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Risk factors for in-hospital stroke mortality in sub-Saharan Africa: Protocol for a systematic review and meta-analysis

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Abstract

Introduction: While individual studies have reported on in-hospital stroke mortality, there is no published systematic review and meta-analysis in sub-Saharan Africa to our knowledge. An inclusive and systematic analysis will help to understand the risk factors for in-hospital stroke mortality in sub-Saharan Africa.

Method and analysis: We will include all retrospective and prospective facility-based observational studies reporting on incidence and/or risk factors for in-hospital stroke mortality in sub-Saharan Africa countries. Electronic databases such as PubMed, Google scholar, AJOL and Cochrane library will be searched for potentially relevant studies on in-hospital stroke mortality and risk factors in sub-Saharan Africa (SSA). Two independent authors will screen titles and abstract to find studies that meet the pre-specified eligibility criteria for inclusion in the review. The pooled in-hospital stroke mortality and its risk factors will be calculated. Random effects model will be used in case of substantial heterogeneity in the included studies, otherwise fixed-effect model will be used. A planned subgroup, sensitivity and meta-regression analyses will be performed.

Ethics and dissemination: Ethical approval is not required as this is a secondary research and will use reported data in scientific literature. A full manuscript will be submitted to a reputable peer-review journal for publication.

PROSPERO registration number: CRD42021227367

Strength and limitation

- To the best of the authors' knowledge, this is the first systematic review and meta-analysis on risk factors for in-hospital stroke mortality in SSA.
- We would incorporate well-validated systematic review and meta-analysis technique that are completely consistent with existing international standards and recommendations.
- Due to regional and geographical differences, there can be variations across studies, therefore, we plan to conduct robust sub-group analyses to detect any sub-group effects

Keywords: Stroke; in-hospital; Mortality; sub-Saharan Africa

Introduction

Stroke is a major cause of death and injury, and post-stroke treatment costs are a significant economic burden worldwide [1,2]. In the management and care of acute stroke, the developed nations have seen significant and substantial improvement [3,4]. Nonetheless, most sub-Saharan countries are unable to say same [4].

The incidence of stroke is rising in low- and middle-income countries (LMICs) in sub-Saharan African countries, and research has shown that between 2002 and 2020, stroke mortality in sub-Saharan Africa will triple [5,6]. For instance, community-based Sub-Saharan African (SSA) studies indicate that 5-10% of all deaths are caused by stroke, partially due to poor health system and rising rates of hypertension [7,8]. Also, in low- and middle-income countries, about 85% of all stroke mortalities are registered, which also accounts for 87% of total stroke losses in terms of disability-adjusted life years (DALYs) [1,9]

In sub-Saharan Africa, epidemiologic studies have shown that in-hospital stroke mortality varied from 18% in Ethiopia to 43% in Ghana [6,10]. Sub-Saharan African countries have insufficient resources for acute and rehabilitation care for stroke, therefore comprehensive and pragmatic preventive efforts directed at risk factors are of utmost important and feasible approach to curtail the burden and in-patient stroke mortality [11]

While individual studies have reported on in-hospital stroke mortality, there is no published systematic review and meta-analysis in sub-Saharan Africa to our knowledge and, therefore, an inclusive and systematic analysis will help to understand the risk factors for in-hospital stroke mortality in sub-Saharan Africa.

. Stroke mortality data is important for tracking disease patterns and coordinating public health strategies [12].

Review questions

- What is the incidence of in-hospital stroke mortality in sub-Saharan Africa?
- What are the risk factors for in-hospital stroke mortality in sub-Saharan Africa?

Objectives

- Primary objective: To determine the incidence of in-hospital stroke mortality in sub-Saharan Africa (SSA)
- Secondary objective: To assess the risk factors for in-hospital stroke mortality in sub-Saharan Africa?

Protocol registration

This systematic review and meta-analysis will follow strict adherence to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [13] (checklist file 1). The current review is registered with International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42021227367)

Eligibility

Types of studies: All retrospective and prospective facility-based observational studies reporting on incidence and/or risk factors for in-hospital stroke mortality in sub-Saharan Africa countries. Animal studies, reviews, commentaries, conference papers and letter to the editor will be excluded.

Types of participants: Studies involving in-hospital stroke participants from sub-Saharan African countries. The review will consider all age groups.

Types of outcome measures: The primary outcome is the in-hospital stroke mortality in sub-Saharan Africa and secondary outcome is the risk factors for in-hospital mortality in sub-Saharan Africa.

Data source and Search strategies

Primary electronic search in English on the incidence and risk factors for in-hospital stroke mortality in sub-Saharan Africa will be conducted in MEDLINE via PubMed, Google Scholar, and AJOL. The search will be limited to studies conducted from January 1990 through December 2020. Table 1 displays the main search term and approaches. The abstracts of all eligible papers will then be reviewed and full articles will be accessed through PubMed, Google Scholar, and AJOL. Reference lists of papers that fulfill the eligibility requirements of the study will be reviewed to identify additional studies not included in our electronic search. To ensure that potential studies that will be missed by electronic searching are included, experts will be consulted.

Table 1: Search string for PubMed, Google scholar and AJOL

Search #	Search term
1)	In-hospital OR in-patient
2)	stroke
3)	1 AND 2
4)	mortality OR death
5)	3 AND 4
6)	risk factors
7)	5 OR 6
8)	sub-Saharan Africa
9)	Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Cote d'Ivoire OR Djibouti OR Equatorial Guinea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Zaire OR Zambia OR Zimbabwe
10)	8 OR 9
11)	Limit to January, 1990-December,2020
12)	Limit to Humans
13)	10 AND 11 AND 12

Screening and selecting studies

Two authors will screen titles and abstract independently to find studies that meet the pre-specified eligibility criteria for inclusion in the review. Full texts of all potentially relevant studies will be accessed and assessed in detail in a similar manner. A third reviewer will be available to resolve any discrepancies between the two independent assessors. A screening guide will be used to ensure that independent reviewers apply the selection criteria reliably. Authors whose full-text documents are not available via a variety of internet-based sources will be contacted directly through the corresponding authors to provide them to help make the final decision about inclusion. If vital

information needed to make the inclusion decision is not obtained, the article will be excluded. Mendeley reference manager will be used to deduplicate studies.

Data extraction and management

Two independent assessors will extract the data from the eligible published articles using a pre-tested and standardized excel spreadsheet. Data such as the last name of the first author, year of publication, study design, sample size, mortality rate, risk factors for in-hospital stroke mortality, type of stroke as well as the demographic information will be extracted. Missing data will be addressed by contacting the corresponding author for insufficient or unclear data. If possible, corresponding authors will be asked to provide us with the raw data to extract the missing data.

Risk of bias and Quality assessment

The Newcastle-Ottawa Quality Assessment tool adapted for cross-sectional studies will be used to assess the quality of the retrieved studies. The purpose of the assessment will be to determine the internal and external validity of the studies and to minimize risk of bias

Data synthesis

The PRISMA flow chart (**Error! Reference source not found.**) will be used to summarized the selection process. When considerable homogeneity exists among the studies, the incidence of in-hospital mortality in sub-Saharan Africa will be pooled. This will be visually represented using the forest plot. The presence of heterogeneity among studies will be quantified by estimating variance using both Cochrane's Q statistics and the I^2 statistics [14]. The I^2 takes values between 0 and 100%, and a value of 0% indicates absence of heterogeneity. I^2 will be interpreted based on Higgins and Thompson classification, percentages of 25%, 50% and 75% will be considered as low, moderate and high heterogeneity, respectively [14].

Meta-regression will be used to assess the factors associated with in-hospital stroke mortality in sub-Saharan Africa. A P≤0.2 will be used to retain variables in the multivariable model. When significant heterogeneity exists in the included studies, a subgroup analysis will be performed to determine the sources of heterogeneity based on the following; type of stroke and study design. If possible**,** a sensitivity analysis will be performed to determine the robustness of the estimates obtained from the meta-analysis. We will do sensitivity analysis on the quality of the studies included in the systematic review and meta-analysis i.e. studies with low quality score will initially be excluded to check their direction and impact on the overall (pooled) estimate.

For comparative studies, the analyses will be performed using Review Manager v 5.4 (The Cochrane Collaboration, Oxford, UK). Otherwise STATA 16 will be used for Effect estimates and presented with the confidence interval.

In event where meta-analysis is not possible due to considerable heterogeneity and low-quality studies, narrative systematic review will be presented.

Grading the quality of evidence

The quality of evidence for all studies will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology. The following domains will be assessed: risk of bias, consistency, directness, precision, publication bias and additional points. The assessments will be classified into four levels: high, moderate, low or very low.[15] Two independent reviewers will assess the GRADE and disagreement will be resolved through discussion

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Expected key results and discussion

Globally, stroke is the third leading cause of death [16]. The bulk of these deaths from strokes are found in developing countries. In these nations, deaths account for up to 87% of all stroke fatalities[12]. This elevated death toll is much greater in sub-Saharan Africa [12]. To the best of the authors' knowledge, there is no comprehensive systematic review and meta-analysis on in-hospital stroke mortality exist in sub-Saharan Africa. Hence, the primary aim of this review is to determine the incidence of in-hospital stroke mortality in sub-Saharan Africa. Secondary objective is to assess the risk factors in-hospital stroke mortality in sub-Saharan Africa.

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Contributors

MA conceived the study. MA, LA and COY drafted the manuscript. MA, LA and COY critically revised the manuscript for methodological and intellectual content. All authors approved the final manuscript. MA is the guarantor of the review

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Competing interest: None declared

Patient consent for publication: Not required

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement: All relevant data are within the manuscript.

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Figure legend

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols flow chart for study selection

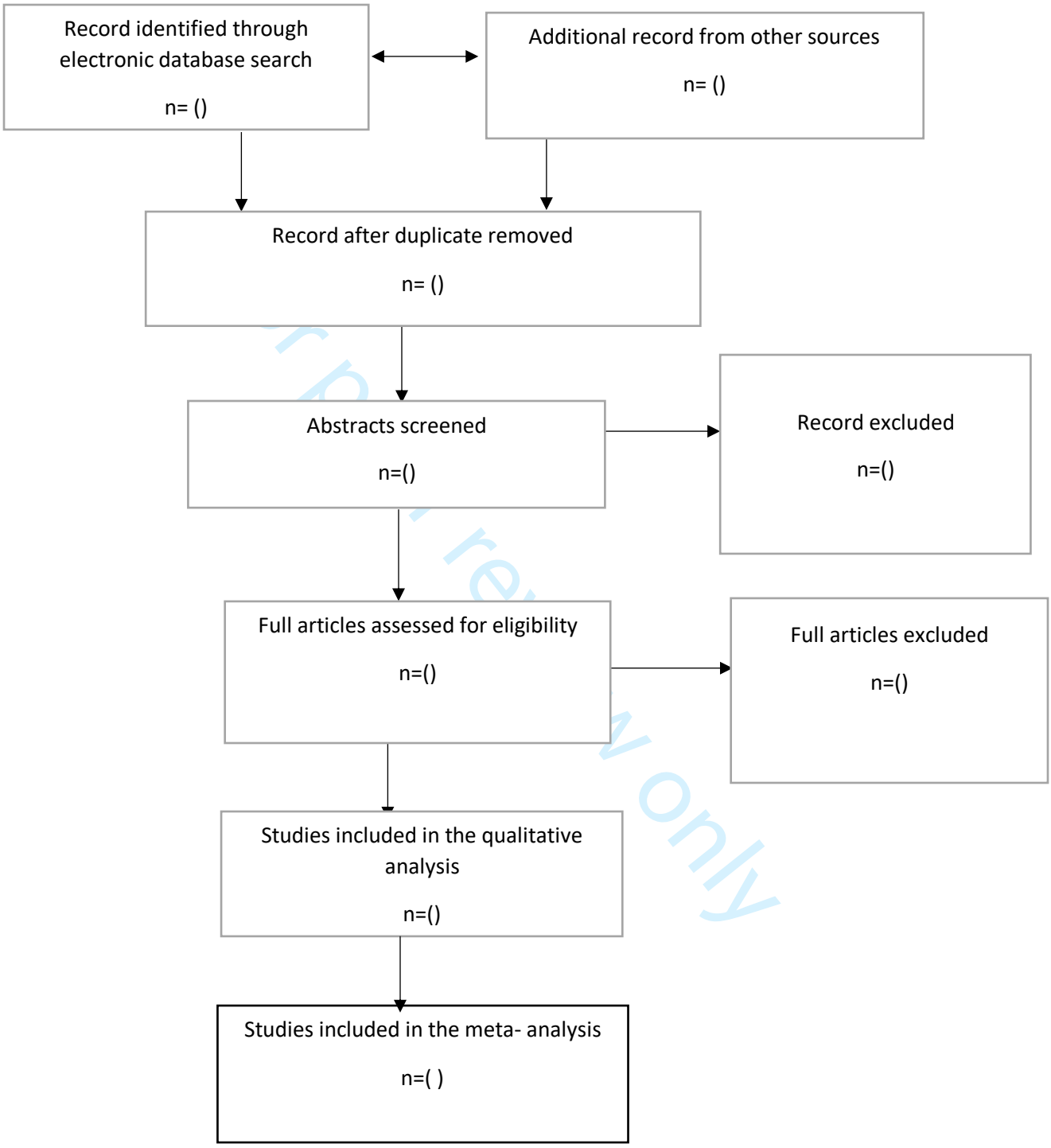

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols flow chart for study selection

Supplementary file 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 4
Authors: contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Authors' contribution	3b	Describe contributions of protocol authors and identify the guarantor of the review	12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
Sources	5a	Indicate sources of financial or other support for the review	12
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4-5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources with planned dates of coverage	5

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such 6 that it could be repeated	6
Study record			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any preplanned data assumptions and simplifications	
Outcome and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in the individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	7-8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7-8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta biases	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

From: 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 [Internet]. 2015;349(January):1–25. Available from: http://dx.doi.org/doi:10.1136/bmj.g7647

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Risk factors for 30-day case fatality rates for in-patients with stroke in Sub-Saharan Africa: Protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Epidemiology, Cardiovascular medicine, Neurology, Rehabilitation medicine
Keywords:	Stroke < NEUROLOGY, EPIDEMIOLOGY, Stroke medicine < INTERNAL MEDICINE

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Risk factors for 30-day case fatality rates for in-patients with stroke in Sub-Saharan Africa: Protocol for a systematic review and meta-analysis

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Abstract

Introduction: While individual studies have reported on in-hospital stroke case fatality rates in Sub-Saharan Africa (SSA), the estimates are highly variable and inconclusive, buttressing the need for precise and reliable estimations. To overcome these inconsistencies, a well-structured systematic review and meta-analytic models are necessary. However, to the best of our knowledge, there is no published systematic review and meta-analysis on risk factors for 30-day case fatality for in-hospital patients with stroke in Sub-Saharan Africa (SSA)

Method and analysis: We will include all retrospective and prospective facility-based observational studies reporting on the incidence and/or risk factors for in-hospital stroke case-fatality in sub-Saharan Africa countries (SSA). Electronic databases such as PubMed, Google scholar, and AJOL will be searched for potentially relevant studies on in-hospital stroke case-fatality and risk factors in sub-Saharan Africa (SSA). The search will be limited to studies conducted from January 1990 through December 2020. Two independent authors will screen titles and abstract to find studies that meet the pre-specified eligibility criteria for inclusion in the review. The pooled in-hospital stroke case-fatality and its risk factors will be calculated. Random effects model will be used in case of substantial heterogeneity in the included studies, otherwise, a fixed-effect model will be used. A planned subgroup, sensitivity and meta-regression analyses will be performed.

Ethics and dissemination: Ethical approval is not required as this is a secondary research and will use reported data in scientific literature. A full manuscript will be submitted to a reputable peer-review journal for publication.

PROSPERO registration number: CRD42021227367

Strength and limitation

- To the best of the authors' knowledge, this is the first systematic review and meta-analysis on risk factors for 30-day in-hospital stroke case-fatality in SSA.
- Sensitivity analyses will be performed to determine the robustness of the estimates obtained from the meta-analysis
- We would incorporate well-validated systematic review and meta-analysis technique that are completely consistent with existing international standards and recommendations.
- Due to regional and geographical differences, there can be variations across studies, therefore, we plan to conduct robust sub-group analyses to detect any sub-group effects.
- Papers/articles that have only been published in English would be considered, which could introduce publication bias.

Keywords: Stroke; in-hospital; case-fatality; Sub-Saharan Africa

Introduction

Stroke is a major cause of death and injury, and post-stroke treatment costs are a significant economic burden worldwide [1,2]. High-income countries have seen rapid and significant reduction in stroke incidence, and long-term survival as a result of expanded use of preventive therapies and significant decreases in premorbid risk factors [3–5]. Nonetheless, most sub-Saharan countries are unable to say same [6]

The incidence of stroke is rising in Low- and Middle-Income Countries (LMICs) in SSA countries, and research has shown that between 2002 and 2020, stroke mortality in sub-Saharan Africa will triple [7,8]. For instance, community-based Sub-Saharan African (SSA) studies indicate that 5-10% of all deaths are caused by stroke, partially due to poor health system and rising rates of hypertension [9,10]. In addition, Low- and Middle-Income Countries (LMICs) account for 85% of all stroke deaths, as well as 87% of total losses due to stroke measured in disability-adjusted life years (DALYs) which total 72 million per year worldwide [1,11]

In sub-Saharan Africa, epidemiologic studies have shown that in-hospital stroke case-fatality rates varied from 18% in Ethiopia to 43% in Ghana [8,12]. Sub-Saharan African countries have insufficient resources for acute medical and rehabilitation care for stroke, therefore comprehensive and pragmatic preventive efforts directed at risk factors are of utmost importance to curtail the burden [13]. In the same vein, early intervention on in-patient with stroke identified with a high risk of case-fatality may increase the survival rate [14]. It is therefore imperative to identify risk factors for 30-day case fatality rates for in-patients with stroke in Sub-Saharan Africa

While individual studies have reported on in-hospital stroke case fatality rates in SSA, the estimates are highly variable and inconclusive, buttressing the need for precise and reliable

estimations. To overcome these inconsistencies, a well-structured systematic review and meta-analytic models are necessary. However, to the best of our knowledge, there is no published systematic review and meta-analysis on risk factors for 30-day case fatality for in-hospital patients with stroke in SSA.

With this in mind, the study seeks to systematically review empirical evidence on risk factors for 30-day case fatality for in-hospital patients with stroke in SSA. It is important for health care providers to learn about the risk factors associated with in-hospital stroke case fatality rates in order to prepare for future patient care as well as to optimize hospital staffing and necessary skills in SSA.

Review questions

- What is the incidence for 30-day case fatality rates for in-patients with stroke in Sub-Saharan Africa?
- What are the risk factors for 30-day case fatality rates for in-patients with stroke in Sub-Saharan Africa?

Objectives

- Primary objective: To determine the incidence for 30-day case fatality rates for in-patients with stroke in Sub-Saharan Africa
- Secondary objective: To assess the risk factors for 30-day case fatality rates for in-patients with stroke in Sub-Saharan Africa

Methods

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Protocol registration and best practices

This systematic review and meta-analysis will follow strict adherence to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [15] (checklist file 1). The current review is registered with International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42021227367)

Eligibility

Types of studies: All retrospective and prospective facility-based observational studies reporting on incidence and/or risk factors for in-hospital stroke mortality and case-fatality in sub-Saharan Africa countries. Animal studies, reviews, commentaries, conference papers and letter to the editor will be excluded.

Types of participants: Studies involving in-hospital stroke participants from sub-Saharan African countries. The review will consider all age groups.

Types of outcome measures: The primary outcome is the in-hospital stroke case-fatality in sub-Saharan Africa and secondary outcome is the risk factors for in-hospital case-fatality in sub-Saharan Africa.

Data source and Search strategies

Primary electronic search in English on the incidence and risk factors for in-hospital stroke case-fatality rate in sub-Saharan Africa will be conducted in MEDLINE via PubMed, Google Scholar, and AJOL. The search will be limited to studies conducted from January 1990 through December 2020. Table 2 displays the main search term and approaches (**Supplementary file 1**). The abstracts of all eligible papers will then be reviewed and full articles will be accessed through PubMed, Google Scholar, and AJOL. Reference lists of papers that fulfill the eligibility requirements of the study will be reviewed to identify additional studies not included in our electronic search. To ensure that potential studies that will be missed by electronic searching are included, experts will be consulted.

Table 2: Search string for PubMed, Google scholar and AJOL

Search #	Search term
1)	In-hospital OR in-patient
2)	Stroke OR cerebrovascular accident OR CVA OR cerebral infarction OR Ischemic stroke OR Lacuna stroke OR cerebral hemorrhage OR haemorrhagic stroke
3)	1 AND 2
4)	mortality OR death OR case-fatality
5)	3 AND 4
6)	risk factors OR associated factors
7)	5 OR 6
8)	sub-Saharan Africa
9)	Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Cote d'Ivoire OR Djibouti OR Equatorial Guinea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa

	OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Zaire OR Zambia OR Zimbabwe
10)	8 OR 9
11)	Limit to January, 1990-December,2020
12)	Limit to Humans
13)	10 AND 11 AND 12

Screening and selecting studies

Two authors will screen titles and abstract independently to find studies that meet the pre-specified eligibility criteria for inclusion in the review. Full texts of all potentially relevant studies will be accessed and assessed in detail in a similar manner. A third reviewer will be available to resolve any discrepancies between the two independent assessors. A screening guide will be used to ensure that independent reviewers apply the selection criteria reliably. Authors whose full-text documents are not available via a variety of internet-based sources will be contacted directly through the corresponding authors to provide them to help make the final decision about inclusion. If vital information needed to make the inclusion decision is not obtained, the article will be excluded. Mendeley reference manager will be used to deduplicate studies.

Data extraction and management

Two independent assessors will extract the data from the eligible published articles using a pre-tested and standardized excel spreadsheet. Data such as the last name of the first author's name, year of publication, study country, study design, sample size, case fatality rate, risk factors for in-hospital stroke case-fatality, severity measure, type of stroke as well as the demographic information (i.e. sex, age, etc.) will be extracted. Missing data will be addressed by contacting the

corresponding author for insufficient or unclear data. If possible, corresponding authors will be asked to provide us with the raw data to extract the missing data.

Risk of bias and Quality assessment

The Newcastle-Ottawa Quality Assessment tool adapted for cross-sectional studies will be used to assess the quality of the retrieved studies. The purpose of the assessment will be to determine the internal and external validity of the studies and to minimize risk of bias

Data synthesis

Extracted data will be exported into Stata (version 16; Stata Cooperation, TX, USA) from Microsoft excel 2013 for all analyses The PRISMA flow chart (**Error! Reference source not found.**) will be used to summarized the selection process. When considerable homogeneity exists among the studies, the incidence of in-hospital case-fatality rate in sub-Saharan Africa will be pooled. This will be visually represented using the forest plot. The presence of heterogeneity among studies will be quantified by estimating variance using both Cochrane's Q statistics and the I^2 statistics [16]. The I^2 takes values between 0 and 100%, and a value of 0% indicates absence of heterogeneity. I^2 will be interpreted based on Higgins and Thompson classification, percentages of 25%, 50% and 75% will be considered as low, moderate and high heterogeneity, respectively [16].

Meta-regression will be used to assess the factors associated with in-hospital stroke case-fatality in sub-Saharan Africa. If possible, sub-group analysis will be performed based on sub-region (West Africa vs. East Africa vs. Southern Africa), publication year and study design (Prospective vs. Retrospective), and quality score (low risk vs. moderate risk vs. high risk of bias) to determine possible source of heterogeneity

If possible, a sensitivity analysis will be performed to determine the robustness of the estimates obtained from the meta-analysis. We will do sensitivity analysis on the quality of the studies included in the systematic review and meta-analysis i.e. studies with low quality score will initially be excluded to check their direction and impact on the overall (pooled) estimate and finally leave one out sensitivity analysis will be performed. Publication bias will be checked by the funnel plot and Egger's test. Furthermore, trim and fill analysis will be used to adjust for publication bias using Duval and Tweedie's method[17] in case publication bias exist.

In event where meta-analysis is not possible due to considerable heterogeneity and low-quality studies, narrative systematic review will be presented.

Grading the quality of evidence

The quality of evidence for all studies will be assessed using the Grading of Recommendations Assessment, Development and Evaluation working group methodology. The following domains will be assessed: risk of bias, consistency, directness, precision, publication bias and additional points. The assessments will be classified into four levels: high, moderate, low or very low.[18] Two independent reviewers will assess the GRADE and disagreement will be resolved through discussion.

Expected key results and discussion

Globally, stroke is the third leading cause of death [19]. The bulk of these deaths from strokes are found in developing countries. In these nations, deaths account for up to 87% of all stroke fatalities[20]. This elevated death toll is much greater in sub-Saharan Africa [20]. To the best of the authors' knowledge, there is no comprehensive systematic review and meta-analysis on in-hospital stroke case-fatality exist in sub-Saharan Africa. Hence, the primary aim of this review is to

determine the incidence of in-hospital stroke case-fatality in sub-Saharan Africa. Secondary objective is to assess the risk factors in-hospital stroke case-fatality in sub-Saharan Africa.

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Contributors

MA conceived the study. MA, LA and COY drafted the manuscript. MA, LA and COY critically revised the manuscript for methodological and intellectual content. All authors approved the final manuscript. MA is the guarantor of the review

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Patient consent for publication: Not required

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement: All relevant data are within the manuscript.

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Figure legend

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols flow chart for study selection

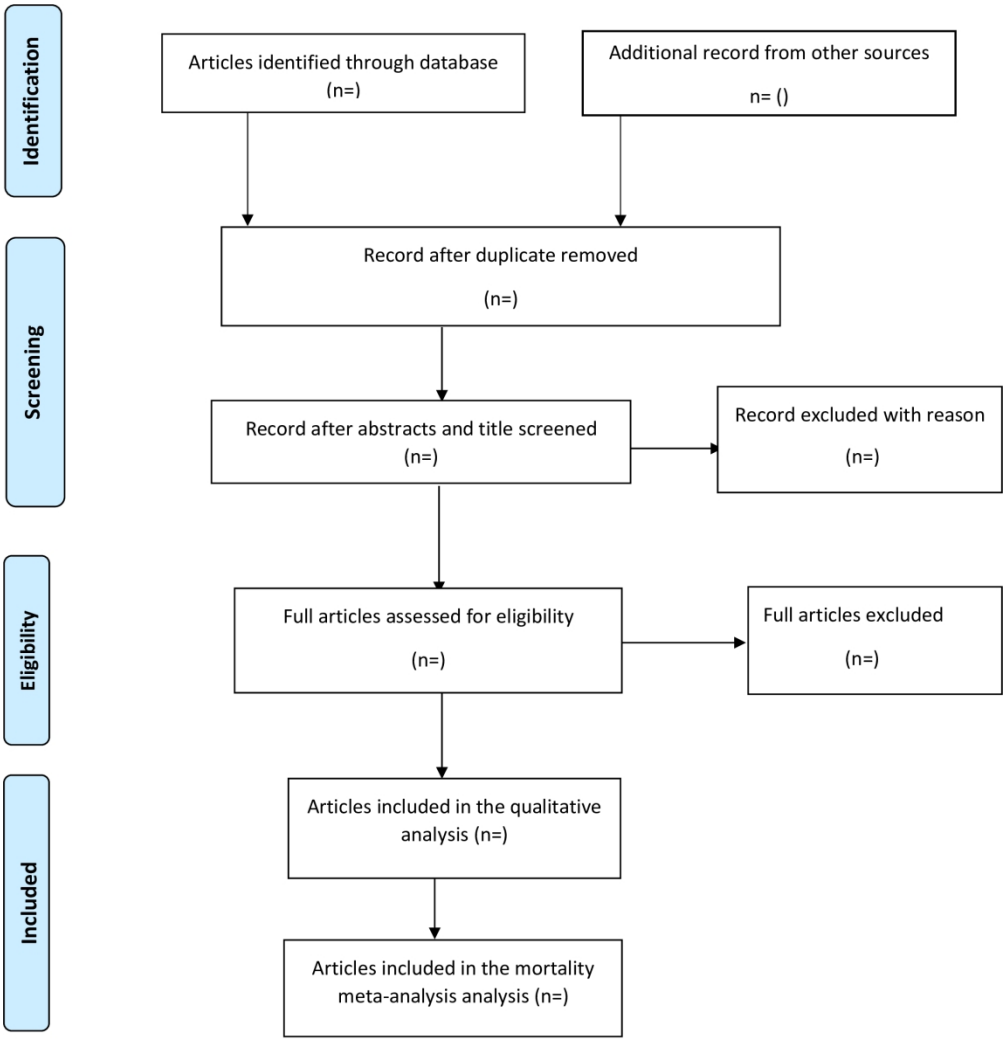

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analysis-Adapted flow showing the results of the search

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analysis-Adapted flowchart showing the results of the search

182x201mm (300 x 300 DPI)

***Supplementary file 1**: Search string for PubMed, Google scholar and AJOL*

Search #	Search term
1)	In-hospital OR in-patient
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3)	1 AND 2
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10)	8 OR 9
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12)	Limit to Humans
13)	10 AND 11 AND 12

Supplementary file 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 6
Authors: contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Authors' contribution	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources with planned dates of coverage	6-7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such 6 that it could be repeated	7
Study record			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any preplanned data assumptions and simplifications	-
Outcome and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in the individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta biases	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

From: 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 [Internet]. 2015;349(January):1–25. Available from: http://dx.doi.org/doi:10.1136/bmj.g7647

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Secondary Subject Heading:	Epidemiology, Cardiovascular medicine, Neurology, Rehabilitation medicine
Keywords:	Stroke < NEUROLOGY, EPIDEMIOLOGY, Stroke medicine < INTERNAL MEDICINE

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Risk factors for 30-day in-hospital mortality for in-patient with stroke in Sub-Saharan Africa: Protocol for a systematic review and meta-analysis

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Abstract

Introduction: While individual studies have reported on in-hospital stroke mortality rates in Sub-Saharan Africa (SSA), the estimates are highly variable and inconclusive, buttressing the need for precise and reliable estimations. To overcome these inconsistencies, a well-structured systematic review and meta-analytic models are necessary. However, to the best of our knowledge, there is no published systematic review and meta-analysis on risk factors for 30-day mortality for in-hospital patients with stroke in SSA

Method and analysis: We will include all retrospective and prospective facility-based observational studies reporting on the incidence and/or risk factors for in-hospital stroke mortality in SSA. Electronic databases such as PubMed, Google scholar, and AJOL will be searched for potentially relevant studies on in-hospital stroke mortality and risk factors in SSA. The search will be limited to studies conducted from January 1990 through December 2020. Two independent authors will screen titles and abstract to find studies that meet the pre-specified eligibility criteria for inclusion in the review. The incidence of 30-day in hospital stroke mortality will be pooled. Meta-regression will be used to assess the factors associated with in-hospital stroke mortality in SSA. If possible, sub-group analysis will be performed based on sub-region, publication year and study design, and quality score to determine possible source of heterogeneity. If possible**,** a sensitivity analysis will be performed to determine the robustness of the estimates obtained from the meta-analysis.

Ethics and dissemination: Ethical approval is not required as this is a secondary research and will use reported data in scientific literature. A full manuscript will be submitted to a reputable peer-review journal for publication.

PROSPERO registration number: CRD42021227367

Strength and limitation

- To the best of the authors' knowledge, this is the first systematic review and meta-analysis on risk factors for 30-day in-hospital stroke mortality rate in SSA.
- Sensitivity analyses will be performed to determine the robustness of the estimates obtained from the meta-analysis
- We would incorporate well-validated systematic review and meta-analysis technique that are completely consistent with existing international standards and recommendations.
- Due to regional and geographical differences, there can be variations across studies, therefore, we plan to conduct robust sub-group analyses to detect any sub-group effects.
- Papers/articles that have only been published in English would be considered, which could introduce publication bias.

Keywords: Stroke; in-hospital; 30-Mortaity; Sub-Saharan Africa; SSA

Introduction

Stroke is a major cause of death and injury, and post-stroke treatment costs are a significant economic burden worldwide [1,2]. High-income countries have seen rapid and significant reduction in stroke incidence, and long-term survival as a result of expanded use of preventive therapies and significant decreases in premorbid risk factors [3–5]. Nonetheless, most sub-Saharan countries (SSA) are unable to say same [6]

The incidence of stroke is rising in Low- and Middle-Income Countries (LMICs) in SSA countries, and research has shown that between 2002 and 2020, stroke mortality in SSA will triple [7,8]. For instance, community-based SSA studies indicate that 5-10% of all deaths are caused by stroke, partially due to poor health system and rising rates of hypertension [9,10]. In addition, LMICs account for 85% of all stroke deaths, as well as 87% of total losses due to stroke measured in disability-adjusted life years (DALYs) which total 72 million per year worldwide [1,11]

In SSA, epidemiologic studies have shown that in-hospital stroke mortality rates varied from 18% in Ethiopia to 43% in Ghana [8,12]. Sub-Saharan African countries have insufficient resources for acute medical and rehabilitation care for stroke, therefore comprehensive and pragmatic preventive efforts directed at risk factors are of utmost importance to curtail the burden [13]. In the same vein, early intervention on in-patient with stroke identified with a high risk of mortality may increase the survival rate [14]. It is therefore imperative to identify risk factors for 30-day in-hospital mortality for in-patients with stroke in SSA. The proportion of patients who die within 30 days from the time of admission to the time of death among all patients hospitalized with stroke is referred to as 30-day in-hospital stroke mortality.

While individual studies have reported on in-hospital stroke mortality rates in SSA, the estimates are highly variable and inconclusive, buttressing the need for precise and reliable estimations. To overcome these inconsistencies, a well-structured systematic review and meta-analytic models are necessary. However, to the best of our knowledge, there is no published systematic review and meta-analysis on risk factors for 30-day mortality for in-hospital patients with stroke in SSA.

With this in mind, the study seeks to systematically review empirical evidence on risk factors for 30-day mortality for in-hospital patients with stroke in SSA. It is important for health care providers to learn about the risk factors associated with in-hospital stroke 30-day mortality in order to prepare for future patient care as well as to optimize hospital staffing and necessary skills in SSA.

Review questions

- What is the incidence for 30-day mortality rates for in-patients with stroke in SSA?
- What are the risk factors for 30-day mortality rates for in-patients with stroke in SSA?

Objectives

- Primary objective: To determine the incidence for 30-day mortality rates for in-patients with stroke in SSA
- Secondary objective: To assess the risk factors for 30-day mortality for in-patients with stroke in SSA

Methods

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics and dissemination

Ethical approval is not required as this is a secondary research and will use reported data in scientific literature. A full manuscript will be submitted to a reputable peer-review journal for publication.

Protocol registration and best practices

This systematic review and meta-analysis will follow strict adherence to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [15] (checklist file 1). The current review is registered with International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42021227367).

Eligibility

Types of studies: All retrospective and prospective facility-based observational studies reporting on incidence and/or risk factors for in-hospital stroke mortality and case-fatality in SSA countries. Also, if any of the countries in SSA have a public reporting of in-hospital 30-day mortality from eventual published quality indicators, such outcome will be included to help contribute to the identification and understanding of risk factors. Animal studies, reviews, commentaries, conference papers and letter to the editor will be excluded.

Types of participants: Studies involving in-hospital stroke participants from sub-SSA countries. The review will consider all age groups.

Types of outcome measures: The primary outcome is the in-hospital stroke 30-day mortality in SSA and secondary outcome is the risk factors for in-hospital mortality in SSA. However, if any study reports on out-of-hospital mortality, it will be extracted and reported separately.

Data source and Search strategies

Primary electronic search in English on the incidence and risk factors for in-hospital stroke case-fatality rate in sub-Saharan Africa will be conducted in MEDLINE via PubMed, Google Scholar, and AJOL. The search will be limited to studies conducted from January 1990 through December 2020. Table 2 displays the main search term and approaches (**Supplementary file 1**). The abstracts of all eligible papers will then be reviewed and full articles will be accessed through PubMed, Google Scholar, and AJOL. Reference lists of papers that fulfill the eligibility requirements of the study will be reviewed to identify additional studies not included in our electronic search. To ensure that potential studies that will be missed by electronic searching are included, experts will be consulted.

Table 2: Search string for PubMed, Google scholar and AJOL

Search #	Search term
1)	In-hospital OR in-patient
2)	Stroke OR cerebrovascular accident OR CVA OR cerebral infarction OR Ischemic stroke OR Lacuna stroke OR cerebral hemorrhage OR haemorrhagic stroke
3)	1 AND 2
4)	Mortality OR 30-day mortality OR death OR case-fatality
5)	3 AND 4
6)	risk factors OR associated factors

7)	5 OR 6
8)	sub-Saharan Africa
9)	Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Cote d'Ivoire OR Djibouti OR Equatorial Guinea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Zaire OR Zambia OR Zimbabwe
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Screening and selecting studies

Two authors will screen titles and abstract independently to find studies that meet the pre-specified eligibility criteria for inclusion in the review. Full texts of all potentially relevant studies will be accessed and assessed in detail in a similar manner. A third reviewer will be available to resolve any discrepancies between the two independent assessors. A screening guide will be used to ensure that independent reviewers apply the selection criteria reliably. Authors whose full-text documents are not available via a variety of internet-based sources will be contacted directly through the corresponding authors to provide them to help make the final decision about inclusion. If vital information needed to make the inclusion decision is not obtained, the article will be excluded. Mendeley reference manager will be used to deduplicate studies.

Data extraction and management

Two independent assessors will extract the data from the eligible published articles using a pre-tested and standardized excel spreadsheet. Data such as the last name of the first author's name, year of publication, study country, study design, sample size, mortality rate, risk factors for in-hospital stroke case-fatality, severity measure, type of stroke as well as the demographic information (i.e. sex, age, etc.) will be extracted. Missing data will be addressed by contacting the corresponding author for insufficient or unclear data. If possible, corresponding authors will be asked to provide us with the raw data to extract the missing data.

Outcome and operationalization

A 30-day in-hospital stroke mortality is operationally defined as the proportion or standardized hospital mortality based on the number of patients who die within 30 days from the time of admission to the time of death among all patients hospitalized with stroke. In this study, a risk factor is defined as a set of variables that are linked to or cause 30-day death in hospitalized stroke patients in SSA. For example, patient related factors that may increase mortality in stroke include poor control of major risk factors to stroke such as hypertension, obesity, smoking, heart disease and diabetes. Hospital related factors such as availability of a stroke unit, availability of an intensive care unit and the capacities of the emergency unit. Treatment delays [i.e. waiting times, time to get to hospital from onset of symptoms]. The severity of stroke and length of stay may also influence 30-day mortality etc.

Risk of bias and Quality assessment

The Newcastle-Ottawa Quality Assessment tool adapted for cross-sectional studies will be used to assess the quality of the retrieved studies. The purpose of the assessment will be to determine the internal and external validity of the studies and to minimize risk of bias.

Data synthesis

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Meta-regression will be used to assess the factors associated with in-hospital stroke 30-day mortality in SSA. If possible, sub-group analysis will be performed based on sub-region (West Africa vs. East Africa vs. Southern Africa), publication year and study design (Prospective vs. Retrospective), and quality score (low risk vs. moderate risk vs. high risk of bias) to determine possible source of heterogeneity.

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In event where meta-analysis is not possible due to considerable heterogeneity and low-quality studies, narrative systematic review will be presented.

Grading the quality of evidence

The quality of evidence for all studies will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology. The following domains will be assessed: risk of bias, consistency, directness, precision, publication bias and additional points. The assessments will be classified into four levels: high, moderate, low or very low.[18] Two independent reviewers will assess the GRADE and disagreement will be resolved through discussion.

Expected key results and discussion

Globally, stroke is the third leading cause of death [19]. The bulk of these deaths from strokes are found in developing countries. In these nations, deaths account for up to 87% of all stroke fatalities[20]. This elevated death toll is much greater in SSA [20]. To the best of the authors' knowledge, there is no comprehensive systematic review and meta-analysis on in-hospital stroke case-fatality exist in SSA. Hence, the primary aim of this review is to determine the incidence of in-hospital stroke 30-day mortality in SSA. Secondary objective is to assess the risk factors for in-hospital stroke mortality in SSA.

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Contributors

MA conceived the study, drafted the manuscript, critically revised the manuscript for methodological and intellectual content. COY drafted the manuscript, critically revised the manuscript for methodological and intellectual content. LA critically revised the manuscript for methodological and intellectual content. All authors approved the final manuscript. MA is the guarantor of the review

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Patient consent for publication: Not required

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement: All relevant data are within the manuscript.

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Figure legend

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols flow chart for study selection

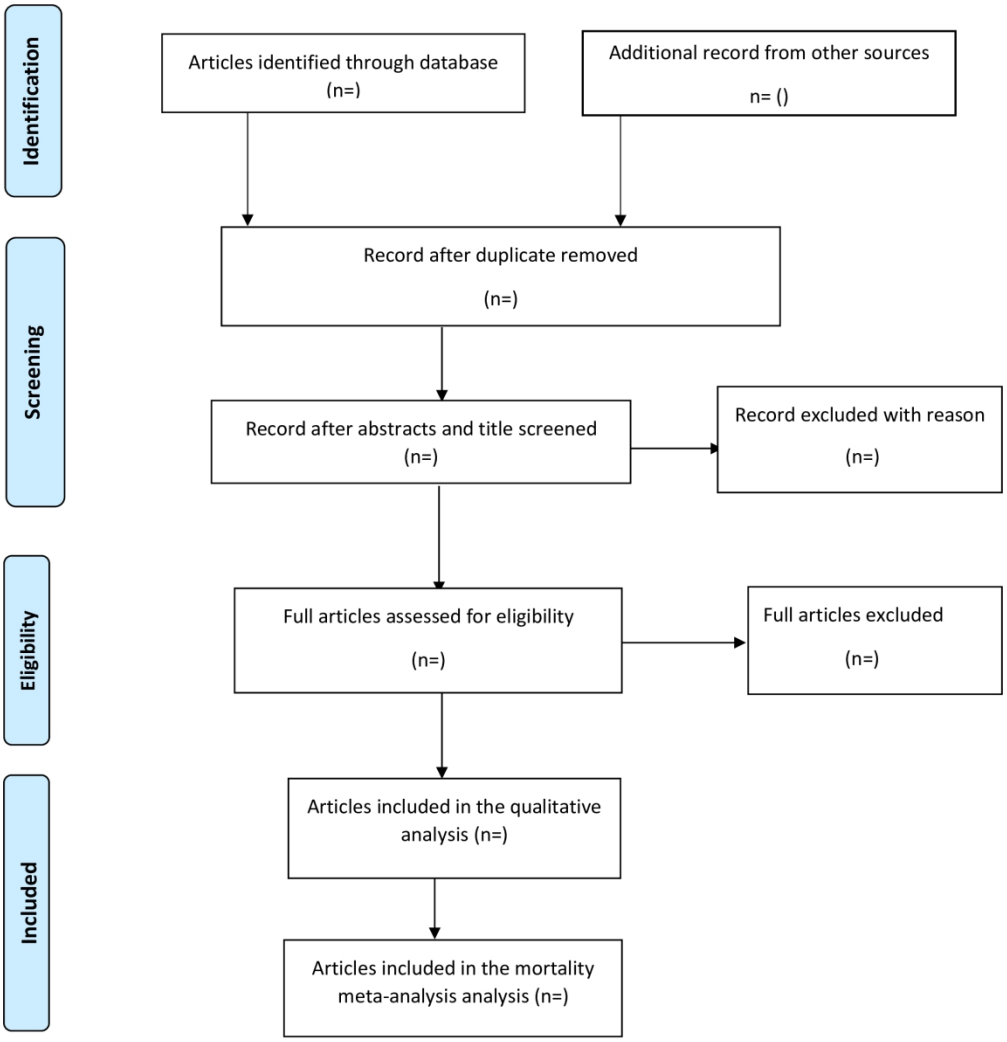

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analysis-Adapted flow showing the results of the search

Figure 1: Preferred Reporting Items for Systematic Review and Meta-Analysis-Adapted flowchart showing the results of the search

182x201mm (300 x 300 DPI)

***Supplementary file 1**: Search string for PubMed, Google scholar and AJOL*

Search #	Search term
1)	In-hospital OR in-patient
2)	Stroke OR cerebrovascular accident OR CVA OR cerebral infarction OR Ischemic stroke OR Lacuna stroke OR cerebral hemorrhage OR haemorrhagic stroke
3)	1 AND 2
4)	mortality OR 30-day mortality OR death OR case-fatality
5)	3 AND 4
6)	risk factors OR associated factors
7)	5 OR 6
8)	sub-Saharan Africa
9)	Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Congo OR Cote d'Ivoire OR Djibouti OR Equatorial Guinea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Zaire OR Zambia OR Zimbabwe
10)	8 OR 9
11)	Limit to January, 1990-December,2020
12)	Limit to Humans
13)	10 AND 11 AND 12

Supplementary file 1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page
ADMINISTRATIVE INFORMATION			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 6
Authors: contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Authors' contribution	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources with planned dates of coverage	6-7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such 6 that it could be repeated	7
Study record			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any preplanned data assumptions and simplifications	-
Outcome and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in the individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9
Meta biases	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

From: 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 [Internet]. 2015;349(January):1–25. Available from: http://dx.doi.org/doi:10.1136/bmj.g7647