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Review article

A systematic review of the cost-effectiveness of emergency interventions for stroke in low- and middle-income countries

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ABSTRACT

Background: Stroke is a leading cause of death and disability globally, with an increasing incidence in low- and middle-income countries (LMICs). The successful treatment of acute stroke requires an organized, efficient and well-resourced emergency care system. However, debate exists surrounding the prioritization of stroke treatment programs given the high costs of treatment and the increased incidence of hemorrhagic stroke in LMICs. Economic data is helpful to guide evidence-based priority setting in health systems development, particularly in low-resource settings where scarcity requires careful stewardship of resources. This systematic review surveys the existing evidence surrounding the cost-effectiveness of interventions to address acute stroke in LMIC settings.
Methods: The authors conducted a PRISMA style systematic review of economic evaluations of interventions to address acute stroke in LMICs. Five databases were systematically searched for articles, which were then reviewed for inclusion.
Results: Of the 153 unique articles identified, 11 met the inclusion criteria. Four studies demonstrate the heavy economic burden on patients and households due to stroke. Two studies estimate that preventive measures are more cost-effective than acute treatments. Four studies directly examine the cost-effectiveness of thrombolysis and thrombectomy in three middle-income countries (Iran, China, and Brazil) with results ranging from roughly $2578 to $34,052 (2019 USD) per quality adjusted life-year saved. These results are similar to the cost-effectiveness ratios estimated in high-income settings. Finally, one study examined a care bundle that included acute treatment elements.
Conclusions: The findings reinforce the need for additional research support informed decision-making. The available evidence suggests that preventive measures should be prioritized over emergency treatment for acute stroke, particularly in settings of resource scarcity. Cost-effectiveness ratios do not compare favorably to estimates for other emergency care interventions in LMICs, such as basic emergency care training, implementation of triage systems, and basic trauma care. Cost-effectiveness is also likely to vary depending on local epidemiology. Overall, decision-makers should balance the economic evidence alongside social, political and cultural priorities when making resource allocation choices.

African relevance

- Since 2008, the incidence of stroke in low-income and middle-income countries (LMICs) has exceeded the incidence in high-income countries.
- Multiple studies in sub-Saharan Africa support not only a higher incidence of hemorrhagic stroke, but also worsened outcomes in cases of hemorrhagic stroke.
- The successful treatment of acute stroke requires an organized, well-resourced and efficient emergency care system.
- The available cost-effectiveness evidence suggests prioritizing basic emergency care interventions and stroke prevention over stroke treatment, to maximize the impact of scarce resources.
- More context relevant research is needed on the cost-effectiveness of treating acute stroke to better inform local decision making in Africa and across LMICs globally.

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Introduction

Stroke is a leading cause of death and disability worldwide [1]. Since 2008, the incidence of stroke in low-income and middle-income countries (LMICs) has exceeded the incidence in high-income countries [2]. The Global Burden of Disease study in 2016 estimated that 5.5 million people died due to cerebrovascular disease, which includes hemorrhagic and ischemic strokes [3]. The successful treatment of acute stroke requires an organized and efficient emergency care system. Emergency care systems in LMICs tend to have few resources, despite studies demonstrating that over 50% of the global disease burden is attributable to conditions amenable to emergency care [4].

The primary intervention to treat acute stroke is thrombolysis. This requires identification of the stroke as ischemic in nature, a rapid risk-benefit assessment based upon level of disability and risk of thrombolysis, and administration of thrombolytic therapy within a short time window from symptom onset [5,6]. Studies have demonstrated that less than 10% of stroke patients in LMICs present to care within a time window that would allow administration of thrombolytics [7,8]. Barriers to optimal emergency care system performance in the treatment of acute stroke include: poor public knowledge about the signs and symptoms of stroke, inadequate access to prehospital emergency care, lack of transport protocols that designate stroke centers, inadequate facility based triage, lack of timely assessment and administration of treatment, poorly resourced facilities, and inadequate financial protection for patients. Process improvements in emergency care systems have been shown to increase the proportion of ischemic strokes that receive thrombolytics [9,10,11,12].

A perception of the high-cost of treatment has sparked calls to focus on prevention strategies rather than acute treatment in these settings [13]. For example, two key resources required to accomplish emergency treatment are computed tomography and thrombolytic drugs, both of which are expensive. The high cost of thrombolytics alone has been hypothesized to contribute to low administration rates in eligible patients [14,15]. Furthermore, the insufficient capacity of health systems in LMICs to handle neuro-critical care patients supports arguments that developing an effective stroke treatment system may require significant capital and human resource investments [16].

Complicating the investment case is a 40% higher incidence of hemorrhagic stroke in LMICs [17]. Multiple studies, particularly in sub-Saharan Africa, support not only the higher incidence, but also worsened outcomes in cases of hemorrhagic stroke [18,19,20,21]. These differences are thought to be due to differing epidemiology of stroke: stroke patients in LMICs tend to be younger, have higher tobacco use rates, a higher prevalence of metabolic syndrome, and lower rates of atrial fibrillation [22]. It is reasonable to assume that the local proportion of strokes that are hemorrhagic will impact the cost-effectiveness of programs that rely on thrombolytics as the primary treatment modality.

The goal of this study is to inform discussions occurring globally regarding emergency care system development and the allocation of scarce resources by providing a systematic review of the economic evidence and summarizing the cost-effectiveness data surrounding interventions for acute stroke in LMICs. While economics should never be the sole driver behind policy or resource decisions, comparing two or more interventions on the basis of costs and effects plays a critical role in priority setting exercises.

Methods

We conducted a systematic review of the literature using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines [23]. Five databases were searched for articles related to the cost-effectiveness of emergency care interventions to treat acute stroke in LMICs. Three databases (PubMed, EMBASE, Ovid Global Health) cover general health sciences literature and two databases (Center for the Evaluation of Value and Risk in Health (CEVR), Center for Reviews and Dissemination) are comprehensive global registries of economic evaluations. A Cochrane LMIC country filter was applied to the results to find studies relevant to our search context. No language restrictions were applied.

Inclusion criteria for an article progressing to data extraction were:

1) An economic evaluation that formally assessed costs and benefits of the studied intervention (e.g. such as a cost-effectiveness analysis). Given the limited number of articles identified, costing-only studies were included.
2) An emergency care intervention to treat acute stroke (e.g. a treatment given during the initial presentation to medical care, usually within hours of onset of symptoms).
3) The intervention took place or was modeled for an LMIC based on 2019 World Bank classification.

Conference abstracts and editorials were excluded. A sample of PubMed search terms is included in Box 1. It was not necessary to include health economics terminology in the search of the health economics databases. After removal of duplicates, the search yielded 153 unique articles. The adequate scope of the search terms was supported by hand-searching references of relevant articles. Hand-searching did not identify any further articles. All articles were uploaded into Covidence for review [24].

Fig. 1 presents our PRISMA flow diagram. Two blinded reviewers (EB, BG) independently screened 153 titles and abstracts for inclusion, with conflicts resolved by a senior reviewer (NR). 34 full-text reviews

Box 1
PubMed search terms.

("costs and cost analysis"[mh] OR "cost-benefit analysis"[mh] OR "cost-benefit" OR "cost analysis" OR "cost analyses" OR "cost effective" OR "cost effectiveness" OR "economics" OR "economic evaluation" OR "Health care costs"[mh])
AND
("Emergency Service, Hospital"[mh] OR "Emergency Medicine"[mh] OR "Emergency medicine"[TW] OR "Emergency services"[TW] OR "Emergency department"[TW] OR "Emergency service"[TW] OR "Emergency departments"[TW] OR "Emergency room"[TW] OR "Emergency rooms"[TW] OR "Emergency ward"[TW] OR "Emergency Unit"[TW] OR "Trauma Centers"[mh] OR "Trauma Center"[TW] OR "Trauma Centers"[TW] OR “emergency health service”[TW] OR “emergency health services”[TW] OR “emergency medical services”[TW] OR “emergency medical service”[TW] OR "accident and emergency"[TW] OR "accident & emergency"[TW] OR "a&e"[TW] OR "A & E"[TW] OR "prehospital"[TW] OR "ambulance"[TW])
AND
("stroke"[mh] OR "cerebrovascular accident" OR "stroke" OR "strokes" OR "cerebral hemorrhage" OR "brain infarction"[mh] OR "brain infarction" OR "brain infarctions" OR "brain stem infarctions"[mh] OR "brain stem infarction" OR "brain stem infarctions" OR "lateral medullary syndrome"[mh] OR "lateral medullary syndrome" OR "wallenberg syndrome" OR "cerebral infarction"[mh] OR "cerebral infarction" OR "cerebral infarctions" OR "Infarction, Anterior Cerebral Artery"[mh] OR "cerebral artery infarction" OR "cerebral artery infarctions" OR "Infarction, middle cerebral artery"[mh] OR "infarction, Posterior cerebral artery"[mh] OR "stroke, lacunar"[mh] OR "lacunar infarct" OR "lacunar infarcts" OR "lacunar infarction" OR "lacunar infarctions")
AND
Cochrane LMIC Filter

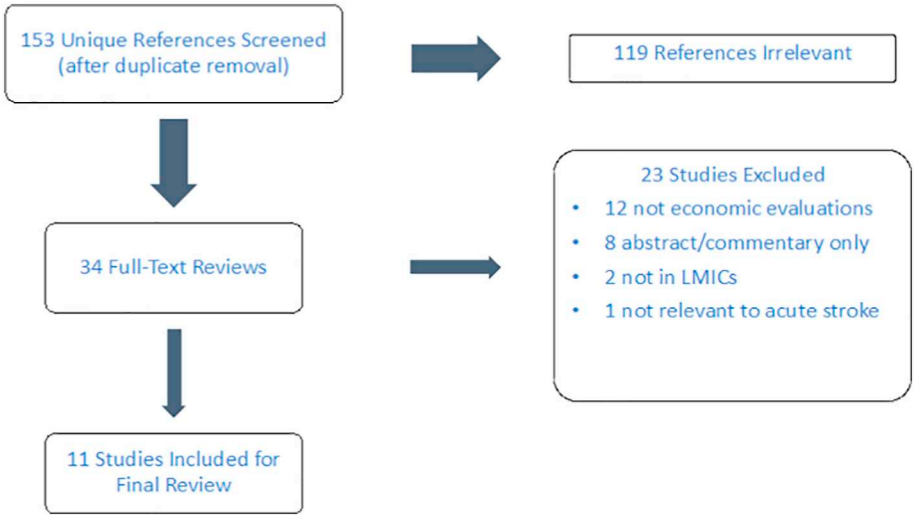

Fig. 1. PRISMA flow diagram.

were conducted independently by two blinded reviewers (EB, BG), with conflicts being resolved by senior review (NR). Data abstraction of 11 included studies and manuscript write-up was conducted by MT, DL and AO. Studies were excluded in the full-text phase for: (12) not being an economic evaluation; (8) conference abstract or editorial only; (2) not an LMIC setting; (1) not an emergency intervention for acute stroke. Due to significant heterogeneity of settings and methods, the results of the studies were not synthesized and are presented individually below.

Results

Costing-only studies

Four of the included studies conducted costing exercises only [25,26,27,28]. Although costing-only studies are less informative due to their lack of generalizability, it was felt that they shed light on the economic burden of acute stroke, which includes the expense of any emergency interventions given. A multi-country study in Argentina, China, India and Tanzania used surveys to evaluate the microeconomic impact of acute cardiovascular disease, including stroke, on households. Catastrophic health spending, defined in this study as spending greater than 40% of non-food household annual income, was identified in over 50% of respondents, along with significant decreases in productivity post stroke [25]. A study in Republic of Congo found the out-of-pocket cost of stroke care to be roughly $113 (USD 2019) per patient, concluding that most local citizens would be unable to bear this cost [26]. In India, two thirds of the medical costs of stroke were found to be direct medical costs, while the other third represented societal costs such as caregiver costs and lost productivity [27]. Finally, in Turkey, annualized stroke costs from the health sector perspective were estimated to be $1381 (USD 2019) per patient. This is broken down into 76% inpatient costs and 24% outpatient treatment costs [28].

Cost-effectiveness of thrombolysis

Four studies specifically examined the cost-effectiveness of thrombolysis or thrombectomy [29,30,31,32]. Araujo et al. modeled intravenous thrombolytics within 3 h compared to no thrombolytics in Brazil, finding a cost of $30,777 to $34,052 (2019 USD) per quality adjusted life year (QALY) saved [29]. The model included a societal perspective and one-year time-horizon. Treatment efficacy estimates were based upon high-income country clinical trials.

Pan et al. (2014) studied the cost-effectiveness of rt-PA versus no rt-PA, within 4.5 h, in China [30]. Cost data utilized Chinese sources, but efficacy data was derived from a mix of local and international sources. They found an incremental cost-effectiveness ratio of $15,703 per QALY saved over a two-year horizon, and $2578 (2019 USD) per QALY saved over a 30-year horizon.

Pan et al. (2018) modeled mechanical thrombectomy within 6 h and rt-PA within 4.5 h, compared to rt-PA within 4.5 h alone [31]. This yielded a cost-effectiveness of $10,142 per QALY gained (2019 USD) with the addition of mechanical thrombectomy for proximal anterior artery occlusion. Both Pan et al. studies utilized high-income country clinical trial data.

Finally, Amiri et al. modeled rt-PA versus no rt-PA in Iran, finding the use of rt-PA produced a cost-effectiveness of $9055 per QALY gained (2019 USD) [32]. This study also relied on clinical trial data from high-income countries.

Cost-effectiveness of packages of care

Yang et al. present a study of the implementation of a care bundle at two health facilities in China [33]. The bundle included a CT scan within 45 min of presentation to facility, rt-PA or urokinase in appropriate patients within 6 h of symptom onset, inpatient initiation of antiplatelets and statins, inpatient vascular function assessment, and pre-discharge health education. They present a negative incremental cost-effectiveness ratio when comparing the intervention to the pre-intervention standard of care, indicating the care bundle improved health outcomes *and* decreased costs. Unfortunately, the cost-effectiveness of individual elements of the package is not presented and change in pre- and post-intervention treatment rates are not transparent.

Cost-effectiveness of acute care compared to prevention

Two macroeconomic modeling studies compared large-scale prevention versus acute care across cardiovascular conditions. Salomon et al. modeled the national implementation over a 10-year horizon of a variety of public health interventions in Mexico, including aspirin for acute stroke [34]. They do not present a specific cost-effectiveness ratio which significantly limits interpretation and utilization of their data. However, the authors present their determination that acute stroke care is not cost-effective by international standards and in Mexico would avert less than 1000 DALYs per year. In comparison, preventive measures for cardiovascular disease were found to be highly cost-effective.

Finally, Ortegon et al. present a cost-effectiveness analysis of over 100 interventions to treat or prevent cardiovascular disease in sub-

Saharan Africa and Southeast Asia [35]. Stroke interventions modeled include aspirin and statin administration in the acute phase and multidisciplinary care in a stroke unit during hospitalization. These interventions were again found to be dominated by (less cost-effective than) preventive measures.

Quality assessment of included studies

In 2013, health economists published consensus driven guidelines for conducting and reporting cost-effectiveness analysis, called the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [36]. Using these guidelines we found that the quality of studies was mixed. Study population, comparators and perspectives were well reported. With regards to analytic and modeling methods, the analyses that directly evaluated thrombolysis tended to have the highest quality methods and reporting, whereas it was difficult to understand the underlying modeling assumptions in the other studies. The presentation of uncertainty and heterogeneity was uniformly poor in included studies.

Discussion

Overall, we identified 11 studies that contribute knowledge towards our research question. For policy-makers interested in comparing treatment versus preventive programs, we identified two macro-level modeling exercises that find prevention of stroke is more cost-effective than treatment after a stroke has occurred. For decision-makers within the emergency care system, we identified four studies that produced cost-effectiveness ratios for the treatment of acute stroke, ranging from roughly $2578 to $34,052 (2019 USD) per QALY saved. For comparison: training lay first-responders in basic trauma care in urban Uganda costs $30–$89 USD/life year saved [37], a prehospital electrocardiogram for patients with acute chest pain in India costs $15 USD per QALY saved [38], and basic paediatric emergency care training and triage costs $165 USD per death averted [39]. Under fiscal constraints the selection of high-cost interventions comes with the opportunity cost of delaying other programmatic priorities, which may be of higher value.

Four of the included studies conducted costing exercises only. These tend to be of limited utility to decision makers because without a cost-effectiveness ratio only the *price* and not the *value* of the intervention can be determined. This makes it difficult to compare across settings and interventions, as the results are highly contextual to place and time. However, three of the studies addressed an evidence gap by including costing from the patient or societal perspective. This allows some assessment of the impact of acute care costs after stroke on patients, their caretakers, and their households. Combined with existing literature on the topic of care-seeking behaviors in acute stroke [40,41,42], it appears that small, upfront out-of-pocket costs are unlikely to dissuade care-seeking behavior, however the long-term economic consequences of acute stroke to households are significant.

The cost-effectiveness of thrombolysis and thrombectomy was studied in three middle-income countries (Iran, China, and Brazil), with a large range of results. The large confidence interval appears to be closely tied to modeling assumptions on the time horizon, which should be informed by the average life expectancy after stroke onset and the cost-benefit of those additional years. One study found intravenous thrombolytics in conjunction with several other acute care interventions would decrease costs and improve health outcomes [43]. This result is an outlier and should be taken with caution, as it differs significantly from the majority of studies in the field. We found it problematic that all of the studies used rt-PA outcome data from high-income country clinical trials. Also concerning was the lack of transparency on data sources for rates of hemorrhagic versus ischemic stroke used in the models. Given these limitations, extrapolating the data from these three countries to the full remainder of LMICs should be done cautiously.

Regarding cost-effectiveness data from high-income countries, a 2012 industry-funded review identified eight cost-effectiveness studies, ranging from roughly $4000 to $75,000 per QALY saved (2019 USD estimates) for intravenous thrombolytics [43]. The World Health Organization (WHO) recommends that an intervention costing less than three times the annual gross domestic product (GDP) or gross national income (GNI) per capita of a country, for each DALY averted or QALY saved, should be considered “cost-effective” [44]. The World Bank has classified 31 countries as low-income for the 2020 fiscal year, having reported GNIs per capita less than $1026 USD. By WHO standards this would imply that thrombolytics for the treatment of acute stroke are not a cost-effective investment for low-income countries and should not be prioritized for health spending. However, it should be noted that interventions deemed as “cost-effective” by these standards often remain unaffordable to LMIC health systems and decision-makers should conduct budgetary impact analyses before moving forward [45].

Our review highlighted several areas for future research. Given the heterogenous epidemiology of stroke, particularly the higher rate of hemorrhage in LMICs, it is critical to have local data to inform local decisions. The higher burden of hemorrhagic stroke may increase the value of prevention in these settings, particularly blood pressure control, one of the predominant risk factors [46]. A global study on the availability of anti-hypertensive medication demonstrated that a large proportion of communities in LMICs do not have adequate access to blood pressure-lowering medication, due both to availability and affordability issues [47]. A 2017 study in Rwanda noted over 50% of stroke patients with previously identified chronic hypertension were not on treatment at the time of the stroke. Notably, hemorrhagic stroke was identified as comprising 65% of that study cohort [20]. These studies highlight the critical need for local data to inform policy.

Another fertile area for research is investigation into the cost-effectiveness of telemedicine interventions to identify stroke patients and accelerate the delivery of definitive care. Early research has suggested large impacts on outcome with few added resources [48,49]. Further research is also needed to assess the costs and capacities surrounding post-stroke care, such as rehabilitation services and palliative care. As the prevalence of stroke survivors increases additional resources will be required for their care.

Conclusion

Stroke in LMICs represents a large and growing portion of overall morbidity and mortality. Emergency care systems in these settings are forced to make difficult decisions on how to allocate scarce resources and decision-makers would benefit from access to cost-effectiveness evidence. Our systematic review identified some evidence relevant to LMICs and highlighted remaining gaps in the literature.

Based on the available economic data, progressive realization of interventions to address acute stroke should begin with investments in prevention followed by treatment, and should consider the importance of financial protection against catastrophic expenditures. In LMIC settings, acute stroke treatment appears to be less cost-effective than other basic emergency care interventions, prompting consideration of the opportunity costs of investment in this area when under fiscal constraints. However, given differences in the epidemiology of stroke across settings, particularly differing rates of hemorrhagic stroke, local data and analysis are needed to inform local decision-making. Finally, though economic data is useful to aid in evidence-based priority setting, it should never be the sole consideration when allocating resources.

Dissemination of results

As a systematic review, this research did not come from a particular community; however it is of importance to decision makers in emergency care systems throughout Africa and across LMICs globally. We aim for wide dissemination of the published manuscript through

conferences, social media, and professional organizations.

Authors' contribution

Authors contributed as follows to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content: EB contributed 20%, BG contributed 20%, MT contributed 15%, DL contributed 15%, OAO contributed 15%, NR contributed 15%. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors declared no conflicts of interest.

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