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Evaluating the predictive capabilities of haematoma expansion scores in patients with acute intracerebral haemorrhage: protocol for a scoping review

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ABSTRACT

Introduction Patients presenting with acute intracerebral haemorrhage are at a high risk of exhibiting haematoma expansion, a phenomenon that can significantly worsen long-term functioning. Numerous clinical and radiological factors are associated with expansion. In a bid to better select patients at increased risk of expanding, these factors have been collated together into clinical scores. Several clinical scores have been developed, but comparisons of diagnostic potential between these scores are limited and the frequency of use in clinical trial enrolment is unknown.

Objective To perform a scoping review of haematoma expansion scores and explore numerous factors such as the methodology of development and diagnostic capabilities.

Methods and analysis MEDLINE, PubMed, EMBASE, CENTRAL and ClinicalTrials.gov will be searched with assistance from an experienced information specialist. Eligible studies will involve adults presenting with spontaneous intracerebral haemorrhage who received baseline assessments, follow-up imaging and risk stratification through a haematoma expansion score. Reviewers will independently extract data from the included studies and will collect data on patient demographics and medical history, details on score development, diagnostic capabilities and usage proportions. Analysis of extracted data will focus on comparing the predictive capability of each score and similarities/differences in score development. The exact analysis technique will be dictated on the type of data extracted.

Ethics and dissemination Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through conference presentations and peer-reviewed publications.

INTRODUCTION
Intracerebral haemorrhage and haematoma expansion

Spontaneous intracerebral haemorrhage, the non-traumatic rupture of cerebral blood vessels, is the most devastating stroke subtype and is a major cause of morbidity and mortality across the world.[1] One-month mortality can be high as 55% and a large proportion of survivors often suffer severe long-term disability.[2] The high morbidity

Strengths and limitations of this study

► This review will perform a detailed assessment of prediction scores in their current form which has not been conducted previously.
► The use of a scoping review methodology allows flexibility in assessment and may assist in the preparation of a formal diagnostic test accuracy systematic review.
► Quality of evidence will not be evaluated in this scoping review.
► Limitations in this study include heterogeneity in the primary outcome measure (several definitions of haematoma expansion exist in the literature, not all studies may use the same definition) and changes in the overall management of intracerebral haemorrhage that may limit the extent of haematoma expansion observed.
► This study may highlight unexpected strengths, weaknesses and areas requiring increased focus for future prediction tool development.

and mortality associated with intracerebral haemorrhage is secondary to the dynamic nature of the disease. The size of an intracerebral haemorrhage is rarely a static fixture: it can change after initial presentation, often enlarging in size. This enlargement of haematoma volume, formally termed as haematoma expansion, is a major cause of the poor long-term outcome.[3] It occurs early in the presentation, and has become the therapeutic target of choice in recent clinical trials.[4–6]

Unfortunately, therapies that are designed to mitigate haematoma expansion date have been largely unsuccessful at improving patient outcomes.[6–8] An inability to precisely select the patients most at risk of expansion, and therefore most likely to benefit from therapy, has been considered a potential reason for this lack of success. As such, investigation into the predictors of haematoma expansion has been a major research focus

for intracerebral haemorrhage experts worldwide. It is the hope that by accurately selecting patients who are at the highest risk of expansion, future trials will be better able to evaluate the effectiveness of their respective treatments.

Predicting haematoma expansion

Given that the diagnosis of intracerebral haemorrhage is confirmed with imaging, the majority of expansion predictors are radiological. A multitude of imaging variables has been identified as potential predictors.[9] [10] Certain clinical variables, such as concomitant antithrombotic use and time of presentation, also play a significant role in influencing expansion.[11] These factors are used together in combination to develop predictive models designed to optimise patient selection accuracy. These models are subsequently simplified into clinical scores for ease of use in day-to-day practice. In the past 5 years alone, several prediction scores were created.[12–14] While the diagnostic capabilities of each score have been assessed by the creating teams on an individual basis, there is no clear consensus of which tool has the best predictive capability. No in-depth or comparative analysis of the scores has been performed and no systematic or scoping review has been conducted to date. It is also unclear whether these tools have been used in recent or ongoing clinical trials.

Objective

Perform a scoping review of the literature assessing the predictive capabilities and extent of use of haematoma expansion scores developed for use in clinical treatment trials. Using the population, concept, context (PCC) elements our clinical objectives are as follows:

1. Describe the characteristics of each score and how each score was developed.
2. Outside of the original derivation studies, have scores been externally validated, used in recent randomised controlled trials or been proposed for use in upcoming studies?
3. Collate and compare the diagnostic capabilities between scores (discrimination, calibration, sensitivity, specificity, positive predictive, negative predictive values).

METHODS

Study registration

This study will be conducted based on the guidelines of the Joanna Briggs Institute (JBI) Methodology for Scoping Reviews.[15] The findings of this study will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting of Scoping Reviews (PRISMA). This protocol will be reported, using PRISMA-Protocols and JBI guidelines.[15] [16]

Inclusion/exclusion criteria

Eligibility criteria were established using the PCC framework. Studies will be selected according to the following criteria:

Participants

Included studies will involve adult patients (≥18 years of age) presenting with spontaneous intracerebral haemorrhage (haemorrhagic stroke), confirmed with either CT or MRI. Eighteen is the threshold age for adulthood used in the majority of haemorrhage trials. Paediatric intracerebral haemorrhage is more often secondary to intravascular lesions and malignancy and hence will not be included in this review. Patients presenting solely with a haemorrhage of another type (subarachnoid, subdural, epidural) with not be included in this review. Haemorrhages with a known secondary aetiology (tumour, vascular malformation, trauma) will also be excluded.

Concept

The major concepts we hope to explore in this scoping review are haematoma expansion and the predictive models, haematoma expansion scores, that have been developed to try and accurately predict this phenomenon in patients presenting with acute intracerebral haemorrhage. An expansion score is defined as a collection of variables, clinical, radiological or both, that have been identified and weighted in a way such that patients presenting with higher cumulative scores are at a higher risk of exhibiting an expansion of their baseline haematoma. We aim to look at the original studies which derived a respective score, subsequent studies that validated and compared different scores to each other, and clinical trials or observational cohorts which used these scores as a clinical tool. Because our primary objective is to learn about both the diagnostic capability and prevalence of use of these scores, we will be evaluating original research contributions, systematic reviews, meta-analysis and guideline documents where appropriate. Studies focused solely on a single clinical or radiological predictor (eg, blend sign) will be excluded from our analysis. There is clear evidence to show that no single variable adequately predicts haematoma expansion.[9] [17]

Haematoma expansion acts as the outcome of interest in this scoping review. Expansion is evaluated by assessing the change in haematoma volume at initial presentation to follow-up imaging usually performed at the 24–48 hours mark. Expansion can be reported as the net change in volume or as a dichotomous outcome via a predetermined definition of haematoma expansion (eg, haematoma enlargement >6 mL). There are several definitions of haematoma expansion in current use today and we will use whichever definitions have been decided on by the study authors. However, only studies that provide a dichotomous definition of haematoma expansion would be used in any subsequent summary analysis.

Context

There is no restriction on healthcare locations, although we expect most studies will involve patients who were treated in an emergency room, intensive care unit or neurological/neurosurgical ward. We also have no restrictions on country of study, ethnicity, gender or socioeconomic status.

Information sources and search strategy

For the purposes of our scoping review, we will include data from primary research studies (with no limitation to study design), previously published systematic reviews, meta-analysis and guidelines that pertain to the topics of haematoma expansion and predictive scores. We will only include studies that are presented in the English language due to constraints in translational resources. A search strategy was developed (see online supplementary appendix) using keywords and Medical Subject Headings (MeSH) terms relating to intracerebral haemorrhage and haematoma expansion. This search strategy will be used on the following four databases: MEDLINE (via Ovid), Embase (via Ovid), PubMed, Cochrane CENTRAL (via Ovid), from date of inception to June 2018. Supplementary searches will include scanning the reference list of included studies and reviews identified through the primary search. Released abstracts from the last 10 years in the International Stroke Conference, European Stroke Organisation Conference or American Academy of Neurology Annual Meeting that have not been published in full manuscript form will also be screened to ensure completeness. Study authors will be contacted for further information as required.

Study records
Data management

Database search results will be downloaded and imported to EndNote Reference Manager Software (Clarivate Analytics, Philadelphia, Pennsylvania, USA) and then transferred to Covidence Systematic Review Software (Covidence, Melbourne, VIC, Australia). After removal of duplicate results, citation titles and abstracts will be screened.

Selection process

At least two reviewers will independently screen articles in a two-level process. Level 1 will involve a title and abstract screening for potentially eligible studies. Studies that score a 'yes' or 'unsure' in this phase will be brought forward for full-text (level 2) evaluation. Full-text screening will use a precreated article screening form. In the event of a disagreement between the two authors in either stage, a third party neurologist will adjudicate. The process of study selection will be described using a PRISMA flow diagram.

Data extraction process and summarisation of results

Reviewers will independently extract data from the included studies using an a priori designed data extraction form. We will collect basic publication data (eg, year and journal of publication, authorship list, funding), study population information (demographic and medical history measures), details on score development (variables involved, development or validation methodology), definition of haematoma expansion used and markers of diagnostic accuracy (c-statistic, calibration, sensitivity/specificity/positive and negative predictive values). The basic make-up of each score will be compared side to side in a tabular format. The underlying methodology used to develop each score will be described descriptively. Study authors will be contacted for further information on score development if deemed necessary.

The analysis of diagnostic summary markers will ultimately be dependent on the data we are able to extract from each study. If possible, we aim to compare the accuracy of each score through multiple pairwise comparisons. Because each score is reported on a continuous scale, multiple positivity thresholds may exist. In this case, we would aim to make comparisons based on the summary reciever operating characteristic (ROC) curves. Due to the potential concern of data paucity, we plan to use test accuracy data from all eligible studies that have evaluated one or more of these scores and will include data from both derivation and validation cohorts. If possible, data from validation cohorts will be examined separately in a sensitivity analysis. To account for changes in clinical practice and intracerebral haemorrhage management, studies published in differing time periods or studies with significant differences in baseline populations may be assessed separately in sensitivity analysis. If the data extracted makes meta-analysis not possible, we will compare the diagnostic summary markers descriptively. As data synthesis is not the primary aim of a scoping review, a formal assessment of the methodological quality of the included studies will not be performed.

Patient and public involvement

Because the collected data within this scoping review originates from previously published studies, patients and the general public were not involved in the development of the research question or choice of outcome measures that we wanted to assess.

Dissemination

The findings of this review and analysis may aid scientists in future clinical trial development and guide future research endeavours, including the development of a formal diagnostic test accuracy systematic review. We will, therefore, disseminate the findings of our work through conference presentations, the popular press and a peer-reviewed publication.

CONCLUSION

Early haematoma expansion presents a compelling therapeutic target for spontaneous intracerebral haemorrhage. Optimal patient selection is critical to identify those at highest risk of expansion for enrolment into future

intracerebral haemorrhage trials. Expansion scores have been proposed as a method to improve patient selection. Our study will inform future clinical trials by systematically assessing the literature to identify, and analyse, the diagnostic abilities and potential limitations of existing haematoma expansion scores.

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