The Development of Pulmonary Edema after Recombinant Tissue Plasminogen Activator in Acute Ischemic Stroke Patient; Neurogenic or Non-Neurogenic?

Ahmad Sulaiman Alwahdy\textsuperscript{a}   Ika Yulieta Margaretha Sihombing\textsuperscript{a}
Fitria Tahta Alfina\textsuperscript{b}   Niken Syahdian\textsuperscript{b}   Putri Nurbati\textsuperscript{b}
Annisa Futihandayani\textsuperscript{b}   Allifka Ramadharti\textsuperscript{b}

\textsuperscript{a}Department of Neurology, Fatmawati Central General Hospital, Jakarta, Indonesia; \textsuperscript{b}Faculty of Medicine, UIN Syarif Hidayatullah, Jakarta, Indonesia

Keywords
Stroke · Ischemic · r-tPA · Neurogenic pulmonary edema · Acute pulmonary edema

Abstract
Recombinant tissue plasminogen activator (r-tPA) is the first-line drug for the treatment of acute ischemic stroke, despite it may lead to a variety of complications in some cases. In patients with extensive stroke, infarction of the brain can cause suppression of the respiratory center in the brain leading to neurogenic pulmonary edema that potentially causes respiratory failure. Its etiology is either due to a neurogenic or non-neurogenic process. Nevertheless, the definite pathophysiology of these circumstances remains unclear. In this study, we reported four cases of post-thrombolytic ischemic stroke patients who suffer from pulmonary edema with different symptoms and onset times as well as we discuss the possible explanation behind these different outcomes.

Introduction

Stroke is a focal or general acute neurological deficit condition during more than 24 h caused by cerebrovascular factors [1]. The current standard of care for the treatment of acute ischemic stroke is intravenous recombinant tissue-type plasminogen activator (IV r-tPA)
and/or mechanical thrombectomy (MT) [2]. In patients with extensive stroke, infarction or large vessel occlusion that involved the insula region is hypothesized to have some effects on suppression of the respiratory center in the brain and lead to complications in the respiratory system such as neurogenic pulmonary edema (NPE) [3, 4].

Pulmonary edema itself can be defined as an abnormal accumulation of extravascular fluid in the lung parenchyma. This process leads to diminished gas exchange at the alveolar level, progressing to potentially causing respiratory failure. Clinical features include progressive worsening dyspnea, rales of lung auscultation, and worsening hypoxia [3, 5]. Regardless of whether the etiology is supposed to be a surge of catecholamines that results in cardiopulmonary dysfunction [6], the exact mechanism remains unclear either due to a neurogenic or non-neurogenic process or it can be mixed processes interact with one another that cannot be separated.

Nevertheless, there are important risks that may affect the cost-benefit calculation when considering recanalization, especially by thrombolysis. Complications that are related to IV r-tPA include symptomatic intracranial hemorrhage, major systemic hemorrhage, and angioedema. Only a few cases are reported to show developing pulmonary edema after IV r-tPA. Consequently, we reported four cases of post-thrombolytic ischemic stroke patients with acute pulmonary edema additionally discussing the possible explanation behind these circumstances. Furthermore, these cases suggest that changes in vital signs should be closely monitored. Additionally, the possibility of pulmonary edema during or after thrombolysis and before treatment at initial presentation should be considered, and corresponding rescue measures should be taken immediately.

Case 1

A 47-year-old male was brought to the emergency room (ER) with shortness of breath, decreased consciousness, and weakness of the left limb for 2 h before hospital admission. Initial blood pressure (BP) was measured as 170/117 mm Hg, heart rate (HR) 127 beats/min, respiratory rate (RR) 26 breaths/min, and there were smooth wet crackles at lung sound. Based on neurological examination, it revealed left side weakness and asymmetrical face with the muscle strength of 1 out of 5 on the left leg and left arm.

The result of brain CT showed infarction at the right insula and nucleus lentiform with Alberta Stroke Program Early CT Score (ASPECTS) was 8 (Fig. 1a). There was cardiomegaly with lung edema, aorta calcification, and elongation investigated by chest X-ray (Fig. 1b). Besides, the electrography (ECG) result showed QS wave and nonspecific ST wave changes (Table 1).

Thrombolytic therapy with alteplase intravenous 0.9 mg/body weight was suggested to be conducted for this case treatment. His National Institutes of Health Stroke Scale (NIHSS) score after IV thrombolytic was reduced from 16 to 12. Unfortunately, the condition of the patient got worst because of massive hemoptysis, severe tachypnea, decreased BP abruptly, and sudden heart attack. Despite the various efforts to save the patient, he eventually died.

Case 2

A 62-year-old male patient was brought to the ER with some symptoms consisting of sudden slurred speech, weakness in the right arm and right leg for 3 h before admission. The patient was diagnosed with atrial fibrillation 2 months ago; however, the patient was neither monitored nor took medication regularly. The patient had a history of taking antituberculosis drugs about 2 years ago. Moreover, he did not have any history of hypertension and diabetes mellitus.
Based on a physical examination conducted in the ER, he was conscious with respective information consisting of 118/89 mm Hg of BP, 113 beats/min of HR, 24 breaths/min of RR, and 36.5°C of body temperature. The pulmonary examination showed the existence of rales in both lung fields, in accordance with the neurological examination that revealed his NIHSS total score was 15.

Concurrently, the patient’s head CT presented the left M4 and M5 infarction, in which the left middle cerebral artery (MCA) territory infarction with ASPECTS 8, old wedge infarct with encephalomalacia in the right occipital lobe, and cerebral atrophy (Fig. 2a). Chest X-ray showed pleural thickening with fibro-infiltrates in the upper, middle, and lower lung fields bilaterally, suggesting pulmonary TB (Fig. 2b).

Thrombolytic therapy with r-tPA was initiated at a dose of 0.9 mg/body weight. The patient’s condition improved as indicated by his NIHSS score of 10. Unfortunately, less than 48 h after thrombolysis, the patient complained of worsening shortness of breath, although a non-rebreathing mask was given. Intubation was performed, and he was transferred to the intensive care unit for further evaluation. Chest X-ray on day 5 of post-thrombolytic showed worsening fibro-infiltrates in both lungs and developing bullae formation in the upper left lung (Fig. 2c). On the tenth day of hospitalization, the patient died due to respiratory failure.

Case 3

A 55-year-old male patient was brought to ER with sudden right-side weakness which started 2 h before admission as well as losing the ability to talk accompanied by other symptoms such as fever, cough, and shortness of breath. He had a history of hypertension, coronary artery disease post percutaneous coronary intervention, and diabetes mellitus type II. Initial BP was measured as 160/88 mm Hg, 96 beats/min of HR, 28 breaths/min of RR with rales in both lung fields, and 37.8°C of body temperature. The neurological examination revealed right-sided weakness, aphasia, and weakness of his right 7th cranial nerve with NIHSS score of 12.
### Table 1. Demographical features and initial clinical presentation at ER of all cases (Pre r-tPA)

| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Reference range |
|-----------|-----------|-----------|-----------|----------------|
| Age       | 47        | 62        | 55        | 61             |
| Sex       | Male      | Male      | Male      | Male           |
| Patient History | | | | |
| Prestroke m-RS | 0 | 0 | 0 | 0 |
| Comorbidities | Hypertension, chronic heart failure | Uncontrolled atrial fibrillation 2 years post-treatment of antituberculosis | Hypertension, diabetes mellitus II, coronary artery disease | Hypertension, chronic heart failure, DM II, dyslipidemia |
| Possible mechanism | Anaphylactic + Neurogenic + Cardiogenic | Pulmonogenic + Neurogenic + Cardiogenic | Neurogenic + Cardiogenic | Neurogenic + Cardiogenic |
| Stroke features | | | | |
| Clinical symptoms | Left-sided weakness, asymmetrical face | Right-sided weakness, aphasiasia, asymmetrical face | Right side weakness, aphasisia, asymmetrical face | Left side weakness, slurred speech, asymmetrical face |
| CT scan findings | Right MCA territory involving the right insula | Left MCA territory involving the left insula | Left MCA territory involving the right insula (confirmed by DSA) | Right MCA territory involving the right insula |
| NIHSS at baseline | 16 | 15 | 12 | 10 |
| NIHSS after r-Tpa | 12 | 10 | 6 | 5 |
| IV r-Tpa | Yes (0.9 mg/body weight) | Yes (0.9 mg/body weight) | Yes (0.9 mg/body weight) | Yes (0.9 mg/body weight) |
| Hemorrhagic transformation | No | No | No | No |
| Complication | Hemoptyrosis | – | – | – |
| Outcome | Death after 2 h with respiratory failure | Death on the 10th day of hospitalization with respiratory failure | Clinical recovery | Clinical recovery |
| Cardiac-pulmonary findings | | | | |
| RR/min | 26 | 24 | 28 | 22 |
| HR/min | 127 | 113 | 96 | 98 |
| Chest X-ray | Cardiomegaly with lung edema; aorta calcification and elongation | Suspected of pulmonary tuberculosis | Infiltrate at a basal right lung with cardiomegaly | Cardiomegaly |
| ECG | QS wave and nonspecific ST wave changes | Atrial fibrillation and poor progression | QS wave and nonspecific T wave changes | QS wave and nonspecific T wave changes |
|                         | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Reference range |
|-------------------------|-----------|-----------|-----------|-----------|-----------------|
| **Blood gas analysis**  |           |           |           |           |                 |
| pH (mm Hg)              | 7.42      | 7.42      | 7.48†     | 7.45†     | 7.37–7.44       |
| PCO₂ (mm Hg)            | 40.8      | 49.6†     | 29.5↓     | 41.5      | 35.0–45.0       |
| PO₂ (mm Hg)             | 151†      | 243.0†    | 146.7†    | 155.3†    | 83.0–108.0      |
| HCO₃⁻ (mmol/L)          | 29.9†     | 32.4†     | 22.3      | 29.2†     | 21.0–28.0       |
| SpO₂ (%)                | 99.9      | 99.9      | 99.9      | 99.9      | 95.0–99.0       |
| Oxygen therapy          | Yes       | Yes       | Yes       | Yes       |                 |
| **Laboratory findings** |           |           |           |           |                 |
| Hemoglobin (g/dL)       | 14.3      | 13.6      | 14.2      | 15.7      | 13.2–17.3       |
| Leucocyte (/µL) × 10⁶   | 10        | 8.6       | 6.6       | 13.1†     | 5–10            |
| Platelets (/µL) × 10⁹   | 241       | 217       | 368       | 150–440   |                 |
| Neutrophils (%)         | 68        | 54        | 72†       | 80†       | 50–70           |
| Lymphocytes (%)         | 21        | 36        | 20        | 8↓        | 20–40           |
| a-PTT (s)               | 27.5↓     | 31.3      | 29.4      | 26.3↓     | 28.6–42.2       |
| PT (s)                  | 13        | 12.5      | 13.4      | 15.7      | 11.7–15.1       |
| INR                     | 0.92      | 1.09      | 0.94      | 0.92      |                 |
| Fibrinogen (mg/dL)      | –         | –         | 369       | 504†      | 200–400         |
| D-dimer (ng/dL) × 10³   | 1,054†    | 219       | 1,254†    | 824†      | ≤500            |
| AST (U/L)               | 21        | 26        | 22        | 19        | ≤32             |
| ALT (U/L)               | 32        | 9         | 15        | 11        | ≤33             |
| Creatinine (mg/dL)      | 1.1       | 1.02      | 1.49†     | 1.29†     | 0.67–1.17       |
| Glucose (mg/dL)         | 138       | 117       | 211†      | 261†      | 70–140          |
| CRP (mg/dL)             | 0.63†     | 0.17      | 0.39      | 0.8†      | ≤0.5            |
The head CT result demonstrated an infarct in the left insula, subcortical parietotemporal lobe, left putamen, and bilateral corona radiata but no hemorrhage (Fig. 3a). His chest X-ray disclosed infiltrate at basal of right and left lung with cardiomegaly (Fig. 3b). Hence, intravenous thrombolysis therapy was initiated with alteplase 0.9 mg/body weight.

In the ward, his clinical condition improved by an NIHSS score of 6. Unfortunately, in less than 24 h, the patient complained of worsening shortness of breath. The treatment of pneumonia was initiated with antibiotics empirically in addition to pulmonary edema’s protocol started immediately after we recognized his symptoms. The patient’s breathlessness reduced on day 7 of hospitalization. Chest X-ray at that time uncovered that the bilateral precardiac infiltrates were no longer visible (Fig. 3c). The patient was discharged after 9 days of hospitalization.

Case 4

The patient came with complaints of sudden left-sided weakness and sudden slurred speech for 3 h. Initial BP was measured as 160/100 mm Hg, HR at 98 beats/min, RR at 22 breaths/min with clear lung sound on auscultation, QS wave, and nonspecific T wave changes on ECG. Neurological examination revealed left side weakness and asymmetrical face with the muscle strength at 1/5 on the left leg and the left arm with NIHSS at 10.

Brain CT disclosed right infarct on frontoparietal and insula with loss of insular ribbon (Fig. 4a). Chest X-ray revealed there was cardiomegaly with no sign of pulmonary edema. Besides, the ECG defined QS wave and nonspecific T wave changes (Table 1).

Thrombolytic therapy was considered to be performed along with alteplase intravenously as bridging therapy before transferring the patient for MT. After performing digital subtraction angiography, recanalization of right M1 was noticed, and MT was restrained (Fig. 4b).

After 3 h of observation in the high care unit, his clinical condition was improved by an NIHSS score of 5 despite the patient complaining of shortness of breath and heavy chest. A repeat chest X-ray showed cardiomegaly with early pulmonary engorgement signed.
for pulmonary edema (Fig. 4c, d). Supplementation of oxygen and diuretic was initiated. The patient was discharged after the 10th day of hospitalization with clinical improvement.

**Discussion**

NPE is a pulmonary compromise condition due to severe damage of the central nervous system that causes symptoms similar to ARDS accompanied by pulmonary edema [7]. NPE is defined as acute respiratory distress characterized by acute onset, extravascular accumulation of interstitial pulmonary fluid [5–7]. Acute onset is seen in less than 4 h usually within 30–60 min, while delayed onset appears approximately 12–72 h after central nervous system event [7–9].
The possible mechanisms of NPE after cerebral infarction include an abrupt increase of intracranial pressure by large infarction or direct destruction of so-called “NPE trigger zones” including the insular cortex, hypothalamus, or ventrolateral medulla. Sudden disruption of blood supply toward the left insular cortex after MCA occlusion is suggested as a possible etiology of NPE [6, 8, 10]. There is a previous report describing NPE after left hemispheric infarction involving the insular cortex, which was associated with cardiac dysfunction but can be rapidly resolved after thrombolytic treatment [9, 10].

NPE usually occurs within minutes to hours after a CNS insult. The clinical symptoms and signs of NPE are nonspecific; although dyspnea, tachypnea, tachycardia, cyanosis, pink frothy sputum, basal pulmonary crackles or rales, and chest radiograph which typically shows bilateral diffuse alveolar infiltrates are common manifestations of NPE [9, 11]. In the first case, the patient died within 2 h after thrombolytic therapy with massive hemoptysis and developing ARDS before finally going into cardiac arrest. We assumed that NPE might already have developed due to its stroke location, and there were signs of brain-heart axis in which the stroke disturbed the heart function as could be seen in the changes in wave or rhythm in ECG of the patient [10, 12].

Nevertheless, in the first case, anaphylactic reaction could not be ruled out either due to the developing massive hemoptysis and abrupt hypotension after r-tPA. It has been reported that the patient died within 53 min after thrombolytic therapy; hence the hypothesis of the case is anaphylaxis reaction of thrombolytic [13]. The patient might not present any common allergic reaction symptoms consisting of rash, pruritus, and orolingual edema. During the autopsy, they found a large amount of bloody edema fluid in the oral, nasal cavity, tracheal cavity, and significant mucosa congestion in both lungs. By this case, it is demonstrated that r-tPA converts plasminogen to plasmin in vivo, which can activate the complement system and the bradykinin pathway that can lead to acute pulmonary edema [13, 14].

The effects of the neurological injury on cardiac function have been acknowledged, and various pathologies of the nervous system can lead to a wide range of alterations in function and structure of the cardiovascular system; ranging from transient and benign electrographic changes to myocardial injury, cardiomyopathy, and even cardiac death [12]. In the second case, the CT scan showed infarction in the MCA territory in accordance with previous studies which showed this territorial infarct can cause NPE [10]. This was not only worsening the patient’s pulmonary edema only but also affected the patient’s cardiac function [12].

Furthermore, pulmonary status is also an important factor for the outcome of the NPE. The X-ray showed the thickening of pleural with fibro infiltrate bilateral, which means the patient had a chronic pulmonary disease that led to the decrease in pulmonary function as well as increased mortality. NPE commonly attacks the lungs with diseases, since the diseased lung has a smaller reserve which would decompensate with smaller insults [15, 16].

In addition, r-tPA is found to function as a cytokine to promote the proliferation of lung fibroblasts that may lead to damage to the alveolar structure [17]. It can activate the complement system and the bradykinin pathway that may worsen the pulmonary edema outcome [13, 14]. As a consequence, we suggest that patients with a chronic lung disease who potentially have the risk of developing NPE due to acute stroke condition should consider the risk and benefit of IV r-tPA, or it is suggested to directly take MT.

In the third case, the infarct location involved the insula area with moderate NIHSS. NIHSS can become a predictor of the prognosis. The higher NIHSS is, the worse prognosis becomes, as seen in all cases above, in which the patients who had a high score of NIHSS were classified as having a severe condition [10]. The X-ray of the third case appeared to have pneumonia, and early empirical antibiotic treatment of community-acquired pneumonia contributed to the patient’s better prognosis [18]. Unfortunately, the patient’s shortness of breath made his
condition worst. Hence, the pulmonary edema protocol treatment was conducted immediately after we recognized his symptoms.

It was hypothesized that heart failure might alter the efficacy of r-tPA in the cerebral circulation by both changes to its pharmacokinetic and pharmacodynamics properties. Nevertheless, it was reported that recanalization rates after intravenous r-tPA use were as high as in patients with normal cardiac function, and the clinical response to r-tPA as reflected by the improvement on the NIHSS was equal and it happened in all our cases [19]. Therefore, we believe that not only stroke location can affect heart function but also the cardiac and pulmonary baseline status might worsen the acute pulmonary edema after r-tPA as well. This should be in consideration as a prognostic value when NPE developed.

This is our limitation that could not perform any serial CT scan to evaluate any hemorrhagic transformation after r-tPA. Nevertheless, all four cases presented improvement from neurological symptoms that were shown by the improvement of NIHSS after IV r-tPA. Therefore, we believe that cerebral hemorrhage as one of r-tPA complications was not the cause of death in our patients. Location of the stroke that might affect the brain-heart axis might cause pulmonary edema, and the cardiac-pulmonary status of the patient might influence the outcome of pulmonary edema.

**Conclusion**

Acute pulmonary edema is a life-threatening illness that is frequently seen by physicians. The causes of the condition are generated by various processes, one of them is NPE in ischemic stroke patients. The risk factors such as anaphylaxis reaction to r-tPA, large location or volume of infarct area, pulmonary underlying disease, cardiovascular disease (heart failure, atrial fibrillation, or any ECG changes, for instance, QS wave and nonspecific ST wave or T wave changes) should be considered before performing recanalization treatment either by IV r-tPA or direct MT in which it will be more influential for this scenario. Comorbidities and conditions of patients during treatment may influence the outcome of NPE as well. Seeing the exact treatment mechanism is still unknown as well as the supporting data about NPE are still limited, the prevention and treatment of NPE remain unclear until today. We should not delay any recanalization treatment for acute stroke patients since the incidence of acute pulmonary edema is very unpredictable. Therefore, close attention should be paid to any change in vital signs during and after thrombolysis so that corresponding treatment can be taken.

**Acknowledgments**

The authors would like to thank to all staff of neurology department and code stroke team of the Fatmawati Central General Hospital for the support and their contribution.

**Statement of Ethics**

Ethical approval is not required for this study in accordance with local or national guidelines. Regarding case 1 and 2, written informed consent was obtained from the patient’s next of kin for publication of the details of their medical case and any accompanying images. Regarding case 3 and 4, written informed consent was obtained from the patients for publication of the details of their medical case and any accompanying images.
Conflict of Interests Statement

None of the authors have any financial disclosure to make or have any conflict of interest.

Funding Sources

This study did not receive any funding in any form.

Author Contributions

Ahmad Sulaiman Alwahdy: care of patient and writing, designing, and editing of the manuscript. Ika Yulieta Margaretha Sihombing: care of patient and writing and editing of the manuscript. Fitria Tahta Alfina, Niken Syahdian, Putri Nurbaeti, Annisa Futihandayani, and Allifika ramadhanti: writing of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1. Boehme AK, Ensenwa C, Elkind MSV. Stroke risk factors, genetics, and prevention. Circ Res. 2017;120(3):472–95.
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for health care professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344–418.
3. Murray JF. Pulmonary edema: pathophysiology and diagnosis. Int J Tuberc Lung Dis. 2011;15(2):155–60, i.
4. Gumanarat PB, Tambunan HS. Management neurogenic pulmonary edema in male 60 years old with massive ischemic stroke in RSUD Jendral A. Yani Kota Metro. Medula. 2020;9(4):699–704.
5. Finsterer J. Neurological perspectives of neurogenic pulmonary edema. Eur Neurol. 2019;81(1–2):94–102.
6. Davison DL, Terek M, Chawla LS. Neurogenic pulmonary edema. Crit Care. 2012;16(2):212.
7. Park MS, Kim JM, Chul YY, Kwon OS, Bae JH. Neurogenic pulmonary edema following acute cerebral infarction. J Neurocrit Care. 2016;9(2):171–3.
8. Probasco JC, Chang T, Victor D, Nyquist P. Isolated pulmonary edema without myocardial stunning in brainstem strokes. J Neurol Transl Neurosci. 2014;2(1):1040.
9. Sedy J, Kunes J, Zicha J. Pathogenetic mechanisms of neurogenic pulmonary edema. J Neurotrauma. 2015;32(15):1135–45.
10. Payabvash S, Taleb S, Benson JC, McKinney AM. Acute ischemic stroke infarct topology; association with lesion volume and severity of symptoms at admission and discharge. AJNR Am J Neuroradiol. 2017;38(1):58–63.
11. Balofsky A, George J, Papadakos P. Neuropulmonology. In: Wijdicks EFM, Kramer AH, editors. Handbook of clinical neurology. Critical Care Neurology, Part I (3rd series), Vol. 140. Amsterdam, The Netherlands: Elsevier; 2017. p. 33–48.
12. Tahsili-Fahadan P, Geocadin RG. Heart-brain axis, effects of neurologic injury on cardiovascular function. Circ Res. 2017;120(3):559–72.
13. Chen XR, Qu D, Zhang Q, Yue X, Qiao DF. Might life-threatening acute pulmonary edema occur after using recombinant tissue plasminogen activator? A case report. BMC Neurol. 2021;21(1):346.
14. Abraham SN, St John AL. Mast cell-orchestrated immunity to pathogens. Nat Rev Immunol. 2010;10(6):440–52.
15. Dutta G, Demetis S. Neurogenic pulmonary edema associated with underlying lung disease after a breakthrough seizure. Case Rep Med. 2012;2012:560942.
16. Malek R, Soufi S. Pulmonary Edema. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557611/ (accessed February 15, 2022).
17. Chen L, Hou J, Fu X, Chen X, Wu J, Han X. tPA promotes the proliferation of lung fibroblasts and activates the Wnt/β-catenin signaling pathway in idiopathic pulmonary fibrosis. *Cell Cycle*. 2019;18(22):3137–46.

18. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):E45–67.

19. Siedler G, Sommer K, Macha K, Marsch A, Breuer L, Stoll S, et al. Heart failure in Ischemic stroke: relevance for acute care and outcome. *Stroke*. 2019;50:3051–6.