Gender differences in mortality of hospitalised stroke patients. Systematic review and meta-analysis

Abdel-Rahman Abdel-Fattah a,⁎, Tiberiu A. Pana a, Toby O. Smith b, Zahra Pasdar a, Maha Aslam a, Mamas A. Mamas c, Phyo K. Myint d

a Agering Clinical and Experimental Research (ACER) Team, Institute of Applied Health Sciences, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, Aberdeen, UK
b Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
c Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, Stoke-on-Trent, UK

d Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute for Primary Care and Health Sciences, Keele University, Stoke-on-Trent, UK

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ABSTRACT

Objective: Gender differences in mortality after stroke remains unclear in the current literature. We therefore aimed to systematically review the gender differences in mortality up to five years after ischaemic (IS) or haemorrhagic stroke (HS) to address this evidence gap.

Methods: The literature was systematically searched using Ovid EMBASE, Ovid Medline, and Web of Science databases, from inception-November 2021. The quality of evidence was appraised using the CASP Cohort-study checklist. Unadjusted and adjusted odds and hazard ratios were meta-analysed, separately for IS and HS and a subgroup analysis of age-stratified mortality data was conducted.

Results: Forty-one studies were included (n = 8,128,700; mean-age 68.5 yrs; 47.1% female). 37 studies were included in meta-analysis (n = 8,808,110). Compared to men, women who had an IS had lower mortality risk in-hospital (0.94; 95%CI 0.91–0.97), at one-month (0.87; 95%CI 0.77–0.98), 12-months (0.94; 95%CI 0.91–0.98) and five-years (0.93 95%CI 0.90–0.96). The subgroup analysis showed that this gender difference in mortality was present in women ≥ 70 years up to one-month post-IS (in-hospital: 0.94; 95% CI 0.91–0.97; one-month: 0.87; 95% CI 0.77–0.98), however, in women < 70 years this difference was no longer present. Nevertheless, analysis of crude data showed women were at higher risk of mortality in-hospital, at 12-months and five-years (in-hospital: 1.05; 95%CI 1.03–1.07, 12-months: 1.10; 95%CI 1.06–1.14, five-years: 1.06; 95% CI 1.02–1.10). After HS, women had higher mortality risk in-hospital (1.03; 95%CI 1.01–1.04) however, no gender differences were found post-discharge.

Conclusion: The gender differences in post-stroke mortality differ by stroke type, age group and follow-up. Crude stroke mortality in women is higher than in men and this appears to be driven by pre-existing comorbidities. In adjusted models, women have a lower mortality risk following IS, independent of duration of follow-up. After HS, women had higher mortality in hospital however, no gender differences after hospital discharge were found.

1. Introduction

There is a growing emphasis on understanding the epidemiology of gender differences in outcomes following a stroke. Stroke remains a worldwide public health concern and is now recognised as the leading cause of long-term disability [1]. Women have higher incidence of stroke than men as well as worse stroke outcomes, which may be attributed to poorer pre-stroke function, older age, and higher prevalence of atrial fibrillation (AF) [2]. More recent literature has emphasised the major influence of confounders such as age, prevalence of AF and poorer premorbid status suggesting that women are less likely to die after a stroke compared to men after adjusting for confounders [3, 4]. This is not uniformly observed across the geographical regions or ethnicities, with two large observational studies form North America suggesting that no gender differences exist in stroke mortality regardless of follow-up time-period [4,50,51]. In contrast, some studies from

⁎ Correspondence to: School of Medicine, Medical Sciences and Nutrition, Rooms 1.129/1.130, West Block, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK.
E-mail address: a.abdelfattah.17@abdn.ac.uk (A.-R. Abdel-Fattah).

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South East Asia and the Indian subcontinent reported higher stroke mortality in women compared to men [3,52,53].

Understanding the gender differences in stroke mortality is of paramount importance to epidemiologists, clinicians and healthcare industries as this understanding may form the basis for the development of gender-specific stroke prevention and management. As a result, this would improve outcomes of stroke in women and reduce its dominant burden on disability-adjusted-life-years (DALYs) worldwide.

We aimed to undertake a systematic review and meta-analysis to assess the gender differences in stroke-type specific mortality at multiple time points from admission through hospital discharge to five-years follow up. We also carried out an exploratory subgroup analysis stratified by age group (mean age <70 years and ≥70 years) to investigate whether age influences gender differences in stroke mortality.

2. Methods

A systematic review and meta-analysis of RCTs was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidance [5].

2.1. Search strategy

Two authors selected studies reporting gender differences in mortality of hospitalised stroke patients by independently carrying out a literature search of the following databases: Ovid MEDLINE, Ovid EMBASE and Web of Science, from inception to November 2021. Detailed search strategy is shown in Supplementary File 1. The articles searched were confined to English-language only. A manual search of reference lists of relevant reviews and their included studies was also performed.

2.2. Eligibility and study selection

The inclusion criteria for the studies included observational studies in English with adult participants > 18 years hospitalised due to stroke. Studies which stratified their data by stroke type (IS or HS) were analysed. Strokes of unspecified type (SUT) were also pooled for meta-analysis. Studies which stratified their data by stroke type (IS or HS) were analysed. Unadjusted and adjusted odds, hazard and risk ratios for in-hospital, one-month, 12-months and five-years mortality were pooled using the generic inverse variance method using fixed-effects model in RevMan 5.4 software. Study heterogeneity was assessed by evaluating the population characteristics and observed value of I², to determine which studies were appropriate to pool. Data with sufficient homogeneity were included in the meta-analysis. The primary outcome was risk of mortality in women compared to men as the baseline after IS, HS or SUT. The outcome of interest was assessed at the following follow-up time periods: in-hospital, up to one month, up to 12-months and up to five-years. Due to heterogeneity in risk reporting; odds ratio (OR), hazard ratio (HR) and risk ratios (RR) were all meta-analysed together and results expressed as ‘risk’, since mortality is a rare event. Descriptive and analytical epidemiological findings were synthesised from separate analyses of unadjusted (crude) and adjusted data, respectively. Whenever studies reported more than one result within an individual time bracket (e.g. three months and six months data) priority was given to the longer-term follow up (e.g. six months).

Mortality data for women and men stratified by age were collated where available to facilitate for an exploratory subgroup analysis stratified by age group. Mean age of study cohort was used where age-stratified data was not available. The age brackets: < 70 years and ≥ 70 years, were chosen based on literature suggesting that elderly patients over 70 years have a different aetiology and epidemiology of stroke mortality [53].

3. Results

3.1. Search results

Forty-one studies were included in the systematic review (N = 8,128,700; mean age 68.5 years; 47.1% female) and 36 studies were deemed appropriate for meta-analysis (n = 8,008,110). The PRISMA flowchart can be found in Supplementary Fig. 1. Justification for exclusion of papers (n = 4) is detailed in Supplementary Table 2.

3.2. Characteristics of included studies

The characteristics of the included studies are presented in Table 1.

| Papers (N = 41) | Population (N = 8,128,700) | % female | Mean female age (years) | Mean male age (yrs) | Region | Time points of mortality | Co-morbidities |
|----------------|-----------------------------|----------|-------------------------|---------------------|--------|--------------------------|---------------|
| Bonkoff, 2021  | 761,106                     | 48.0     | 75.3                    | 69.4                | Germany| In-hospital mortality    | Age, diabetes mellitus (DM), hypertension (HTN), atrial fibrillation (AF), ischaemic heart disease (IHD), previous stroke, hypercholesterolaemia (HL), stroke severity using NIHSS scale and pre-stroke functional status |
| Eriksson, 2021 | 335,183                     | 48.3     | 78.1                    | 73.3                | Sweden | 7, 28 and 90 days       | Age, DM, smoking, HTN, AF, previous stroke |
| Irie, 2021     | 17,956                      | 41.3     | n/a                     | n/a                 | Japan  | 30 days                  | Age and stroke severity |

(continued on next page)
Table 1 (continued)

| Papers (N = 41) | Population (N = 8 128,700) | % female (Mean – 47.1) | Mean female age (years) (Mean – 68.7 yrs) | Mean male age (yrs) (Mean – 68.2 yrs) | Region | Time points for mortality | Co-morbidities |
|-----------------|----------------------------|------------------------|-------------------------------------------|-------------------------------------|--------|--------------------------|----------------|
| Phan, 2021      | 9441                       | 46.0                   | 78.8                                      | 72.0                                | Australasia | 1 year                  | Age, stroke severity. Co-morbidities: dementia, HTN, smoking, HL, AF, HF, renal disease, liver disease, COPD, DM and cancer |
| Uchida, 2019    | 2399                       | 45.3                   | 79.7                                      | 72.8                                | Japan       | 90 days                  | Age, past and current smoker, HTN, DM, AF, history of stroke, pre-modified Rankin scale (mRS), baseline NIHSS score, baseline blood glucose, baseline LDL cholesterol and baseline creatinine |
| Weber, 2019     | 1,112,570                  | 48.9                   | 74.0                                      | 74.0                                | Germany     | In-hospital mortality    | Not stated |
| James, 2017     | 192,826                    | 48.9                   | 75                                        | 67                                  | USA and Canada | In-hospital mortality | Race, AF, transient ischaemic attack (TIA) or stroke, coronary artery disease (CAD), myocardial infarction (MI), carotid stenosis, DM, HTN, peripheral vascular disease (PVD), dyslipidemia, smoking, international normalized ratio (INR), glucose, systolic blood pressure (SBP), creatinine, prior anti-platelet and/or anti-coagulant use, region, number of beds and hospital type, annual intracerebral haemorrhage (ICH) volume, rural location, The Joint Commission Primary Stroke Center Status |
| Mapoure, 2017   | 818                        | 44.4                   | 62.3                                      | 58.4                                | Cameroon     | In-hospital mortality    | AF, DM, stroke history |
| Ong, 2017       | 4278                       | 41.1                   | 72.2                                      | 69.9                                | Taiwan       | In-hospital mortality    | AF, DM, stroke history |
| Renoux, 2017    | 2553                       | 50.6                   | 76.5                                      | 71.4                                | United Kingdom | 1 year                  | Age, HTN, DM, angina, MI, PVD, CHF, prior TIA/stroke, HL, VHD, cancer, VTE, dementia, current and past smokers and migraine |
| Xing, 2017      | 1325                       | 32.3                   | 63.1                                      | 59.1                                | China        | 3, 12 and 36 months      | HTN, AF, DM, stroke history |
| Hsieh, 2016     | 1196                       | 42.5                   | 66.3                                      | 62.2                                | Singapore    | 30 days                  | HTN, DM, HL |
| Dehlendorff, 2015 | 79,617                  | 47.2                   | 74.4                                      | 69.5                                | Denmark      | 7 and 30 days            | HTN, AF, DM, stroke and alcohol history and intermittent arterial claudication |
| Li, 2015        | 810                        | 44                      | > 75                                      | > 75                                | China        | 12 and 36 months         | Age, stroke type, HTN, AF, DM, dyslipidemia, stroke history, anaemia, HF, rehabilitation, chronic kidney disease (CKD) |
| Talebi, 2014    | 341                        | 56.0                   | 69.9                                      | 67.7                                | Iran         | 7 days                   | HTN, DM, HL, IHD |
| Zhou, 2014      | 615                        | 35.8                   | 63.5                                      | 62.7                                | China        | 3, 6 and 12 months       | HTN, AF, HL |
| Denti, 2013     | 1993                       | 49.5                   | 76.9                                      | 71.4                                | Italy        | 1 month                  | Age, stroke severity and premorbid disability |
| Ganti, 2013     | 245                        | 51                      | 77                                        | 69                                  | Worldwide    | 7 days                   | HTN, AF, DM, stroke and alcohol history |
| Koton, 2013     | 5034                       | 45.4                   | 73.3                                      | 68.7                                | Israel       | In-hospital mortality and 3 months | Age, prior disability, modified Rankin Scale, NIHSS score, prior stroke, CHD, previous acute coronary syndrome (ACS) or HF, HTN, DM, HL, AF, Dyslipidemia, IHD, cancer, PAD and smoking |
| Santalucia, 2013 | 367                       | 48.2                   | 77.2                                      | 72.3                                | Italy        | In-hospital mortality    | AF, HTN, dyslipidemia, DM, obesity, TIA, AF |
| Lewsey, 2012    | 157,639                    | 55                      | 74                                        | 69                                  | Scotland     | 30 days                  | Admission and socioeconomic deprivation. Co-morbidities: DM, cancer, respiratory disease, HF, PVD, AF, HTN, renal failure, CAD, rheumatic/ valvar heart disease, venous thromboembolism (VTE), depression, parkinsonism, dementia, falls and fractures and alcohol misuse. |
| Park, 2012      | 6635                       | 42.7                   | 70                                        | 64                                  | Korea        | In-hospital mortality    | HTN, previous IHD and previous stroke |
| Olsen, 2012     | 26,818                     | 48.5                   | 73.9                                      | 68.9                                | Denmark      | 3 months                 | HTN, AF, DM, stroke and alcohol history and intermittent arterial claudication |
| Watila, 2012    | 91                         | 33.0                   | 55.6                                      | 56.2                                | Nigeria      | 30 days                  | HTN, AF, DM and Human immunodeficiency virus (HIV) infection |
| Wu, 2012        | 103,689                    | 46.7                   | 73.4                                      | 68.8                                | Hong Kong    | 30 days                  | Age, year of hospitalisation |
| DeVries, 2011   | 15,806                     | 51.6                   | 75                                        | 75                                  | USA          | 30 days                  | AF, HF, CKD and anaemia |
| Ovbiagile, 2011 | 2,553,742                  | > 84                    | 80.3                                      | 77.6                                | USA          | Age, race, ethnicity, hospital region and location, stroke type and number of major procedures. Co-morbidities: HF, AUTS, DM, race, education and smoking |

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The mean age in women was 75.3 years and 69.4 years in men. Sample populations of the included studies were from various regions worldwide including Germany [3,6], Sweden [7], Denmark [8–14], Japan [4,15], Australia [16], North America [17], United States [18–20], Canada [21], Cameroon [22], Taiwan [23], China [24–26], Hong Kong [27], Singapore [28], Iran [29], Italy [30,31], Israel [32], Scotland [33], United Kingdom [34], Korea [35,36], Nigeria [37], Spain [38], Poland [39], Palestine [40], Netherlands [41], Greece [42], Di Carlo Europe [43] and worldwide [44].

### 3.3. Quality appraisal

Forty studies were analysed using the CASP cohort study tool (Table 2). One study had no full-text available therefore quality appraisal was not feasible [4]. All studies clearly addressed a research question (100%). Thirty-seven studies recruited the study cohort appropriately (92.5%), although only 34 studies measured mortality accurately (85%). Confounding was a major limitation as 30 studies identified confounders poorly (75%). One study did not have any access to information on confounding [6]. Data reported were overall precise in 34 studies (85%), however attrition bias may have been introduced due to incomplete follow-up data in 13 studies (32.5%).

### 3.4. Results of meta-analysis

#### 3.4.1. Ischaemic stroke (IS)

Fifteen studies reported data on IS-specific mortality between women and men. Compared to men, analysis of adjusted data (Table 3) showed that women had lower mortality risk after IS at all time points, from in-hospital (Risk 0.94; 95% CI 0.91–0.97, n = 793,976) to one month (Risk 0.87; 95% CI 0.77–0.98, n = 20,040), 12 months (Risk 0.94; 95% CI 0.91–0.98, n = 63,255) and five years (Risk 0.93 95% CI 0.90–0.96, n = 31,485) (Fig. 1).

When analysing crude data, women were at a higher risk of in-hospital mortality (Risk 1.05; 95% CI 1.03–1.07, n = 903,223), up to 12 months (Risk 1.10; 95% CI 1.06–1.14, n = 81,889) and up to five years (Risk 1.06; 95% CI 1.02–1.10, n=50 119). In the immediate period after discharge and up to one-month post-IS, there was no gender difference in risk of mortality (Risk 1.12; 95% CI 0.98–1.27, n = 23,161).

Data from the subgroup analysis (Table 3) showed no gender difference in mortality in of women < 70 years after IS up to one-month from onset of stroke (in hospital, Risk 1.05; 0.69–1.60, n = 25,269; one month, Risk 1.41; 0.70–2.68, n = 91), however, women ≥ 70 years had lower mortality risk compared to men (in hospital, Risk 0.94; 0.91–0.97, n = 768,707; one month, Risk 0.87; 0.77–0.98, n = 19,949).

### Table 1 (continued)

| Papers (N = 41) | Population (N = 8 128,700) | % female (Mean) | Mean female age (years) | Mean male age (years) | Region | Time points for mortality | Co-morbidities |
|-----------------|-----------------------------|-----------------|------------------------|----------------------|--------|--------------------------|---------------|
| Towfighi, 2011  | 2,537,997                   | 47.5            | 35.64 (no mean stated) | 35.64 (no mean stated) | USA    | In-hospital mortality (2005–2006) | MI, chronic pulmonary disease, cerebrovascular disease, hemiplegia, paraplegia, dementia, DM, malignancy, metastatic solid tumour, liver disease, peptic ulcer disease, PVD, renal disease and acquired immune deficiency syndrome (AIDS) |
| Martinez-Sanchez, 2010 | 310                       | 41.3            | 41.1                   | 42.1                 | Spain  | In-hospital mortality | Migraine, HTN, HL |
| Olsen, 2010     | 40,155                      | 48.1            | 74.5                   | 69.7                 | Denmark| 1 week, 1 and 3 months, 1 year | HTN and cardiovascular risk factors |
| Wiszniewska, 2010 | 2534                      | 54.4            | 74.3                   | 68.8                 | Poland | 30 days | HTN, HF, AF, TIA, CAD, DM and alcohol abuse |
| Oh, 2009        | 18,634                      | 43.4            | 68.4                   | 63.4                 | Korea  | 25 months | Age, civil status, type of residence, stroke severity, AF, HTN, DM, intermittent claudication, Charlson comorbidity index score, smoking, and alcohol intake and hospital department. |
| Palnum, 2009    | 29,549                      | 63.1            | > 80                   | > 80                 | Denmark| 30 and 90 days | HTN, HF, AF, DM, stroke and alcohol history, smoking, intermittent claudication, and previous stroke |
| Olsen, 2009     | 25,607                      | 45.3            | 72.6                   | 68.5                 | Denmark| 1 week | Hypertension, diabetes, congestive heart failure, atrial fibrillation, ischaemic heart disease, smoking, recurrent stroke attack, chronic kidney disease, obesity |
| Swileh, 2009    | 186                         | 51.1            | 68.7                   | 69.5                 | Palestine | In-hospital mortality | Alcohol, smoking, diabetes, HTN, AF, Intermittent arterial claudication |
| Vaartjes, 2009  | 30,675                      | 51.9            | 72.9                   | 69.3                 | Netherlands| 1 and 5 years | HTN, IHD, AF, other disabling disease |
| Olsen, 2007     | 39,484                      | 48.0            | 75.3                   | 70.3                 | Denmark| 7, 30, 90, 150 days | Age, Charlson comorbidity index score (of comorbidities), level of consciousness, stroke type, CNS score, hospital consent rate, marital status and living situation. |
| Andersen, 2005  | 999                         | 56.0            | 77.0                   | 70.9                 | Denmark| 1, 5 and 10 years | Comorbidities: previous stroke, DM, HT, smoking, HL, AF, MI, Dementia |
| Kapral, 2004    | 3323                        | 46.0            | 73                     | 69                   | Canada  | In-hospital and 6 months | HTN, AF, DM |
| Di Carlo, 2003  | 4,499                       | 50.2            | 74.5                   | 69.2                 | Europe  | 48 h and 3 months | Age, smoker, HT, HL, alcohol, DM, TIA, AF, MI, angina, CHF and VHD |
| Venmos, 2000    | 555                         | 44.4            | 76.1                   | 75.1                 | Greece  | 1 year | **Note:** No data provided in original article.
Table 2
CASP quality assessment tool.

| Question assessed (Success rate) | De Carlo, 2009 | Olsen, 2010 | Denis, 2013 | Sundquist, 2013 | Anderson, 2005 | Davies, 2013 | Olsen, 2012 | Michalski, 2004 | Teng, 2004 | Watilla, 2012 | Olsen, 2008 | Oh, 2009 | Vanrell, 2009 | Sanchez, 2010 | Wu, 2011 | Jannsens, 2012 | Lawley, 2012 | Polham, 2009 | Yannos, 2009 | Eriksson, 2021 |
|---------------------------------|---------------|-------------|-------------|----------------|---------------|--------------|-------------|----------------|------------|-------------|-------------|--------|--------------|--------------|---------|----------------|---------|--------------|-------------|----------------|
| 1. Did the study address a clearly focused issue? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 2. Was the cohort recruited in an acceptable way? (92.5%) | Y | Y | Y | N | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 3. Was the exposure accurately measured to minimise bias? (85%) | Y | Y | Y | N | Y | N | Y | Y | Y | Y | N | Y | Y | Y | Y | N | Y | Y | Y | Y | N | Y | Y |
| 4. Was the outcome accurately measured to minimise bias? (100%) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 5a. Have the authors identified all important confounding factors? (25%) | N | N | N | N | N | N | N | N | N | N | N | Y | N | Y | N | Y | N | Y | N | Y | N | Y | N |
| b. Have they taken account of the confounding factors in the design and/or analysis? (47.5%) | Y | Y | Y | N | N | N | Y | N | Y | N | N | Y | N | Y | N | Y | N | Y | N | Y | N | Y | N |
| 6a. Was the follow up of subjects complete enough? (67.5%) | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y |
| b. Was the follow up of subjects long enough? (70%) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y |
| 7. Are the results clearly presented? (97.5%) (clearly presented – Y/N) | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| 8. Are the results precise? (85%) | N | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y |
| 9. Can the results be applied to the general population? (80%) | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Total (/11): | 9 | 10 | 10 | 4 | 8 | 8 | 10 | 9 | 9 | 8 | 10 | 9 | 8 | 10 | 8 | 9 | 8 | 9 | 7 | 9 |

*Y=1 and N=0
No adjusted data were available beyond one-month post-IS. Crude data showed that women < 70 years were at higher risk of mortality post-IS up to five years after stroke (in hospital, Risk 1.22; 1.03–1.45, n = 25,269; 12 months Risk 1.11; 1.01–1.21, n = 49, 309; five years, Risk 1.07; 1.00–1.15, n = 49,309). However, apart from the in-hospital period, there was no difference in women ≥ 70 years, compared to men, in mortality up to five years after IS.

3.6. Haemorrhagic stroke (HS)

Six studies reported data on HS-specific mortality between women and men. The analysis of data adjusted for confounding variables (detailed in Supplementary Table 1) showed that women had higher risk of mortality in hospital (Risk 1.03; 95% CI 1.01–1.04, n = 192,826) yet no difference was found after discharge and up to five years following discharge. Data from meta-analysis of unadjusted estimates yielded a similar result (in-hospital: Risk 1.04; 95% CI 1.03–1.05, n = 192,826) (Fig. 2).

Data from the subgroup analysis were consistent with adjusted and crude results from the primary analyses. The data show that there was no gender difference in mortality after HS in both the < 70 years and ≥ 70 years groups. No in-hospital data were available for HS patients to compare with the primary analysis findings.

3.6. Stroke of unspecified type (SUT)

Seventeen studies reported on mortality after stroke without specifying stroke type. Analysis of adjusted data (Table 3) showed higher mortality risk in women during the in-hospital period (Risk 1.02; 95% CI 1.00–1.04, n = 5,254,065), however, lower risk after one-month (up to 12-months) (Risk 0.95; 95% CI 0.90–0.99, n = 120,145) post-SUT (Fig. 3). No gender difference was found in the first month after discharge (Risk 0.98; 95% CI: 0.94–1.04, n = 202,992).

On the other hand, meta-analysis of crude data showed no gender difference in risk of mortality was found in-hospital (Risk 0.98; 95% CI 0.95–1.01, n = 5,120,945), however, higher mortality risk up to one-month (Risk 1.11; 95% CI 1.06–1.15, n = 114,647) and 12-months post-SUT (Risk 1.11; 95% CI 1.06–1.15, n = 114,647). and 12-months post-SUT (Risk 1.11; 95% CI 1.06–1.15, n = 114,647).

Results from the subgroup analysis of patients after SUT were consistent with the primary analysis for subjects ≥ 70 years. Compared to men, women in this group had higher mortality in-hospital (Risk 1.03; 1.01–1.05, n = 202,994) however, lower mortality after one-month post-SUT (Risk 0.95; 0.90–0.99, n = 79,029). In women < 70 years, there was no difference in mortality from stroke onset through to 12-months. No adjusted data were available beyond 12-months follow-up post-SUT.

Crude data showed no gender difference after SUT in the < 70 years age group. On the other hand, consistent with the primary analysis,
**A) In-hospital mortality**

![Forest plots of meta-analysis and subgroup analysis results for mortality in women, compared to men, after ischaemic stroke (IS); Risk and corresponding 95% confidence intervals (CI) reported.](image)

*IS = Ischaemic stroke*
B) Mortality up to one-month

| Study or Subgroup | log[Risk Ratio] | SE | Weight | Risk Ratio IV, Fixed, 95% CI | Risk Ratio IV, Fixed, 95% CI |
|-------------------|----------------|----|--------|----------------------------|----------------------------|
| 23.1.1 Up-to-1mth post-Is (Unadjusted) | | | | | |
| Denti, 2013 | 0.06069784 | 0.16836735 | 3.6% | 1.06 [0.76, 1.48] | |
| Oh, 2009 | 0.12839927 | 0.07806122 | 16.8% | 1.14 [0.98, 1.32] | |
| Wiszniewska, 2010 | 0.07918125 | 0.19642857 | 2.7% | 1.08 [0.74, 1.59] | |
| Subtotal (95% CI) | | | 23.1% | 1.12 [0.98, 1.27] | |
| Heterogeneity: Chi² = 3.16, df = 2 (P = 0.21); I² = 0% | |
| Test for overall effect: Z = 1.68 (P = 0.09) | |
| 23.1.2 <70 years (Unadjusted) | | | | | |
| Oh, 2009 | 0.12839927 | 0.07806122 | 16.8% | 1.14 [0.98, 1.32] | |
| Subtotal (95% CI) | | | 16.8% | 1.14 [0.98, 1.32] | |
| Heterogeneity: Not applicable | |
| Test for overall effect: Z = 1.64 (P = 0.10) | |
| 23.1.3 ≥70 years (Unadjusted) | | | | | |
| Denti, 2013 | 0.06069784 | 0.16836735 | 3.6% | 1.06 [0.76, 1.48] | |
| Wiszniewska, 2010 | 0.07918125 | 0.19642857 | 2.7% | 1.08 [0.74, 1.59] | |
| Subtotal (95% CI) | | | 6.3% | 1.07 [0.83, 1.38] | |
| Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0% | |
| Test for overall effect: Z = 0.54 (P = 0.59) | |
| 23.1.4 Up-to-1mth post-Is (Adjusted) | | | | | |
| Denti, 2013 | -0.18708664 | 0.10459184 | 9.4% | 0.83 [0.68, 1.02] | |
| Irie, 2021 | -0.11918641 | 0.07653061 | 17.5% | 0.89 [0.76, 1.03] | |
| Wattia, 2012 | 0.34044411 | 1.50510204 | 0.0% | 1.00 [0.07, 26.85] | |
| Subtotal (95% CI) | | | 26.9% | 0.87 [0.77, 0.98] | |
| Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0% | |
| Test for overall effect: Z = 2.30 (P = 0.02) | |
| 23.1.5 <70 years (Adjusted) | | | | | |
| Wattia, 2012 | 0.34044411 | 1.50510204 | 0.0% | 1.00 [0.07, 26.85] | |
| Subtotal (95% CI) | | | 0.0% | 1.00 [0.07, 26.85] | |
| Heterogeneity: Not applicable | |
| Test for overall effect: Z = 0.23 (P = 0.82) | |
| 23.1.6 ≥70 years (Adjusted) | | | | | |
| Denti, 2013 | -0.18708664 | 0.10459184 | 9.4% | 0.83 [0.68, 1.02] | |
| Irie, 2021 | -0.11918641 | 0.07653061 | 17.5% | 0.89 [0.76, 1.03] | |
| Subtotal (95% CI) | | | 26.9% | 0.87 [0.77, 0.98] | |
| Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0% | |
| Test for overall effect: Z = 2.31 (P = 0.02) | |
| Total (95% CI) | | | 100.0% | 0.98 [0.92, 1.04] | |
| Heterogeneity: Chi² = 16.75, df = 11 (P = 0.12); I² = 34% | |
| Test for overall effect: Z = 0.77 (P = 0.44) | |
| Test for subgroup differences: Chi² = 15.93, df = 5 (P = 0.007), I² = 68.6% | |

*IS= Ischaemic stroke

Fig. 1. (continued).
### C) Mortality up to 12-months

| Study or Subgroup | log[Risk Ratio] | SE | Weight | Risk Ratio (IV, Fixed, 95% CI) | Risk Ratio (IV, Fixed, 95% CI) |
|-------------------|----------------|----|--------|-------------------------------|-------------------------------|
| **24.1.1 Up-to-12mths post-IS (Unadjusted)** | | | | | |
| Li, 2015 | 0.49831055 | 1.48979592 | 0.0% | 1.65 [0.09, 30.52] |  |
| Oh, 2009 | 0.10788803 | 0.04745918 | 4.9% | 1.11 [1.01, 1.22] |  |
| Olsen, 2012 | 0.15745677 | 0.04081633 | 6.7% | 1.17 [1.08, 1.27] |  |
| Renoux, 2017 | 0.12057393 | 0.07908163 | 1.8% | 1.13 [0.97, 1.32] |  |
| Uchida, 2019 | 0.10720997 | 0.16836735 | 4.0% | 1.11 [0.80, 1.55] |  |
| Vaartjes, 2009 | 0.06069784 | 0.0255102 | 17.1% | 1.06 [1.01, 1.12] |  |
| **Subtotal (95% CI)** | | | | | 30.8% 1.10 [1.06, 1.14] |
| **Heterogeneity:** $\chi^2 = 4.40$, df = 5 ($P = 0.49$); $I^2 = 0\%$ | | | | | Test for overall effect: $Z = 4.91$ ($P < 0.00001$) |
| **24.1.2 <70 years (Unadjusted)** | | | | | |
| Oh, 2009 | 0.10788803 | 0.04745918 | 4.9% | 1.11 [1.01, 1.22] |  |
| Vaartjes, 2009 | 0.05690485 | 0.13010204 | 0.7% | 1.06 [0.82, 1.37] |  |
| **Subtotal (95% CI)** | | | | | 5.6% 1.11 [1.01, 1.21] |
| **Heterogeneity:** $\chi^2 = 0.14$, df = 1 ($P = 0.71$); $I^2 = 0\%$ | | | | | Test for overall effect: $Z = 2.29$ ($P = 0.02$) |
| **24.1.3 ≥70 years (Unadjusted)** | | | | | |
| Li, 2015 | 0.49831055 | 1.48979592 | 0.0% | 1.65 [0.09, 30.52] |  |
| Olsen, 2012 | 0.15745677 | 0.04081633 | 6.7% | 1.17 [1.08, 1.27] |  |
| Renoux, 2017 | 0.12057393 | 0.07908163 | 1.8% | 1.13 [0.97, 1.32] |  |
| Uchida, 2019 | 0.10720997 | 0.16836735 | 4.0% | 1.11 [0.80, 1.55] |  |
| Vaartjes, 2009 | -0.026872 | 0.022959 | 21.1% | 0.97 [0.93, 1.02] |  |
| **Subtotal (95% CI)** | | | | | 29.9% 1.03 [0.99, 1.06] |
| **Heterogeneity:** $\chi^2 = 17.44$, df = 4 ($P = 0.002$); $I^2 = 77\%$ | | | | | Test for overall effect: $Z = 1.29$ ($P = 0.20$) |
| **24.1.4 Up-to-12mths post-IS (Adjusted)** | | | | | |
| Li, 2015 | 0.50105926 | 1.5255102 | 0.0% | 1.65 [0.08, 32.82] |  |
| Olsen, 2012 | -0.05517133 | 0.06377551 | 2.7% | 0.95 [0.83, 1.07] |  |
| Renoux, 2017 | -0.08618615 | 0.05612245 | 3.5% | 0.92 [0.82, 1.02] |  |
| Uchida, 2019 | -0.1079054 | 0.11967976 | 0.8% | 0.90 [0.71, 1.14] |  |
| Vaartjes, 2009 | -0.05517133 | 0.02040816 | 26.7% | 0.95 [0.91, 0.98] |  |
| **Subtotal (95% CI)** | | | | | 33.7% 0.94 [0.91, 0.98] |
| **Heterogeneity:** $\chi^2 = 0.57$, df = 4 ($P = 0.97$); $I^2 = 0\%$ | | | | | Test for overall effect: $Z = 3.30$ ($P = 0.0010$) |
| **Total (95% CI)** | | | | | 100.0% 1.02 [1.00, 1.04] |
| **Heterogeneity:** $\chi^2 = 60.20$, df = 17 ($P < 0.00001$); $I^2 = 72\%$ | | | | | Test for overall effect: $Z = 2.06$ ($P = 0.04$) |
| **Test for subgroup differences:** $\chi^2 = 37.66$, df = 3 ($P < 0.00001$); $I^2 = 92.0\%$ | | | | | |

*IS= Ischaemic stroke

Fig. 1. (continued).
D) Mortality up to five-years

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Fixed, 95% CI | Risk Ratio IV, Fixed, 95% CI |
|-------------------|----------------|----|--------|----------------------------|----------------------------|
| 26.1.1 Up-to-Syr5 post-IS (Unadjusted) | | | | | |
| Li, 2015 | 0.54654266 | 2.18367347 | 0.0% | 1.73 [0.02, 124.77] | |
| Oh, 2009 | 0.07954301 | 0.03979592 | 4.5% | 1.08 [1.00, 1.17] | |
| Vaartjes, 2009 | 0.0307844 | 0.02040816 | 16.9% | 1.05 [1.01, 1.10] | |
| Subtotal (95% CI) | | | 21.4% | 1.06 [1.02, 1.10] | |
| Heterogeneity: Chi² = 0.40, df = 2 (P = 0.82); I² = 0% | | | | | |
| Test for overall effect: Z = 3.23 (P = 0.001) | | | | | |
| 26.1.2 <70 years (Unadjusted) | | | | | |
| Oh, 2009 | 0.07954301 | 0.03979592 | 4.5% | 1.08 [1.00, 1.17] | |
| Vaartjes, 2009 | 0.00432137 | 0.1071428 | 0.6% | 1.00 [0.81, 1.24] | |
| Subtotal (95% CI) | | | 5.1% | 1.07 [1.00, 1.15] | |
| Heterogeneity: Chi² = 0.43, df = 1 (P = 0.51); I² = 0% | | | | | |
| Test for overall effect: Z = 1.89 (P = 0.06) | | | | | |
| 26.1.3 ≥70 years (Unadjusted) | | | | | |
| Li, 2015 | 0.54654266 | 2.18367347 | 0.0% | 1.73 [0.02, 124.77] | |
| Vaartjes, 2009 | -0.0177287 | 0.0127551 | 43.4% | 0.98 [0.96, 1.01] | |
| Subtotal (95% CI) | | | 43.4% | 0.98 [0.96, 1.01] | |
| Heterogeneity: Chi² = 0.07, df = 1 (P = 0.80); I² = 0% | | | | | |
| Test for overall effect: Z = 1.39 (P = 0.17) | | | | | |
| 26.1.4 Up-to-Syr5 post-IS (Adjusted) | | | | | |
| Li, 2015 | 0.53147892 | 2.19387755 | 0.0% | 1.70 [0.02, 125.39] | |
| Vaartjes, 2009 | -0.07058107 | 0.01530612 | 30.1% | 0.91 [0.90, 0.96] | |
| Subtotal (95% CI) | | | 30.1% | 0.93 [0.90, 0.96] | |
| Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0% | | | | | |
| Test for overall effect: Z = 4.61 (P < 0.00001) | | | | | |
| Total (95% CI) | | | 100.0% | 0.99 [0.97, 1.00] | |
| Heterogeneity: Chi² = 35.81, df = 8 (P < 0.0001); I² = 78% | | | | | |
| Test for overall effect: Z = 1.53 (P = 0.13) | | | | | |
| Test for subgroup differences: Chi² = 34.83, df = 3 (P < 0.00001), I² = 91.4% | | | | | |

*IS= Ischaemic stroke

Fig. 1. (continued).
A) In-hospital mortality

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Fixed, 95% CI | Risk Ratio IV, Fixed, 95% CI |
|-------------------|----------------|----|--------|-----------------------------|-----------------------------|
| 27.1.1 In-hospital mortality post-HS (Unadjusted) | | | | | |
| James, 2017       | 0.04099769 | 0.00633775 | 53.8% | 1.04 [1.03, 1.05] | |
| Subtotal (95% CI) | | | | | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 6.43 (P < 0.00001) |
| 27.1.2 In-hospital mortality post-HS (Adjusted) | | | | | |
| James, 2017       | 0.02694163 | 0.00688776 | 46.2% | 1.03 [1.01, 1.04] | |
| Subtotal (95% CI) | | | | | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 3.91 (P < 0.00001) |
| Total (95% CI)    | 100.0%     | 1.04 [1.03, 1.04] | |
| Heterogeneity: Chi² = 2.24, df = 1 (P = 0.13); I² = 55% |
| Test for overall effect: Z = 7.37 (P < 0.00001) |
| Test for subgroup differences: Chi² = 2.24, df = 1 (P = 0.13), I² = 55.4% |

*HS= Haemorrhagic stroke

**Results available from one study only; James et al., 2017.

B) Mortality up to one-month

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Fixed, 95% CI | Risk Ratio IV, Fixed, 95% CI |
|-------------------|----------------|----|--------|-----------------------------|-----------------------------|
| 28.1.1 Up to 1-month post-HS (Unadjusted) | | | | | |
| Ganti, 2013       | 0.26481782 | 0.5892857 | 2.3% | 1.30 [0.41, 4.14] | |
| Hsieh, 2016       | 0.07554696 | 0.15561224 | 32.7% | 1.08 [0.79, 1.46] | |
| Subtotal (95% CI) | | | | | |
| Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0% |
| Test for overall effect: Z = 0.58 (P = 0.56) |
| 28.1.2 <70 years (Unadjusted) | | | | | |
| Hsieh, 2016       | 0.07554696 | 0.15561224 | 32.7% | 1.08 [0.79, 1.46] | |
| Subtotal (95% CI) | | | | | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.49 (P = 0.63) |
| 28.1.3 >70 years (Unadjusted) | | | | | |
| Ganti, 2013       | 0.26481782 | 0.5892857 | 2.3% | 1.30 [0.41, 4.14] | |
| Subtotal (95% CI) | | | | | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.45 (P = 0.65) |
| 28.1.4 Up to 1-month post-HS (Adjusted) | | | | | |
| Ganti, 2013       | 0.48144263 | 1.67091837 | 0.3% | 1.62 [0.06, 42.79] | |
| Hsieh, 2016       | 0.09287537 | 0.23214857 | 14.7% | 1.09 [0.69, 1.71] | |
| Subtotal (95% CI) | | | | | |
| Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0% |
| Test for overall effect: Z = 0.39 (P = 0.69) |
| 28.1.5 <70 years (Adjusted) | | | | | |
| Hsieh, 2016       | 0.08278537 | 0.23214857 | 14.7% | 1.09 [0.69, 1.71] | |
| Subtotal (95% CI) | | | | | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.36 (P = 0.72) |
| 28.1.6 >70 years (Adjusted) | | | | | |
| Ganti, 2013       | 0.48144263 | 1.67091837 | 0.3% | 1.62 [0.06, 42.79] | |
| Subtotal (95% CI) | | | | | |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.29 (P = 0.77) |
| Total (95% CI)    | 100.0%     | 1.09 [0.92, 1.30] | |

*HS= Haemorrhagic stroke

Fig. 2. Forest plots of meta-analysis and subgroup analysis results for mortality in women, compared to men, after haemorrhagic stroke (HS); Risk and corresponding 95% confidence intervals (CI) reported.
**C) Mortality up to 12-months**

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Fixed, 95% CI |
|-------------------|----------------|----|--------|------------------------------|
| **29.1.1 Up-to-12mths post-HS (Unadjusted)** | | | | |
| Vaartjes, 2009 | -0.00436481 | 0.03826531 | 24.0% | 1.00 [0.92, 1.07] |
| Xing, 2017 | 0.1271048 | 0.25510204 | 0.5% | 1.14 [0.69, 1.87] |
| Zhou, 2014 | 0 | 0.18877551 | 1.0% | 1.00 [0.69, 1.45] |
| **Subtotal (95% CI)** | | | | |
| | | | | 25.5% | 1.00 [0.93, 1.07] |

Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%

Test for overall effect: Z = 0.04 (P = 0.97)

| **29.1.2 <70 years (Unadjusted)** | | | | |
| Vaartjes, 2009 | 0.09691001 | 0.2346939 | 0.6% | 1.10 [0.70, 1.75] |
| Xing, 2017 | 0.1271048 | 0.25510204 | 0.5% | 1.14 [0.69, 1.87] |
| Zhou, 2014 | 0 | 0.18877551 | 1.0% | 1.00 [0.69, 1.45] |
| **Subtotal (95% CI)** | | | | 2.2% | 1.06 [0.83, 1.36] |

Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² = 0%

Test for overall effect: Z = 0.47 (P = 0.64)

| **29.1.3 ≥70 years (Unadjusted)** | | | | |
| Vaartjes, 2009 | -0.0409586 | 0.0459184 | 16.7% | 0.96 [0.88, 1.05] |
| **Subtotal (95% CI)** | | | | 16.7% | 0.96 [0.88, 1.05] |

Heterogeneity: Not applicable

Test for overall effect: Z = 0.89 (P = 0.37)

| **29.1.4 Up-to-12mths post-HS (Adjusted)** | | | | |
| Vaartjes, 2009 | -0.03621217 | 0.03571429 | 27.6% | 0.96 [0.90, 1.03] |
| Zhou, 2014 | 0.13987909 | 0.36989796 | 0.3% | 1.15 [0.56, 2.37] |
| **Subtotal (95% CI)** | | | | 27.8% | 0.97 [0.90, 1.04] |

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%

Test for overall effect: Z = 0.97 (P = 0.33)

| **29.1.5 <70 years (Adjusted)** | | | | |
| Zhou, 2014 | 0.13987909 | 0.36989796 | 0.3% | 1.15 [0.56, 2.37] |
| **Subtotal (95% CI)** | | | | 0.3% | 1.15 [0.56, 2.37] |

Heterogeneity: Not applicable

Test for overall effect: Z = 0.38 (P = 0.71)

| **29.1.6 ≥70 years (Adjusted)** | | | | |
| Vaartjes, 2009 | -0.03621217 | 0.03571429 | 27.6% | 0.96 [0.90, 1.03] |
| **Subtotal (95% CI)** | | | | 27.6% | 0.96 [0.90, 1.03] |

Heterogeneity: Not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

**Total (95% CI)**

| | | | | |
| Heterogeneity: Chi² = 2.02, df = 10 (P = 1.00); I² = 0% |
| Test for overall effect: Z = 1.34 (P = 0.18) |
| Test for subgroup differences: Chi² = 1.34, df = 5 (P = 0.93), I² = 0% |

*HS= Haemorrhagic stroke

Fig. 2. (continued).
D) Mortality up to five-years

| Study or Subgroup                  | log(Risk Ratio) | SE    | Weight | Risk Ratio IV, Fixed, 95% CI | Risk Ratio IV, Fixed, 95% CI |
|-----------------------------------|-----------------|-------|--------|----------------------------|----------------------------|
| 30.1.1 Up-to-5yrs post-HS (Unadjusted) |                 |       |        |                            |                            |
| Vaartjes, 2009                    | 0.00432137      | 0.03316327 | 26.6%  | 1.00 [0.94, 1.07]           |                             |
| Xing, 2017                        | 0.08278537      | 0.23214286 | 0.5%   | 1.09 [0.69, 1.71]           |                             |
| Subtotal (95% CI)                 |                 |       |        | 27.2% 1.01 [0.94, 1.07]      |                             |
| Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0% |     |       |        | Test for overall effect: Z = 0.18 (P = 0.86) |  |

| 30.1.2 <70 years (Unadjusted)      |                 |       |        |                            |                            |
| Vaartjes, 2009                    | 0.827853        | 0.21173469 | 0.7%   | 2.29 [1.51, 3.47]          |                             |
| Xing, 2017                        | 0.08278537      | 0.23214286 | 0.5%   | 1.09 [0.69, 1.71]          |                             |
| Subtotal (95% CI)                 |                 |       |        | 1.2% 1.63 [1.20, 2.22]      |                             |
| Heterogeneity: Chi² = 5.62, df = 1 (P = 0.02); I² = 82% |     |       |        | Test for overall effect: Z = 3.13 (P = 0.002) |  |

| 30.1.3 ≥70 years (Unadjusted)      |                 |       |        |                            |                            |
| Vaartjes, 2009                    | 0.01772876      | 0.02551102 | 45.0%  | 0.98 [0.93, 1.03]          |                             |
| Subtotal (95% CI)                 |                 |       |        | 45.0% 0.98 [0.93, 1.03]    |                             |
| Heterogeneity: Not applicable      |                 |       |        | Test for overall effect: Z = 0.69 (P = 0.49) |  |

| 30.1.4 Up-to-5yrs post-HS (Adjusted) |                 |       |        |                            |                            |
| Vaartjes, 2009                    | 0.04095861      | 0.03316327 | 26.6%  | 0.96 [0.90, 1.02]          |                             |
| Subtotal (95% CI)                 |                 |       |        | 26.6% 0.96 [0.90, 1.02]    |                             |
| Heterogeneity: Not applicable      |                 |       |        | Test for overall effect: Z = 1.24 (P = 0.22) |  |

Total (95% CI)                     |                 |       |        | 100.0% 0.99 [0.96, 1.02]   |                             |
| Heterogeneity: Chi² = 17.12, df = 5 (P = 0.004); I² = 71% |     |       |        | Test for overall effect: Z = 0.67 (P = 0.50) |  |
| Test for subgroup differences: Chi² = 11.39, df = 3 (P = 0.010), I² = 73.7% | | | | |

*HS= Haemorrhagic stroke

**Adjusted results available from one study only; Vaartjes et al., 2009

Fig. 2. (continued).
Fig. 3. Forest plots of meta-analysis and subgroup analysis results for mortality in women, compared to men, after stroke of unspecified type (SUT); Risk and corresponding 95% confidence intervals (CI) reported.

*SUT= Stroke of unspecified type*
### B) Mortality up to one-month

| Study or Subgroup | log(Risk Ratio) | SE | Weight | Risk Ratio IV, Fixed, 95% CI |
|-------------------|----------------|----|--------|----------------------------|
| **32.1.1 Up-to-1mth post-SUT (Unadjusted)** |
| Dehlendorff, 2015 | 0.1417632 | 0.02806122 | 12.3% | 1.15 [1.09, 1.22] |
| Di Carlo, 2003   | 0.09096308 | 0.08826531 | 1.2% | 1.10 [0.92, 1.30] |
| Olsen, 2007      | 0.1383027 | 0.03316327 | 8.8% | 1.15 [1.08, 1.23] |
| Olsen, 2009      | 0.03463284 | 0.07753102 | 1.6% | 1.04 [0.89, 1.21] |
| Palnum, 2009     | 0.0211893 | 0.05357143 | 3.4% | 1.02 [0.92, 1.13] |
| Wu, 2012         | 0.05690485 | 0.04591837 | 4.6% | 1.06 [0.97, 1.16] |
| **Subtotal (95% CI)** | **31.8%** | **1.11 [1.08, 1.15]** |
| Heterogeneity: | Chi² = 7.08, df = 5 (P = 0.21); I² = 29% |
| Test for overall effect: | Z = 6.23 (P < 0.00001) |
| **32.1.2 <70 years (Unadjusted)** |
| Palnum, 2009     | 0.0374265 | 0.107143 | 0.8% | 1.04 [0.84, 1.28] |
| Wu, 2012         | -0.1249378 | 0.09438775 | 1.1% | 0.88 [0.73, 1.06] |
| **Subtotal (95% CI)** | **1.9%** | **0.95 [0.82, 1.09]** |
| Heterogeneity: | Chi² = 1.29, df = 1 (P = 0.26); I² = 23% |
| Test for overall effect: | Z = 0.76 (P = 0.45) |
| **32.1.3 ≥70 years (Unadjusted)** |
| Dehlendorff, 2015 | 0.1417632 | 0.02806122 | 12.3% | 1.15 [1.09, 1.22] |
| Di Carlo, 2003   | 0.09096308 | 0.08826531 | 1.2% | 1.10 [0.92, 1.30] |
| Olsen, 2007      | 0.1383027 | 0.03316327 | 8.8% | 1.15 [1.08, 1.23] |
| Olsen, 2009      | 0.03463284 | 0.07753102 | 1.6% | 1.04 [0.89, 1.21] |
| Palnum, 2009     | 0.0211893 | 0.05357143 | 3.4% | 1.02 [0.92, 1.13] |
| Wu, 2012         | 0.05690485 | 0.04591837 | 4.6% | 1.06 [0.97, 1.16] |
| **Subtotal (95% CI)** | **31.8%** | **1.11 [1.08, 1.15]** |
| Heterogeneity: | Chi² = 7.08, df = 5 (P = 0.21); I² = 29% |
| Test for overall effect: | Z = 6.23 (P < 0.00001) |
| **32.1.4 Up-to-1mth post-SUT (Adjusted)** |
| DeVries, 2011    | 0.06032003 | 0.05841837 | 2.8% | 1.06 [0.95, 1.19] |
| Lewsey, 2012     | 0.0374265 | 0.03571429 | 7.6% | 1.04 [0.97, 1.11] |
| Palnum, 2009     | -0.14874165 | 0.04591837 | 4.6% | 0.86 [0.79, 0.94] |
| **Subtotal (95% CI)** | **15.0%** | **0.98 [0.94, 1.04]** |
| Heterogeneity: | Chi² = 12.30, df = 2 (P = 0.002); I² = 84% |
| Test for overall effect: | Z = 0.60 (P = 0.55) |
| **32.1.5 <70 years (Adjusted)** |
| Lewsey, 2012     | 0.0413927 | 0.05102041 | 3.7% | 1.04 [0.94, 1.15] |
| Palnum, 2009     | -0.0409586 | 0.1122449 | 0.8% | 0.96 [0.77, 1.20] |
| **Subtotal (95% CI)** | **4.5%** | **1.01 [0.94, 1.13]** |
| Heterogeneity: | Chi² = 0.45, df = 1 (P = 0.50); I² = 0% |
| Test for overall effect: | Z = 0.59 (P = 0.56) |
| **32.1.6 ≥70 years (Adjusted)** |
| DeVries, 2011    | 0.06032003 | 0.05841837 | 2.8% | 1.06 [0.95, 1.19] |
| Lewsey, 2012     | 0.0374265 | 0.03571429 | 7.6% | 1.04 [0.97, 1.11] |
| Palnum, 2009     | -0.14874165 | 0.04591837 | 4.6% | 0.86 [0.79, 0.94] |
| **Subtotal (95% CI)** | **15.0%** | **0.98 [0.94, 1.04]** |
| Heterogeneity: | Chi² = 12.30, df = 2 (P = 0.002); I² = 84% |
| Test for overall effect: | Z = 0.60 (P = 0.55) |
| **Total (95% CI)** | **100.0%** | **1.07 [1.05, 1.09]** |

*SUT= Stroke of unspecified type

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Fig. 3. (continued)
### C) Mortality up to 12-months

| Study or Subgroup | log[Risk Ratio] | SE | Weight | IV, Fixed, 95% CI | IV, Fixed, 95% CI |
|-------------------|----------------|----|--------|-------------------|-------------------|
| 33.1.1 Up-to-12mths post-SUT (Unadjusted) | | | | | |
| Andersen, 2005 | 0.07040732 | 0.13775502 | 0.7% | 1.07 [0.82, 1.41] | |
| Di Carlo, 2003 | 0.10311925 | 0.0744898 | 2.4% | 1.11 [0.96, 1.28] | |
| Olsen, 2007 | 0.11272713 | 0.02704082 | 18.4% | 1.12 [1.07, 1.19] | |
| Palnum, 2009 | 0.03342376 | 0.04846939 | 5.7% | 1.03 [0.94, 1.14] | |
| Phan, 2021 | 0.21748394 | 0.125 | 0.9% | 1.24 [0.97, 1.59] | |
| Venmos, 2000 | 0.09691001 | 0.17857143 | 0.4% | 1.10 [0.78, 1.56] | |
| Subtotal (95% CI) | | | | 28.5% [1.11, 1.15] | |
| Heterogeneity: Chi² = 3.22, df = 5 (P = 0.67); I² = 0% | | | | |
| Test for overall effect: Z = 4.64 (P < 0.00001) | | | | |
| 33.1.2 <70 years (Unadjusted) | | | | | |
| Palnum, 2009 | 0.02532107 | 0.09438776 | 1.5% | 1.03 [0.85, 1.23] | |
| Subtotal (95% CI) | | | | 1.5% [1.03, 1.23] | |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 0.27 (P = 0.79) | | | | |
| 33.1.3 ≥70 years (Unadjusted) | | | | | |
| Andersen, 2005 | 0.07040732 | 0.13775502 | 0.7% | 1.07 [0.82, 1.41] | |
| Di Carlo, 2003 | 0.10311925 | 0.0744898 | 2.4% | 1.11 [0.96, 1.28] | |
| Olsen, 2007 | 0.11272713 | 0.02704082 | 18.4% | 1.12 [1.07, 1.19] | |
| Palnum, 2009 | 0.03342376 | 0.04846939 | 5.7% | 1.03 [0.94, 1.14] | |
| Phan, 2021 | 0.21748394 | 0.125 | 0.9% | 1.24 [0.97, 1.59] | |
| Venmos, 2000 | 0.09691001 | 0.17857143 | 0.4% | 1.10 [0.78, 1.56] | |
| Subtotal (95% CI) | | | | 28.5% [1.11, 1.15] | |
| Heterogeneity: Chi² = 3.22, df = 5 (P = 0.67); I² = 0% | | | | |
| Test for overall effect: Z = 4.64 (P < 0.00001) | | | | |
| 33.1.4 Up-to-12mths post-SUT (Adjusted) | | | | | |
| Koton, 2013 | -0.02227639 | 0.3 | 0.1% | 0.98 [0.54, 1.76] | |
| Olsen, 2007 | -0.03794192 | 0.0358469 | 10.7% | 0.96 [0.90, 1.03] | |
| Palnum, 2009 | -0.1130927 | 0.0436375 | 7.1% | 0.89 [0.82, 0.97] | |
| Phan, 2021 | 0.07554696 | 0.09693878 | 1.4% | 1.08 [0.89, 1.30] | |
| Venmos, 2000 | -0.03621217 | 0.14030612 | 0.7% | 0.96 [0.73, 1.27] | |
| Subtotal (95% CI) | | | | 20.1% [0.90, 0.99] | |
| Heterogeneity: Chi² = 3.89, df = 4 (P = 0.42); I² = 0% | | | | |
| Test for overall effect: Z = 2.19 (P = 0.03) | | | | |
| 33.1.5 <70 years (Adjusted) | | | | | |
| Palnum, 2009 | -0.04577549 | 0.09693877 | 1.4% | 0.96 [0.79, 1.16] | |
| Subtotal (95% CI) | | | | 1.4% [0.79, 1.16] | |
| Heterogeneity: Not applicable | | | | |
| Test for overall effect: Z = 0.47 (P = 0.64) | | | | |
| 33.1.6 ≥70 years (Adjusted) | | | | | |
| Koton, 2013 | -0.02227639 | 0.3 | 0.1% | 0.98 [0.54, 1.76] | |
| Olsen, 2007 | -0.03794192 | 0.0358469 | 10.7% | 0.96 [0.90, 1.03] | |
| Palnum, 2009 | -0.1130927 | 0.0436375 | 7.1% | 0.89 [0.82, 0.97] | |
| Phan, 2021 | 0.07554696 | 0.09693878 | 1.4% | 1.08 [0.89, 1.30] | |
| Venmos, 2000 | -0.03621217 | 0.14030612 | 0.7% | 0.96 [0.73, 1.27] | |
| Subtotal (95% CI) | | | | 20.1% [0.90, 0.99] | |
| Heterogeneity: Chi² = 3.89, df = 4 (P = 0.42); I² = 0% | | | | |
| Test for overall effect: Z = 2.19 (P = 0.03) | | | | |
| Total (95% CI) | | | | 100.0% [1.04, 1.06] | |
| Heterogeneity: Chi² = 58.36, df = 23 (P < 0.00001); I² = 61% | | | | |
| Test for overall effect: Z = 2.97 (P = 0.003) | | | | |
| Test for subgroup differences: Chi² = 44.13, df = 5 (P < 0.00001), I² = 88.7% | | | | |

*SUT* = Stroke of unspecified type

Fig. 3. (continued).
women ≥ 70 years had higher mortality after one and 12-months post-SUT (one-month: Risk 0.96; 0.92–1.00, n = 2,583,848; 12 months: Risk 1.11; 1.06, 1.15, n = 84,527).

4. Discussion

The results of our systematic review provide robust evidence that there are important gender differences in medium- and long-term mortality after stroke, which are dependent on stroke type and length of follow-up. After ischaemic stroke, women consistently had lower risk of mortality than men, ranging from 6% in-hospital to 13% lower risk by one-month and 7% by five years, after adjusting for important confounders, such as: age, history of previous strokes, hypertension, hyperlipidaemia, atrial fibrillation, ischaemic heart disease. Nevertheless, meta-analysis of unadjusted estimates showed up to 10% higher mortality post-IS in women at all follow-up points, suggesting that this higher raw mortality is mostly explained by gender-based characteristics of female stroke patients, such as higher age at stroke onset and prevalence of comorbidities. The results of our age-stratified subgroup analysis show that older women (≥70 years) had a lower mortality after IS compared to men, however this gender difference was not apparent in younger women (<70 years). Unadjusted data appears to unmask the higher mortality in women compared to men regardless of age group. These findings support current literature which suggests that age-adjusted data may obscure the complex relationship of sex differences at specific ages [2].

A retrospective analysis of participants from the International Stroke Trial (IST) showed a higher raw mortality 24.5% in women (24.5%) compared to men (19.3%) at six-months [45]. However, when they adjusted for age, stroke severity, atrial fibrillation, and blood pressure, women had lower mortality at six months (OR 0.90; 95% CI 0.83–0.98). Other previous studies also yielded similar findings of higher post-stroke raw mortality in women, but lower mortality after adjustment for relevant confounders [2,3].

Two important conclusions pertaining to gender equity in stroke care can be drawn from this study. Firstly, the higher stroke mortality in women is unlikely to be driven independently by intrinsic biological differences in stroke pathophysiology, but largely by age as well as co-morbid disease burden. Thereby, it is essential to recognise that the differences in raw mortality seen in routine clinical practice can be reduced by changes in clinical practice, namely; better primary prevention of comorbidities including cardiovascular disease and smoking cessation as well as more tailored clinical management of these comorbidities in women. In terms of HS, it can be concluded that beyond discharge, no gender difference appears between the risks of mortality of women and men after a HS, irrespective of confounders or age group. Our data is concordant with that of one study which concluded no gender differences in unadjusted or adjusted risk of mortality risk irrespective of confounding (OR 1.19; 95% CI 0.92–1.53 and OR 0.188; 95% CI 0.84–1.75), respectively [28]. Nevertheless, more studies assessing risk of mortality in women compared to men post-HS are crucial for more robust evidence. Cellular-level investigations into the role of cell-death pathways and inflammatory signalling cascades, influenced by the effects of oestrogen in women, appear to provide some basis to the gender-specific biology of ischaemia in IS. One study highlighted that the neuroprotection offered by higher levels of oestrogen in women as well as slowing large artery atherosclerosis build-up [46]. Although these studies suggest women have less severe strokes, it is important to highlight that lack of adjustment for stroke subtype, severity and comorbidities is an important notable limitation of these studies.

Geographical, racial and socio-economic factors are also important to highlight as potential confounders to differences in stroke mortality between women and men. Excess stroke mortality in women is of particular concern in Asian populations, where there are clear differences in patient biology and epidemiology documented in the literature compared to Western populations [19,47,48]. The prevalence of intracranial plaques causing IS has been reported as 38.5% in Caucasians compared to 69.1% in Chinese populations (p = 0.02) [19]. Large racial-ethnic disparities in Black and Hispanic individuals compared to white individuals have also been highlighted in the literature [51]. In these populations, the higher rates of stroke mortality, particularly in women, were due to key geopolitical and economic factors including: poorer health literacy, a large
gender pay gap resulting in lower income and poorer healthcare affordability in women, differences in socio-economic status and differing beliefs [49,53] in African countries, unique barriers to the provision of quality stroke care include a shortage of medical transport, specialist staff and well-equipped stroke units, economic recessions resulting in inability to support the cost of brain imaging, thrombolysis or out-patient rehabilitation. These reasons are responsible for inter-continental disparities in stroke care and outcomes [51].

Due to the wide distribution of the included studies across the globe, analysing data from specific regions by time period or stroke type was not possible due to insufficient data for pooling (Table 5). In addition, as shown in Table 4, the Western hemisphere represents 98% (n = 7, 835,

Table 4
Studies included in meta-analysis of gender differences in stroke mortality; by geographical region.

| Region           | No. of studies | Name of study                  | No. of participants (%) Total= 8, 008, 110 |
|------------------|----------------|--------------------------------|-------------------------------------------|
| USA and Canada   | 5              | James, 2017                    | 5, 302, 794 (66.2%)                       |
|                  |                | DeVries, 2011                  |                                           |
|                  |                | Orbiagele, 2011                |                                           |
|                  |                | Towfighi, 2011                 |                                           |
|                  |                | Kapral, 2004                   |                                           |
| Europe           | 16             | Bonkhoff, 2021                 | 2, 532, 686 (31.6%)                       |
|                  |                | Eriksson, 2021                 |                                           |
|                  |                | Weber, 2019                    |                                           |
|                  |                | Renaux, 2017                  |                                           |
|                  |                | Denti, 2013                    |                                           |
|                  |                | Santalucia, 2013               |                                           |
|                  |                | Lewsey, 2012                   |                                           |
|                  |                | Olsen, 2012                    |                                           |
|                  |                | Wiszniewska, 2010             |                                           |
|                  |                | Palnum, 2009                   |                                           |
|                  |                | Olsen, 2009                   |                                           |
|                  |                | Vaartjes, 2009                 |                                           |
|                  |                | Olsen, 2007                   |                                           |
|                  |                | Andersen, 2005                 |                                           |
|                  |                | Di Carlo, 2003                 |                                           |
|                  |                | Vemmos, 2000                   |                                           |
| East Asia        | 10             | Irie, 2021                     | 157, 537 (1.97%)                           |
|                  |                | Uchida, 2021                   |                                           |
|                  |                | Org, 2017                      |                                           |
|                  |                | Xing, 2017                     |                                           |
|                  |                | Hsieh, 2016                    |                                           |
|                  |                | Li, 2015                       |                                           |
|                  |                | Zhou, 2014                     |                                           |
|                  |                | Park, 2012                     |                                           |
|                  |                | Wu, 2012                       |                                           |
|                  |                | Oh, 2009                       |                                           |
| Australia        | 1              | Phan, 2021                     | 9441 (0.12%)                               |
| Africa           | 1              | Watila, 2012                   | 91 (0.0011%)                              |
| Middle East      | 2              | Sweiabieh, 2009                | 527 (0.0066%)                             |
|                  |                | Talebi, 2014                   |                                           |
| Near East        | 1              | Koton, 2013                    | 5034 (0.063%)                             |
| Worldwide        | 1              | Ganti, 2013                    | 245 (0.0031%)                             |

Table 5
Names and population of studies for age-stratified subgroup analysis of gender differences in stroke mortality: mean age < 70 years and ≥ 70 years.

| Follow-up time period | Ischaemic stroke | Haemorrhagic stroke |
|-----------------------|------------------|---------------------|
|                       | < 70 years       | ≥ 70 years          |
|                       | Unadjusted       | Adjusted            | Unadjusted       | Adjusted            |
| In-hospital mortality | Oh, 2009         | Oh, 2009            | Bonkhoff, 2021  | Bonkhoff, 21        |
|                       | Park, 2012       | Park, 2012          | Weber, 2019     | Kapral, 2004        |
| No. of participants (N = ) | N = 25,269         | N = 25,269          | N = 1,907,954   | N = 768,707         |
| Up to 1 month         | Oh, 2009         | Watila, 2012        | Denti, 2013     | Denti, 2013         |
| No. of participants (N = ) | N = 18,634        | N = 91              | Wiszniewska, 2010 | Irie, 2021 |
| Up to 12 months       | Oh, 2009         | –                   | Li, 2015        | –                   |
|                       | Vaartjes, 2009 * | –                   | Olsen, 2012     | –                   |
|                       | –                | –                   | Renaux, 2017    | –                   |
|                       | –                | –                   | Uchida, 2019    | –                   |
|                       | –                | –                   | Vaartjes, 2009 * | –                   |
|                       | –                | –                   | Vaartjes, 2009 * | –                   |
| No. of participants (N = ) | N = 49,309 *     | N = 31,485          | N = 19,949      | –                   |
| Up to 5 years         | Oh, 2009         | –                   | Li, 2015        | –                   |
|                       | Vaartjes, 2009 * | –                   | –              | –                   |
| No. of participants (N = ) | N = 49,309 *     | –                   | –              | –                   |
| Haemorrhagic stroke   | –                | –                   | –              | –                   |
of further research for haemorrhagic aetiology of stroke. The gender differences in risk of mortality following HS and the necessity for observational studies comparing risk of mortality between women and men after IS and HS, from diagnosis to five-years follow up. The participants of the studies represented a large demographic spread from various different healthcare systems which increases the generalisability and global applicability of our findings. All literature searches, data extraction, meta-analysis and quality appraisal were put through a rigorous cross-check by at least two independent researchers at each stage. There are also some limitations worth highlighting. There was a high degree of heterogeneity in the variables that were adjusted for as well as a lack of adjustment of stroke severity. Further, the majority of studies in the current literature are those with Western study cohorts. Therefore, it is important to note that East Asia and Africa are under-represented in the existing analysis and would be statistically underpowered if analysis was stratified by region. In addition, there was an inadequate number of studies available to meta-analysis results at individual post-operative follow-up time points therefore, time brackets were utilised.

Clinicians treating stroke patients must be cognisant of the important risk factors including age, HTN and AF which put women at higher risk of mortality than men. Equally however, they should understand that this relationship is an interplay of various confounding factors that when adjusted for, women have a lower risk of mortality than men post-IS. Finally, it is important to recognise the lack of evidence surrounding the gender differences in risk of mortality following HS and the necessity of further research for haemorrhagic aetiology of stroke.

### 5. Conclusion

The gender differences in mortality risk after stroke is dependent on stroke type, age group and duration since stroke onset. Crude stroke mortality in women was found to be higher than in men however this appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time. In HS, beyond the in-hospital period appears to be driven by pre-existing comorbidities. The current literature suggests that once age, stroke severity and comorbidities are adjusted for, women were at lower risk of mortality, compared to men following IS, irrespective of time.

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### Conflict of interest

None declared.

### CRediT authorship contribution statement

**Abdel-Rahman Abdel-Fattah**: Primary reviewer, Literature review, Data-analysis and Drafting manuscript. **Tiberiu A. Pana**: Statistical analysis and Supervision, Drafting manuscript. **Toby O. Smith**: Senior reviewer for systematic review, Supervision of systematic review, drafting manuscript. **Zahra Pasdar**: Second data extraction, Drafting manuscript. **Maha Aslam**: Second reviewer, Drafting manuscript.

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**Table 5 (continued)**

| In-hospital mortality | Up to 1 month | Up to 12 months | No. of participants (N = ) | Adjusted | Unadjusted | Adjusted | Unadjusted |
|-----------------------|--------------|----------------|----------------------------|----------|------------|----------|------------|
| In-hospital mortality | Hsieh, 2016 | Vaartjes, 2009 * | N – 1196 | – | – | N – 425 | N – 245 |
| No. of participants (N = ) | – | Zhou, 2014 | N – 1196 | – | – | – | – |
| Up to 5 years | Vaartjes, 2009 * | – | N – 615 | – | – | – | – |
| No. of participants (N = ) | – | Xing, 2017 | N – 32,000 | – | – | N – 30,675 | – |
| Stroke of unspecified type (SUT) | – | – | – | – | – | – | – |

*Age-stratified data was available in the paper and extracted for subgroup analysis (see Supplementary Tables 3-6 for age-stratified data).*
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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2022.107359.
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