View Point

Prognosticating Acute Ischemic Stroke and Estimating the Feasibility of Mapping Stroke Volume to the Functional Outcomes Using Diffusion-Weighted Images: A Systematic Review Protocol

Priyanka Shridharan, Tarun Gangil[1], Sankar Prasad Gorthi[2], Prakashini K[3]

Departments of Neurology, and [1]Radiotherapy and Oncology, Kasturba Medical College (KMC), Manipal Academy of Higher Education (MAHE), Manipal, Karnataka, [2]Department of Neurology, Bharati Vidyapeeth (DTU), Medical College and Hospital, Pune, Maharashtra, [3]Department of Radiology, KMC, MAHE, Manipal, Karnataka, India

Abstract

Introduction: Diffusion-weighted image or DWI is commonly used to provide valuable and diverse information on acute stroke in tertiary care hospitals. DWI is a sensitive and accurate method for identifying the infarct core and can expose the area of cerebral infarction within a few hours of onset. This systematic review is planned to evaluate the measurement of stroke volume on DWI and correlate it with functional outcomes (modified ranking scale). **Method:** We have adhered to the PRISMA-P checklist to report this systematic review protocol. PubMed, Web of Science, Scopus, and TRIP (Turning Research into Practice) databases will be searched. Two independent reviewers will screen the records, extract data, and critically appraise the studies. A checklist for critical appraisal will be applied for data abstraction, and data extraction will be done using predictive modeling for systematic reviews. The risk of bias will be measured by the Prediction Model Risk of Bias Assessment Tool (PROBAST). The meta-analysis will be considered only if included studies have adequate data, and STATA statistical package version 13.1 will be used for performing a meta-analysis. A narrative synthesis will be performed if meta-analysis is not possible. **Ethics and Dissemination:** As this review will focus on secondary information, there is no ethical consideration required. We will disseminate our findings by publishing our analysis in a peer-reviewed journal.
Protocol Registration: In Prospective Register of Systematic Reviews (CRD42019141840).

Keywords: Acute ischemic stroke, DWI, functional outcome, Modified Rankin Scale (mRS), MRI, stroke volume

Background

Stroke and ischemic heart diseases (IHDs) are the prime causes of death and are the leading cause of disability in most developing countries.[1] A long-term follow-up of stroke survivors showed that 31% of patients were dependent on others for daily routine activities, 20% needed support for ambulation, and 71% had impaired vocational capacities. The prophecy of stroke is extremely variable and difficult to predict at presentation because it is influenced by various factors such as neurological, psychosocial, and functional.[2] What causes a stroke to the brain is reduced or interrupted blood supply to the part of the brain which in turn leads to the death of brain cells within a minute due to deprivation of oxygen and nutrients. Prompt treatment is essential for stroke, which can minimize brain damage and potential complications. Functional outcomes after a stroke are highly irregular or fluctuating, which creates more difficulties in estimating the likelihood of recovery after the stroke.[3]

Since the 1980s, magnetic resonance imaging (MRI) has been an essential tool for examining acute stroke patients recent advancements in neuroimaging empower therapeutic decision-making. DWI is the most accurate and sensitive method for the detection of stroke and can reveal the areas of cerebral infarction within the hour of symptoms onset. Recently published guidelines by the American Heart Association suggested that computed tomographic perfusion, DWI, or magnetic resonance perfusion scans should be obtained within 6 h after the last known normal status to identify the acute changes in the brain and size of vessel occlusion.[4] Studies of early DWI to foretell recovery have resulted in different inferences. Many experts found a strong alliance between DWI and outcomes, while many do not favor the association.[5-9]

Address for correspondence: Dr. Sankar Prasad Gorthi, Department of Neurology, Bharati Vidyapeeth (DTU), Medical College and Hospital, Pune, Maharashtra, India.
E-mail: sankarprasadgorthi@gmail.com

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Stroke volume is the common index for assessing the extent of ischemic brain injury following focal cerebral ischemia and can be measured manually by software applications such as the 3D slicer, the ITK SNAP tool, the ABC/2 method, and artificial intelligence (Machine Learning tools). A few studies have shown that ischemic stroke on DWI sequences of MRI is measured within seven days and reliably predicts health outcomes. An important parameter reflecting the primary pathological condition is believed to be lesion volume, and the extent of this pathological condition is related to the neurologic deficits and functional outcome. Hence, infarct volume may serve as a predictor of the severity of neurological impairments.[10,11]

The Modified Rankin Scale (mRS) is a widely used measure in patients with a brain stroke to assess functional outcomes and can also provide a common language for describing the degree of disability.[12,13] The mRS has many advantages; it covers the whole gamut of functional outcomes and is applicable at every stage, from asymptomatic stroke to death[14] [Table 1]. Strong correlation with stroke pathological parameters such as infarct volumes and agreement with other stroke scales demonstrated the coinciding rationality of mRS.[15] A limited number of levels in mRS may restrict customization in comparison to other stroke scales such as the National Institute of Health Stroke Scale. However, a single-point change shows clinical significance in mRS.

This review focuses on the measurement of stroke volume on DWI and correlates it with the functional outcome, which can be considered a potential marker for predicting neurological deficits. We have proposed the following review question: In patients with acute ischemic stroke in the anterior circulation, whether the stroke volume measured from DWI by manual and artificial intelligence technique within three to five days of onset correlates with the functional outcome as assessed by the mRS at the end of 30 and 90 days?

Methods

This review will stick to the "Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol, 2015" (PRISMA)[16] and report this protocol we have followed PRISMA-P. The protocol has been registered in the Prospective Register of Systematic Review (CRD42019141840).

Table 1: mRS Scale

mRS Score	Description
0	No Symptoms
1	No Significant Disability (able to carry out all usual activities, despite some symptoms)
2	Slight disability (able to look after own affairs without assistance, but unable to carry out all previous activities)
3	Moderate disability (require some help, but able to walk unassisted)
4	Moderately Severe Disability (unable to attend to own bodily needs without assistance and unable to walk unassisted
5	Severe disability (require constant nursing care and attention, bedridden, incontinent)
6	Dead

Searches

Identification of records from the databases and other sources

Four online databases will be searched, viz. PubMed, Scopus, Web of Science, and TRIP (Turning Research Into Practice). Only human studies in English will be included in the review. Back and forward references of included studies will be examined based on our eligibility criteria.

Search terms

We plan an all-inclusive search strategy using database-specific search terms like MESH for PubMed, which will be subsequently customized to other databases. The following search terms will be used to retrieve relevant studies (by using Boolean operators, "AND" and "OR"): stroke, prognosis, stroke volume, Modified Rankin Scale, functional outcome, artificial intelligence, diffusion-weighted image.

Inclusion and exclusion criteria

Types of studies

Randomized control trials (RCTs) prospective and retrospective cohort, prognostic, diagnostic, and case-control studies will be included in this systematic review. Studies investigating prediction models using neuroimaging with or without a combination of clinical variables assessed using clinical/subjective scales for the prognosis of acute ischemic stroke will be included. Case series, case reports, pilot trials, conference proceedings, dissertations, commentaries, guidelines on clinical practice, and handouts for patient education will be excluded.

Population

Individuals with acute stroke within three to five days of onset, hospitalized, aged 18 years and above, will be included. Stroke patients who have undergone MRI (DWI) should have measured the stroke volume using the tool by manual method (such as ITK SNAP, 3D Slicer, ABC/2 method) or artificial intelligence (Machine learning tools). Acute stroke is defined as the presentation/occurrence of clinical manifestations of focal disturbances of cerebral functions (less than 24 hours). During the acute stage, stroke patients may experience FAST (**F**ace drop, weakness, loss of function in arms or legs, difficulty in **S**peaking, and **T**imely treatment is crucial) symptoms. Patients with co-morbidities such as Dementia, Parkinson's disease, Alzheimer's disease, and existing physical disabilities and those who have not undergone MRI DWI will be excluded.

Outcomes

Functional outcomes measured using mRS assessed at a particular time post-stroke (acute), such as 30 or 90 days. The functional outcome of mRS is measured on a scale from 0 (perfectly healthy) to 6 (dead)[14] [Table 1].

Selection of studies

A three-step screening process will be followed for the studies that have to be included. De-duplication of titles will be done across databases using Mendeley. Two reviewers (PS and SG) will screen the title independently, abstracts, and full-text articles for relevance using an Excel spreadsheet. We will discuss consensus, and in case of any disagreement, the senior reviewer (PK) will be consulted to achieve a consensus. Reasons for exclusion will be documented. The article selection process will be depicted using the PRISMA flow diagram, as shown in Figure 1.

Data abstraction

Included studies will be shared by the two reviewers (SG and PK). One of them, on one's own, will take out the data from each article, while the other reviewers will verify and confirm the data. To manage all the recovered data, it will be exported to an MS Excel spreadsheet. A checklist for critical appraisal and data extraction for systematic reviews of prediction modeling studies (CHARMS) will be used to abstract the data from studies.[17] The checklist will be adjusted as per the specific need of the systemic review [Table 2]. Reviewers will resolve any dispute through discussion. The corresponding author of the study will be the contact person if there is any unclear or unreported targeted information. If we do not receive a reply within a fortnight of sending an email, the study will be excluded.

Risk of bias-assessment

Two independent reviewers (SG and PK) will perform the risk of bias assessment of the included studies independently by using the Prediction Model Risk of Bias Assessment Tools (PROBAST).[18] PROBAST, by its prediction models

Table 2: Data extraction form

General Study Information	Title, Author, Unique ID, Publication year, and Eligibility
Methods	Study design and duration
Participants	The setting, Method of recruitment, Age, Gender, Ethnicity, Stratification according to stroke severity, Time post-stroke, Functional outcomes, Diagnostic/ Prognostic tools used, whether the prognostic model was devised or not, Validation of the model, predictability of outcome at a later time point.
Outcome	Functional outcomes measured using MRS assessed at a certain time post-stroke (acute), such as 30, or 90 days

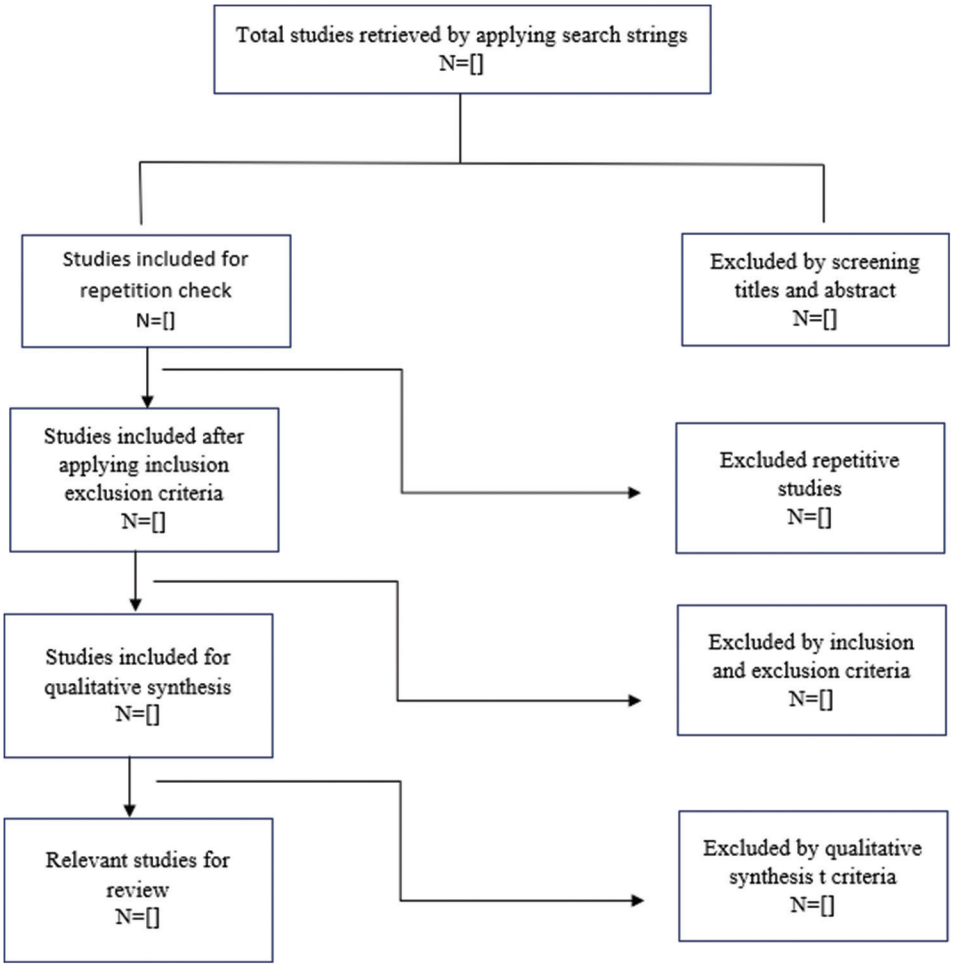

Figure 1: PRISMA Flow Chart

and individual predictors, evaluates the applicability of the studies in the intended population and context. PROBAST will categorize the risk of bias into high, low, and unclear risk of bias. Disagreements between the reviewers shall be resolved by discussion. If required, another reviewer (TG) will be available to resolve any disagreements and reach a consensus and record their final decisions in a "risk of bias" table.

Strategy for data synthesis

If the included studies provide adequate data, a meta-analysis will be performed to obtain the pooled estimate. In this case, the correlation coefficients provided by the individual studies will be pooled to obtain the pooled correlation coefficient. Statistical heterogeneity will be determined using Chi-squared and I-squared statistics. The random-effects model will be adopted for meta-analysis. The STATA statistical package, version 13.1, will be used for performing meta-analysis.[19,20] If heterogeneity persists, we plan to conduct subgroup analysis based on various criteria such as the risk of bias, study type, duration of a stroke, etc. If meta-analysis is not possible, we plan to narratively synthesize the findings.

Handling missing data

Any missing participants and relevant data values from studies will be reported. For any missing and unreported data, the corresponding authors of the studies will be contacted. If data are missing (or do not receive unpublished data from study authors), then data analysis will be conducted only on available data. We will label the possible consequences of lost data in our outcomes in the discussion segment.

Mapping clinical features to prognosticate clinical outcomes

In addition to recently being created for prognostication in stroke, machine-learning models for prognostication have shown useful in cancer. To create the maximum margin hyperplane decision border for binary categorization, support vector machine (SVM), the most widely used high-performance machine learning algorithm in illness prediction, nonlinearly maps input vectors to a high-dimension feature space. The training process for deep neural networks (DNNs) involves computing the gradients of the loss function to update the weights of the interconnected layers of neurons. Because of this, the model is better able to distinguish between significant traits and unimportant changes through many levels of representation learning. Both SVM and DNN models have a proven track record as promising, high-performance algorithms with numerous potential uses in medical prognostication.

Artificial neural networks have been used to forecast 6-month functional outcomes and 30-day death. Even though these models demonstrated good accuracy and discrimination, they (1) omitted variables on anticoagulation or pre-morbid functional status that may have significant prognostic information in SICH, and (2) did not directly compare the prognostic accuracy of machine-learning models to existing clinical prognostic scores when using the same variables. Additionally, SVMs have been employed to predict SICH hematoma expansion as a factor in 30-day mortality. However, the authors did not forecast functional results and did not assess the prognostic efficacy of current models.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Author contributions

All authors have made a considerable significant contribution to the systematic review protocol design, article drafting, and finalizing of the draft version to be submitted. SPG will act as a guarantor of the review.

References

1. Global Health Estimates. Geneva: World Health Organization; 2012. Available from: http://www.who.int/healthinfo/global_burden_disease/en/.
2. Chriki L, Stern T, Bullion S. The recognition and management of psychological reactions to stroke: A case discussion. Prim Care Companion J Clin Psychiatry 2006;08:234-40.
3. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361-87.
4. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, *et al*. 2018 Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46-110.
5. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke was studied by whole-brain echo-planar diffusion-weighted magnetic resonance imaging. Ann Neurol 1995;37:231-41.
6. Baird AE, Dambrosia J, Janket S, Eichbaum Q, Chaves C, Silver B, *et al*. A three-item scale for the early prediction of stroke recovery. Lancet 2001;357:2095-9.
7. Thijs VN, Lansberg MG, Beaulieu C, Marks MP, Moseley ME, Albers GW. Is early ischemic lesion volume on diffusion-weighted imaging an independent predictor of stroke outcome? A multivariable analysis. Stroke 2000;31:2597-602.
8. Hand PJ, Wardlaw JM, Rivers CS, Armitage PA, Bastin ME, Lindley RI, *et al*. MR diffusion-weighted imaging and outcome prediction after ischemic stroke. Neurology 2006;66:1159-63.
9. Wardlaw JM, Keir SL, Bastin ME, Armitage PA, Rana AK. Is diffusion imaging appearance an independent predictor of outcome after ischemic stroke? Neurology 2002;59:1381-7.
10. Bederson JB, Pitts LH, Tsuji M, Nishimura MC, Davis RL, Bartkowski H. Rat middle cerebral artery occlusion: Evaluation of the model and development of a neurologic examination. Stroke 1986;17:472-6.
11. Brint S, Jacewicz M, Kiessling M, Tanabe J, Pulsinelli WA. Focal brain ischemia in the rat: Methods for reproducible neocortical infarction using tandem occlusion of the distal middle cerebral and ipsilateral common carotid arteries. J Cereb Blood Flow Metab 1988;8:474-85.
12. Rankin L. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 1957;2:200-15.
13. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604-7.
14. Quinn TJ, Dawson J, Walters M. Dr. John Rankin; his life, legacy and the 50th anniversary of the Rankin Stroke Scale. Scott Med J 2008;53:44-7.
15. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: Clinometric and clinical considerations. Clin Interv Aging 2013;8:201-11.

16. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 2015;349:g7647-9.
17. Moons KGM, de Groot JAH, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, *et al*. Critical appraisal and data extraction for systematic reviews of prediction modeling studies: The CHARMS checklist. PLoS Med 2014;11:e1001744.
18. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, *et al*. PROBAST: A tool to assess the risk of bias and applicability of prediction model studies. Ann Intern Med 2019;170:51-8.
19. Deeks JJ, Higgins JPT, Altman DG. Analyzing data and undertaking meta-analyses. Cochrane Handb Syst Rev Interv 2019. p. 241-84.
20. Duval S, Tweedie R. Trim and fill: A simple funnelplot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455-63.