










Original Research

Impact of adherence to key performance indicators on mortality among patients managed for ischemic stroke

Mustapha MOHAMMED , Hadzliana ZAINAL , Balamurugan TANGIISURAN , Sabariah N. HARUN , Siti M. GHADZI , Irene LOOI , Norsima N. SIDEK , Keng L. YEE , Zariah A. AZIZ .
Received (first version): 27-Nov-2019 Accepted: 9-Feb-2020 Published online: 9-Mar-2020

Abstract

Background: Stroke is a leading cause of death worldwide. The cases of acute ischemic stroke are on the increase in the Asia Pacific, particularly in Malaysia. Various health organizations have recommended guidelines for managing ischemic stroke, but adherence to key performance indicators (KPI) from the guidelines and impact on patient outcomes, particularly mortality, are rarely explored.

Objective: This study aims to evaluate the impact of adherence to key performance indicators on mortality among patients managed for ischemic stroke.

Methods: We included all first-ever ischemic stroke patients enrolled in the multiethnic Malaysian National Neurology Registry (NNeuR) - a prospective cohort study and followed-up for six months. Patients' baseline clinical characteristics, risk factors, neurological findings, treatments, KPI and mortality outcome were evaluated. The KPI nonadherence (NAR) and relationship with mortality were evaluated. NAR>25% threshold was considered suboptimal.

Results: A total of 579 first-ever ischemic stroke patients were included in the final analysis. The overall mortality was recorded as 23 (4.0%) in six months, with a median (interquartile) age of 65 (20) years. Majority of the patients (dead or alive) had partial anterior circulation infarct, PACI (43.5%; 34.0%) and total anterior circulation infarct, TACI (26.1%; 8.8%). In addition, DVT prophylaxis (82.8%), anticoagulant for atrial fibrillation (AF) patients (48.8%) and rehabilitation (26.2%) were considered suboptimal. NAR < 2 was significantly associated with a decrease in mortality (odds ratio 0.16; 0.02-0.12) compared to NAR>2. Survival analysis showed that death is more likely in patients with NAR>2 (p=0.05).

Conclusions: KPI nonadherence was associated with mortality among ischemic stroke patients. The adherence to the KPI was sub-optimal, particularly in DVT prophylaxis, anticoagulant for AF patients and rehabilitation. These findings reflect the importance of continuous quality measurement and implementation of evidence recommendations in healthcare delivery to achieve optimal outcome among stroke patients.

Keywords

Stroke; Brain Ischemia; Risk Factors; Anticoagulants; Guideline Adherence; Professional Practice; Mortality; Registries; Prospective Studies; Survival Analysis; Malaysia

INTRODUCTION

Stroke is a leading cause of mortality and disability globally, and its burden over the past decades has increased significantly.¹⁻⁴ The economic, psychological and social costs implications of stroke have run into huge budgets.^{2,5} The burden of stroke is projected to keep rising until more effective prevention strategies are widely adopted.⁴ Ischemic stroke is more common; however, hemorrhagic stroke is responsible for more deaths, and disability-

adjusted life-years lost.^{4,6} All strokes should be considered for immediate treatments.⁵ Acute treatment for ischemic strokes aims to restore brain tissue perfusion and could be achieved using thrombolytic agents or endovascular procedures, or both. Reports have shown an increasing number of patients being diagnosed with acute stroke, especially in Asia Pacific.⁷ Data from the National Neurology Registry (NNeuR) of Malaysia shows that the incidence of ischemic stroke has increased by 29.5% annually from 2010 to 2014.⁸ In Malaysia, stroke is among the top five leading causes of death and as one of the top 10 causes of hospitalization.⁹ It is also among the top five diseases with the highest burden of disease based on disability-adjusted life years. The NNeuR and other studies have revealed that adherence to the evidence-based guidelines and outcomes in stroke care has not been systematically evaluated in clinical practice.⁸⁻¹¹

Acute ischemic stroke (AIS) is a medical emergency.¹² The chances of poor outcomes with stroke increase with delay in time to treatment.¹³ Intravenous recombinant tissue plasminogen activator (rtPA) is an FDA approved drug for AIS to be given within 3 - 4.5 hours of stroke onset.¹⁴ Clinical evidence demonstrates the significance of timely evaluation and initiation of treatment for optimal stroke outcomes.^{15,16} Furthermore, improving the quality of stroke care has become a global priority.¹⁷⁻²¹ Data from the Get with the Guidelines-Stroke (GWTG-Stroke) program

Mustapha MOHAMMED. School of Pharmaceutical Sciences. University of Science Malaysia. Pulau Pinang (Malaysia). macreener88@gmail.com

Hadzliana ZAINAL. School of Pharmaceutical Sciences. University of Science Malaysia. Pulau Pinang (Malaysia). hadz@usm.my

Balamurugan TANGIISURAN. National Poison Centre, University of Science Malaysia. Pulau Pinang (Malaysia). bala@usm.my

Sabariah Noor HARUN. School of Pharmaceutical Sciences. University of Science Malaysia. Pulau Pinang (Malaysia). sabariahnoor@usm.my

Siti Maisharah Sheikh GHADZI. School of Pharmaceutical Sciences. University of Science Malaysia. Pulau Pinang (Malaysia). maisharah@usm.my

Looi IRENE. Clinical Research Centre, Hospital Seberang Jaya, Pulau Pinang (Malaysia). irenelooi@yahoo.com

Norsima Nazifah SIDEK. Clinical Research Centre, Hospital Sultanah Nur Zahirah. Terengganu (Malaysia). norsima@crc.moh.gov.my

Keng Lee YEE. National Institute of Health, Ministry of Health. Selangor (Malaysia). leekengyee@crc.moh.gov.my

Zariah Abdul AZIZ. Clinical Research Centre, Hospital Sultanah Nur Zahirah. Terengganu (Malaysia). zaraziz_ayie@yahoo.com

demonstrate significant and sustained improvements in the United States' stroke care.^{16,17,23} However, treatment of AIS has mainly remained conservative with usual clinical practice, which often falls short of guideline-established goals and only a small percentage of Asian patients undergo thrombolysis.²⁴

Although Malaysia lacks stroke units, it has in place KPIs, which serve as a quality measurement of stroke healthcare delivery. Nine KPIs, adapted from the Centers for Disease Control and Prevention's Paul Coverdell National Acute Stroke Registry, are used to assess the compliance rate of stroke care delivery: (1) thrombolytic therapy administration, (2) antiplatelet therapy within 48 hours of admission, (3) venous thromboembolism prophylaxis, (4) anticoagulation therapy for atrial fibrillation, (5) discharge on antiplatelet therapy, (6) discharge on statin medication, (7) dysphagia screening, (8) stroke education, and (9) rehabilitation.^{8,25} The performance indicators are standards of care that show inadequacy if eligible patients do not receive that standard of care. Thus, these indicators are used to monitor adherence to guidelines, and support transfer of new evidence into routine practice.²⁶

Many countries produce their guidelines, and updates occur at varying intervals, but the impact on outcomes remain unvalidated.²⁷ Despite the wide the availability of guidelines for the prevention and treatment of stroke, many patients do not still receive these recommended interventions.^{28,29} Stroke Council of the Malaysian Society of Neurosciences has developed a guideline on ischemic stroke management with the latest version in 2012.¹¹ While the guidelines are developed to bridge the research - clinical practice gap, evidence regarding their use, implementation, and impact on patients' outcome, including mortality, disability, and costs remain limited.^{10,19,20} To date, there is no report on the mortality outcome in association with adherence to guidelines for stroke care and performance in Malaysia. Therefore, our study was aimed to assess the impact of KPI adherence on mortality among ischemic stroke patients.

METHODS

The Stroke Registry in Malaysia was founded in 2009. The multiethnic NNeuR is a prospective cohort program that gathers data on patient's admitted into the hospital in any of the participating hospitals of the states in the country and diagnosed with stroke. NNeuR is a multicenter, hospital-based registry which aims to introduce extensive epidemiological information on the stroke statistics, trend, and management in Malaysia. It is funded by the Ministry of Health Malaysia (MOH) with the support from the National Network Clinical Research Centre, Ministry of Health. The complete details on the stroke registry have been previously described elsewhere.^{8,9,10,30} Further details about the registry can also be found through the link <http://acrm.org.my/nneur/>. NNeuR study protocol was approved by the Ministry of Health Medical Research and Ethics Committee (MREC) (NMRR-08-1631-3189).

Patients' data were extracted from the Malaysian National Stroke Registry, NNeuR (2009-2016). Only adult patients (>18 years of age), diagnosed with first-ever acute ischemic stroke (AIS) based on the WHO's criteria were included in the study.³¹ Clinical first-ever ischemic stroke was defined as an acute focal neurological deficit lasting >24 hours with no cause other than a cerebrovascular disease in patients who have not had a previous stroke. We excluded recurrent stroke, non-ischemic stroke, and stroke mimics. Based on the features of the initial neurological examination, the patients were grouped according to the Oxfordshire Community Stroke Project (OCSP) stroke subtypes; total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI) and posterior circulation infarct (POCI).³² The clinical diagnosis was also confirmed by neuro-imaging findings; computer tomography (CT) or magnetic resonance imaging (MRI). Other patients baseline characteristics reviewed include; socio-demographics, vascular risk factors such as hypertension, diabetes, hyperlipidaemia, ischemic heart disease, atrial fibrillation, hyperuricaemia, medical history, stroke family history, smoking, alcohol, medication use, stroke KPIs and patient status during hospitalization and

Features	Death (%)	Alive (%)	p-value
Age [Median, interquartile]	65 (20)	59 (16)	0.011 [#]
Female gender	9 (39.1)	234 (42.1)	0.478
OCSP classification			0.004*
LACI	4 (17.4)	235 (42.8)	
PACI	10 (43.5)	189 (34.0)	
POCI	2 (8.7)	69 (12.4)	
TACI	6 (26.1)	49 (8.8)	
Unclassified	1 (4.3)	10 (1.8)	
Risk Factors			
Hypertension	19 (82.6)	376 (67.6)	0.096
Diabetes Mellitus	13 (56.5)	226 (40.6)	0.098
Hyperlipidaemia	8 (34.8)	172 (30.9)	0.426
Ischemic heart disease	4 (17.4)	53 (9.5)	0.182
Atrial fibrillation	1 (4.3)	17 (3.1)	0.523
Hyperuricaemia	1 (4.3)	21 (3.8)	0.597
Family history	1 (4.3)	58 (10.4)	0.299
Smoking	18 (78.3)	274 (49.3)	0.005*
Alcohol	0 (0)	16 (2.9)	0.518

Oxfordshire community stroke project (OCSP); Lacunar infarct (LACI); Partial anterior circulation infarct (PACI); Posterior circulation infarct (POCI); Total anterior circulation infarct (TACI); *; # = significance at p<0.05 using Chi-square and Mann-Whitney U tests respectively

Areas of KPI nonadherence		Frequency	Percentage (%)
In-hospital indicators			
	Anti-platelet within 48 hours	27	4.7
	Dysphagia screening	9	1.6
	DVT prophylaxis	480	82.8 [‡]
Discharge indicators			
	Stroke education	34	5.9
	Rehabilitation	152	26.2 [‡]
	Anticoagulant for AF patient	289	49.8 [‡]
	Antiplatelet upon discharge	15	2.6
	Lipid-lowering therapy upon discharge	11	1.9
Deep vein thrombosis (DVT); Atrial fibrillation (AF); KPI nonadherence = (NAR) [‡] = NAR Threshold ≥ 25%			

discharge as described in the NNeuR. Patients were followed up for six months for mortality. These evaluations were made by the attending physicians and data uploaded onto the NNeuR. In the event of a patient's death, the date and cause of death were noted and identified as either given by relatives or general practitioners.

The primary outcome, KPI nonadherence (NAR) was calculated based on the eight KPIs for each included ischemic stroke patient. The NAR value initially starts at zero and increase by one, for each practice not according to the guideline recommendation, to a maximum of 8. The KPIs included are anti-platelet within 48 hours of admission, dysphagia screening before feeding, DVT prophylaxis within 48 hours of admission for non-ambulatory patients, stroke education, rehabilitation, anticoagulant for AF patients, antiplatelet upon discharge and lipid-lowering therapy upon discharge. All measures indicate the proportion of eligible patients who received the intervention as described. The optimal adherence is defined as the proportion of patients who received all of the performance measure interventions for which they were eligible.¹⁷ The NAR, >25% threshold was considered sub-optimal. The secondary study outcome was death within 6-months follow-up. The NAR was categorised into two groups (NAR <2 vs NAR >2), as the NAR recorded ranged from 0 to 5, and NAR >2 is reported to be sub-optimal, as supported by previous studies.³³

Data were presented descriptively as frequencies, percentages, median and interquartile range in tables and figures. Chi-square test, Mann-Whitney U test, and Kaplan-Meier survival analysis were conducted using IBM SPSS Statistics version 20.0. $p < 0.05$ was considered statistically significant.

RESULTS

Patients demographics, stroke sub-type and vascular risk factors are shown in Table 1. This study involved a total of five hundred and seventy-nine (579) first-ever ischemic stroke patients. The results also showed a total of 23 (4.0%) patients died within six months, with a median (interquartile) age of 65 (20) years. Also, the deceased were

mostly PACI 10 (43.5%) and TACI 6 (26.1%) with hypertension 19 (82.6%), smoking 18 (78.3%) and diabetes 13 (56.5%) as the most common risk factors. The overall survival status was found to be significantly associated with smoking ($p=0.005$) and OCSF classification ($p=0.004$).

The major areas of nonadherence based on KPIs and the relative percentage are reported in Table 2. Of the 579 patients included in this study, and considering NAR >25% threshold, NAR was common in DVT prophylaxis 480 (82.8%), anticoagulant for AF 289 (49.8%), and rehabilitation 152 (26.2%). The best performance based on NAR was in dysphagia screening before oral intake 9 (1.6%) and lipid-lowering agent at discharge 11 (1.9%).

This study also revealed that most of the stroke patients had NAR <2 according to their survival status. Also, NAR <2 was significantly associated with a decrease in mortality (OR 0.16; 95%CI 0.02-0.12) compared to NAR >2. Further details are shown in Table 3.

The survival curves of the two groups of patients with NAR <2 and >2 are illustrated in Figure 1. The Kaplan-Meier survival analysis for mortality event among the stroke patients showed a significant difference of survival rate with NAR ($p=0.05$), with the patients in the group of NAR >2 having a higher chance of death during the 6-months follow up compared to those in NAR <2, as shown in Figure 1.

DISCUSSION

This study was designed to investigate the quality of ischemic stroke care based on key performance indicators enshrined in the Malaysian stroke registry and the management guideline, and to establish a possible relationship with stroke patients' short-term survival. Using the standard set of performance indicators, we found significant gaps in the quality of care provided for ischemic stroke patients. Some areas of stroke care quality were found to be suboptimal, cutting across the in-hospital and discharge indicators, particularly in DVT prophylaxis, anticoagulant for AF, and rehabilitation. These encounters may have impacted negatively to the short-term survival outcome of the stroke patients. The consequences might widen further with longer follow-ups.^{17,18,21,22,34} While it is

Features	KPI nonadherence (%)		p-value	OR (95% CI)
	NAR ≤ 2	NAR > 2		
Status				
Death	22 (95.7)	1 (4.3)	0.039*	0.16 (0.02-0.12)
Alive	433 (77.9)	123 (22.1)	Ref	Ref
KPI nonadherence (NAR); *significant at $p < 0.05$				

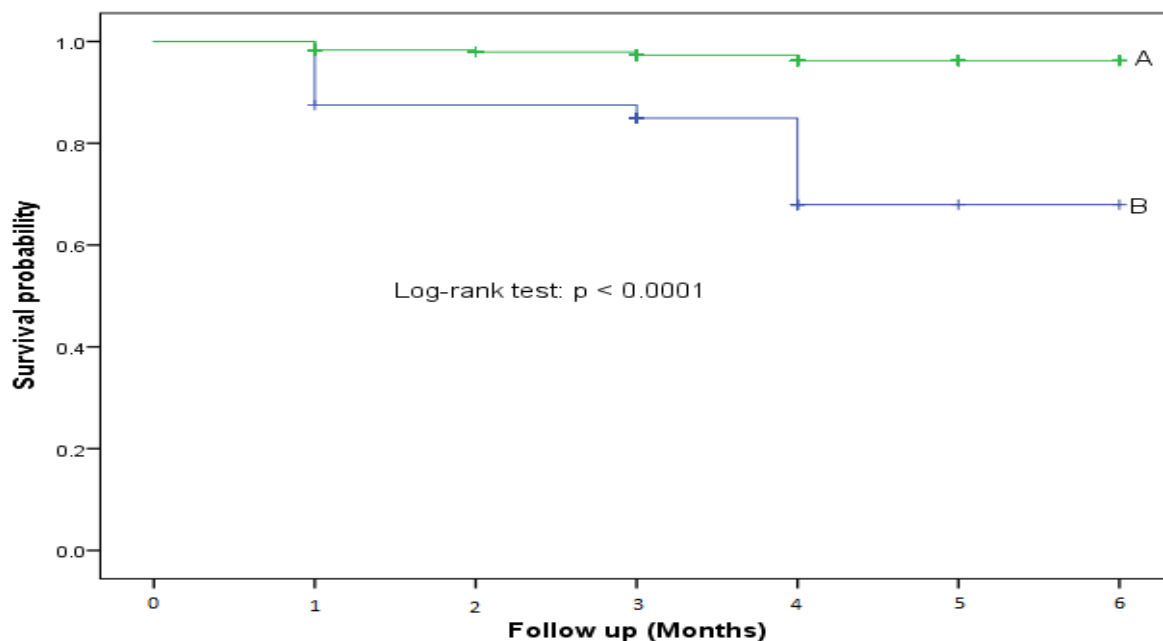


Figure 1. Kaplan-Meier survival curves for the different groups of KPI nonadherence NAR=KPI nonadherence; A=NAR>2; B=NAR≤2; Significant at p<0.05

possible that in our setting, physicians still prefer a medical approach based on personal experience to an evidence-based one, especially in the choice of pharmacological treatments. Inadequate documentation could also explain the low performance. Studies have demonstrated that adherence to stroke performance indicators and other processes of care were associated with improved outcomes among acute stroke patients.^{22,35}

The management of vascular risk factors is essential to reduce the risk of recurrent stroke.²⁸ Our study also identifies sub-optimal adherence with secondary prevention measures, particularly at discharge, including the use of anticoagulant for AF patients. For stroke patients with atrial fibrillation, only advanced tertiary hospitals have the facility to monitor international normalised ratio.³⁶ Many physicians, especially in the lower-level hospitals, therefore, may be reluctant to prescribe warfarin. This might be a reason for the reduced use of anticoagulants in NNeuR. It could also be possible that the status of bleeding risk in this cohort is unknown; therefore, a high risk of bleeding may also explain why the anticoagulants are not being prescribed. For patients with ischemic stroke, the use of antiplatelets on admission or discharge is strongly recommended to reduce the risk of recurrence.²⁸ However, only less than 5% of eligible patients did not receive antiplatelets during hospitalisation or at discharge, which is consistent with findings of other studies about the use of secondary prevention methods for stroke care.^{11,28,37}

This study established an association between mortality and performance indicators non-adherence, though not adjusted for confounders. The risk of death was found to be associated with increasing NAR. Previous studies have reported a reduction in mortality and the risk of death to be directly associated with the level of compliance to stroke guidelines. Besides, an improved functional

outcome, such as motor and daily activities, was linked to higher compliance.³³ Our study also established a significant association between OCSP clinical type of stroke and smoking with survival status. Also, the most common risk factors identified were hypertension, diabetes and hyperlipidemia may have partly contributed to the deterioration of health status and possibly the death among the stroke patients. A strong relationship between stroke risk factors such as hypertension, diabetes, dyslipidemia, smoking, age, and poor outcome have been reported.^{38,39} Smoking remains a singular most significant social risk in stroke. A study reported that smoking might be related to up to 49% (95%CI, 22-67) of the strokes cases of the population.⁴⁰ This finding suggests that smoking exposed individuals to the risk of stroke and complications such as death.

Standard stroke management procedures recommended by both local (e.g. Malaysian stroke CPG) and international (e.g. AHA/ASA guidelines) organizations include but not limited to complete history, vital signs, physical, neurological and cardiovascular assessment, early reperfusion and mobilization, secondary prevention modalities. These procedures may have strongly influenced the outcomes of stroke patients. Though our study did not evaluate whether an individual nonadherence area was related to evidence of prior failure to proceed with further management, the importance of such specific areas, like early mobilization, investigations, and acute monitoring have been established in previous studies.^{41,42} This real importance of these results reflects that a good clinical practice achieved through the adoption of guidelines can improve the health professionals' approach to managing stroke cases. It means that patients are routinely managed better from presentation to discharge and follow-ups.

Our study also demonstrated significant association between KPI nonadherence and mortality. Implying that with stroke patients with less NAR, there is a less likelihood of mortality cases. Our findings are supported by similar studies that demonstrated optimal compliance with in-hospital and discharge measures to be associated with better clinical and functional outcomes.^{21,35} Patients with better outcome might have been those admitted to hospitals with a higher quality of stroke care and might have received an additional in-hospital intervention. Improving the quality of care must, therefore, be a national priority. DVT prophylaxis has been consistently associated with significant benefits in the USA and Canada.^{21,39} Early anticoagulant use for ischemic stroke patients with AF is associated with a reduction in early and late case fatality.⁴⁴ Similarly, stroke rehabilitation is one key measure that ensures continuity of care and is associated with improved patient short and long-term outcomes.²⁶

Our study is the first attempt to verify the possible impact of KPI adherence on stroke short-term survival outcome from the Malaysian stroke population. The findings of this study could further be validated with a more robust extensive multi-randomized study. The study is not without limitations. It is a longitudinal observational study based on secondary data from the Malaysian stroke registries. As of 2016, there were only 15 participating hospitals in the whole country. As such the sample size may be small to generalise our findings. Also, the initial objectives of the register are to determine epidemiologic data including the demographic pattern of stroke patients, the stroke types, the risk factors for stroke, stroke management and complications, and not to improve the adherence of stroke performance measures. Nevertheless, the registry includes all necessary information to treat, measure clinical evolution, and define etiology with the indicators that contribute to a quality evaluation in stroke care. It is also

possible that some performance measures were not properly documented on the medical records before transfer into the registry, and it would mean that some of the performance measures may be wrongly estimated. To account for this, only patients with complete data were included in the analysis.

CONCLUSIONS

Nonadherence to key performance indicators was demonstrated to be associated with mortality among ischemic stroke patients. The adherence to guidelines in acute ischemic stroke management was sub-optimal, particularly in DVT prophylaxis, rehabilitation and anticoagulant for AF patients. These findings suggest the importance of continuous quality improvement in stroke care in Malaysia. Our study also reflects the need for full implementation of guidelines, raising awareness and professional education on stroke management among health professionals.

ACKNOWLEDGEMENT

We thank the Director-General of Health Malaysia for his permission to publish this article.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

FUNDING

This project did not receive any funding. All costs associated were entirely borne by the authors.

References

1. Johnston SC, Mendis S, Mathers CD. Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modelling. *Lancet Neurol.* 2009;8(4):345-354. [https://doi.org/10.1016/S1474-4422\(09\)70023-7](https://doi.org/10.1016/S1474-4422(09)70023-7)
2. Rajsic S, Gothe H, Borba HH, Sroczynski G, Vujicic J, Toell T, Siebert U. Economic burden of stroke: a systematic review on post-stroke care. *Eur J Health Econ.* 2019;20(1):107-134. <https://doi.org/10.1007/s10198-018-0984-0>
3. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18(5):439-458. [https://doi.org/10.1016/S1474-4422\(19\)30034-1](https://doi.org/10.1016/S1474-4422(19)30034-1)
4. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol.* 2017;16(11):877-897. [https://doi.org/10.1016/S1474-4422\(17\)30299-5](https://doi.org/10.1016/S1474-4422(17)30299-5)
5. Benjamin EJ, et al. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association. *Circulation.* 2019 Mar 5;139(10):e56-e528. <https://doi.org/10.1161/CIR.0000000000000659>
6. Katan M, Luft A. Global Burden of Stroke. *Semin Neurol.* 2018;38(2):208-211. <https://doi.org/10.1055/s-0038-1649503>
7. Mehndiratta MM, Khan M, Mehndiratta P, Wasay M. Stroke in Asia: Geographical variations and temporal trends. *J Neurol Neurosurg Psychiatry.* 2014 Dec;85(12):1308-1312. <https://doi.org/10.1136/jnnp-2013-306992>
8. Aziz ZA, Lee YY, Ngah BA, Sidek NN, Looi I, Hanip MR, Basri HB. Acute stroke registry Malaysia, 2010-2014: Results from the National Neurology Registry. *J Stroke Cerebrovasc Dis.* 2015;24(12):2701-2709. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.07.025>
9. Loo KW, Gan SH. Burden of stroke in Malaysia. *Int J Stroke.* 2012;7(2):165-167. <https://doi.org/10.1111/j.1747-4949.2011.00767.x>
10. Tharakan J. Stroke registry-relevance and contributions. *Med J Malaysia.* 2012;67(3):251-252.
11. Hwong WY, Aziz ZA, Sidek NN, Bots ML, Selvarajah S, Kappelle LJ, Sivasampu S, Vaartjes I. Prescription of secondary preventive drugs after ischemic stroke: Results from the Malaysian National Stroke Registry. *BMC Neurol.* 2017;17(1):203. <https://doi.org/10.1186/s12883-017-0984-1>

12. Hasan TF, Rabinstein AA, Middlebrooks EH, Haranhalli N, Silliman SL, Meschia JF, Tawk RG. Diagnosis and management of acute ischemic stroke. *Mayo Clin Proc.* 2018;93(4):523-538. <https://doi.org/10.1016/j.mayocp.2018.02.013>
13. Goyal M, Fargen KM, Menon BK. Acute stroke, Bayes' theorem and the art and science of emergency decision-making. *J Neurointerv Surg.* 2014;6(4):256-259. <https://doi.org/10.1136/neurintsurg-2013-011056>
14. Romano JG, Smith EE, Liang L, Gardener H, Camp S, Shuey L, Cook A4, Campo-Bustillo I, Khatri P, Bhatt DL, Fonarow GC, Sacco RL, Schwamm LH. Outcomes in mild acute ischemic stroke treated with intravenous thrombolysis: a retrospective analysis of the Get With the Guidelines–Stroke registry. *JAMA Neurol.* 2015;72(4):423-431. <https://doi.org/10.1001/jamaneurol.2014.4354>
15. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. 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):750-758. <https://doi.org/10.1161/CIRCULATIONAHA.110.974675>
16. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Xian Y, Hernandez AF, Peterson ED, Schwamm LH. 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):1632-1640. <https://doi.org/10.1001/jama.2014.3203>
17. Fonarow GC, Reeves MJ, Smith EE, Saver JL, Zhao X, Olson DW, Hernandez AF, Peterson ED, Schwamm LH; GWTG-Stroke Steering Committee and Investigators. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in get with the guidelines-stroke. *Circ Cardiovasc Qual Outcomes.* 2010;3(3):291-302. <https://doi.org/10.1161/CIRCOUTCOMES.109.921858>
18. Heuschmann PU, Berger K. International experience in stroke registries: German Stroke Registers study group. *Am J Prev Med.* 2006;31(6 Suppl 2):S238-S239. <https://doi.org/10.1016/j.amepre.2006.08.005>
19. Wang Y, Li Z, Zhao X, Liu L, Wang C, Wang C, Peterson ED, Schwamm LH, Fonarow GC, Smith SC Jr, Bettger J, Wang D, Li H, Xian Y, Wang Y. Evidence-Based Performance Measures and Outcomes in Patients With Acute Ischemic Stroke: Findings From the China National Stroke Registry. *Circ Cardiovasc Qual Outcomes.* 2018;11(12):e001968. <https://doi.org/10.1161/CIRCOUTCOMES.115.001968>
20. Hsieh F, et al. Taiwan stroke registry investigators. Get with the guidelines-stroke performance indicators: surveillance of stroke care in the Taiwan stroke registry: get with the guidelines-stroke in Taiwan. *Circulation.* 2010;122(11):1116-1123. <https://doi.org/10.1161/CIRCULATIONAHA.110.936526>
21. LaBresh KA, Reeves MJ, Frankel MR, Albright D, Schwamm LH. Hospital treatment of patients with ischemic stroke or transient ischemic attack using the "Get With The Guidelines" program. *Arch Intern Med.* 2008;168(4):411-417. <https://doi.org/10.1001/archinternmed.2007.101>
22. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel MR, Smith EE, Ellrodt G, Cannon CP, Liang L, Peterson E, Labresh KA. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation.* 2009;119(1):107-115. <https://doi.org/10.1161/CIRCULATIONAHA.108.783688>
23. Ellrodt AG, Fonarow GC, Schwamm LH, Albert N, Bhatt DL, Cannon CP, Hernandez AF, Hlatky MA, Luepker RV, Peterson PN, Reeves M, Smith EE. Synthesizing lessons learned from get with the guidelines: the value of disease-based registries in improving quality and outcomes. *Circulation.* 2013;128(22):2447-2460. <https://doi.org/10.1161/01.cir.0000435779.48007.5c>
24. Kalkonde YV, Alladi S, Kaul S, Hachinski V. Stroke Prevention Strategies in the Developing World. *Stroke.* 2018;49(12):3092-3097. <https://doi.org/10.1161/STROKEAHA.118.017384>
25. Centers for Disease Control and Prevention (CDC). Prevention. Use of a registry to improve acute stroke care--seven states, 2005-2009. *MMWR Morb Mortal Wkly Rep.* 2011;60(7):206-210.
26. Grube MM, Dohle C, Djouchadar D, Rech P, Bienek K, Dietz-Fricke U, Jöbges M, Kohler M, Missala I, Schönherr B, Werner C, Zeytounchian H, Wissel J, Heuschmann PU. Evidence-based quality indicators for stroke rehabilitation. *Stroke.* 2012;43(1):142-146. <https://doi.org/10.1161/STROKEAHA.111.627679>
27. Rohde A, Worrall L, Le Dorze G. Systematic review of the quality of clinical guidelines for aphasia in stroke management. *J Eval Clin Pract.* 2013;19(6):994-1003. <https://doi.org/10.1111/jep.12023>
28. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(7):2160-2236. <https://doi.org/10.1161/STR.0000000000000024>
29. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. 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(3):870-947. <https://doi.org/10.1161/STR.0b013e318284056a>
30. Nazifah SN, Azmi IK, Hamidon B, Looi I, Zariah A, Hanip M. National Stroke Registry (NSR): Terengganu and Seberang Jaya experience. *Med J Malaysia.* 2012;67(3):302-304.
31. Amarenco P, Bogousslavsky J, Caplan L, Donnan G, Hennerici M. Classification of stroke subtypes. *Cerebrovasc Dis.* 2009;27(5):493-501. <https://doi.org/10.1159/000210432>
32. Appleton JP, Woodhouse LJ, Adami A, Becker JL, Berge E, Cala LA, Casado AM, Caso V, Christensen HK, Dineen RA, Gommans J, Koumellis P, Szatmari S, Sprigg N, Bath PM, Wardlaw JM; ENOS Investigators. Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. *Neurology.* 2020;94(5):e439-e452. <https://doi.org/10.1212/WNL.0000000000000881>

33. Micieli G, Cavallini A, Quaglini S; Guideline Application for Decision Making in Ischemic Stroke (GLADIS) Study Group. Guideline compliance improves stroke outcome: a preliminary study in 4 districts in the Italian region of Lombardia. *Stroke*. 2002;33(5):1341-1347. <https://doi.org/10.1161/01.str.0000013663.27776.db>
34. Rudd AG, Williams LS. Advances in health policy and outcomes. *Stroke*. 2009 May;40(5):e301-e304. <https://doi.org/10.1161/STROKEAHA.108.544551>
35. Bravata DM, Wells CK, Lo AC, Nadeau SE, Melillo J, Chodkowski D, Struve F, Williams LS, Peixoto AJ, Gorman M, Goel P, Acompora G, McClain V, Ranjbar N, Tabereaux PB, Boice JL, Jacewicz M, Concato J. Processes of Care Associated With Acute Stroke Outcomes. *Stroke Outcomes and Processes of Care*. *Arch Intern Med*. 2010;170(9):804-810. <https://doi.org/10.1001/archinternmed.2010.92>
36. Sargin M, Tasdemir MM, Kuplay H, Erdogan SB, Tandogar N, Akansel S, Kurc E, Orhan G, Aka SA. Retrospective cohort study for evaluating the INR monitoring patterns in patients with deep vein thrombosis in daily practice: Analysis of 2010–2013 database of a tertiary care center. *Phlebology*. 2019;34(5):317-323. <https://doi.org/10.1177/0268355518806117>
37. Wei JW, Wang J-G, Huang Y, Liu M, Wu Y, Wong LK, Cheng Y, Xu E, Yang Q, Arima H, Heeley EL, Anderson CS; ChinaQUEST Investigators. Secondary prevention of ischemic stroke in urban China. *Stroke*. 2010;41(5):967-974. <https://doi.org/10.1161/STROKEAHA.109.571463>
38. Gallacher KI, McQueenie R, Nicholl B, Jani BD, Lee D, Mair FS. Risk factors and mortality associated with multimorbidity in people with stroke or transient ischaemic attack: a study of 8,751 UK Biobank participants. *J Comorb*. 2018;8(1):1-8. <https://doi.org/10.15256/joc.2018.8.129>
39. Habibi-koolaee M, Shahmoradi L, Niakan Kalhori SR, Ghannadan H, Younesi E. Prevalence of Stroke Risk Factors and Their Distribution Based on Stroke Subtypes in Gorgan: A Retrospective Hospital-Based Study - 2015-2016. *Neurol Res Int*. 2018;2018:2709654. <https://doi.org/10.1155/2018/2709654>
40. Shinton R. Lifelong exposures and the potential for stroke prevention: the contribution of cigarette smoking, exercise, and body fat. *J Epidemiol Community Health*. 1997;51(2):138-143. <https://doi.org/10.1136/jech.51.2.138>
41. Evans A, Perez I, Harraf F, Melbourn A, Steadman J, Donaldson N, Kalra L. Can differences in management processes explain different outcomes between stroke unit and stroke-team care? *Lancet*. 2001;358(9293):1586-1592. [https://doi.org/10.1016/S0140-6736\(01\)06652-1](https://doi.org/10.1016/S0140-6736(01)06652-1)
42. Indredavik B, Bakke F, Slørdahl S, Rokseth R, Haheim L. Treatment in a combined acute and rehabilitation stroke unit: which aspects are most important? *Stroke*. 1999;30(5):917-923. <https://doi.org/10.1161/01.str.30.5.917>
43. Saposnik G, Fang J, O'Donnell M, Hachinski V, Kapral MK, Hill MD; Investigators of the Registry of the Canadian Stroke Network (RCSN) for the Stroke Outcome Research Canada (SORCan) Working Group. Escalating levels of access to in-hospital care and stroke mortality. *Stroke*. 2008;39(9):2522-2530. <https://doi.org/10.1161/STROKEAHA.107.507145>
44. Urimubenshi G, Langhorne P, Cadilhac DA, Kagwiza JN, Wu O. Association between patient outcomes and key performance indicators of stroke care quality: A systematic review and meta-analysis. *Eur Stroke J*. 2017;2(4):287-307. <https://doi.org/10.1177/2396987317735426>