Mortality rate and predictors of Stroke: A Meta-Analysis and Systematic Review

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Abstract

Background Global data on stroke mortality remained to be sparse. In light of this, we aimed to conduct a Meta-analysis and systematic review of observational studies to estimate the mortality of stroke and to identify risk factors that predispose patients for stroke-related death. Methods This study was conducted based on the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) guidelines. Overall mortality, in-hospital and 30-day mortality due to stroke were the primary outcome measures of the study. The meta-analysis was performed using Stata (Version 14, Stata Corp, College Station, Texas). Random-effect models were used for estimating pooled effects. Findings Overall, thirty-two studies assessed overall mortality due to stroke. A total number of 2,885,126 patients were recruited for the study. Pooled estimate indicated that the overall mortality of stroke was reported to be 20% (19%-22%). Whereas, the 30-day and in-hospital mortality were found to be 18% (16%-20%) and 16% (16%-19%), respectively. A subgroup analysis revealed that Africa registered the highest stroke-related death 29% (23%-36%). Hypertension was found to be an important risk factor for mortality secondary to stroke 61.9% (52.8%-71.1%). Conclusion Overall mortality of stroke was estimated to be twenty percent. The burden of stroke mortality was prominent in Africa region. Hypertension remained to be an independent risk factor for stroke mortality. Mortality of stroke can be minimized by establishing stroke centers that promptly deliver emergency management of stroke event.

Background

The American Heart Association (AHA)/American Stroke Association (ASA) expert consensus document defines "stroke" as a range of disorders including ischemic stroke (IS), silent central nervous system (CNS) infarction, intra-cerebral hemorrhage (ICH), silent cerebral hemorrhage, subarachnoid hemorrhage (SAH), cerebral venous thrombosis, and stroke not otherwise specified [1]. According to the global burden of diseases (GBDs), stroke was the second most common cause of deaths (11.8%) worldwide, next to ischemic heart disease (14.8%) and the third most common cause of disability (4.5%) [1-2]. Stroke produces substantial health and economic impact in the world [2-3]. IS remained the most common type of stroke in both developed and developing countries [4]. In 2013, there were around 25.7 million stroke survivors in the world, of which 71% were with IS. The number of deaths from stroke and Disability Adjusted Life Years (DALYs) due to stroke were 6.5 million and 113 million, respectively. There were also 10.3 million new cases of stroke in the same year [2-3].

There are several risk factors for the occurrence of stroke and related mortalities. When ranking these risk factors to stroke by DALYs, hypertension tops the ranks followed by diet low in fruits, high BMI, diet high in sodium, smoking [5]. Modifiable risk factors contribute to 90.5% of the global stroke burden when measured in terms of DALYs [5]. The most important of these are behavioral factors such as smoking, alcohol consumption and low physical activity and metabolic factors such as high systolic blood pressure, high body mass index, diabetes, and high total cholesterol [2, 5]. In addition, environmental factors also contribute to stroke-related DALYs. Non-modifiable risk factors such as genetics also have their own contribution [2]. The increase in modifiable risk factors could be the driving force behind the higher incidence of stroke in younger adults. The high contribution of modifiable risk factors means that much focus should be given on these factors to bring significant changes on the global burdens of stroke [5].

Over the past few decades, the incidence of stroke showed divergent trends between high-income countries (HICs) and low- to middle-income countries (LMICs). While the annual incidence of stroke declined in HICs, it increased in the LMICs by more than 100% to surpass that of the HIC. The burden in LMICs has also been higher in terms of prevalence, deaths, and DALY lost [3,6]. Previous studies reported different rate of mortality of stroke ranged from (11.97%-60%) [7-8] which indicate the requirement of comprehensive data on stroke mortality globally.

Advancement in technology and management of stroke led to the emergence of stroke units. According to the world health organization (WHO) action plan, access to elements of stroke unit care are considered essential [9]. Compared to general wards, these resource-intensive facilities have been associated with improved treatment outcomes in stroke patients in terms of mortality and dependency [10]. Though stroke units improve stroke outcomes both in HICs and LMICs, there are several barriers and only limited stroke units in LMICs [11-13]. This coupled with the delay in hospital arrival, lack of stroke experts, shortage of medications, and cost could have potentially contributed to the poorer stroke treatment outcomes in LMICs when compared to HICs [2-3].

Currently, the global prevalence, mortality and DALY lost secondary to stroke showed a significant increase [3]. However, global data on stroke mortality remained to be sparse. In light of this, we aimed to conduct a Meta-analysis and systematic review of observational studies to estimate the mortality of stroke and to identify risk factors that predispose for stroke-related death.

Methods

Literature search strategies

This study was conducted based on the Meta-Analyses of Observational Studies in Epidemiology (MOOSE) guidelines [14]. We utilized four electronic databases (google scholar, Scopus, PubMed, Embase) to retrieve articles using the following key words and mesh terms: stroke OR “ischemic stroke” OR “acute stroke” [Mesh] OR “cerebral stroke”[Mesh] or hemorrhagic stroke AND *overall mortal* or “30-day mortal” or in-hospital mortal*[all field] OR outcome OR prognostic*[all field]. The search- date ranged from January, 1, 2000 to December, 25, 2017).

Eligibility criteria

We included studies measuring mortality of stroke. However, mortality from heat stroke and electric shock stroke was excluded. Age was restricted to adults (18 years of age or older). Interventional and review articles were not included in the present study.

Outcome measures of the study
Overall mortality due to stroke, in-hospital and 30-day mortality were the primary outcome measures of the study. Risk factors for stroke which constitute factors that predict the incidence of stroke and mortality were also identified.

Data Collection Process

A preliminary reading of titles and abstracts was carried out to include all relevant papers. Final inclusion of articles was made upon a thorough reading of full texts. Three investigators namely (TMA, BMG, MAS) undertook the independent review of all articles. In cases of disagreement, a fourth author (EAG) was involved and any discrepancy was resolved in consensus.

Data extraction

All records that were found from searches of the electronic databases were exported into the ENDNOTE software version X5 (Thomson Reuters, USA) so as to avoid duplication. Specific datasheet was prepared using Microsoft Excel software version 2013. Information on studies including year of publication, objectives of the study, sociodemographic and clinical characteristics of participants, complications of stroke, risk factors and types of stroke was taken from each study. The mortality rate of stroke reported as overall mortality, in-hospital mortality and 30-days mortality was fetched and stored in an independent sheet stated/levled as “main analysis”.

Data analysis

The meta-analysis was performed using Stata (Version 14, Stata Corp, College Station, Texas) [15]. Heterogeneity and publication bias were assessed using Comprehensive Meta-analysis version-3 (Biostat, Englewood, New.Jersey, USA). Results were summarized using conventional forest plots. Random-effects models for estimating pooled effects were considered preferable rather than fixed-effect models because high variability across the included studies was expected. The heterogeneity in pooled estimation was determined by the DerSimonian-Laird (DL) approach and was assessed using $I^2$. Sensitivity analysis was conducted to determine the robustness of the results and sources of variation in pooled estimation, respectively. Subgroup analysis was performed based on study design and geography of study subjects. Moreover, publication bias for the primary outcome was assessed by Egger test and inspection of funnel plots. The quality of the studies was evaluated using STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) scale [16]. Accordingly, we arbitrarily classified included studies into high quality (≥75% of the STROBE checklist) and low quality (<75% of the STROBE checklist).

Results

Study characteristics and the selection process

Overall, 8408 records were generated from four electronic databases including PubMed (1654), Scopus (2857), Google scholar (3670) and Embase databases (227), respectively. No grey literature was included. The preliminary screening based on titles and abstracts identified forty-one papers as potentially relevant for the full-text review and thirty two articles were finally deemed eligible for the systematic review and meta-analysis (fig 1).

Thirty two studies assessed overall mortality due to stroke. Twelve studies were from Africa [7-8, 17-26], six from Europe [27-32], six from Asia [33-38], five from North America [39-43] and two from Latin America [44-45]. Seventeen studies reported 30-day mortality rate of stroke whereas twenty two studies measured in-hospital mortality. Detailed explanations on study characteristics are shown in the supplementary table (table 1).

Patient Characteristics

A total number of 2,885,126 patients were recruited for the study. The mean age of participants was found to be 69.8± 13.8 years. There were 1,172,581(40.64%) males and 1,712,545(59.36%) females, respectively. Overall stroke mortality was documented for 302,592 (10.49%) patients. The rate of 30-day mortality was reported in 190,570(0.66%) subjects while in-hospital mortality was recorded in 108,368 (3.75%) participants.

Types of stroke

About 121,3064 (42%) patients experienced ischemic stroke. Hemorrhagic stroke was identified in 190,906(6.6%) of patients. The remaining stroke events were undifferentiated or unclassified.

Risk factors

The following risk factors were reported hypertension 115,9461 (40.2%) with mean systolic blood pressure of 154.29±21.45 mmHg, diabetes 195,612 (6.78), AF: 216,097 (7.49%), hypercholesterolemia: 420,144 (14.5%), alcohol consumption: 309,02 (1.71%), smoking: 163,583 (5.67%), cardiomyopathy 39,870(0.14%) and previous stroke attack 39,833(1.4%). The risk factors for rest of the population were not distinguished.

Complications of stroke

Complications were reported in 10,622 subjects. Specific complications include confusion 46,294(3.57%), thromboembolism 170(1.6%), mobility disorder 1573(14.81%), speech disorder 1550(14.59%), infection 465(4.38%), cognitive problem 731(6.9%), neurologic complications 1504(14.16%).

Mortality of stroke

Pooled estimate indicated that the overall mortality of stroke was reported to be 20% (19%-22%). Whereas, the 30-day mortality was found to be 18% (16%-20%). In-hospital mortality was estimated as 16% (16%-19%) (Fig 2-4).
Subgroup analysis

To examine the difference in the epidemiology of stroke mortality among continents and type of study designs, a subgroup analysis was undertaken based on the location of the studies and study designs. Consequently, it was found that Africa registered the highest stroke-related death 29% (23%-36%) followed by Europe 22% (16%-27%). (Fig. 5) America, 16% (12%-20%) and Asia 16% (10%-21%) showed a comparable rate of overall stroke mortality (Figure 5). Mortality was higher among prospective studies 26% (22%-31%) versus retrospective 17% (15%-20%) (Additional file 1).

Determinants of mortality

Pooled odds ratio of precipitating factors revealed that hypertension was found to be an important risk factor for mortality secondary to stroke 61.9% (52.8%-71.1%). The probability of death has increased in a quarter among stroke patients who were having hypercholesterolemia 20.2% (10.0%-30.4%) and alcohol consumption 21.5% (10.4%-32.6%), respectively (table 2).

Sensitivity and subgroup analysis

The sensitivity analysis showed that omission of anyone of the included studies did not significantly affect the pooled mortality of stroke (all P < 0.05) (additional file 2). We performed subgroup analysis based on geographic area of the studies and the type of study design. Accordingly, overall mortality was found to be higher in Africa 29% (23%-36%) than any other continents (fig 5). In addition, mortality was higher among prospective studies 26% (22%-31%) versus retrospective 17% (15%-20%) (Additional file 3).

Discussion

Stroke is a sudden cerebrovascular accident that poses significant mortality and morbidity. Stroke mortality can be summarized as overall mortality, 30-day mortality and in-hospital mortality. Post-stroke complications of stroke denotes a constellation of disabilities including: neurologic sequelae, infection, psychiatric disorder, pain, movement disorders, cognitive and speech problems [46]. The determinants of mortality secondary to stroke represent an array of modifiable and non-modifiable risk factors including diabetes [47], hypertension [48], hypercholesterolemia [49], alcohol consumption [50], cigarette smoking [51] and atrial fibrillation [52]. Despite the hassle burden of stroke, data regarding stroke mortality and its determinants were found to be scarce. To this end, a systematic review and meta-analysis of observational studies has been designed so as to explore the mortality rate of stroke on the basis of gross, thirty-day and in-hospital mortalities. In addition, the current review highlighted risk factors that implicate with stroke mortality.

A rigorous review of 32 articles provided a total of 2,885, 126 stroke patients. According to the pooled analysis, the overall mortality of stroke was reported to be 20% (CI: 19%-22%). This figure falls between ranges of mortality values reported by different studies. Subgroup analysis confirmed greater incidence of overall stroke mortality in Africa 29% (23%-36%). In Africa, the burden of stroke appeared to be in unprecedented rise which cause international inequality in relative to developed nations. Contemporary reports indicated 316 per 100,000 incidence rate of stroke per year. Socio-demographic and lifestyle changes in the general population including population growth and longevity were supposed to attribute for this substantial burden [53-54]. Ironically, there is limited intervention to reduce the impact of stroke on the lives of individuals. For instance, African counties lack national strategies to stop smoking, alcohol consumption and to promote physical activity [54-55]. To date, there is no “state of the art” stroke care in African countries. Rather, the management of stroke is directed to supportive therapies. Further, diagnosis is speculative and complex due to lack of imaging modalities. Patients’ pre hospital delay precludes the timely initiation of thrombolytic therapy [56]. In contrary, low rate of crude mortality was observed in Europe (22%), America (16%), and Asia (16%). Recent advances in system and processes enable developed countries to efficiently use reperfusion therapy. Reperfusion improves outcomes by reducing the volume of brain tissue injury. Tele-stroke and mobile stroke units in the pre hospital setting have increased thrombolytic utilization and reduced delays to treatment. However, these technologies are hardly implemented in low and middle income countries despite their effectiveness [57].

30-day mortality was found to be 18% (16%-20%) in the present review. Different explanations have been forwarded for the escalated burden of mortality in stroke patients within thirty days of the stroke event. Among ischemic stroke patients, the mortality of stroke depends on the efficacy of anticoagulation and the mortality associated with intracranial hemorrhage due to the supra-therapeutic anticoagulation [58]. We can extrapolate that the 30-day mortality is not independently attributed from stroke, rather it could be secondary to the bleeding related to anticoagulation. In addition, the thirty-day mortality could be influenced by integrated system of stroke care. For instance, retrospective analysis of a large data base of Canadian stroke registry reported a significant decline of 30-day mortality to 12.7% in well-organized stroke center. However, the magnitude of 30-day mortality of stroke is expected to be significant in developing countries where advanced stroke service and nursing care is inadequate [59]. A prospective evaluation of death among Nigerian stroke patients with thirty days of ictus reported a 19.69% of mortality which is nearly a similar figure with the pooled estimate [17]. A multi-center analysis of large data of acute ischemic stroke patients in United States revealed 15.32% 30-day mortality. In United Kingdom, time-trend analysis of the general practice research stroke database indicated similar rate of mortality (15.32%) [32].

Further, the present review included 108,368 subjects from 22 articles to determine the in-hospital mortality of stroke. Accordingly, the pooled in-hospital mortality was found to be 16% (14%-19%). The frequency of in-hospital mortality was reported among different countries such Iran 20.52% [34] Sweden (15.47%) [19] and Cameroon 20.62% [30]. Even though hospital incidence facilitates the recovery of stroke patients, in the meantime, it predisposes patients for hospital acquired infections which complicate the survival of stroke patients. More importantly, the likelihood of in-hospital mortality is substantially affected by the prompt and vigilant care. In addition, the coincidence of comorbidities such as diabetes, AF and other cardiovascular disorders deteriorates the prognosis of patients admitted with stroke. Increased risk of in-hospital mortality was also noted in patients who were presented with severe form of stroke and middle cerebral artery occlusion with hemiation, basilar artery occlusion, and hemorrhagic transformation. Therefore, the contribution of in-hospital mortality for the burden of overall mortality of stroke could be minimized through delivery of pragmatic care for hospitalized stroke patients.
Our review highlighted that, hypertension was the most common precipitating factor for the onset of stroke and subsequent death. HTN accounted to a 61.9% (52.8-71.1) increase in the incidence of mortality. The occurrence of stroke on the top of elevated blood pressure is viewed as one of the hypertensive crisis encountered in emergency department. The prompt management of hypertensive emergency determines the prognosis of patients. Hemorrhagic transformation of ischemic stroke is a clinical deterioration and the most fatal scenario observed in patients who are not properly managed in critical setting. Poor outcome was noticed in hemorrhagic stroke patients due to the development of hematoma. Therefore, adequate blood pressure should be a priority so as to reduce the mortality of stroke [48, 63]. We also investigated other risk factors such as diabetes, AF and dyslipidemia as independent determinants that influence stroke outcomes. Additional studies are warranted to explore strategies to minimize the consequence of these risk factors on stroke mortality.

In general, the current review revealed that the mortality of stroke found to be more significant worldwide to the extent that it becomes a huge hassle for the global health. But, the study was not without limitations. Firstly, some of the studies included in the review showed higher level of heterogeneity and we could not detect the source of variation with the available data. However, we conducted a sensitivity analysis to avoid the ‘drowning effect’ from large sample size studies. For example, one-on-one exclusion of Margaret C et al 2014 [41] and Agarwal S et al 2015 [42] found that the overall mortality did not differ from the original overall estimates. Secondly, it should be noticed that data regarding mortality might not be comprehensive since information from grey literatures were not searched.

**Conclusions**

Overall mortality of stroke was estimated to be twenty percent. The burden of stroke mortality was prominent in Africa region. Hypertension remained to be an independent risk factor for stroke mortality. On the basis of the findings of the present review, it is recommended that the overall mortality of stroke can be minimized by establishing stroke centers that promptly deliver emergency management of stroke event. Particularly, these services should be extended in African region which represent the highest rate of mortality due to stroke. Further, blood pressure control should be given a due attention to reduce the risk of mortality secondary to cerebrovascular incidence.

**Abbreviations**

| Abbreviation | Definition |
|--------------|------------|
| AHA          | American Heart Association |
| ASA          | American Stroke Association |
| CNS          | central nervous system |
| DALYs        | Disability Adjusted Life Years |
| GBD          | Global Burden of Diseases |
| HICs         | high-income countries |
| HTN          | Hypertension |
| IS           | ischemic stroke |
| ICH          | intracerebral hemorrhage |
| LMICs        | Low- to middle-income countries |
| MOOSE:       | Meta-Analyses of Observational Studies in Epidemiology |
| SAH          | subarachnoid hemorrhage |
| STROBE       | Strengthening the Reporting of Observational Studies in Epidemiology |
| WHO          | world health organization |

**Declarations**

**Ethics approval and consent to participate**
Not applicable

**Consent to publish**
Not applicable

**Availability of data and materials**
All data are included in the main manuscript and additional files

**Competing interests**
Authors declared no conflict of interest

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Authors' Contributions

TMA conceived the study, prepared the study protocol, involve in acquisition of data, performed review, and analyze the data and write-up of the final part of the manuscript. MAS, EAG, AGM, ASB, MBA and BMG prepared the study protocol, interpret and analyzed the data and wrote the initial draft of manuscript. All the authors read, approved the final manuscript and agreed to be accountable for all aspects of the work.

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Tables
Table 1. Overview of studies included in the systematic review and meta-analysis

| Study                  | Design          | Location     | Sample size | Mean age, years, Sex(M:F) | Sex(M:F) | Overall mortality | 30-days mortality | In-hospital mortality | HTN | DM | AF | Alcohol | Smoking | H   |
|-----------------------|-----------------|--------------|-------------|---------------------------|----------|-------------------|--------------------|----------------------|-----|----|----|---------|---------|-----|
| Sanya EO et al 2015   | Prospective     | Nigeria      | 302         | 60.47 ± 13.60             | 161:133  | 64                | 64                 | 64                   | ✓   | -  | ✓ | -       | ✓       | ✓   |
| Mapoure NY et al 2014 | Prospective     | Cameroon     | 325         | 58.66 ± 13.6              | 201:124  | 87                | 87                 | 87                   | ✓   | ✓ | - | -       | -       | ✓   |
| Lekoubou A et al 2016 | Retrospective   | Cameroon     | 1688        | 62.7                      | 846:840  | 348               | 348                | 348                  | ✓   | ✓ | - | ✓       | ✓       | ✓   |
| Golestanian E et al 2009 | Retrospective | USA          | 31303       | 79.9 ± 7.6                | 11738:19563 | 10626             | 4795               | 3248                 | ✓   | ✓ | - | -       | -       | ✓   |
| Walker RW et al 2013  | Cross-sectional | Tanzania     | 130         | 68.8 ± 14.8               |          | 78                | 31                 |                      | ✓   | ✓ | - | -       | -       | ✓   |
| Gnolonfoun DD et al 2014 | Cross-sectional | Benin        | 100         | 58.42                     | 29       |                    |                    |                      | ✓   | ✓ | - | -       | -       | ✓   |
| Mathisen SM et al 2015 | Retrospective  | Norway       | 1137        | 66.8 ±14.3                | 611:526  | 589               |                    |                      | ✓   | ✓ | ✓ | -       | ✓       | ✓   |
| Loes CA et al 2013    | Prospective     | Netherlands  | 959         |                          |          | 192               | 43                 |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Atadzhanov M et al 2012 | Cross-sectional | Zambia       | 250         | 55 ±18                    | 103:147  | 101               | 101                | 101                  | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Sennay A et al 2016   | Retrospective   | Ethiopia     | 142         | 62.8 ± 15.6               | 77:65    | 17                | 17                 | 17                   | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Heikinheimo T et al 2012 | Prospective    | Malawi       | 147         | 54.2 ±16.9                | 76:71    | 59                |                    |                      | ✓   | ✓ | - | -       | -       | ✓   |
| Deresse B et al 2015  | Prospective     | Ethiopia     | 163         | 53.1 ± 16.9               | 108:55   | 24                | 24                 | 24                   | ✓   | ✓ | ✓ | -       | ✓       | ✓   |
| Ekeh B et al 2015     | Prospective     | Nigeria      | 120         | 55±15.2                   | 74:46    | 42                | 30                 |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Nura H et al 2013     | Prospective     | Nigeria      | 272         | 56.4 ± 12.7               | 168:104  | 51                | 51                 | 49                   | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Nakibuka J et al 2015 | Prospective     | Uganda       | 127         | 59±68                     | 42:42    | 23                |                    |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Ledwina et al 2013    | Retrospective   | USA          | 28143       |                          |          | 13416:14727       | 3943               | 3943                  | 2506 | ✓ | ✓ | ✓       | ✓       | ✓   |
| Armin J et al 2001    | Retrospective   | Germany      | 5017        | 65.9 ± 18.4               | 2890:2127 | 519               | 519                |                      | ✓   | ✓ | ✓ | -       | ✓       | ✓   |
| Garcia-Ptacek S et al 2017 | Retrospective  | Sweden       | 9662        | >65 years                 | 4164:5498 | 2364              | 1495               |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Margaret C et al 2014 | Cross-sectional | USA          | 1051342     |                          |          | 366065:552059     | 127129             |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Glendehart K et al 2007 | Retrospective  | Iran         | 16351       | 63.4 ± 17.2               | 8759:7592 | 3354              | 3354               |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Farhoudi M et al 2017 | Retrospective   | Iran         | 5355        | 67.6 ± 13.8               | 2708:2647 | 1099              | 1099               | 1099                 | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Wang W et al 2017     | Nationwide survey | China       | 9315        | 46.6 ±16.3                | 5120:4195 | 758               |                    |                      | ✓   | ✓ | ✓ | -       | ✓       | ✓   |
| Ying Tan Y et al 2017 | Retrospective   | China        | 913         | 65.1 ± 11.8               | 1288:625  | 121               |                    |                      | ✓   | ✓ | ✓ | -       | ✓       | ✓   |
| Freitas de Carvalho et al 2011 | Prospective study | Brazil      | 2407        | 66.86±14.38              | 1160:1247 | 503               | 503                |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Nayak AR et al 2016   | Prospective     | India        | 104         | 73±31                     | 53       |                    | 17                 |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Sylaja PN et al 2018  | Prospective     | India        | 2066        | 58.3±14.7                | 1389:678  | 163               |                    |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Agarwal S et al 2015  | Retrospective   | USA          | 775 905     | 71.65±14.47              | 357547:418358 | 43425            | 43425              |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| goldacre MJ et al 2008 | Retrospective  | England      | 586525      |                          |          | 233410:353115     | 55000              |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| Ganesha A et al 2016  | Retrospective   | Canada       | 319972      | 73.1 ± 14.3              | 158965:161007 | 46756           |                    |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| kuster GW et al 2014  | Prospective     | Brazil       | 341         | 66.8 ± 15.7              | 178:163  | 28                |                    |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
| lee S et al           | Retrospective   | UK           | 32151       | 74.6 ± 12.52             | 14359:17792 | 4926              | 4926               |                      | ✓   | ✓ | ✓ | -       | -       | ✓   |
Table 2: Pooled odds ratios of precipitating factors of mortality in Stroke patients

| Precipitating factors   | Number of studies | Events/Total (n/N) | Pooled event rate % (95% CI) | Z-value |
|-------------------------|-------------------|-------------------|------------------------------|---------|
| Hypertension            | 27 studies        | 1,159,461/2,244,341 | 61.9% (52.8-71.1)** | 13.27   |
| Diabetes                | 20 studies        | 195,612/1,106,985  | 16.6% (14.1-19.0)** | 13.30   |
| Atrial Fibrillation     | 18 studies        | 216,097/1,443,642  | 10.3% (7.9-12.8)** | 8.40    |
| Hypercholesterolemia    | 19 studies        | 420,144/1,080,155  | 20.2% (10.0-30.4)** | 3.88    |
| Alcohol                 | 12 studies        | 30,902/794,300     | 21.5% (10.4-32.6)** | 3.79    |
| Cigarette smoking       | 21 studies        | 163,130/1,196,417  | 16.3% (13.6-19.0)** | 11.85   |

**p<0.001; CI- confidence interval

Figures

Figure 1

Flow chart indicating the selection process of studies
Figure 2

The overall mortality of stroke patients
Figure 3

The thirty-day mortality of stroke patients
### Figure 4

The in-hospital mortality of stroke patients

| Study                          | ES (95% CI) | % Weight |
|-------------------------------|-------------|----------|
| Senya EO et al (2015)         | 0.21 (0.17, 0.28) | 4.31     |
| Mapoun NY et al (2014)        | 0.27 (0.22, 0.32) | 4.26     |
| Lekoubou A et al (2016)       | 0.21 (0.19, 0.23) | 4.03     |
| Golestani E et al (2009)      | 0.10 (0.10, 0.11) | 4.06     |
| Atadzhianov M et al (2012)    | 0.40 (0.35, 0.47) | 3.93     |
| Sennay A et al (2016)         | 0.12 (0.08, 0.18) | 4.12     |
| Heikinheimo T et al (2012)    | 0.22 (0.16, 0.30) | 3.75     |
| Deresse B et al (2015)        | 0.15 (0.10, 0.21) | 4.10     |
| Nura H et al (2013)           | 0.18 (0.14, 0.23) | 4.32     |
| Nakwabua K et al (2015)       | 0.18 (0.12, 0.26) | 3.76     |
| Ledneva et al (2013)          | 0.09 (0.09, 0.09) | 4.96     |
| Garcia-Placek S et al (2017)  | 0.15 (0.15, 0.18) | 4.94     |
| Ghandehar K et al (2007)      | 0.07 (0.06, 0.09) | 4.90     |
| Borham-Haghghi A et al (2015) | 0.21 (0.20, 0.21) | 4.95     |
| Farhoudi M et al (2017)       | 0.21 (0.19, 0.22) | 4.92     |
| Freitas de Carvalho J et al (2013) | 0.21 (0.19, 0.23) | 4.87     |
| Nayak AR et al (2016)         | 0.16 (0.10, 0.25) | 3.65     |
| Sylaja PN et al ( )           | 0.08 (0.07, 0.09) | 4.91     |
| Agarwal S et al (2015)        | 0.06 (0.06, 0.06) | 4.96     |
| Ganesh A et al (2016)         | 0.15 (0.14, 0.15) | 4.96     |
| Kuster GW et al (2014)        | 0.08 (0.06, 0.12) | 4.80     |
| Lee S et al (2011)            | 0.15 (0.15, 0.18) | 4.96     |
| Overall (I² = 99.91%, p = 0.00) | 0.16 (0.14, 0.19) | 100.00   |
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