

Factors associated with delay in seeking treatment by patients with acute stroke: The National Neurology Registry (NNeuR) of Malaysia

Malinee Neelamegam¹, Sharad Malavade¹, Irene Looi², Norsima Nazifah Sidek³, Zariah Abdul Aziz³

¹College of Public Health, University of South Florida, ²Hospital Seberang Jaya, Malaysia, ³Hospital Sultanah Nur Zahirah, Terengganu

BACKGROUND

The World Health Organization defines stroke as “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin” (Aho, Harmsen, Hatano, Marquardsen, Smirnov, & Strasser, 1980). This definition includes ischemic strokes, which are due to cerebral infarct, and hemorrhagic strokes, which are either intracerebral or subarachnoid hemorrhages. (Aho et al., 1980).

Past research has shown that almost 85% of global strokes occur in developing countries (Bonita, Mendis, Truelsen, Bogousslavsky, Toole & Yatsu, 2004; Feigin, 2005; Johnston, Mendis, & Mathers, 2009). Interestingly, while stroke incidence in developed countries reduced by 42%, the incidence rates in developing countries increased by almost 100% (Feigin, Lawes, Bennett, Barker-Collo, & Parag, 2009).

Post stroke outcome can be devastating and in acute stroke patients, the outcome trajectory is heavily influenced by timely access to treatment upon a stroke event (Lees, Bluhmki, von Kummer, Brott, Toni, grotto & Albers, 2010). With the availability of thrombolysis treatment using recombinant tissue-type plasminogen activator (rTPA), acute ischemic stroke can be treated effectively (The National Institute of Neurological Disorders and Stroke rt-PA stroke study group, 1995). However, for thrombolysis treatment to be effective, it must be administered within 4.5 hours of symptom onset (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995).

Therefore, the identification of factors that lead to timely treatment upon a stroke event has significant public health importance. By understanding the factors that result in timely healthcare seeking behaviour, targeted efforts can be made to reduce the proportion of individuals who delay seeking treatment upon a stroke event.

OBJECTIVES

The purpose of this study was to investigate delayed arrival to the hospital among acute ischemic stroke patients in Malaysia through secondary data analysis of the National Neurology Registry of Malaysia

Primary Objective:

The primary objective of this study is to determine the factors that are associated with delayed arrival to the hospital in acute stroke patients seeking treatment in Hospital Seberang Jaya, Malaysia and Hospital Sultanah Nur Zahirah, Malaysia from 2010 to 2013.

Secondary Objective:

Secondary objectives of this study are to determine the association between delayed arrival to the hospital and post stroke functional outcome and length of hospital stay in acute stroke patients in the study population from the year 2010 to 2013.

METHODS

Overview of the National Neurology Registry of Malaysia

The National Neurology Registry (NNeuR) of Malaysia is a project funded and conducted by the Ministry of Health Malaysia. The registry began in the year 2010 in two pioneer sites, Hospital Seberang Jaya and Hospital Sultanah Nur Zahirah, Terengganu. As of the year 2014, the registry has 12 active source data provider sites throughout Malaysia.

The National Neurology Registry of Malaysia is a multi-center, observational cohort study designed to evaluate the health outcomes of patients with acute stroke at participating government clinical centers. The NNeuR study population consists of male and female participants with acute stroke or epilepsy seeking medical care for these two conditions at the participating study site. Participation in the registry is voluntary. To be included in the stroke section of NNeuR, patients must be diagnosed with acute stroke, with acute stroke defined as stroke onset within the last two weeks and patients must be above the age of 12 years.

Study Design

This is a cross-sectional study conducted in 2014 using data from the National Neurology Registry of Malaysia from January 2010 to December 2013. This secondary data analysis is conducted using data from two source data providers of the registry, which are,

Hospital Seberang Jaya and Hospital Sultanah Nur Zahirah in Malaysia. Data from these two sites were used upon obtaining approval from the respective principal investigators of the sites.

Study Population

The study population comprised of individuals with acute stroke. Data of 3856 individuals who participated in the NNeuR from January 2010 to December 2013 were analysed. Only individuals participating in two of the source data provider sites, Hospital Seberang Jaya and Hospital Terengganu, were included in this study. Patients with transient ischemic attacks were excluded from this analysis. No other inclusion or exclusion criteria were employed in this study.

Data Collection Methods

Data collection for the National Neurology Registry of Malaysia is done by a team of physicians and allied health professionals. Data is collected by interviewing patient/proxies, medical examinations and laboratory tests. All data collection interviews, medical examinations and laboratory tests were performed in the respective government hospitals using a uniformed laboratory protocol and reference ranges across all government laboratories.

Data collection was done using electronically implemented Case Report Forms (eCRFs). Clinical database management of the National Neurology Registry is done to ensure that the collected data is complete, accurate and sufficiently clean to support the further statistical analysis.

Study Variables:

Demographic variables: Demographic variables for this study are gender, ethnic group, marital status, age and education level of study participants. Ethnic group of participants is categorized as Malay, Chinese, Indian, Other Malaysian and Foreigner. Marital status of study participants is categorized as single, married, divorced, widowed and domestic partnership. Age in years of the participant during data collection is used. Education level of the study participant is categorized as no formal education, primary school education, secondary school education, tertiary school education.

Outcome of interest: The outcome of interest in this study is the time taken from the onset of acute stroke symptom to presentation at an emergency medical care facility. The continuous variable “Duration” from the dataset will be used for this analysis. This variable, measured in minutes, is an auto-calculated variable on the eCRF. The variable is derived by deducting the date and time of arrival of patients to the hospital from the date and time of symptom onset. Duration is further categorized as arrival in within 3 hours of symptom onset and arrival after more than 3 hours of symptom onset.

Factors assessed for association with outcome: There are several potential factors that will be assessed to examine their association with the duration in seeking treatment among acute stroke patients. These factors are mode of arrival to the emergency department, type of stroke, type of stroke symptom at onset, stroke severity and stroke event. Mode of arrival is categorized as arrival by ambulance, own transport or other transport. The World Health Organization (WHO) stroke classification is used to categorize stroke type to ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage. Stroke severity is measured by using the National Institutes of Health Stroke Scale (NIHSS). Based on the total NIHSS score, patients will be categorized as not having a stroke (NIHSS=0), minor stroke (NIHSS= 1 to 4), moderate stroke (NIHSS= 5-15), moderately severe stroke (NIHSS = 15 to 20) and severe stroke (NIHSS = 21 to 42). To determine the type of stroke symptoms present at onset, patient’s response is categorized as absent or present for headache, nausea, vertigo, altered sensorium, visual alteration, speech disturbances, hemiparesis (weakness on one side of the body), tetraparesis (weakness on all 4 limbs) and monoparesis (weakness on anyone limb). Stroke event was classified as first-ever stroke event or recurrent stroke.

Additionally, duration from symptom onset to arrival in the emergency department was assessed for association with functional outcome and length of hospital stay. Functional outcome at discharge was assessed using the Modified Rankin Scale (MRS). Based on the total MRS score, patients were categorised as having no significant post stroke disability (MRS=0 to 1), slight disability (MRS=2), moderate disability (MRS=3), moderately severe disability, (MRS=4), severe disability (MRS=5) and death (MRS=6). Length of hospital stay is a continuous variable measuring in days, the length the patient was admitted in the medical facility.

Statistical Methods

Statistical analysis for the study was performed using SAS for windows version 9.3. (SAS Institute, Cary, NC). All statistical analysis was done based on a predefined data analysis plan.

Univariate analysis was done for all continuous variables to examine the normality of the variable. Normality was determined by visual examination of the normal plots. Study subjects were categorized into the non-delayed group if they arrived at the hospital within 3 hours of the onset of stroke symptoms. Study subjects arriving after 3 hours of symptom onset were categorized into the delayed group.

Descriptive statistics were obtained to understand the baseline characteristics of the delayed and non-delayed group in the study population. Means and standard deviations were generated for continuous variables, while frequencies and percentages were generated for the categorical variables.

Bivariate analysis was done to assess the association of predetermined factors with delay in seeking treatment. Analysis for continuous variables was done using independent t-test and Mann-Whitney test. Chi-square and Fisher's exact test was used for categorical variables. Statistical significance was determined as $p \leq 0.05$.

Multiple logistic regression analysis was done to estimate the contribution of variables associated with time from symptom onset to hospital arrival. A model consisting of variables found to be significant in bivariate analysis was used to build a parsimonious model using stepwise model selection. Statistical significance value was determined as $p \leq 0.05$.

Additionally, patient outcome was assessed for patients arriving within three hours of symptom onset and those arriving after more than three hours. Analysis for continuous variables was done using independent t-test and Mann-Whitney test. Chi-Square analysis was used for categorical variables after adjusting for stroke severity. Multiple logistic regression was done to estimate the contribution of time from symptom onset to hospital arrival, to patient's functional outcome at discharge (MRS score) while adjusting for stroke severity and stroke type. Statistical significance was determined as $p \leq 0.05$.

RESULTS

In this study, of the 6547 individuals who participated in the NNeuR, data of 3856 individuals who participated in the selected sites, namely Hospital Seberang Jaya and

Hospital Sultanah Nur Zahirah, were extracted and analysed. Of the 3856 individuals analysed in this study, 3219 (83.48%) individuals sought treatment at Hospital Sultanah Nur Zahirah, while the remaining 637 (16.52%) individuals sought treatment at Hospital Seberang Jaya.

Of the 3856 individuals included in the study, 2917 (75.65%) were categorized as delayed arrival (arrival > 3hours from symptom onset). Only 939 individuals (24.35%) were categorized as non-delayed arrival.

The NNeuR dataset used in this analysis had missing values for several variables of interest in this study. Due to missing values, education status could not be determined for 342 individuals (8.81%) and marital status was not available for 86 individuals (2.21%). Missing values were also present for other variables used in this analysis. Information on the age of 13 individuals (0.33%), mode of arrival of 46 individuals (1.18%), stroke severity (NIHSS score) of 13 individuals (0.33%), stroke event classification of 1 individual (0.03%), smoking status of 1227 individuals (31.60%) and length of hospital stay of 828 individuals (21.32%) was missing. In terms of symptom type, information on headache for 85 individuals (2.19%), nausea for 57 individuals (1.47%), vertigo for 83 individuals (2.14%), altered sensorium for 86 individuals (2.21%), visual disruption for 104 individuals (2.68%), speech impairment for 48 individuals (1.24%), hemiparesis for 41 individuals (1.06%), tetraparesis for 70 individuals (1.80%) and monoparesis for 85 individuals (2.19%) was missing in this dataset.

Baseline demographic characteristics of non-delayed and delayed arrival are shown in **Table 1**. Due to missing values, the number of observations in several variables was lower than the total number of individuals included in this analysis. Mean age of individuals with delayed arrival was 62.91 years and was comparable to the mean age of individuals with non-

delayed arrival, which was 61.66 years. The distribution of males in the non-delayed arrival group was slightly higher at 58.89% compared to 54.41% in the delayed arrival group. Although in both groups, ethnic Malay individuals were the largest group, there was a slightly higher percentage of non-Malays in the non-delayed arrival group. The education and marital status distribution in the delayed arrival and non-delayed arrival group were similar.

Table 1: Characteristics of individuals with non-delayed arrival and delayed: National Neurology Registry of Malaysia (NNeuR), 2010 -2013

| Variable | Delayed arrival (n=2917) | Non-Delayed Arrival (n=939) | p-value |
|----------------------------------|-------------------------------------|--|----------------|
| Age (<i>years</i>), mean (std) | 62.91 (12.22) | 61.66 (11.88) | 0.298 |
| Gender, n (%) | | | |
| Male | 1587 (54.41) | 553 (58.89) | 0.016 |
| Female | 1330 (45.59) | 386(41.11) | |
| Ethnicity, n (%) | | | |
| Malay | 2583 (88.55) | 790 (84.13) | <0.001 |
| Chinese | 239 (8.19) | 99 (10.54) | |
| Indian | 62 (2.13) | 39 (4.15) | |
| Others | 7 (0.24) | 5 (0.53) | |
| Foreigners | 26 (0.89) | 6 (0.64) | |
| Education, n (%) | | | |
| No formal education | 442 (16.43) | 111 (13.25) | 0.074 |
| Primary level education | 1434 (53.29) | 447 (53.34) | |
| Secondary level education | 758 (28.17) | 256 (30.55) | |
| Tertiary level education | 57 (2.12) | 24 (2.86) | |
| Marital Status, n (%) | | | |
| Single | 86 (3.01) | 19 (2.08) | 0.2695 |
| Married | 2680 (93.77) | 856 (93.76) | |
| Divorced | 24 (0.84) | 10 (1.10) | |
| Domestic Partnership | 68 (2.38) | 28 (3.07) | |

The association of the mode of arrival, stroke severity, stroke event and type of stroke with the time from symptom onset to arrival at hospital is presented in **Table 2**. Mode of arrival, stroke severity and stroke type was significantly associated with time from symptom onset to arrival at the hospital ($p < 0.001$). However stroke event, either first ever stroke or recurrent stroke, was not associated with time of arrival at hospital after symptom onset.

Table 2: Association between mode of arrival, stroke severity, stroke event and type of stroke with the time from symptom onset to arrival at hospital: National Neurology Registry of Malaysia (NNeuR), 2010 -2013

| Variable | Delayed arrival (n=2917) | Non-Delayed Arrival (n=939) | p-value |
|--------------------------------|-------------------------------------|--|----------------|
| Mode of arrival, n (%) | | | |
| Ambulance | 1705 (59.14) | 474(51.02) | <0.001 |
| Own Transport | 1171 (40.62) | 452 (48.65) | |
| Others | 7 (0.24) | 3 (0.32) | |
| Stroke severity (NIHSS), n (%) | | | |
| Mild | 2071 (71.29) | 609 (64.86) | <0.001 |
| Moderate | 511 (17.59) | 227 (24.17) | |
| Severe | 323 (11.12) | 103 (10.97) | |
| Stroke event, n (%) | | | |
| First ever stroke | 2184 (74.90) | 701 (74.65) | 0.8813 |
| Recurrent stroke | 732 (25.10) | 238 (25.35) | |
| Stroke type, n (%) | | | |
| Ischemic stroke | 2888 (99.01) | 214 (22.79) | <.0001 |
| Intracranial haemorrhage | 29 (0.99) | 725 (77.21) | |

Results from multiple logistic regression indicated that only stroke severity (NIHSS score) and stroke type were factors that were associated with time from symptom onset to arrival at hospital. Compared with patients with severe stroke, patients with mild to moderate stroke were less likely to arrive in the hospital within 3 hours of symptom onset (OR 0.386,

95% CI, 0.214 – 0.698). Additionally patients with ischemic stroke were less likely to arrive at the hospital within 3 hours of symptom onset compared to patients with intracerebral haemorrhage (OR 0.002, 95% CI 0.002-0.004).

The association of the symptom type at onset with the time from symptom onset to arrival at hospital is presented in **Table 3**. Symptoms such as headache, nausea, altered speech and hemiparesis were significantly associated with time from symptom onset to arrival to hospital. However, no significant association was found for symptoms such as vertigo, altered vision, tetraparesis and monoparesis.

Table 3: Association between symptom type at onset and the time from symptom onset to arrival at hospital; National Neurology Registry of Malaysia (NNeuR), 2010 -2013

| Variable | Delayed arrival (n=2917) | Non-Delayed Arrival (n=939) | p-value |
|-----------------------|-----------------------------|--------------------------------|---------|
| Headache, n (%) | | | |
| Yes | 580 (20.29) | 283 (31.00) | <0.001 |
| No | 2278 (79.71) | 630 (69.00) | |
| Nausea, n (%) | | | |
| Yes | 451 (15.65) | 257 (28.03) | <0.001 |
| No | 2431 (84.35) | 660 (71.97) | |
| Vertigo, n (%) | | | |
| Yes | 400 (13.98) | 148 (16.25) | 0.090 |
| No | 2462 (86.02) | 763 (83.75) | |
| Altered vision, n (%) | | | |
| Yes | 141 (4.95) | 43 (4.76) | 0.8138 |
| No | 2707 (95.05) | 861 (95.24) | |
| Altered speech, n (%) | | | |
| Yes | 1561 (54.09) | 450 (48.81) | 0.005 |
| No | 1325 (45.91) | 472 (51.19) | |
| Hemiparesis, n (%) | | | |
| Yes | 2226 (76.97) | 620 (67.17) | <0.001 |

| | | | |
|---------------------|--------------|-------------|-------|
| No | 666 (23.03) | 303 (32.83) | |
| Tetraparesis, n (%) | | | |
| Yes | 21 (0.73) | 10 (1.10) | 0.280 |
| No | 2856 (99.27) | 899 (98.90) | |
| Monoparesis, n (%) | | | |
| Yes | 50 (1.74) | 16 (1.77) | 0.963 |
| No | 2816 (98.26) | 889 (98.23) | |

Assessment of post stroke outcome and time from symptom onset to arrival at hospital is presented in **Table 4**. Functional outcome, measured using the Modified Rankin Scale (MRS), was significantly associated with time from symptom onset to arrival at hospital. Similarly, length of hospital stay was also significantly associated with time from symptom onset to arrival at hospital. However, the mean difference in length of hospital stay between the delayed arrival and non-delayed arrival group was approximately one day.

Table 4: Association between post stroke outcome and the time from symptom onset to arrival at hospital: National Neurology Registry of Malaysia (NNeuR), 2010 -2013

| Variable | Delayed arrival (n=2917) | Non-Delayed Arrival (n=939) | p-value |
|--|-----------------------------|-----------------------------------|---------|
| Functional outcome (MRS score), n (%) | | | |
| No significant disability | 225 (7.71) | 214 (23.65) | <0.001 |
| Moderate disability | 689 (23.62) | 94 (10.39) | |
| Moderately severe disability | 822 (28.18) | 170 (18.78) | |
| Severe disability | 1030 (35.31) | 209 (23.09) | |
| Death | 151 (5.18) | 218 (24.09) | |
| Length of hospital stay (days), mean (std) | 5.108 (7.984) | 6.097 (9.052) | <0.001 |

Multiple logistic regression analysis indicated that patients with moderate to severe disability at discharge were 93.194 times more likely (95% CI, 50.369-172.427) to have arrived in the hospital after 3 hours of symptom onset compared to patients with no

significant stroke related disability at discharge, after adjusting for stroke severity and stroke type.

DISCUSSION

In this study, the factors associated with time from stroke symptom onset to arrival in the hospital were investigated in individuals participating in the National Neurology Registry of Malaysia (NNeuR). The results of the study indicate that mode of arrival, stroke severity, and stroke type were significantly associated with the time from symptom onset to presentation to the hospital in this study population. In terms of symptom type, headache, nausea, altered speech and hemiparesis were associated with time from symptom onset to arrival at the hospital. Additionally, functional outcome and length of hospital stay post stroke were also significantly associated with time from symptom onset to arrival at the hospital.

This study also found that patients with mild to moderate stroke were less likely to arrive at the hospital within 3 hours of symptom onset compared to those with severe stroke. Similarly, patients with ischemic stroke were less likely to arrive within 3 hours of symptom onset compared to those with intracerebral hemorrhage. After adjusting for stroke severity and stroke type, individuals who developed moderate to severe post stroke disabilities at discharge were more likely to have arrived at the hospital after more than 3 hours of symptom onset compared to individuals who had no significant post-stroke disability at discharge.

In this study, only 25% of the study participants arrived to the hospital within 3 hours of symptom onset. This figure is comparable to past studies (Kay, Woo & Poon, 1992; Alberts, Bertels & Dawson, 1990; Barsan, Brott & Broderick, 1993). This study also found

that demographic factors such as age, education and marital status do not influence the delay in seeking treatment in acute stroke patients. .

Similar to this study, one study conducted in Spain found that previous stroke was not associated with delay in seeking treatment upon stroke onset (Geffner, Soriano, Perez, Vilar & Rodriguez, 2012). This could be explained by the theory that having a previous stroke may have increased the knowledge level of a patient but does not necessarily improve health seeking behaviour in an individual.

Multivariate logistic regression analysis indicated that in this study, stroke severity was associated with lower odds of delayed arrival at the hospital. This finding was similar to the findings of the South London Stroke Registry (Addo, Leon, Rudd, McKevitt & Wolfe, 2012). Additionally, Geffner et al (2012) found that stroke severity was significantly associated with timely arrival to the hospital following stroke symptom onset. Severe strokes are more likely to result in more prominent onset symptoms, encouraging patients to seek medical attention promptly. On the other hand, milder strokes may result in mild, resolving symptoms that are less likely to be viewed as critical thus resulting in delayed arrival to the hospital. Rosamond, Gorton, Hinn, Hohenhaus & Morris (1998), found that familiarity with stroke symptoms may influence the delay in seeking treatment. .

This study also found that post-stroke functional outcome at discharge, assessed using the Modified Rankin Scale, is associated with time from symptom onset to arrival at hospital. Although Jorgensen and colleagues reported that functional outcome reflects stroke severity and is not independently associated with delay in seeking treatment, we found that even after adjusting for stroke type and stroke severity, individuals with lower post-stroke functional outcome at discharge were more likely to have arrived at the hospital after 3 hours of symptom onset (Jorgensen, Nakayama, Reith, Raaschou, & Olsen, 1996). Results of this

study concur with the findings of Kwon, Yoon & Chang (2010) who reported that arrival to the hospital within 3 hours of symptom onset was significantly associated with improved post-stroke functional outcome after adjusting for stroke severity.

This study has several distinct strengths. The large population based sample size of the NNeuR gives the study significant power to assess the research question. Additionally, the NNeuR also boasts a high participation rate and good quality control on data collected, thus further increasing the internal validity of the study.

As the effect of random error on the internal validity can be decreased by increasing the sample size, by using a large database such as the NNeuR, we can be confident that the internal validity of the study was not highly affected by random error. NNeuR also follows a standardized protocol on data collection, physical examination and measurements and this minimizes measurement error and promotes the internal validity of our study.

However, this study also has some limitations. The study sample consists of individuals seeking treatment in only two of the registry's source data provider sites, generalizability of study results is limited. This is reflected in the ethnic distribution of the study population that varies from the national distribution of ethnicity in the Malaysian population, thus limiting our findings to only individuals in the two states in Malaysia, namely Penang and Terengganu.

The NNeuR may be affected by selection bias as data is not collected among individuals seeking treatment in private medical institutions. Excluding these individuals may have biased the findings of this study. Additionally, proxy interviews were also used in the NNeuR for individuals who were unable to respond independently. Although this is important to reduce the non-response rate in the study, proxy interviews may introduce information bias in the study. Although post stroke outcome was assessed for association

with timely arrival to the hospital in this study, the association may have also been due to stroke severity.

Additionally, no information was available regarding location of the patient at onset of symptom. Therefore, the impact of location on the association of symptom type and delay was not determined in the study. Studies have shown that in stroke patients, location of symptom onset is associated with delayed hospital arrival (Barsan et al., 1993; Alonzo, 1986). The association of delay in seeking treatment and long term prognosis and functional outcome could not be assessed as this data was not available.

The essential key in the management of acute stroke is the time it takes for patients to identify their stroke symptoms and to seek treatment. Intravenous tissue plasminogen activator (tPA) is the only approved medical therapy for acute ischemic stroke, however, administration must be within 3 hours of symptom onset. (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). Therefore, timely presentation to the hospital is vital for improved outcome post stroke. Therefore, public health interventions to effectively reduce the delay in seeking treatment in acute stroke patients must be made based on understanding the factors associated with timely health seeking behaviour in the target population.

REFERENCE

- Addo J, Ayis S, Leon J, Rudd AG, McKeivitt C, Wolfe CDA. (2012) Delay in presentation after an acute stroke in a multiethnic population in South London: the South London Stroke Register. *J Am Heart Assoc.* 6, 13.
- Aho, K., Harmsen, P., Hatano, S., Marquardsen, J., Smirnov, V.E., & Strasser, T. (1980). Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*, 58, 113-130.
- Alberts MJ, Bertels C, Dawson DV (1990). An analysis of time of presentation after stroke. *JAMA* 263, 65-69.
- Alonzo, AA (1986) The impact of the family and lay others on care seeking during life-threatening episodes of suspected coronary artery disease. *Soc So Med*, 22, 1297- 1298
- Barsan, WG, Brott, TG, Broderick, JP, Haley, EC, Levy, DE & Marler, JR (1993). Time of hospital presentation in patients with acute stroke. *Arch Intern Med.* 159, 2558-2561
- Bonita, R., Mendis, S., Truelsens, T., Bogousslavsky, J., Toole, J., & Yatsu, F. (2004) The global stroke initiative. *Lancet Neurol*, 3, 391–393.
- Feigin, V.L. (2005). Stroke epidemiology in the developing world. *Lancet*, 365, 2160–2161.
- Feigin, V.L., Lawes, C.M., Bennett, D.A., Barker-Collo, S.L., & Parag, V. (2009). Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol*, 8, 355–369.
- Geffner, D., Soriano, C., Perez, T, Vilar, C, & Rodriguez, D (2012) Delay in seeking treatment by patients with stroke: Who decides, where they go, and how long it takes. *Clinical Neurology and Neurosurgery*, 114, 21-25.
- Johnston, S.C., Mendis, S., & Mathers, C.D. (2009). Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. *Lancet Neurol*, 8, 345–354.

- Jorgensen, HS., Nakayama, H., Reith, J., Raaschou, HO, & Olsen, TS (1996). Factors delaying hospital admission in acute stroke: The Copenhagen Stroke Study. *Neurology*, 47, 383-387
- Kay R, Woo J, Poon S (1992) Hospital arrival times after onset of stroke. *J Neurol Neurosurg Psychiatry*. 55 : 973-974.
- Kwon, YD., Yoon, SS., & Chang, H. (2010) Association of hospital arrival time with modified rankin scale at discharge in patients with acute cerebral infarction. *Eur Neurol*, 64, 207-213
- Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW (2010) Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 375(9727):1695–1703.
- Rosamond, WD, Gorton, RA, Hinn, AR, Hohenhaus, SM, & Morris, DL. (1998) Rapid response to stroke symptoms: the Delay in Accessing Stroke Healthcare (DASSH) study. *Acad Emerg Med*. 5, 45-51
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995). Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*, 333:1581-1587.