doi.org/10.1001/archneur.62.3.393

Wong, L. K. (2006). Global burden of intracranial atherosclerosis. International Stroke Society, 1(3), 158–159. https://doi.org/10.1111/j.1747-4949.2006.00045.x

Yang, J., Yu, F., Liu, H., An, H., Xiong, R., & Huang, D. (2016). A retrospective study of thrombolysis with 0.6 mg/kg recombinant tissue plasminogen activator (rt-PA) in mild stroke. Scientific Reports, 6, 31344. https://doi.org/10.1038/srep31344

Zinkstok, S. M., Beenen, L. F., Majoe, C. B., Marquering, H. A., de Haan, R. J., & Roos, Y. B. (2014). Early deterioration after thrombolysis plus aspirin in acute stroke: A post hoc analysis of the antiplatelet therapy in combination with recombinant t-PA thrombolysis in ischemic stroke trial. Stroke, 45(10), 3080–3082. https://doi.org/10.1161/STROKEAHA.114.006268

How to cite this article: Hou X, Chen W, Xu H, Zhu Z, Xu Y, Chen H. The rate of early neurological deterioration occurring after thrombolytic therapy: A meta-analysis. Brain Behav. 2019;9:e01210. https://doi.org/10.1002/brb3.1210