Translational Perioperative and Pain Medicine

ISSN: 2330-4871

Review Article | Open Access Volume 6 | Issue 3

Pre- and In-Hospital Management of Stroke

Yue Lu[#], Tong Sun[#], Yi-ping Ding, Shan-shan Diao, Tan Li, Xiu-ying Cai[*], Zhuan Xu[*] and Yan Kong[*]

Department of Neurology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China

[#]These authors contributed equally to this work.

Abstract

Background: For acute ischemic stroke (AIS), intravenous thrombolysis (IVT) is an effective but time-dependent therapy. However, patients are usually too late for treatment, mainly because of pre- and in-hospital delays.

Method: Papers were identified through the PubMed search, with keywords such as: 'stroke', 'thrombolysis', 'management', 'prehospital delay', 'in-hospital delay'.

Results: In pre-hospital stroke management, factors related to pre-hospital delays include demographic characteristics, social factors, clinical factors, behavioral factors, and cognitive factors. Great significance should be assigned to the implementation of stroke preparedness interventions, stroke assessment instruments, the use of emergency medical service (EMS), mobile stroke units (MSUs), and the Stroke Emergency Map. With regard to in-hospital stroke management, there are some tasks related to the in-hospital delays, such as registering patients, waiting for the stroke team, CT availability, lab resources, and making a decision for thrombolytic therapy. With good communication between the EMS and the emergency department (ED), delays can be significantly reduced.

Conclusions: With the streamlining of all aspects of pre-hospital and in-hospital thrombolysis processes and the increase of hospital experience, we can achieve a shorter onset-to-treatment time (OTT), and more patients may benefit from timely thrombolytic therapy.

Keywords

Acute ischemic stroke, Thrombolysis, Management, Pre-hospital delay, In-hospital delay, Mobile stroke units

Introduction

Stroke is a leading cause of death and disability [1], which brings a considerable socioeconomic impact as a result of the loss of labor productivity and high health-care costs. Surprisingly, in the United States, someone suffers a stroke every 40 seconds on average, and someone dies of one approximately every four minutes [2].

Intravenous recombinant tissue plasminogen activator (rt-PA), a medical reperfusion therapy [3], is beneficial for stroke patients to reduce irreversible brain damage, prevent death, and improve long-term quality of life [4,5]. However, this treatment has a time window of 4.5 hours, which should be initiated as soon as possible [6]. Better functional outcome is linked to shorter onset-to-treatment time (OTT) [7-10]. Furthermore, the benefit is highly time-dependent within the therapeutic time window [11,12]. As a pooled analysis of randomized trials shows, comparing the patients treated between 3 and 4.5 hours with those treated in the first three hours, the number of people needing treatment to recover without disabilities doubles [11]. Another study indicates that every 15 minutes of expediting rt-PA is advantageous in extending stroke patients' healthy lives by one month [13]. The documented presence of delays increases the odds of symptomatic intracranial hemorrhage and in-hospital mortality, and decreases the odds of independent ambulation at discharge [14]. Therefore, the sooner rt-PA is initiated, the better the outcome for stroke patients.

In AIS thrombolysis, OTT consists of onset-to-door time (ODT) and door-to-needle time (DNT). In this review of stroke management, we stress the need to optimize each link of the stroke rescue chain. With the streamlining of all aspects of pre-hospital and in-hospital thrombolysis processes and the increase of hospital experience, we can achieve a shorter OTT, and more patients may benefit from timely thrombolytic therapy.

Prehospital Stroke Management

Among the factors hindering reperfusion therapy, delayed presentation at the hospital is a significant one [15], especially in non-English speaking and less developed regions and countries [16]. In some comprehensive stroke centers, although the DNT was much lower than 30 minutes, the ODT remained stagnant above 60 minutes over a period of nearly 20 years [17,18].

In 2018, an international symposium was held in China, which focused on the prehospital delays and some novel strategies to effectively address them [16]. The symposium discussed the possibility that long prehospital delay times may be attributable of the poor public awareness, poor usage of EMS, or even lack of EMS.

Table 1: The factors associated with prehospital delay in acute stroke.

Factors	early arrival	Late arrival	References
Demographic	High level of education	Low level of education	[25,27]
	High income	Low income	
		Ethnic minorities	[28]
Medical	Atrial fibrillation		[22]
	Knowing someone who had suffered a stroke		[23]
	Onset location was at outside the home	Onset location was at home	[23,24]
	Onset during daytime	Onset during nighttime	[20,22]
	Greater stroke severity		[21,22,24]
	Coma		[19,20,26]
	By an emergency medical service	By other means of transportation	[22]
Social	Someone else noticed the symptom onset first	Patients noticed the symptom onset first	[20,23]
	Shorter distance from the onset place to the first hospital	Further distance from the onset place to the first hospital	[23]
Cognitive and behavioral	Calling emergency number, going to hospital directly, asking others for help	Doing nothing and waiting	[23]

The factors related to prehospital delays in AIS

Various determinants of prehospital delays have been identified; these include demographic characteristics, social factors, clinical factors, behavioral factors, and cognitive factors [19-28], as shown in Table 1.

Some other factors are unclear, such as age [20], sex [20,29,30], a history of stroke [23,31,32], and transferred from community-based hospitals [23,33,34].

Stroke preparedness

The recognition of stroke-like symptoms by EMS personnel, patients, and their families is the first step in timely workup and treatment of AIS. Furthermore, inappropriate care-seeking behaviors (i.e., visiting a general physician, using a private vehicle, or taking a "wait-and-see" approach), contribute to increased prehospital delay [8]. Timely care-seeking is significantly associated with patients' awareness of AIS [22]. However, in a Greek study, 24% of the study participants surveyed did not know any stroke symptoms [35]; in Spain, 11% did not know any symptoms [36]; in the United States, 32% did not know any symptoms [27], and in Hubei Province in China, around 60% of patients did not recognize initial stroke symptoms [37]. Even in family physicians and non-neurologists, this phenomenon also exists [16,38-41].

With inconclusive and inconsistent results, stroke awareness campaigns have been evaluated in several studies [28,42-48]. Some campaigns indicated that there was no significant reduction in pre-hospital delay after exposure to public education campaigns regarding AIS [28,42,43]. On the other hand, in recent years, some educational campaigns have had a positive effect; among the stroke preparedness campaigns, mass media campaigns may encourage stroke patients to present to the hospital via EMS and bypass their general practitioners, which indicates that these mass media campaigns can not only improve public's recognition and response to stroke, but can also change the behaviors of stroke patients [46]. However, some limitations exist, such as high advertising costs, low penetration of ethnic minority populations [47], lack of cultural customization, and a possible decline in effectiveness once media campaigns end [44]. Besides that, education in schools is attracting more and more attention as an alternative to mass media. Recently, in America, a randomized controlled trial of a school-based stroke education program for minorities who are economically disadvantaged showed that both parents and children have made significant and relatively large advances in stroke preparedness [48].

More endeavors should be made to reach target groups of different ages and backgrounds (i.e., medical students, the neighbors of stroke survivors, the elderly, minorities, children who may be future physicians, patients, and relatives) [16,49,50]. Firstly, to inform the younger generation, who may make decisions to seek medical treatment for elderly family members, education programs could be incorporated into the school system. Secondly, it is critical to educate family doctors and community hospital physicians, which may increase the use of expedited ambulance transportation in the event of a suspected stroke. Thirdly, educating EMS personnel is of great significance, as they could help to identify and prioritize ambulances for potential stroke patients. Since far fewer facilities are available to perform thrombectomies, it is critical for EMS staff on site to identify potential major vessel occlusion according to the stroke scale, which could help them to act quickly in transferring stroke patients to the appropriate hospitals. Fourthly, in-hospital education

aimed at addressing subsequent stroke events should also be developed, because of the higher disability rates and mortality risk associated with recurrence. Such educational work is a long-term task which requires the efforts of several generations.

Stroke assessment instruments

There are several stroke assessment instruments available to help the public and healthcare workers quickly assess and triage patients with acute stroke, such as the Cincinnati Pre-Hospital Stroke Scale (CPSS) and the Los Angeles Prehospital Stroke Screen (LAPSS) in the US, the Face Arm Speech Test (FAST) in the UK, the “Stroke 112” in the Taiwan [38], and the “Stroke 120” in mainland China [51,52].

The CPSS is used to assess whether patients have the following conditions: Facial palsy, asymmetric arm weakness, and speech disturbance (this is measured by having the patient repeat a sentence) [53]. In addition to the analysis of motor weakness, the LAPSS also contains a blood glucose measurement and four historical items [54]. It has a high specificity (97%) and sensitivity (91%) for the diagnosis of prehospital stroke [54]. However, it may exclude some conditions that mimic stroke and consume more time, and it is not useable for public education. The FAST is based on the three elements of the CPSS, but it assesses possible speech disorders during normal conversation [55]. With FAST, 88.9% of patients with TIA or stroke can be identified, and it has the advantage of being easily performed so that it can be used as a public message.

However, for non-English speaking people, it is sometimes difficult to remember “FAST” and the related meaning of each character because of the linguistic barriers. In recent years, Taiwan has developed “Stroke 112”, a national stroke education program designed to penetrate the language barrier [38]. The three numbers can be transformed into three stroke symptoms used in FAST (Face, Arm, Speech, and Time): 1 uneven face (crooked mouth); 1 weak arm (arm weakness); 2 incoherent lips (slurred speech). Similarly, in mainland China, due to language barriers, “Stroke 120” was developed, where “120” is used as an emergency phone number [51,52]. The numbers can be converted into three types of AIS recognition actions, with 1 meaning "First, look for an uneven face", 2 meaning "Second, examine for arm weakness" and 0 meaning "no clear language". Also, the Chinese pronunciation of "zero" is "ling", which means "listening". During the past several years, “Stroke 120” and “Stroke 112” have been well-accepted in mainland China and Taiwan respectively [16]. Therefore, it is more acceptable for non-English speaking countries to remember such novel stroke awareness programs than it is to rely on FAST to recognize the signs of stroke.

The use of EMS

A lot of evidence showed that the use of EMS is a significant factor in increasing the likelihood of early arrival [21,22] and appropriate therapy with rt-PA [56,57]. However, the rate of EMS utilization differed in countries. The EMS utilization rate is 15.4% among stroke patients in Hubei Province in China [37], and in India, less than 15% of people make timely use of EMS [16], which was significantly lower than that in Sweden (53%) [34], the United States (51%) [58], Korea (36%) [59], England (78%) [60] and Germany (72%) [61]. EMS utilization was related to the following factors: Previous use of EMS, early recognition of stroke symptoms, sudden stroke attack, severe stroke, or living in urban communities [37,62]. A study indicated that patients with a history of stroke had a reduced tendency to use EMS [37], while another report showed no relation between EMS utilization and previous stroke [62]. A study showed that patients who recognized initial stroke signs tended to use EMS, which indicates that early identification of stroke signs was a significant factor that influences EMS utilization [37].

Firstly, the poor awareness of when to use EMS is a leading cause of prolonged prehospital delays, so public education plays a significant role in reducing prehospital delays and increasing the utilization of EMS [63-65]. In a study, implementation of the EMS training program successfully reduced the on-scene time (OST) of thrombolysis candidates by 10% [66]. Education programs on stroke risk and the effective use of emergency calls ought to be implemented for patients as well as family members [20]. Therefore, more health education programs should be launched to highlight the need to contact with EMS as soon as a stroke occurs.

Secondly, EMS is not well established in some developing countries, which may account for the low usage of EMS. For instance, India has a very limited number of ambulances, which are operated by different entities, and most of them do not have any necessary medical management equipment [39]. Likewise, in remote areas of many countries, EMS is not well-developed and there are not enough ambulances.

Thirdly, the inconsistent emergency phone numbers are an important cause of pre-hospital delays. In China, some hospitals use their hospital-specific emergency telephone numbers which are too long to remember [52].

A review suggests that the EMS threshold for suspected stroke ought to be lowered to enhance its sensitivity rather than its specificity [67]. Simple stroke evaluations such as FAST or “Stroke 120” should be used as soon as an emergency call has been made and the EMS alerted [68]. Similar to trauma or myocardial infarction, every potential stroke patient ought to be evaluated as

an emergency; meanwhile, ambulances should be sent first. In many cases, EMS staff do not know which hospitals are capable of stroke management, causing some patients to be re-transferred to hospitals with stroke management facilities. Due to referral procedures and extra travel, access to thrombolytic treatment is further delayed. Therefore, EMS personnel should be clearly aware of the hospitals with stroke centers, which is significant for appropriate dispatch, especially in areas where there are many hospitals [22]. Meanwhile, EMS personnel ought to contact stroke centers in advance, which can not only ensure that a particular hospital is equipped to perform thrombolysis treatment, but also prepare the hospital for the arrival of patients.

Prehospital mobile stroke units

As we know, specialized mobile stroke units (MSUs) are presently deployed in Berlin, Germany; Houston, Texas; and Cleveland, Ohio. Equipped with a point-of-care laboratory, an imaging system, proper medications, and a telemedicine connection to the hospital [69,70], MSUs aim to pre-hospital diagnosis and treatment and to divert diagnosis-based patients to the most fitting target hospital [71].

By issuing the diagnosis at the emergency site, MSUs can prevent additional hospitalization delays in inspection, transfer, and secondary (inter-hospital) transport, reducing the transport time during the prehospital and in-hospital phase. In Homburg, Germany, a randomized single-center controlled trial was conducted to compare the time from alarm to therapy decision between MSU and hospital intervention [72]. With an MSU trial, the median time from symptom onset to treatment decision was 56 minutes (IQR 43-103) and the median time of OTT was 72 minutes (53-108), far lower than that of the hospital intervention group (104 minutes (IQR 80-156) and 153 minutes (IQR 136-198) respectively) [72]. Similar trends in time savings were seen in an observational study in Houston, TX, USA [73], as well as in the PHANTOM-S (Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke) study [74].

"The golden hour" is a term attributed to a trauma surgeon who found that the earlier patients are treated within the first hour after a trauma, the better their chances of survival. This term is also used in AIS management to emphasize the time sensitivity. However, very few stroke patients received treatment within 60 minutes, which indicates that there may be a ceiling effect of the timing of conventional stroke management [75,76]. With the first MSU trial, the treatment decision rate within 60 minutes was much higher than that of the hospital intervention group (57% vs. 4%), breaking the "golden hour" limit [72]. Further studies such as the PHANTOM-S trial [77] and the Houston MSU program [78] also increased the rate of treatment within 60 minutes, supporting this conclusion.

However, significant questions remain about clinical efficacy, safety, cost-effectiveness, and best setting for interventions [71]. In the future, MSUs may allow new diagnostics (eg., automated imaging evaluation and biomarkers) and treatments (eg., neuroprotective drugs and treatments for hemorrhagic stroke) to be developed in a pre-hospital setting. With such functions, MSUs may serve as valuable research tools for the pre-hospital management of AIS [71].

The stroke emergency map

As we know, the Stroke Emergency Map unites all the qualified centers and local hospitals capable of providing intravenous thrombolysis and/or endovascular thrombectomy, which could guide the EMS to send stroke patients to nearby hospitals with appropriate stroke care. The first Stroke Emergency Map of China was established in Shenzhen by Dr. Ren in 2016 [16]. Subsequently, the Stroke Emergency Map was established in many regions of China, and the rate of thrombolysis was improved.

The Thrombolysis Map is supported by local health administrations and it consists of EMS staff training, ambulance dispatch and triage guidelines, as well as stroke center standards. Besides that, it can not only direct policymakers to establish new stroke centers in under-served areas, but can also promote improvement in the quality of stroke centers, reducing both pre-hospital and in-hospital delays [16].

In-Hospital Stroke Management

In-hospital delays are another major barrier to the availability of thrombolysis. The American Heart Association and American Stroke Association has recommended that DNT be no more than 60 minutes [79]. However, less than half of stroke patients in the United States [18] and even fewer in China [80,81] receive rt-PA treatment within this time frame. Lots of time is often consumed in trivial non-medical processes (i.e., registering patients, excessive patient transfers, filling out request forms, or waiting for the stroke team, CT availability, or lab resources).

Taking the history

It usually takes a lot of time to take a patient history, particularly for aphasic patients, and information can be distorted or lost in the communication process. The initial history relayed by the EMS, may not always be accurate, and reaching eyewitnesses or next of kin afterward for treatment decisions is often time-consuming and difficult.

Therefore, the treating stroke team can communicate with the original information provider over a phone

already at prenotification, during EMS contact on-scene. It is also preferable to have the next of kin transported by EMS with the patient to allow for additional history to be communicated rapidly if needed.

Laboratory tests and CT scans

Of all the potential in-hospital delays, waiting for the laboratory tests is an essential element, and blood biochemistry tests play a significant role [82]. One study suggests that door-to-laboratory time (DTL) has an independent relationship with in-hospital delays [81], and relevant testing can be conducted during patient transportation. In particular, blood glucose and the international normalized ratio (INR) are the two indices which directly affect treatment decisions; fortunately, glucose can be measured by the EMS and point-of-care (POC) INR samples can be taken immediately upon admission and reported within a minute.

CT scans sometimes also hinder acute thrombolysis treatment. Door-to-imaging time (DTI) was considered to be a factor related to in-hospital delay [81,83,84]. It is time-consuming to write a patient into a computer system as well as to order CT scans. To address these issues, such clerical and administrative duties can be completed before the patient arrives while transferring the patient straight from the ambulance onto the CT table, which can save a lot of time.

Physicians delay thrombolysis

A study indicated that physicians may have a tendency to delay thrombolysis treatment if they believe that thrombolysis would be less beneficial or if they have more time before the end of the thrombolytic treatment window [85].

In consequence, it is of great significance to improve adherence to guidelines and treat patients as soon as possible after arrival at the hospital, no matter how much time is left to the end of the thrombolytic treatment window.

Decision-making for IVT

Before thrombolytic treatment, all patients and family members present are informed of the benefits and risks of stroke treatment, which usually takes less than a minute. In a few countries, informed consent for thrombolytic therapy is not even required. However, in some countries, such as China, the decision-making process for thrombolytic treatment can be a factor in increasing in-hospital delay [81]. Because of the threat of violence from patients or their proxies [86-88], as well as situations wherein doctors are not fully understood by the public [89], doctor-patient relations in China are strained, and the benefits and risks of treatment are often biased by the physicians.

The difference between the healthcare system of western countries and that of China may account for such a phenomenon [90]. Firstly, patients in China usually have so many offspring that it is often difficult for physicians to know which of the patient's relatives is the primary decision-maker. Secondly, clinicians are inclined to exaggerate the risk of increased hemorrhagic complications. Thirdly, the high cost of thrombolysis may also be an obstacle to a smooth decision-making process.

Measures to Reduce Treatment Delays

Before a patient's arrival, prompt reactions based on prenotification play key roles in reducing treatment delays; efficient, coordinated reactions involve seamless collaboration between the prehospital and inpatient

Table 2: Measures to reduce treatment delays [17,67,91-94].

Measure	Description
Pre-hospital phase	
EMS involvement	Education of EMS staff to recognize and prioritise acute stroke. And the ambulance personnel ensuring vital functions, measuring blood glucose, and inserting an intravenous line.
Hospital prenotification	Ambulance calls stroke consultant on mobile phone, who accepts patients, takes history, checking additional medical history from patient records.
Registration and preorder of tests	Patient registration, CT request electronically and pre-order of laboratory tests before patient arrival.
Stroke team	Gathering the stroke team, including a stroke neurologist, an ER nurse, and a lab nurse, at the CT
Medications preparation	Having the medications and infusion pumps ready for the patient at the CT.
In-hospital phase	
Transfer onto CT-table	Direct transfer onto CT-table upon hospital arrival. The CT is performed and immediately interpreted by a stroke neurologist.
Neurologic evaluation and blood withdrawal	Simultaneously EMS briefing, neurological evaluation, and blood withdrawal on CT-table. POC INR if needed.
Decision	Treatment decision before laboratory results are available.
rt-PA on CT table	rt-PA can be initiated on CT table, but usually in adjacent room where the drug is kept.

Table 3: Studies of effects of stroke management.

	Site	Year	OTT (min) with and without intervention	OTD (min) with and without intervention	DTN (min) with and without intervention	DTI (min) with and without intervention	Thrombolysis rates (%) with and without intervention	The rate of DTN ≤ 60 min (%) or DNT ≤ 30 min (%)
Meretoj, et al. [67,93]	Helsinki, Finland	1998-2011	119 (80-176) vs. 195 (164-250)	89 (62-138) vs. 75 (45-145)	20 (14-32) vs. 105 (65-120)	-	31% in 2011, no earlier rates specified	94% in 2011, no earlier rates Specified (DTN ≤ 60 min)
Sanne M. Zinkstok, et al. [94]	Amsterdam, Netherlands	2000-2012	105 (75-160) vs. 158 (135 - 177), p < 0.001	71 (48-120) vs. 65 (50-90), P = 0.156	28 (20-37) vs. 75 (60-105), P < 0.001	6 (4-10) vs. 35 (27-47), P < 0.001	-	62.7% vs. 0.0% (DNT ≤ 30 min)
Meretoja, et al. [17]	Australia	2011-2012	115 vs. 140	73 (50-108) vs. 77 (53-113)	46 (24-79) vs. 61 (43-75), P = 0.040	-	-	-
Qiang Huang, et al. [91]	Beijing, China	2011-2015	173 (130-225) vs. 229 (185-270), P < 0.001	106 (67-140) vs. 110 (67-164), P = 0.510	53 (43-86) vs. 116 (93-135), P < 0.001	24 (16-29) vs. 28 (15-40), P = 0.002	-	60.3% vs. 9.9%; P < 0.001 (DTN ≤ 60 min)
Sang-Beom Jeon, et al. [92]	Seoul, Korea	2014-2016	102.5 (49.0-153.5) vs. 129.0 (84.3-183.3), p = 0.024	91.0 (36.0-199.0) vs. 107.0 (45.5-218.5), P = 0.144	20.5 (15.8-32.5) vs. 46.0 (36.0-57.0), p < 0.001	13.0 (8.0-19.0) vs. 18.0 (15.0-23.0), P < 0.001	15.8% vs. 9.8%, P = 0.002	-

*Data are presented as median (IQR).

OTT: onset to thrombolysis; OTD, onset-to-door time; DTN, door-to-needle time; DTI, door-to-imaging time.

DOI: 10.31480/2330-4871/091

components of stroke treatment [17,67,91-94] as shown in Table 2.

Some studies have examined the effect of stroke management in thrombolytic treatment [17,67,91-94] as shown in Table 3. Surprisingly, the Helsinki model had a median DNT of only 20 minutes [93] and the Acute Brain Care (ABC) intervention study showed the median DNT decreased from 75 to 28 minutes [94].

A study in China showed that the intervention improved all parameters (all $P < 0.05$) including door-to-examination, door-to-laboratory, door-to-imaging, final-test-to-needle times, and DTN with net reductions of 2, 28, 4, 23 and 63 minutes, respectively [91]. Another study in Korea showed that after SAT implementation, the median door-to-laboratory, door-to-CT and door-to-MRI time decreased to 8 minutes, 13 minutes, and 37.5 minutes respectively ($P < 0.001$) [92]. The median DNT time was reduced from 46 minutes to 20.5 minutes. The thrombolysis rate increased from 9.8% to 15.8%, and the post-thrombolysis intracranial hemorrhage rate decreased from 12.6% to 2.1%.

In view of the mixed results of several studies, it may be of significant benefit to optimize management protocols.

Conclusions

This review clearly demonstrates that each part in the pre- and in-hospital stroke rescue chain is significant; further studies are needed to assess the efficacy of other potential improvements.

Since these delays depend on many factors, improved public awareness, pre- and in-hospital management, education of ambulance teams, increased information for the public, and the optimization of acute management strategies at hospitals should all enable more stroke patients to get timely treatment of rt-PA as well as to attain functional recovery. Additional research is required in order to develop the most effective public awareness programs to affect the behavior of patients, relatives, and bystanders in an actual emergency situation. EMS is a key factor in reducing prehospital delays, and it is important to make good use of MSUs and the Stroke Emergency Maps. Furthermore, the in-hospital portion of stroke treatment is another significant challenge to manage. Seamless collaboration between prehospital and inpatient care is an integral part of stroke treatment, which is necessary to reduce overall delays and thus improve patient outcomes.

Acknowledgments

This work supported by a grant from National Key R&D Program of China (2017YFC0114300), the National Basic Research Priorities Program of Jiangsu Province (Grant No. BK20160347), Jiangsu Province's Key Provincial Talents Program (Grant No. QNRC2016730) and Health and Family Planning Commission of Jiangsu Province (Grant No. Z2017011).

Conflict of interest

We declare that we have no conflict of interest.

References

1. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151-210.PMID:28919116.
2. Writing Group M, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK et al. Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association. Circulation 2016;133:447-54. PMID:26811276.
3. Jauch EC, Saver JL, Adams HP, Jr., Bruno A, Connors JJ 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 2013;44:870-947. PMID:23370205.
4. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2014;10.1002/14651858.CD000213.pub3:CD000213. PMID:25072528.
5. Kim YD, Nam HS, Kim SH, Kim EY, Song D et al. Time-Dependent Thrombus Resolution After Tissue-Type Plasminogen Activator in Patients With Stroke and Mice. Stroke 2015;46:1877-82.PMID:25967573.
6. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE et al. 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.PMID:26696642.
7. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet 2010;375:1695-703. PMID:20472172.
8. Saver JL, Smith EE, Fonarow GC, Reeves MJ, Zhao X et al. The "golden hour" and acute brain ischemia: presenting features and lytic therapy in >30,000 patients arriving within 60 minutes of stroke onset. Stroke 2010;41:1431-9. PMID:20522809.
9. Gumbinger C, Reuter B, Stock C, Sauer T, Wietholter H et al. 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.PMID:24879819.
10. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. JAMA 2013;309:2480-8.PMID:23780461.
11. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G et al. 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;384:1929-35. PMID:25106063.

12. Khatri P, Yeatts SD, Mazighi M, Broderick JP, Liebeskind DS et al. Time to angiographic reperfusion and clinical outcome after acute ischaemic stroke: an analysis of data from the Interventional Management of Stroke (IMS III) phase 3 trial. Lancet Neurol 2014;13:567-74.PMID:24784550.

13. Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW et al. Stroke thrombolysis: save a minute, save a day. Stroke 2014;45:1053-8.PMID:24627114.

14. Kamal N, Sheng S, Xian Y, Matsouaka R, Hill MD et al. Delays in Door-to-Needle Times and Their Impact on Treatment Time and Outcomes in Get With The Guidelines-Stroke. Stroke 2017;48:946-54.PMID:28228574.

15. de Los Rios la Rosa F, Khoury J, Kissela BM, Flaherty ML, Alwell K et al. Eligibility for Intravenous Recombinant Tissue-Type Plasminogen Activator Within a Population: The Effect of the European Cooperative Acute Stroke Study (ECASS) III Trial. Stroke 2012;43:1591-5.PMID:22442174.

16. Zhao J, Ren L, Abraham SV, Li D, Kung D et al. The Stroke Prehospital Delay Summary Statement: A Global Battlefield. Translational Perioperative and Pain Medicine 2019;6 20-6.

17. Meretoja A, Weir L, Ugalde M, Yassi N, Yan B et al. Helsinki model cut stroke thrombolysis delays to 25 minutes in Melbourne in only 4 months. Neurology 2013;81:1071-6. PMID:23946303.

18. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ 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;311:1632-40.PMID:24756513.

19. Hong ES, Kim SH, Kim WY, Ahn R, Hong JS. Factors associated with prehospital delay in acute stroke. Emerg Med J 2011;28:790-3.PMID:20732862.

20. Jiang B, Ru X, Sun H, Liu H, Sun D et al. Pre-hospital delay and its associated factors in first-ever stroke registered in communities from three cities in China. Sci Rep 2016;6:29795.PMID:27411494.

21. Fassbender K, Balucani C, Walter S, Levine SR, Haass A et al. Streamlining of prehospital stroke management: the golden hour. Lancet Neurol 2013;12:585-96. PMID:23684084.

22. Song D, Tanaka E, Lee K, Sato S, Koga M et al. Factors Associated with Early Hospital Arrival in Patients with Acute Ischemic Stroke. J Stroke 2015;17:159-67.PMID:26060803.

23. Zhou Y, Yang T, Gong Y, Li W, Chen Y et al. Pre-hospital Delay after Acute Ischemic Stroke in Central Urban China: Prevalence and Risk Factors. Mol Neurobiol 2017;54:3007-16.PMID:27032390.

24. Jin H, Zhu S, Wei JW, Wang J, Liu M et al. Factors associated with prehospital delays in the presentation of acute stroke in urban China. Stroke 2012;43:362-70. PMID:22246693.

25. Mosley I, Nicol M, Donnan G, Patrick I, Dewey H. Stroke symptoms and the decision to call for an ambulance. Stroke 2007;38:361-6.PMID:17204685.

26. Yanagida T, Fujimoto S, Inoue T, Suzuki S. Prehospital delay and stroke-related symptoms. Intern Med 2015;54:171-7. PMID:25743008.

27. Kleindorfer D, Khoury J, Broderick JP, Rademacher E, Woo D et al. Temporal trends in public awareness of stroke: warning signs, risk factors, and treatment. Stroke 2009;40:2502-6.PMID:19498187.

28. Addo J, Ayis S, Leon J, Rudd AG, McKevitt C et al. Delay in presentation after an acute stroke in a multiethnic population in South london: the South london stroke register. J Am Heart Assoc 2012;1:e001685.PMID:23130144.

29. Mandelzweig L, Goldbourt U, Boyko V, Tanne D. Perceptual, social, and behavioral factors associated with delays in seeking medical care in patients with symptoms of acute stroke. Stroke 2006;37:1248-53.PMID:16556885.

30. Palomeras E, Fossas P, Quintana M, Monteis R, Sebastian M et al. Emergency perception and other variables associated with extra-hospital delay in stroke patients in the Maresme region (Spain). Eur J Neurol 2008;15:329-35. PMID:18312404.

31. Geffner D, Soriano C, Perez T, Vilar C, Rodriguez D. Delay in seeking treatment by patients with stroke: who decides, where they go, and how long it takes. Clin Neurol Neurosurg 2012;114:21-5.PMID:21944574.

32. Fang J, Yan W, Jiang GX, Li W, Cheng Q. Time interval between stroke onset and hospital arrival in acute ischemic stroke patients in Shanghai, China. Clin Neurol Neurosurg 2011;113:85-8.PMID:20889252.

33. Srivastava AK, Prasad K. A study of factors delaying hospital arrival of patients with acute stroke. Neurol India 2001;49:272-6.PMID:11593245.

34. Wester P, Radberg J, Lundgren B, Peltonen M. Factors associated with delayed admission to hospital and in-hospital delays in acute stroke and TIA: a prospective, multicenter study.Seek- Medical-Attention-in-Time Study Group. Stroke 1999;30:40-8.PMID:9880386.

35. Hatzitolios AI, Spanou M, Dambali R, Vraka K, Doumarapis E et al. Public awareness of stroke symptoms and risk factors and response to acute stroke in Northern Greece. Int J Stroke 2014;9:E15.PMID:24798041.

36. Lundelin K, Graciani A, Garcia-Puig J, Guallar-Castillon P, Taboada JM et al. Knowledge of stroke warning symptoms and intended action in response to stroke in Spain: a nationwide population-based study. Cerebrovasc Dis 2012;34:161-8.PMID:22907330.

37. Yin X, Yang T, Gong Y, Zhou Y, Li W et al. Determinants of Emergency Medical Services Utilization Among Acute Ischemic Stroke Patients in Hubei Province in China. Stroke 2016;47:891-4.PMID:26768208.

38. Zhao J, Eckenhoff MF, Sun WZ, Liu R. Stroke 112: A Universal Stroke Awareness Program to Reduce Language and Response Barriers. Stroke 2018;49:1766-9. PMID:29925649.

39. Abraham SV, Krishnan SV, Thaha F, Balakrishnan JM, Thomas T et al. Factors delaying management of acute stroke: An Indian scenario. Int J Crit Illn Inj Sci 2017;7:224-30.PMID:29291175.

40. Farrag MA, Oraby MI, Ghali AA, Ragab OA, Nasreldein A et al. Public stroke knowledge, awareness, and response to acute stroke: Multi-center study from 4 Egyptian governorates. J Neurol Sci 2018;384:46-9.PMID:29249376.

41. Kim YS, Park SS, Bae HJ, Heo JH, Kwon SU et al. Public awareness of stroke in Korea: a population-based national survey. Stroke 2012;43:1146-9.PMID:22156687.

42. Denti L, Caminiti C, Scoditti U, Zini A, Malferrari G et al. Impact on Prehospital Delay of a Stroke Preparedness Campaign: A SW-RCT (Stepped-Wedge Cluster Randomized Controlled Trial). Stroke 2017;48:3316-22. PMID:29101258.

43. Dombrowski SU, Mackintosh JE, Sniehotta FF, Araujo-Soares V, Rodgers H et al. The impact of the UK 'Act FAST' stroke awareness campaign: content analysis of patients, witness and primary care clinicians' perceptions. BMC Public Health 2013;13:915.PMID:24088381.

44. Rasura M, Baldereschi M, Di Carlo A, Di Lisi F, Patella R et al. Effectiveness of public stroke educational interventions: a review. Eur J Neurol 2014;21:11-20.PMID:24102755.

45. Mellon L, Doyle F, Rohde D, Williams D, Hickey A. Stroke warning campaigns: delivering better patient outcomes? A systematic review. Patient Relat Outcome Meas 2015;6:61-73.PMID:25750550.

46. Bray JE, Finn J, Cameron P, Smith K, Straney L et al. Temporal Trends in Emergency Medical Services and General Practitioner Use for Acute Stroke After Australian Public Education Campaigns. Stroke 2018;49:3078-80. PMID:30571429.

47. Robinson TG, Reid A, Haunton VJ, Wilson A, Naylor AR. The face arm speech test: does it encourage rapid recognition of important stroke warning symptoms? Emerg Med J 2013;30:467-71.PMID:22764171.

48. Williams O, Leighton-Herrmann Quinn E, Teresi J, Eimicke JP, Kong J et al. Improving Community Stroke Preparedness in the HHS (Hip-Hop Stroke) Randomized Clinical Trial. Stroke 2018;49:972-9.PMID:29567762.

49. Bray JE, Johnson R, Trobbiani K, Mosley I, Lalor E et al. Australian public's awareness of stroke warning signs improves after national multimedia campaigns. Stroke 2013;44:3540-3.PMID:24135926.

50. Skolarus LE, Murphy JB, Zimmerman MA, Bailey S, Fowlkes S et al. Individual and community determinants of calling 911 for stroke among African Americans in an urban community. Circ Cardiovasc Qual Outcomes 2013;6:278-83.PMID:23674311.

51. Zhao J, Liu R. Calling for a rapid recognition and response program for stroke in China. Transl Perioper Pain Med 2016;1:1-4.PMID:28105445.

52. Zhao J, Liu R. Stroke 1-2-0: a rapid response programme for stroke in China. Lancet Neurol 2017;16:27-8. PMID:28029517.

53. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati Prehospital Stroke Scale: reproducibility and validity. Ann Emerg Med 1999;33:373-8.PMID:10092713.

54. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke 2000;31:71-6.PMID:10625718

55. Harbison J, Massey A, Barnett L, Hodge D, Ford GA. Rapid ambulance protocol for acute stroke. Lancet 1999;353:1935. PMID:10371574.

56. Laurencin C, Philippeau F, Blanc-Lasserre K, Vallet AE, Cakmak S et al. Thrombolysis for Acute Minor Stroke: Outcome and Barriers to Management. Results from the RESUVAL Stroke Network. Cerebrovasc Dis 2015;40:3-9. PMID:25998791.

57. Hsieh MJ, Tang SC, Chiang WC, Huang KY, Chang AM et al. Utilization of emergency medical service increases chance of thrombolytic therapy in patients with acute ischemic stroke. J Formos Med Assoc 2014;113:813-9. PMID:24296308.

58. Kamel H, Navi BB, Fahimi J. National trends in ambulance use by patients with stroke, 1997-2008. JAMA 2012;307:1026-8.PMID:22416095.

59. Hong KS, Bang OY, Kim JS, Heo JH, Yu KH et al. Stroke Statistics in Korea: Part II Stroke Awareness and Acute Stroke Care, A Report from the Korean Stroke Society and Clinical Research Center For Stroke. J Stroke 2013;15:67-77.PMID:24324942.

60. Price CI, Rae V, Duckett J, Wood R, Gray J et al. An observational study of patient characteristics associated with the mode of admission to acute stroke services in North East, England. PLoS One 2013;8:e76997.PMID:24116195.

61. Minnerup J, Wersching H, Unrath M, Berger K. Effects of emergency medical service transport on acute stroke care. Eur J Neurol 2014;21:1344-7.PMID:24471796.

62. Ekundayo OJ, Saver JL, Fonarow GC, Schwamm LH, Xian Y et al. Patterns of emergency medical services use and its association with timely stroke treatment: findings from Get With the Guidelines-Stroke. Circ Cardiovasc Qual Outcomes 2013;6:262-9.PMID:23633218.

63. Miyamatsu N, Okamura T, Nakayama H, Toyoda K, Suzuki K et al. Public awareness of early symptoms of stroke and information sources about stroke among the general Japanese population: the Acquisition of Stroke Knowledge Study. Cerebrovasc Dis 2013;35:241-9.PMID:23548748.

64. Miyashita F, Yokota C, Nishimura K, Amano T, Inoue Y et al. The effectiveness of a stroke educational activity performed by a schoolteacher for junior high school students. J Stroke Cerebrovasc Dis 2014;23:1385-90.PMID:24389379.

65. Sakamoto Y, Yokota C, Miyashita F, Amano T, Shigehatake Y et al. Effects of stroke education using an animated cartoon and a manga on elementary school children. J Stroke Cerebrovasc Dis 2014;23:1877-81.PMID:24794944.

66. Puolakka T, Kuisma M, Lankimaki S, Puolakka J, Hallikainen J et al. Cutting the Prehospital On-Scene Time of Stroke Thrombolysis in Helsinki: A Prospective Interventional Study. Stroke 2016;47:3038-40.PMID:27827326.

67. Meretoja A, Kaste M. Pre- and in-hospital intersection of stroke care. Ann N Y Acad Sci 2012;1268:145-51. PMID:22994234.

68. Nor AM, McAllister C, Louw SJ, Dyker AG, Davis M et al. Agreement between ambulance paramedic- and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. Stroke 2004;35:1355-9. PMID:15118173.

69. Balucani C, Levine SR. The "almost magical" mobile stroke unit revolution. Neurology 2012;78:1809-10. PMID:22592365.

70. Yong E. First response: race against time. Nature 2014;510:S5.PMID:24964025.

71. Fassbender K, Grotta JC, Walter S, Grunwald IQ, Ragoschke-Schumm A et al. Mobile stroke units for prehospital thrombolysis, triage, and beyond: benefits and challenges. Lancet Neurol 2017;16:227-37. PMID:28229894.

72. Walter S, Kostopoulos P, Haass A, Keller I, Lesmeister M et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. Lancet Neurol 2012;11:397-404.PMID:22497929.

73. Bowry R, Parker S, Rajan SS, Yamal JM, Wu TC et al. Benefits of Stroke Treatment Using a Mobile Stroke Unit Compared With Standard Management: The BEST-MSU Study Run-In Phase. Stroke 2015;46:3370-4. PMID:26508753.

74. Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: a randomized clinical trial. JAMA 2014;311:1622-31.PMID:24756512.

75. Wahlgren N, Ahmed N, Davalos A, Hacke W, Millan M et al. Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. Lancet 2008;372:1303-9.PMID:18790527.

76. Kim JT, Fonarow GC, Smith EE, Reeves MJ, Navalkele DD et al. Treatment With Tissue Plasminogen Activator in the Golden Hour and the Shape of the 4.5-Hour Time-Benefit Curve in the National United States Get With The Guidelines-Stroke Population. Circulation 2017;135:128-39.PMID:27815374.

77. Ebinger M, Kunz A, Wendt M, Rozanski M, Winter B et al. Effects of golden hour thrombolysis: a Prehospital Acute Neurological Treatment and Optimization of Medical Care in Stroke (PHANTOM-S) substudy. JAMA Neurol 2015;72:25-30.PMID:25402214.

78. Parker SA, Bowry R, Wu TC, Noser EA, Jackson K et al. Establishing the first mobile stroke unit in the United States. Stroke 2015;46:1384-91.PMID:25782464.

79. Adams HP, Jr., del Zoppo G, Alberts MJ, Bhatt DL, Brass L et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38:1655-711.PMID:17431204.

80. Wang Y, Liao X, Zhao X, Wang DZ, Wang C et al. Using recombinant tissue plasminogen activator to treat acute ischemic stroke in China: analysis of the results from the Chinese National Stroke Registry (CNSR). Stroke 2011;42:1658-64.PMID:21512182.

81. Huang Q, Ma QF, Feng J, Cheng WY, Jia JP et al. Factors Associated with In-Hospital Delay in Intravenous Thrombolysis for Acute Ischemic Stroke: Lessons from China. PLoS One 2015;10:e0143145.PMID:26575839

82. Breuer L, Huttner HB, Kiphuth IC, Ringwald J, Hilz MJ et al. Waiting for platelet counts causes unsubstantiated delay of thrombolysis therapy. Eur Neurol 2013;69:317-20. PMID:23548890.

83. Sauser K, Levine DA, Nickles AV, Reeves MJ. Hospital variation in thrombolysis times among patients with acute ischemic stroke: the contributions of door-to-imaging time and imaging-to-needle time. JAMA Neurol 2014;71:1155-61.PMID:25023407.

84. Ford AL, Williams JA, Spencer M, McCammon C, Khoury N et al. Reducing door-to-needle times using Toyota's lean manufacturing principles and value stream analysis. Stroke 2012;43:3395-8.PMID:23138440.

85. Mikulik R, Kadlecova P, Czlonkowska A, Kobayashi A, Brozman M et al. Factors influencing in-hospital delay in treatment with intravenous thrombolysis. Stroke 2012;43:1578-83.PMID:22426311.

86. Yang T, Zhang H, Shen F, Li JW, Wu MC. Appeal from Chinese doctors to end violence. Lancet 2013;382:1703-4. PMID:24267999.

87. Sun P, Zhang X, Sun Y, Ma H, Jiao M et al. Workplace Violence against Health Care Workers in North Chinese Hospitals: A Cross-Sectional Survey. Int J Environ Res Public Health 2017;14.PMID:28106851.

88. Sun T, Gao L, Li F, Shi Y, Xie F et al. Workplace violence, psychological stress, sleep quality and subjective health in Chinese doctors: a large cross-sectional study. BMJ Open 2017;7:e017182.PMID:29222134.

89. Bogardus ST, Jr., Holmboe E, Jekel JF. Perils, pitfalls, and possibilities in talking about medical risk. JAMA 1999;281:1037-41.PMID:10086441.

90. Blumenthal D, Hsiao W. Lessons from the East--China's rapidly evolving health care system. N Engl J Med 2015;372:1281-5.PMID:25830419.

91. Huang Q, Song HQ, Ji XM, Cheng WY, Feng J et al. Generalization of the Right Acute Stroke Prevention Strategies in Reducing in-Hospital Delays. PLoS One 2016;11:e0154972.PMID:27152854.

92. Jeon SB, Ryoo SM, Lee DH, Kwon SU, Jang S et al. Multidisciplinary Approach to Decrease In-Hospital Delay for Stroke Thrombolysis. J Stroke 2017;19:196-204. PMID:28592785.

93. Meretoja A, Strbian D, Mustanoja S, Tatlisumak T, Lindsberg PJ et al. Reducing in-hospital delay to 20 minutes in stroke thrombolysis. Neurology 2012;79:306-13.PMID:22622858.

94. Zinkstok SM, Beenen LF, Luitse JS, Majoie CB, Nederkoorn PJ et al. Thrombolysis in Stroke within 30 Minutes: Results of the Acute Brain Care Intervention Study. PLoS One 2016;11:e0166668.PMID:27861540.

Corresponding Author: *Yan Kong, Zhuan Xu and Xiuying Cai; Department of Neurology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China, E-mail: kong0919@163.com*

Editor: *Tianzuo Li, MD, PhD, Department of Anesthesiology, Sijitan Hospital, Capital University, China, E-mail: trmzltz@126.com*

Additional publication details

Journal short name: Transl Perioper & Pain Med

Received Date: January 16, 2019

Accepted Date: April 11, 2019

Published Date: April 16, 2019

Citation: Lu Y, Sun T, Yi-ping D, Shan-shan D, Li T, et al. Pre- and In-Hospital Management of Stroke. Transl Perioper & Pain Med 2019; 6 (3):64-74