Clinical outcomes of ischemic stroke patients after thrombolytic therapy

Desfechos clínicos de pacientes com acidente vascular cerebral isquêmico após terapia trombolítica

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Abstract

Objective: To analyze outcomes and associated factors in ischemic stroke patients submitted to thrombolytic therapy.

Methods: This was a retrospective cohort study of ischemic stroke patients submitted to thrombolytic therapy. Comorbidities, neurologic deficits and time of thrombolysis were described. The chi-squared test was used to assess association among comorbidities, time of thrombolysis, and occurrence of hemorrhagic transformation.

Results: There was a high frequency of comorbidities. Mean neurological deficit score was 15 points. Mean time window was 98 minutes and needle-to-door time, 89.9 minutes. Hemorrhagic transformation was observed in 20 patients. Bivariate analysis revealed that hemorrhagic transformation was associated with greater neurologic deficit score, atrial fibrillation and heart disease. Neurologic deficit fell from 51% to 12.5% between admission and discharge.

Conclusion: Thrombolytic therapy presented positive outcomes, regardless of long thrombolysis time and high neurologic deficit scores.

Resumo

Objetivo: Analisar desfechos e fatores associados em pacientes com acidente vascular cerebral isquêmico após terapia trombolítica.

Métodos: Estudo do tipo coorte retrospectivo de pacientes com acidente vascular cerebral isquêmico submetidos à terapia trombolítica. Foram descritas as comorbidades; os défices neurológicos e os tempos de atendimento. Utilizou-se o teste qui quadrado para associação entre comorbidades, tempos de atendimento e ocorrência de transformação hemorrágica.

Resultados: Houve elevada frequência de comorbidades. Défices neurológicos pontuaram média de 15 pontos. A janela de tempo obteve média de 98 minutos e o tempo porta-agulha, 89,8 minutos. Observou-se transformação hemorrágica em 20 pacientes. Na análise bivariada, a ocorrência de transformação hemorrágica esteve associada com maior défice neurológico, fibrilação atrial e cardiopatia. Houve redução dos défices neurológicos de 51% para 12,5 entre a admissão e alta.

Conclusão: A terapia trombolítica apresentou resultados positivos, apesar de tempos de atendimento elevados e pacientes com défices neurológicos com elevada pontuação.

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Introduction

Stroke and ischemic heart disease are the leading causes of premature death worldwide. Strokes are also one of the main events responsible for reducing functional capacity in activities of daily living.[1]

The occurrence of strokes is related to risk factors, which are dependent on lifestyle habits that increase the probability of developing the disease.[2]

There are two types of strokes, ischemic and hemorrhagic, depending on the determining ischemic mechanisms or predominant brain lesion topography. Approximately 80% of strokes are ischemic and, for the most part, involve the thromboembolic occlusion of the arterial territory corresponding to the neurologic manifestation, causing reduced cerebral perfusion pressure.[3]

Stroke treatment promotes arterial rechanneling, dissolving occlusive thrombi or emboli through chemical (systemic or intra-arterial use of thrombolytic drugs) or mechanical thrombolysis (surgical removal of clots). These procedures restore cerebral blood flow to the region of ischemic penumbra, leading to functional recovery.[4]

Since the early 2000s, the standard pharmacological treatment for acute ischemic stroke has been thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA).[5]

The effectiveness of this therapy has been demonstrated; however, there are still challenges in the implementation of thrombolytic treatment protocols and few ischemic stroke patients benefit from this therapy. One of the main limiting factors is time. The shorter the time window between onset of stroke symptoms and drug infusion, greater the chances of a good prognosis.[6]

The main clinical outcomes associated with this treatment are: significantly improved National Institute of Health Stroke Scale NIHSS score, hospital discharge, low occurrence of symptomatic hemorrhagic transformation, and low treatment-related deaths.[7,8]

In Brazil, intravenous thrombolysis for ischemic stroke is conducted in several hospitals. However, there are few national reports on the demographic and clinical characteristics of patients submitted to this treatment. There is also little information on the frequency of complications due to this therapy, such as hemorrhagic transformation. More information is needed on how epidemiological and health system characteristics influence the treatment's safety, considering ischemic stroke as an extensively undertreated event.

In this context, the objective of this study was to analyze outcomes and associated factors in ischemic stroke patients at a hospital after receiving rt-PA thrombolytic therapy.

Methods

This was a quantitative retrospective cohort study. It was approved by the ethics committee of the Federal University of Triângulo Mineiro, under resolution 1.040.479.

The investigation took place at a public teaching hospital that covers 27 municipalities in the south of the Minas Gerais Triangle Region, Brazil. This facility provides high-complexity care, exclusively via the Brazilian Unified Health System (SUS). It has 301 active beds, of which 25 belong to the emergency department. The hospital is a certified teaching hospital and meets the professional training demands of health undergraduate programs, medical, nursing and multiprofessional residencies, and graduate-level programs.

Between January 2012 and January 2015, 828 stroke patients diagnosed were admitted. Of these, 78 received rt-PA treatment. The chart numbers of patients submitted to thrombolysis during this period were obtained from the institution's electronic system, requested at the medical archive service. Data were gathered using an instrument specifically designed to gather information on the variables of interest of this study.

This study included the medical charts of patients 18 years or older diagnosed with ischemic stroke and International Disease Classification IDC 10 (I 64.0) duly registered with the pharmacy and the medical archive service for intravenous thrombolytic treatment.

Medical charts that were not found in the archive service's registration system after five attempts and those that were incomplete in terms of research variables were excluded.

Seventy-nine patients were included in the initial sample; however, 14 charts were not found after five attempts with the hospital's medical archive service. Thus, the sample comprised 64 medical charts that met the inclusion criteria.

The studied sociodemographic variables were: age, gender, ethnicity and origin, and comorbidities as recorded on the admission form or diagnosed during hospital stay. Tobacco use and alcohol consumption were considered as risk factors.

Etiology of ischemic stroke was classified as per Adams et al.[9] into large artery atherosclerosis, small artery atherosclerosis, heart embolism, undetermined, and other causes.

In this study, time window was defined as the time between stroke symptom onset and hospital admission, in minutes; door-to-needle time was understood as the time between hospital admission and intravenous thrombolysis, in minutes; time of thrombolysis was the time between onset of stroke symptoms and rt-PA infusion, in minutes; time of admission corresponded to time between admission and discharge, in days.

Hemorrhagic transformation due to hospital admission (pneumonia, urinary tract infection and pressure ulcers), discharge, and death comprised the clinical outcomes.

The NIHSS was used to assess stroke-related neurologic deficit. Minimum score is zero and maximum is 42, and, in general, the scale is used to estimate stroke severity, predict size of injury, patient evolution and prognosis.[10] Yaghi et al.[11] considers an NIHSS score lesser or equal to 7 as indicative of minor neurologic deficit, 8 to 14, as moderate deficit, and greater or equal to 15, severe deficit.

The data were inserted in an electronic spreadsheet using Excel® for Windows®, validated via dual data entry. Next, they were exported and processed using the Statistical Package for the Social Sciences (SPSS), version 22 for Windows 8®, for data processing and analysis.

Descriptive statistics were computed for quantitative variables using measures of central tendency (mean and median) and dispersion (standard deviation). The chi-square test was used to determine association between time of thrombolysis and NIHSS score after rt-PA infusion.

To assess statistical significance of NIHSS score improvement at the time of admission and discharge, scores were categorized into minor, moderate and severe.[11] After this procedure, the Wilcoxon test was applied.

Qualitative variables were analyzed according to descriptive statistics via simple univariate frequencies, and association measures via contingency tables.

Significance was set at 5% ($p<0.05$), with a 95% confidence interval.

Results

Between January 2012 and January 2015, 828 stroke patients were admitted; of these, 657 (79.4%) were ischemic and (11.8%) received rt-PA treatment. For this study, 64 patient charts were evaluated.

Of the analyzed charts (n=64), the age range of the study subjects was 39 to 85 years (mean 65.7 years, standard deviation 11.3)

The sociodemographic data revealed that most patients were men 34 (59.6%), white 31 (54.4%) and from the city of Uberaba 48 (84.2%).

The most prevalent comorbidities were systemic arterial hypertension (76.6%), atrial fibrillation (28.1%), heart disease (25%) and diabetes *mellitus* (17.2%).

The site of stroke for most patients (73.4%) was the middle cerebral artery. In terms of etiology, most of the events were caused by heart embolism (50%), followed by large artery occlusion (28%).

According to the NIHSS, neurologic deficit score at the time of admission varied between 6 and 30 points, with mean score 14.7 and median 15. At the time of admission, scores varied between zero and 25 points, with a mean and median of 7.7 and 15, respectively.

Level of severity of neurologic deficit as measured by the NIHSS at admission and discharge is demonstrated in table 1. There were improvements in scores by deficit category whose statistical significance was appraised via the Wilcoxon test, p< 0.01.

The results of the time intervals involved in thrombolytic therapy were: mean time window of 98.4 minutes and standard deviation of 61.2. Door-to-needle time obtained a mean of 89.9 minutes and standard deviation of 39.8. Time of thrombolysis had a mean of 191.4 minutes and standard deviation 52.9.

Complications due to thrombolytic therapy and hospital admission were: symptomatic hemorrhagic transformation 20 (31%), pneumonia 13 (20.4%), urinary tract infection 5 (7.9%) and pressure ulcer 4 (6.3%).

Table 1. National Institute Health Stroke Scale (NIHSS) scores on hospital admission and discharge of investigated patients (n=64)

Classification	Admission n(%)	Discharge n(%)	p-value
Deficit			
Minor (0-7)	5(7.8)	34(53.1)	<0.01
Moderate (8-14)	26(40.6)	18(28.3)	
Severe (≥15)	33(51.6)	6(12.5)	
Death	-	4(0.6)	
Total	64(100)	64(100)	

Regarding clinical outcomes (discharge and death), most of the investigated patients (90.6%) were discharged to home, 4.7% died from other causes, 3.1% were discharged to another hospital, and 1.6% died from thrombolysis.

Length of hospital stay ranged between 3 and 31 days, with a mean of 11.7 days.

Results of the association test between age and NIHSS score at time of admission did not find any association between age and NIHSS score (chi square with p>0.05).

There was no association between time window, divided into two categories (zero to 180 minutes and >180 minutes) and NIHSS score subdivided into categories zero to 14 points and 15 to 42 points (chi square with p>0.05).

Table 2 shows the correlation between the occurrence of hemorrhagic transformation according to the studied variables. Patients with NIHSS >15 were 2.8 times more likely to develop hemorrhaging after the procedure when compared to those with a score <15 points (p=0.01). There was no statistical significance between the occurrence of hemorrhages and age, door-to-needle time, and thrombolysis time.

Patients who presented atrial fibrillation had two times the risk to develop symptomatic hemorrhagic transformation; those with heart disease were two and half times more likely to suffer hemorrhagic transformation in comparison to individuals who did not present these diseases. These associations are shown in table 3.

Table 2. Association between age, National Institute Health Stroke Scale (NIHSS) score, door-to-needle time and thrombolysis time; and occurrence of hemorrhagic transformation in selected patients (n=64)

Variables	Hemorrhagic transformation				p-value
	Yes n(%)	No n(%)	RR (95%CI)	OR (95%CI)	
Age, years			0.4 (0.2-1.2)	0.3(0.1-1.1)	0.1
18-60	4(17.4)	19(82.6)			
>60	16(39.0)	25(61.0)			
NIHSS, score			0.4(0.1-0.7)	0.2(0.1-0.9)	0.01
0-14	5(16.1)	26(83.9)			
15-42	15(45.5)	18(55.5)			
Door-to-needle, minutes					
<60	5(26.3)	14(73.7)	0.8(0.3- 1.9)	0.7(.2- 2.4)	0.6
≥60	15(33.3)	30(66.7)			
Thrombolysis, hours			1.1(0.5-2.2)	1.1(0.4-3.2)	0.9
<3	9(32.1)	19(67.9)			
≥ 3	11(30.6)	25(69.4)			

RR - relative risk; 95%CI - 95% confidence interval

Table 3. Association between comorbidities and occurrence of hemorrhagic transformation in investigated patients (n= 64)

Comorbidities	Hemorrhagic transformation				p-value
	Yes n(%)	No n(%)	RR (95%CI)	OR (95%CI)	
SAH			0.7(0.3-1.5)	0.6(0.2-2)	0.4
Yes	14(28.6)	35(71.4)			
No	6(40)	9(60)			
Diabetes			1.6(0.7-3.4)	2.1(0.6-8)	0.3
Yes	5(45.5)	6(54.5)			
No	15(28.3)	38(71.7)			
AF			2(1-4)	3.2 (1-10)	0.04
Yes	9(50)	9(50)			
No	11(30.6)	35(69.4)			
Heart disease			2.5(1.3-4.8)	4.3(1.3-14.2)	0.01
Yes	9(53.6)	7(46.4)			
No	11(22.9)	37(77.1)			
Dyslipidemia			0.5(0.102)	0.4(0.1-2)	0.3
Yes	2(18.2)	9(81.8)			
No	18(34)	35(66)			

RR - relative risk; 95%CI - 95% confidence interval; SAH - systemic arterial hypertension; AF - atrial fibrillation

Discussion

In this study, only 78 (11.8%) of the patients admitted underwent thrombolytic therapy, being that a frequency above 20% is considered adequate.[12]

The main events that explain such low rates of thrombolysis for stroke patients are: lack of public awareness about stroke symptoms to activate emergency medical services; lack of training for prehospital transportation professionals; patients' referrals to hospitals that do not perform thrombolysis; inefficient screening at emergency services to identify stroke cases; and lack of protocols that integrate all health professionals to avoid delays in patient presentation.[12,13]

In this investigation, most patients were male and white, similar to other studies.[14,15] There was no association between skin color and gender and rt-Pa treatment outcomes.[14]

Mean patient age was 65.7 years, close to that reported by the literature,[2,12] and was not associated with patient severity on the NIHSS neither to the occurrence of hemorrhagic transformation. The benefits of thrombolysis do not depend on patient age or NIHSS score. [8]

The selected cases presented high frequency of comorbidities. Arterial hypertension was the most prevalent risk factor, followed by heart disease, atrial fibrillation, and diabetes, data similar to those of other studies about rt-PA infusion.[2] In this investigation, patients with atrial fibrillation and heart disease presented greater risk for hemorrhagic transformation. Saposnik et al.[16] described the presence of atrial fibrillation as associated with greater risk for hemorrhagic transformation and higher death rates after intravenous thrombolysis.

The most common etiology for ischemic stroke was heart embolism, corroborating the findings of other studies.[17,18] Ischemic strokes caused by heart embolism represent approximately one-fourth of ischemic stroke cases, with worse symptomology and greater risk of developing hemorrhagic transformation.[19]

The researched patients presented severe neurologic deficit on hospital admission as scored by the NIHSS, with a mean of 15 points, i.e., higher than those found in other retrospective studies. A study in the United States developed with 7,193 patients found a mean NIHSS score of 11.[15] Al-Khaled et al.[20] obtained a mean score of 11.6 in a study with 1,007 patients. Patients with symptomatic hemorrhagic transformation obtained NIHSS scores higher than 15 points on admission, with statistical significance ($p<0.01$), corroborating the data presented in the literature.[15,21]

When compared with the literature,[8,18] this study found a higher percentage of patients with 15 points or more on the NIHSS. The percentage fell after thrombolytic treatment, dropping from 56% to 12.5%, a statistically significant difference

($p<0.01$). This satisfactory result among the studied patients was primarily due to their greater stroke severity, presence of comorbidities, and delayed time of treatment.

The difference between time windows in Brazilian and international studies is noteworthy. In a Brazilian study by Tosta et al.[7] the mean time window was 118 minutes. In the most important Brazilian study conducted at 19 hospitals with 2,407 stroke patients, the mean time window was 12.9 hours. Of these, 19 (1.1%) were treated with rt-Pa. In Canada, Ganesh et al.[22] found a mean time of 190 minutes. A prolonged time window is associated with delays due to the general public's failure to recognize stroke symptoms and the consequent delay in prehospital care and transportation. Thus, prolonged time window is one of the main barriers to conducting thrombolysis at hospitals.[15,22]

In this study, door-to-needle time was elevated and higher than that recommended by Brazilian guidelines on ischemic stroke treatment,[23] which establish a maximum of 60 minutes. Strbian et al.[24] and Fonarow et al.[25] obtained 77- and 40-minute door-to-needle times, respectively. A multicenter trial with 25,504 patients conducted by Fonarow et al.[26] in the United States indicated a direct relationship between adequate door-to-needle time and better patient outcomes. Thrombolysis is a complex process and in order to decrease door-to-needle time, health teams involved in stroke treatment must be organized and trained. This requires experience and changes that demand time.[24]

The mean time of thrombolysis in this study was 191 minutes, greater than those found in other studies, such as Tong et al.,[15] with 125 minutes and Gumbinger et al.,[27] 140 minutes. According to Mikulik et al.,[28] factors such as delayed hospital presentation and unsatisfactory door-to-needle time interfere in thrombolysis time. Measures to reduce thrombolysis time are necessary, for the sooner treatment is administered, the better the outcomes for ischemic stroke patients.[26]

Frequency of symptomatic hemorrhagic transformation was greater in comparison to other studies. Al-Khaled et al.[20] found 6%; Tong et al.,[15] 5%; Tosta et al.[7] and Cougo-Pinto et al.[21] found a frequency of 6%. The higher frequency of hemorrhagic transformation in this study can be explained by higher NIHSS scores and the presence of comorbidities such as atrial fibrillation and heart disease.

The occurrence of hospital pneumonia following rt-PA treatment diverges in the literature. Hoffmeister et al.[6] found 23.6% patients with pneumonia. Bruening and Al-Khaled[29] obtained 22.7%, while Gumbinger et al.[27] registered 8% of patients with hospital-acquired pneumonia. Hospital-acquired pneumonia following ischemic stroke treatment is considered a potentially avoidable complication, associated with high NIHSS scores and prolonged hospital stay.[29] This can explain the occurrence of the complication in the present study, as the patients presented higher NIHSS scores and longer hospital stays than in other studies.

Over 90% of the patients were discharged to home, and 6% died during the hospital stay. The death rate in this study was similar to that found by Schmidt et al.,[30] Al-Khaled et al.,[20] Ganesh et al.[22] and Tong et al.,[15] with 6%, 8.2%, and 7.2%, respectively. In clinical practice, ischemic stroke patients treated with rt-PA present better outcomes when compared to those who do not receive rt-PA. This points to the need to increase treatment availability, with actions aimed at improving therapy, prevention measures and recognition of the disease.[27]

Limitations of this study include its retrospective nature and the inclusion of only one specialized center. Incomplete data on patient charts limited the sample size, but did not compromise reaching the goals established by the researchers.

The results of this study can contribute to increasing the effectiveness of thrombolysis protocols for ischemic stroke patients and help support public policies in favor of more effective treatment in the healthcare system, resulting in improved neurologic recovery and quality of life for patients and family members.

Conclusion

Treatment with intravenous rt-PA for ischemic stroke resulted in lower NIHSS scores at the time of hospital discharge. It is worth noting the occur-

rence of symptomatic hemorrhagic transformation and the data obtained from a sample with a high frequency of comorbidities, severe neurologic deficits, and prolonged therapeutic windows.

Collaborations

Nascimento KG, Chavaglia SRR, Pires PS, Ribeiro SBF and Barbosa MH contributed with the project's conception, data analysis and interpretation, relevant critical review of its intellectual content and final approval of the version for publication.

References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, Moran AE, Sacco RL, Anderson L, Truelsen T, O'Donnell M, Venketasubramanian N, Barker-Collo S, Lawes CM, Wang W, Shinohara Y, Witt E, Ezzati M, Naghavi M, Murray C; Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245-54. Review. Erratum in: Lancet. 2014; 383(9913):218.
2. de Carvalho JJ, Alves MB, Viana GÁ, Machado CB, dos Santos BF, Kanamura AH, et al. Patterns of management, and outcomes in Fortaleza, Brazil: A hospital-Based Multicenter Prospective Study. Stroke. 2011; 42(12):3341-6.
3. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee JM, Moseley ME, Peterson ED, Turan TN, Valderrama AL, Vinters HV; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism. An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2013; 44(7):2064-89.
4. Martins SC, Freitas GR, Pontes-Neto OM, Pieri A, Moro CH, Jesus PA, Longo A, Evaristo EF, Carvalho JJ, Fernandes JG, Gagliardi RJ, Oliveira-Filho J; Executive Committee from the Brazilian Stroke Society and the Scientific Department in Cerebrovascular Diseases of the Brazilian Academy of Neurology. Guidelines for acute ischemic stroke treatment: part II: stroke treatment. Arq Neuropsiquiatr. 2012; 70(11):885-93.
5. Anani N, Mazya MV, Bill O, Chen R, Koch S, Ahmed N, et al. Changes in European Label and Guideline Adherence After Updated Recommendations for Stroke Thrombolysis Results From the Safe Implementation of Treatments in Stroke Registry. Circ Cardiovasc Qual Outcomes. 2015; 8(6 Suppl 3):S155-62.
6. Hoffmeister L, Lavados PM, Comas M, Vidal C, Cabello R, Castells X. Performance measures for in-hospital care of acute ischemic stroke in public hospitals in Chile. BMC Neurol. 2013; 13:23. doi: 10.1186/1471-2377-13-23.
7. Tosta ED, Rebello LC, Almeida SS, Neiva MS. Treatment of ischemic stroke with r-tPA: implementation challenges in a tertiary hospital in Brazil. Arq Neuropsiquiatr. 2014; 72(5):368-72.
8. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, Grotta J, Howard G, Kaste M, Koga M, von Kummer R, Lansberg M, Lindley RI, Murray G, Olivot JM, Parsons M, Tilley B, Toni D, Toyoda K, Wahlgren N, Wardlaw J, Whiteley W, del Zoppo GJ, Baigent C, Sandercock P, Hacke W; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014; 384(9958):1929-35.
9. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993; 24(1):35-41.
10. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. Clin Interv Aging. 2013; 8:201-11.
11. Yaghi S, Harik SI, Hinduja A, Bianchi N, Johnson DM, Keyrouz SG. Post t-PA transfer to hub improves outcome of moderate to severe ischemic stroke patients. J Telemed Telecare. 2015; 21(7):396-9
12. Eissa A, Krass I, Bajorek BV. Barriers to the utilization of thrombolysis for acute ischaemic stroke. J Clin Pharm Ther. 2012; 37(4):399-409.
13. Berkowitz AL, Mittal MK, McLane HC, Shen GC, Muralidharan R, Lyons JL, et al. Wordwide reported use of IV tissue plasminogen activador for acute ischemic stroke. Int J Stroke. 2014; 9(3):349-55.
14. Boehme AK, Siegler JE, Mullen MT, Albright KC, Lyerly MJ, Monlezun DJ, et al. Racial and gender differences in stroke severity, outcomes, and treatment in patients with acute ischemic stroke. J Stroke Cerebrovasc Dis. 2014; 23(4):e 255-61.
15. Tong X, George MG, Yang Q, Gillespie C. Predictors of in-hospital death and symptomatic intracranial hemorrhage in patients with acute ischemic stroke treated with thrombolytic therapy: Paul Coverdell Acute Stroke Registry 2008-2012. Int J Stroke. 2014; 9(6):728-34.
16. Saposnik G, Gladstone D, Raptis R, Zhou L, Hart RG; Investigators of the Registry of the Canadian Stroke Network (RCSN) and the Stroke Outcomes Research Canada (SORCan) Working Group. Atrial fibrillation in ischemic stroke predicting response to thrombolysis and clinical outcomes. Stroke. 2013; 44(1):99-104.
17. Kim BJ, Park JM, Kang K, Lee SJ, Ko Y, Kim JG, et al. Case characteristics, hyperacute treatment, and outcome information from the clinical research center for stroke-fifth division registry in South Korea. J Stroke. 2015; 17(1):38-53. Erratum in: J Stroke. 2015; 17(3):377-8.
18. Aoki S, Hosomi N, Sueda Y, Kono T, Takamatsu K, Ohyama H, Torii T, Kitamura T, Nomura E, Noda K, Ohtsuki T, Matsumoto M; HARP Registry Study Group. Multicenter Study of Intravenous Recombinant Tissue Plasminogen Activator Infusion around Hiroshima, Japan: The Hiroshima Acute Stroke Retrospective and Prospective Registry Study. J Stroke Cerebrovasc Dis. 2015; 24(12):2747-53.
19. Wang XG, Zhang LQ, Liao XL, Pan YS, Shi YZ, Wang CJ, Wang YL, Liu LP, Zhao XQ, Wang YJ, Li D, Wang CX; Thrombolysis Implementation and Monitoring of acute ischemic Stroke in China (TIMS-China) Investigators. Unfavorable outcome of thrombolysis in Chinese patients with cardioembolic stroke: a prospective cohort study. CNS Neurosci Ther. 2015; 21(8):657-61.
20. Al-Khaled M, Matthis C, Eggers J. Predictors of in-hospital mortality and the risk of symptomatic intracerebral hemorrhage after thrombolytic therapy with recombinant tissue plasminogen activator in acute ischemic stroke. J Stroke Cerebrovasc Dis. 2014; 23(1):7-11.

21. Cougo-Pinto PT, Santos BL, Dias FA, Fabio SR, Werneck IV, Camilo MR, et al. Frequency and predictors of symptomatic intracranial hemorrhage after intravenous thrombolysis for acute ischemic stroke in a Brazilian public hospital. Clinics (Sao Paulo). 2012; 67(7):739-43.

22. Ganesh A, Camden M, Lindsay P, Kapral MK, Coté R, Fang J, Zagorski B, Hill MD; Canadian Stroke Audit Group. The quality of treatment of hyperacute ischemic stroke in Canada: a retrospective chart audit. CMAJ Open. 2014; 2(4):E233-9.

23. Oliveira-Filho J, Martins SC, Pontes-Neto OM, Longo A, Evaristo EF, Carvalho JJ, et al. Guidelines for acute ischemic stroke treatment: part I. Arq Neuropsiquiatr. 2012; 70(8):621-9.

24. Strbian D, Ahmed N, Wahlgren N, Lees KR, Toni D, Roffe C, Surakka IL, Tatlisumak T; SITS Investigators. Trends in door-to-thrmbolyisis time in the safe implementation of stroke thrombolyisis registry. Effect of center volume and duration of registry membership. Stroke. 2015; 46(5):1275-80.

25. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, et al. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. JAMA. 2014; 311(16):1632-40.

26. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, et al. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation. 2011; 123(7):750-8.

27. Gumbinger C, Reuter B, Stock C, Sauer T, Wiethölter H, Bruder I, Rode S, Kern R, Ringleb P, Hennerici MG, Hacke W; AG Schlaganfall. Time to treatment with recombinant tissue plasminogen activator and outcome of stroke in clinical practice: retrospective analysis of hospital quality assurance data with comparison with results from randomised clinical trials. BMJ. 2014; 348:g3429.

28. Mikulík R, Kadlecová P, Czlonkowska A, Kobayashi A, Brozman M, Svigelj V, Csiba L, Fekete K, Kõrv J, Demarin V, Vilionskis A, Jatuzis D, Krespi Y, Ahmed N; Safe Implementation of Treatments in Stroke-East Registry (SITS-EAST) Investigators. Factors influencing in-hospital delay in treatment with intravenous thrombolysis. Stroke. 2012; 43(6):1578-83.

29. Bruening T, Al-Khaled M. Atroke-associate pneumonia in thrombolyzed patients: incidence and outcome. J Stroke Cerebrovasc Dis. 2015; 24(8):1724-9.

30. Schmidt A, Heroum C, Caumette D, Le Lay K, Bénard S. Acute Ischemic Stroke (AIS) patient management in French stroke units and impact estimation of thrombolysis on care pathways and associated costs. Cerebrovasc Dis. 2015; 39(2):94-101.