Clinical study

Thrombolysis safety and effectiveness in acute ischemic stroke patients with pre-morbid disability

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ABSTRACT

Introduction: Recombinant tissue plasminogen activator (rt-PA) is the first-line therapy demonstrated to be safe and effective in acute ischemic stroke. People with pre-existing severe dementia or physical disability are usually excluded from rt-PA. The aim of our study was to investigate rt-PA safety and effectiveness in acute stroke with pre-existing disability (mRS $\geq$ 2).
Methods: The study encompassed 35 acute ischemic stroke patients with mRS $\geq$ 2 treated with rt-PA. In order to assess the differences in clinical outcome in three disability groups (mRS = 2; 3; 4/5), the following parameters were evaluated: intracerebral hemorrhage, mortality, NIHSS, ΔNIHSS and mRS.
Results: Baseline-NIHSS and age were not significantly different among groups. Mortality was higher in the pre-morbid mRS 4/5 group (44%) than in the pre-morbid mRS 2 (16.7%) and mRS 3 groups (21.4%). In survived patients, median ΔNIHSS% was higher in the mRS 2 and 3 groups (-63.3% and −92.3%, respectively) than in the mRS 4/5 group (−9.1%). The 247 rt-PA treated subjects with mRS < 2 in the same period showed lower mortality rate (4.7%), lower sICH (5%), lower mRS at discharge (median 1; range 0–6) and similar ΔNIHSS% (−75%).
Conclusion: Patients with mRS 2 and 3 may benefit from rt-PA with a moderate risk of sICH and mortality.

1. Introduction

Treatment with recombinant tissue plasminogen activator (rt-PA) within the first 4.5 h from symptoms onset is the first-line approved therapy for stroke patients [1,2]. The treatment availability has significantly improved over time and different exclusion criteria have been discussed over decades to guarantee the best possible stroke treatment to an increasing number of patients.

People with severe dementia or physical disability before stroke do not usually undergo interventional treatment for acute ischemic stroke. This subgroup of patients has not been studied because clinical trials generally exclude patients with pre-existing disability. In particular, patients with pre-existing disabling neurological disease have been excluded from the European Cooperative Acute Stroke Study (ECASS) and from the Third International Stroke Trial (IST-3) rt-PA trials [3–6].

The modified Rankin Scale (mRS) is a commonly used scale to measure the degree of disability or dependence in daily activities of people with neurological and non-neurological disability owing to stroke or other causes. It has become the most widely used clinical outcome measurement for stroke clinical trials [7,8]. mRS ranges from 0 to 6, from perfect health without symptoms to death.

Stroke patients with pre-existing disability are usually older (>80 years old), which comprise a more complicated management, in particular as far as reperfusion therapy decision making is concerned. It is known that elderly patients tend to have worse post-stroke functional outcome than younger patients, despite adjustment for stroke risk factors and other comorbidities [9]. Older patients generally present greater stroke severity at onset, higher premorbid disability and more frequent medical complications in the acute phase. However, recent studies have reported that age does not negatively affect rt-PA treatment effectiveness [9–11]. A recent study evaluating the safety and effectiveness of thrombolysis in a large cohort of patients older and younger than 80 years showed higher degree of prior-to-stroke disability in the elderly patients which did not significantly affect the thrombolysis

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outcome [12]. Pre-existing disability is reported in up to 12.5% of treated cases in registry studies, with a greater proportion (24.8%) among patients older than 80 years old [13–15]. Recently, in actual clinical practice in Central and Eastern Europe, patients with at least slight pre-existing disability accounted for 8% of all cases treated with rt-PA [16]. Pre-stroke disability did not increase the risk of symptomatic intracerebral hemorrhage (sICH), but it may be associated with less neurological improvement and higher mortality.

Considering the above-mentioned high rate of stroke occurrence in these patients and the lack of studies regarding the safety and outcome of rt-PA in pre-stroke disability, the aim of our study was to investigate rt-PA effectiveness in a cohort of acute stroke patients with pre-existing disability (mRS $\geq$ 2).

2. Materials and methods

We retrospectively analyzed the clinical and imaging data of patients with acute ischemic stroke admitted to the Stroke Unit of the University Hospital and Health Services of Trieste (Italy) from September 2015 to October 2017. Inclusion criteria were acute ischemic stroke symptoms, admission within 4.5 h or wake-up stroke or undetermined onset, pre-existing disability (mRS $\geq$ 2), rt-PA treatment. We excluded patients with stroke mimic and hemorrhagic stroke.

mRS ranges from 0 to 6, from perfect health without symptoms to death, and it was calculated as follows: (0) No symptoms; (1) No significant disability. Able to carry out all usual activities, despite some symptoms; (2) Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities; (3) Moderate disability. Requires some help, but able to walk unassisted; (4) Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted; (5) Severe disability. Requires constant nursing care and attention, bedridden, incontinent; (6) Dead. Barthel score [17], NIHSS score [18] and MMSE [19] were also used to assess patient's ability to perform daily life tasks, cognitive ability and stroke severity.

Following data of included patients were collected: (1) demographic details (age, sex); (2) stroke risk factors (hypertension, diabetes, dyslipidemia, smoke, ischemic cardiopathy, atrial fibrillation); (3) NIHSS score, Barthell score and mRS at baseline; (4) NIHSS score, Barthell score and mRS at discharge; (5) symptomatic intracerebral hemorrhage (sICH); (6) time from symptom onset to reperfusion therapy; (7) side of ischemic area; (8) stroke subtype classification at discharge classified by TOAST [20]; (9) OCST Classification [21]; (10) ASPECT [22]; (11) neuroimaging data (non-enhanced CT ad admission and non-enhanced CT at 24 h; CT angiography and CT Perfusion at admission).

In order to assess the differences in clinical outcome among the three disability groups (mRS = 2; mRS = 3 and mRS = 4 and 5) following parameters were evaluated: intracerebral hemorrhage, mortality rate, changing of NIHSS and mRS score, as well as ΔNIHSS calculated as percentage of NIHSS decrease from admission to discharge in order to measure the patient recovery.

$$\Delta\mathrm{NIHSS}(\%) = \frac{\mathrm{NIHSS}_{\mathrm{discharge}} - \mathrm{NIHSS}_{\mathrm{admission}}}{\mathrm{NIHSS}_{\mathrm{admission}}} \cdot 100\%$$

The research was conducted according to the principles of the Declaration of Helsinki. All participants released their informed consent to participate in the study after all procedures had been fully explained. Approval for the study had been obtained from the local ethics committee.

Continuous variables were presented as mean ± SD or medians (ranges) depending on their distribution (normal or not) and non-continuous variables as percentages. The differences in NIHSS at admission and in ΔNIHSS among three disability groups (mRS = 2; mRS = 3 and mRS = 4 and 5) were assessed by Kruskal-Wallis test. A level of $p < 0.05$ was regarded as statistically significant.

3. Results

After a retrospective review of 282 acute ischemic stroke patients who underwent reperfusion therapy, a total of 35 subjects (26F; 9 M) with mRS $\geq$ 2 formed the final study population. All subjects were Caucasian and median age at admission was 87 years old (range 45–95). At admission, median mRS was 3 (range 2–5), median NIHSS was 14.5 (range 1–24), median Barthel score was 27.5 (range 0–100). In 15 patients with pre-stroke dementia median MMSE was 20/30. Mean time from stroke onset to intravenous treatment was 185 ± 42 min. In 3 cases, patients were admitted due to wake-up stroke. Other 3 patients underwent thrombectomy after rt-PA. Most treatments were performed during day time, in only 8 cases rt-PA was administered after 8:00 PM. Anterior cerebral infarct (TACI) was observed in 22 cases, while partial syndrome (PACI) in 9 cases and lacunar stroke (LACI) in 3 cases. Stroke involving the posterior circulation (POCI) was not observed. Arterial hypertension affected 26 patients (74%), Dyslipidemia 13 patients (37%), Diabetes Type II 9 patients (26%), Atrial fibrillation 16 patients (46%) and Ischemic cardiopathy 12 patients (34%). Stroke's pathogenesis atherothrombotic infarction due to damage of larger vessel was identified in 6 patients; in 4 cases, small vessels were involved; cardioembolic mechanism was reported in 15 cases; after all diagnostic evaluation, cryptogenic stroke was diagnosed in 9 subjects. In 18 subjects the lesion was in the left side, while in 17 in the right side. Median ASPECT score was 9.0 (range 7–10), 17 of the 35 patients had ASPECT 10. In 3 cases a major vessel occlusion was found (middle cerebral artery). Out of 35 patients, 7 reported hemorrhagic transformation with significant clinical deterioration, causing death in 6 cases. Median days of hospitalization was 15 (range 1–56). Median NIHSS at discharge was 5.5 (range 0–21), median ranking scale at discharge was 4 (range 2–6), median Barthel at discharge was 15 (range 0–100). Mortality rate was 25.7% (9 out of 35 patients). Baseline clinical and neuroimaging findings are summarized in Table 1.

Table 1
Clinical characteristics and neuroimaging findings at admission.

Age (years)	87 (45–95)
Gender (M:F)	9:26
Time from onset to rt-PA (minutes)	185 ± 42
Comorbidities	
Hypertension (%)	74%
Diabetes mellitus (%)	26%
Atrial fibrillation (%)	46%
Dyslipidemia (%)	37%
Ischemic cardiopathy (%)	34%
NIHSS baseline	14.5 (1–24)
mRS	3 (0–5)
Barthel	15 (0–100)
ASPECT	9 (7–10)
Lesion side (R:L)	17:18
OCSP Classification (N)	
PACI	9 (25.7%)
POCI	0 (0%)
TACI	22 (62.8%)
LACI	3 (8.6%)
TOAST Classification (N)	
Large-artery atherosclerosis	6 (17.1%)
Cardioembolism	15 (43.1%)
Small-vessel occlusion	4 (11.4%)
Stroke of undetermined etiology	9 (25.7%)
Stroke of other determined etiology	0

Mortality rate, sICH, and changes in NIHSS and mRS score were reported in Table 2 for each of the three disability groups (mRS = 2; mRS = 3 and mRS = 4 and 5). NIHSS at admission and age were not significantly different among groups. Mortality was higher in the pre-morbid mRS 4 and 5 group (44%) than in pre-morbid mRS 2 (16.7%) and 3 groups (21.4%). In patient who survived, median ΔNIHSS% was higher in groups with mRS 2 and 3 (-63.3% and −92.3%, respectively) than in group with mRS 4 and 5 (-9.1%), although not statistically significant.

In order to evaluate these results in respect to the 247 subjects with rankin < 2, who underwent rt-PA therapy in the same period, we observed lower mortality rate (4.7%), lower sICH (5%), lower mRS at discharge (Median 1; range 0–6). In survived subjects with mRS < 2, ΔNIHSS% was similar (−75%) to those with pre-morbid mRS 2 and 3.

4. Discussion

rt-PA treatment within the first 4.5 h from symptoms onset has been widely debated and is actually contraindicated for patients with acute stroke and pre-existing disability. Despite the high stroke occurrence in these patients, there is a lack of studies regarding the reperfusion treatment safety and effectiveness in pre-stroke disability patients. The main finding of this study was that patients with mRS 2 and 3 may benefit from thrombolytic therapy with moderate risk of sICH and mortality.

In our study, almost all patients with mRS 2 and 3 treated with rt-PA improved the neurological deficit measured by the admission/discharge NIHSS score and their recovery is similar to that of patients without or with mild disability at admission. For higher pre-morbid disability patients with mRS 4 and 5, risks are higher and recovery is limited. Despite in patients with pre-existing disability death was higher compared to those without pre-existing disability, our results suggested that patients with and without pre-existing disability may return to their premorbid functional status following intravenous thrombolysis, in accordance with previous study [23]. Our findings are consistent with a previous studies supporting the hypothesis that moderate disability alone should not be considered as a contraindication to IVT treatment [24,25].

It is a critical issue deciding how to manage and treat older patients with acute ischemic stroke and pre-existing disability. In clinical practice, physicians can count on modern neuroimaging techniques. Different neuroimaging techniques may guide the patient selection for reperfusion therapy and discriminate between ischemic core and penumbra [26]. In the past years, great research interest was shown toward CT perfusion (CTP), which is progressively becoming more widespread and available in emergency departments [26–29]. A recent study showed that CTP assessed perfusion deficit is related to neurological disability at admission [28] and allows the identification of patients eligible for reperfusion treatment [30] in cases of wake-up stroke, too [31]. In our study, CTP imaging, which was performed in 74% of our sample, supported the decision to apply reperfusion therapy. However, results showed that considering mRS at admission too, proves to be important when higher than 3. Fig. 1 shows two cases with different pre-existing disability, both with large penumbra area and with different outcome after rt-PA treatment.

Furthermore, older and disability patients often show cognitive impairment. In our study population, besides pre-existing disability, a large number of patients suffered from cognitive impairment. The relation between stroke and dementia is complex: cerebral infarction itself is a risk factor for post-stroke dementia and pre-stroke cognitive impairment or dementia is a risk factor for stroke [32,33]. How to best manage stroke patients with pre-existing

Table 2
Mortality, sICH, and changes in NIHSS and mRS score in acute stroke patients with mRS = 2; mRS = 3 and mRS = 4 and 5.

Rankin	Number of patients	Age Median (range)	Mortality N (%)	sICH N (%)	mRS at discharge Median (range)	mRS at 3 months Median (range)	NIHSS at admission Median (range)	NIHSS discharge Median (range)	ΔNIHSS% Median (range)
2	12	82 (45;89)	2 (16.7%)	3 (25%)	4(2;6)	4 (2;6)	14.5 (2;18)	7 (1;18)	−63.3% (-100; 55)
3	14	89 (79;95)	3 (21.4%)	2 (14%)	4 (3;6)	4 (3;6)	11 (1;24)	1 (0;19)	−92.1% (-100;19)
4 and 5	9	88 (71;94)	4 (44%)	2 (22%)	5 (4;6)	5 (4;6)	15 (11;23)	17 (3;21)	−9.1% (-80; 46)

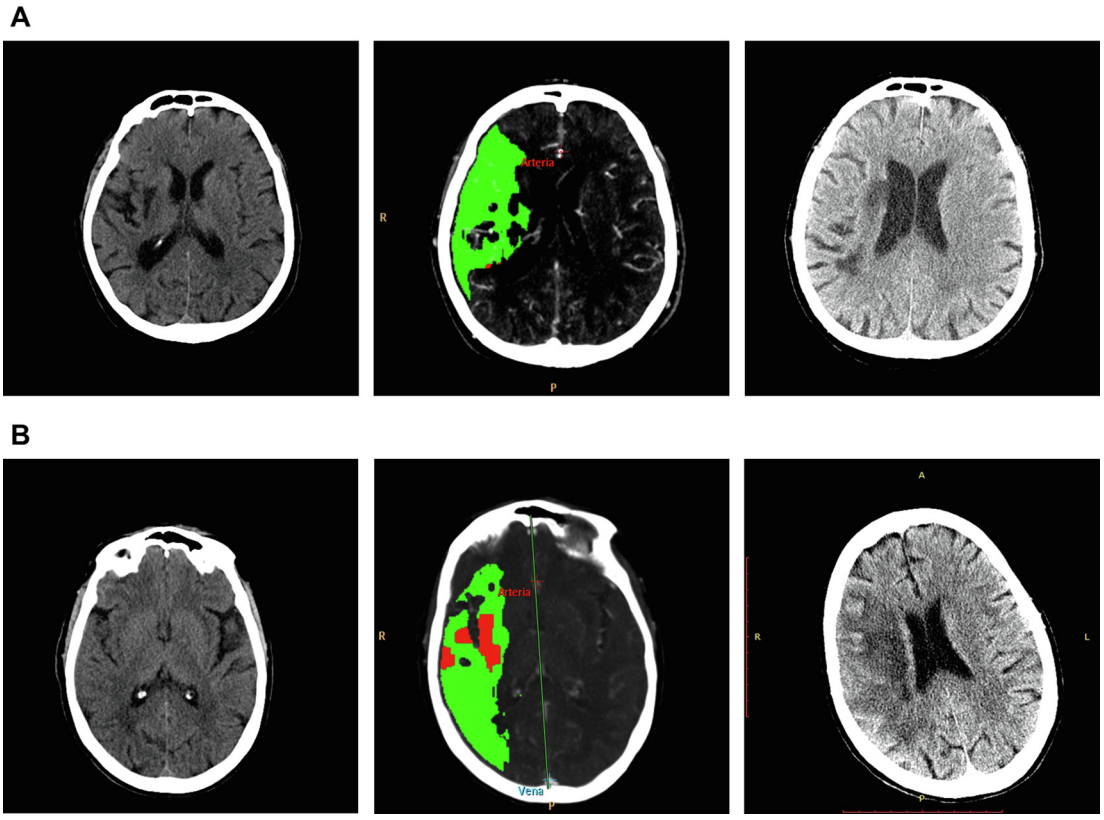

Fig. 1. Neuroimaging assessment. From left to right: Direct CT at admission; CT perfusion identified core penumbra areas; 24 h Direct CT: (A) Male patient 87 years old and pre-existing disability with mRS = 3, with moderate left hemiparesis and dysarthria (NIHSS = 15), brain CT Perfusion scan shows a wide penumbral area in the territory of the right middle cerebral artery, brain CT scan performed after 24 h from thrombolysis shows a small infarcted area. After 7 days the patient was discharged and transferred to the rehabilitation unit with NIHSS of 6. (B): Female 78 years old and pre-existing disability with mRS = 4, with severe left hemiparesis and dysarthria (NIHSS = 18), brain CT Perfusion scan shows a large penumbral area. In the territory of the right middle cerebral artery with a small core extended from the subcortical area to the cortical ones, brain CT scan performed after 24 h from thrombolysis shows the lesion in the territory of the right middle cerebral artery. After 5 days the patient died.

dementia is still debated. Moreover, patients with history of dementia tended to be older, with higher prevalence of comorbidities and more severe stroke. However, as reported in literature, medical complications, intracerebral hemorrhage, and survival were similar among patients receiving thrombolysis, whether they had dementia or any pre-existing disability or not [34]. The results of our study are in line with these findings.

The European guidelines recommend that only patients with pre-stroke mRS equal to 0 should be selected for acute stroke interventions and it does not give clear guidance on treatment management for pre-stroke mRS ≥ 2 patients [35]. The American Heart Association Stroke Council is starting to consider that disability does not increase the risk of post-thrombolysis bleeding and that thrombolysis/thrombectomy may be reasonable in selected cases, even if they may be associated with less neurological improvement and higher mortality [36,37]. Recently, patients with stroke and premorbid disability have been regarded as subjects with higher mortality, institutionalization, and costs if they accumulate additional disability due to stroke, thus recommending acute interventions, which are currently routinely withheld in patients with mild-moderate premorbid disability [38]. The results of our study in a limited sample support the aforementioned considerations. Indeed, our population with mRS 2–3 (despite moderately higher mortality risk compared to patients with mRS 0–1) have shown great improvement in terms of NIHSS score after rt-PA treatment, with some of them returning to their previous quality of life without substantial additional disability.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333: 1581-7.
[2] The NINDS. t-PA stroke study group. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA stroke trial. Stroke 1997;28:2119–25.
[3] Hacke W, Kaste M, Bluhmki E, Investigators ECASS, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317e1329.
[4] Foell RB, Silver B, Merino JG, Wong EH, Demaerschalk BM, Poncha F, et al. Effects of thrombolysis for acute stroke in patients with preexisting disability. CMAJ 2003;169:193–7.
[5] Saposnik G, Cote R, Rochon PA, Mamdani M, Liu Y, Raptis S, Kapral MK, Black SE. Registry of the Canadian Stroke Network; Stroke Outcome Research Canada

(SORCan) Working Group. Care and outcomes in patients with ischemic stroke with and without preexisting dementia. Neurology 2011;77(18):1664–73. https://doi.org/10.1212/WNL.0b013e31823648f1.
[6] Mazya M, Egido JA, Ford GA, Lees KR, Mikulik R, Toni D, et al. Predicting the risk of rymptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: Safe Implementation of Treatment in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke 2012;43:1524–31.
[7] Wilson JL, Hareendran A, Grant M, et al. Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale. Stroke 2002;33(9):2243–6.
[8] Saver JL, Filip B, Hamilton S, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: the Rankin Focused Assessment (RFA). Stroke 2010;41(5):992–5.
[9] Denti L, Scoditti U, Tonelli C, et al. The poor outcome of ischemic stroke in very old people: a cohort study of its determinants. J Am Geriatr Soc 2010;58:12e17.
[10] Bhalla A, Grieve R, Tilling K, et al. BIOMED II European Study of Stroke Care: older stroke patients in Europe: stroke care and determinants of outcome. Age Ageing 2004;33:618e624.
[11] Sandercock P, Wardlaw JM, Lindley RI, et al. IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST- 3]): a randomised controlled trial. Lancet 2012;23:352e363.
[12] Paolo Immovilli, Eugenia Rota, Nicola Morelli, Paola De Mitri, Fabiola Magnifico, Andrea Mascolo, Emilio Terlizzi, Ilaria Iafelice, Andrea Magnacavallo, Emanuele Michieletti, Donata Guidetti. Intravenous Thrombolysis for Acute Ischemic Stroke in the Elderly: An Italian Cohort Study in a "Real World" Setting. International Journal of Gerontology 9 (2015; 20e23).
[13] Wahlgren N, Ahmed N, Davalos A. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275–82.
[14] Simpson MA, Dewey HM, Churilov L. Thromboly-sis for acute stroke in Australia: outcomes from the Safe Implementation of Thrombolysis in Stroke registry (2002–2008). Med J Aust 2010;193:439–43.
[15] Ahmed N, Lees KR, Ringleb PA. Outcome after stroke thrombolysis in patients >80 years treated within 3 hours vs>3-4.5hours. Neurology 2017;89:1561–8.
[16] Karlinski M, Kobayashi A, Czlonkowska A. Role of preexisting disability in patients treated with intravenous thrombolysis for ischemic stroke. Stroke 2014;45:770–5.
[17] Loewen SC, Anderson BA. Reliability of the modified motor assessment scale and the barthel index. Phys Ther 1988;68(7):1077–81.
[18] Kwah Li Khim, Diong Joanna. National Institutes of Health Stroke Scale (NIHSS). J. Physiother. 2014;60(1):61. https://doi.org/10.1016/j.jphys.2013.12.012.
[19] Folstein MF, Folstein SE, McHugh PR, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, in Journal of Psychiatric Research, vol. 12, n 3; 1975, pp. 189–98, DOI:10.1016/0022-3956 (75) 90026-6, PMID 1202204.
[20] P. Adams Jr., MD, Birgitte H. Bendixen, PhD, MD, L. Jaap Kappelle, MD, Jose Biller, MD, Betsy B. Love, MD, David Lee Gordon, MD, E. Eugene Marsh III, MD, and the TOAST Investigators. Classification of Subtype of Acute Ischemic Stroke Definitions for Use in a Multicenter Clinical Trial Harold. Stroke 1993; 24: 35-41.
[21] Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet 1991;337(8756):1521–6.
[22] Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, et al. Use of the alberta stroke program early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol. 2001;22(8):1534–42.
[23] Zhang Wenwen, Coote Skye, Frost Tanya, Dewey Helen M, Choi Philip MC. Acute stroke patients with mild-to-moderate pre-existing disability should be considered for thrombolysis treatment. J. Stroke Cerebrovas. Dis. 2018;27 (10):2707–11. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.05.051.
[24] Gensicke H, Strbian D, Zinkstok SM, Scheitz JF, Bill O, Hametner C, et al. Intravenous thrombolysis in patients dependent on the daily help of others before stroke. Stroke 2016;47(2):450–6.
[25] Merlino G, Corazza E, Lorenzut S, Gigli GL, Cargnelutti D, Valente M. Efficacy and safety of intravenous thrombolysis in patients with acute ischemic stroke and pre-existing disability. J Clin Med 2019;8(3):400.
[26] González RG. Imaging-guided acute ischemic stroke therapy: from "time is brain" to "physiology is brain". Am J Neuroradiol 2006;27:728–35.
[27] Manganotti P, Furlanis G, Ajčević M, et al. CT perfusion and EEG patterns in patients with acute isolated aphasia in seizure-related stroke mimics. Seizure 2019;71:110–5.
[28] Furlanis G, Ajčević M, Stragapede L, Lugnan C, Ridolfi M, Caruso P, et al. Ischemic Volume and Neurological Deficit: Correlation of Computed Tomography Perfusion with the National Institutes of Health Stroke Scale Score in Acute Ischemic Stroke. J Stroke Cerebrovas Dis 2018;27(8):2200–7.
[29] Stragapede L, Furlanis G, Ajčević M, Ridolfi M, Caruso P, Naccarato M, et al. Brain oscillatory activity and CT perfusion in hyper-acute ischemic stroke. J Clin Neurosci 2019. https://doi.org/10.1016/j.jocn.2019.07.068.
[30] Parsons MW. Perfusion CT: is it clinically useful? Int J Stroke 2008;3:41–50.
[31] Caruso P, Naccarato M, Furlanis G, Ajčević M, Stragapede L, Ridolfi M, et al. Wake-up stroke and CT perfusion: effectiveness and safety of reperfusion therapy. Neurol Sci. 2018. https://doi.org/10.1007/s10072-018-3486-z.
[32] Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet Neurol 2005;4:752–9.
[33] Zhu L, Fratiglioni L, Guo Z, et al. Incidence of dementia in relation to stroke and the apolipoprotein E epsilon4allele in the very old: findings from a population-based longitudinal study. Stroke 2000;31:53–60.
[34] G. Saposnik, MD, MSc, FAHA, R. Cote, MD, FRCPC, FAHA, P.A. Rochon, MD, MPH, FRCPC, M. Mamdani, PharmD, MPH, MA, Y. Liu, MSc, S. Raptis, MSc, M.K. Kapral, MD, MSc, FRCPC, S.E. Black, MD, FRCPC. Care and outcomes in patients with ischemic stroke with and without preexisting dementia. Neurology® 2011; 77: 1664–1673.
[35] Fiehler J, Cognard C, Gallitelli M, Jansen O, Kobayashi A, Mattle HP, et al. European recommendations on organisation of interventional care in acute stroke (EROICAS). Int J Stroke 2016;11:701–16. https://doi.org/10.1177/1747493016647735.
[36] Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al. American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016;47:581–641. https://doi.org/10.1161/STR.0000000000000086.
[37] Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, American Heart Association Stroke Council, et al. 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 2018;2018(49):e46–e110. https://doi.org/10.1161/STR.0000000000000158.
[38] Aravind Ganesh, MD; Ramon Luengo-Fernandez, DPhil; Sarah T. Pendlebury, DPhil; Peter M. Rothwell, FMedSci; on behalf of the Oxford Vascular Study Long-Term Consequences of Worsened Poststroke Status in Patients With Premorbid Disability Implications for Treatment. Stroke. 2018; 49: 2430–2436. Doi: 10.1161/STROKEAHA.118.022416.