Prevalence, Characteristics and Outcomes of Undetermined Intracerebral Hemorrhage: A Systematic Review and Meta-Analysis

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Abstract

Background and Purpose: There are scarce data regarding the prevalence, characteristics and outcomes of intracerebral hemorrhage (ICH) of undetermined (unknown or cryptogenic) etiology. We sought to determine the prevalence, radiological characteristics and clinical outcomes of undetermined ICH.

Methods: Systematic review and meta-analysis of studies involving patients with spontaneous ICH was conducted to primarily assess the prevalence and clinical-radiological characteristics of undetermined ICH. Additionally, we assessed the rates for ICH secondary to hypertensive arteriopathy (HTN-A) and cerebral amyloid angiopathy (CAA). Subgroup analyses were performed based on the use of a) etiology-oriented ICH classification, b) detailed neuroimaging, and c) Boston criteria among CAA-ICH. We pooled the prevalence rates using random-effect models, and assessed the heterogeneity using Cochran Q and I^2 statistics.

Results: We identified 24 studies comprising 15,828 spontaneous ICH patients (mean age: 64.8 years, males: 60.8%). The pooled prevalence of HTN-A ICH, undetermined ICH and CAA-ICH were 50% (95%CI: 43-58%), 18% (95%CI: 13-23%), and 12% (95%CI: 7-17%; p<0.001 between subgroups). The volume of ICH was largest in CAA-ICH 24.7mL (95%CI: 19.7-29.8mL), followed by HTN-A ICH 16.2mL (95%CI: 10.9-21.5mL) and undetermined ICH 15.4mL (95%CI: 6.2-24.5mL). Among patients with undetermined ICH, the rates of short-term mortality (within 3 months) and concomitant intraventricular hemorrhage were 33% (95%CI: 25-42%) and 38% (95%CI: 28-48%), respectively. Subgroup analysis demonstrated a higher rate of undetermined ICH among studies that did not use an etiology-oriented classification (22%; 95%CI: 15-29%). No

difference was observed between studies based on the completion of detailed neuroimaging to assess the rates of undetermined ICH (p=0.62).

Conclusions: The etiology of spontaneous ICH remains unknown or cryptogenic among one in seven patients in studies using etiology-oriented classification and among one in four patients in studies that avoid using etiology-oriented classification. The short-term mortality in undetermined ICH is high despite the relatively small ICH volume.

Non-standard Abbreviations and Acronyms

ICH: Intracerebral Hemorrhage

HTN: Hypertension

CAA: Cerebral Amyloid Angiopathy

IVH: Intraventricular Hemorrhage

Text

Introduction

Spontaneous intracerebral hemorrhage (ICH) is a significant cause of morbidity and mortality worldwide.[1] Although ICH accounts for 10 to 20% of total stroke cases,[2, 3] more than two-third of ICH survivors suffer from functional dependence.[4, 5] ICH is associated with a higher mortality rate compared with either ischemic stroke or subarachnoid hemorrhage, and fatality rates range from 40% at one month to 54% at one year after index event.[6] Due to the risk for early neurological impairment and worse clinical outcomes, current American Heart Association/American Stroke Association (AHA/ASA) guidelines recommend early, aggressive, goal-directed treatment for ICH patients.[1] Since optimal treatment might differ according to underlying etiology, early assessment of the underlying ICH etiology remains critical for rapid management and swift utilization of resources in the acute setting.

The etiology of ICH has been classified as either spontaneous (80%), involving hypertensive arteriopathy (HTN-A; 65%) and cerebral amyloid angiopathy (CAA; 15%), or secondary causes (20%).[7] Another classification method is based on the ICH location: deep ICH (70%) involving the basal ganglia, internal capsule, brainstem or cerebellum, and lobar ICH (15-30%) involving cortical-subcortical locations.[3] Although these classifications provide an insight into possible causes of ICH, the etiology remains unknown in approximately 10-35% of spontaneous ICH patients.[8-11] ICH of undetermined etiology refers to patients for whom the etiology remains unknown or cryptogenic after performing a detailed diagnostic evaluation. Etiological ICH classifications have been proposed that underscore the use of unknown or

cryptogenic etiology of ICH, especially during acute and subacute stroke care.[9, 12] However, due to limited and scarce data, the prevalence rates of unknown or cryptogenic etiology of ICH remains unclear. We conducted a systematic review and meta-analysis of spontaneous ICH studies to assess the prevalence rates of undetermined (unknown or cryptogenic) etiology of ICH. We also evaluated the clinical and radiographic outcomes among these patients.

Methods

The meta-analysis adopted the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[13] and is reported in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal.[14] Systematic search of Ovid MEDLINE, CINAHL and CENTRAL databases was performed on April 24, 2020. The complete search algorithm used in MEDLINE is described in Figure 1. The details on database search is included in methods section of online supplement.

Study selection

We included studies involving: (1) patients with spontaneous ICH; (2) available data on the prevalence of undetermined (unknown or cryptogenic) cause of ICH; and (3) adult patients (≥18 years old). We excluded studies that did not report the prevalence of undetermined cause of ICH or studies with overlapping data.

Primary analyses

We primarily assessed the prevalence rate of undetermined ICH. Additionally, we evaluated the prevalence rates of ICH secondary to HTN-A and CAA related etiologies. We also

assessed the rates of short-term mortality, intraventricular hemorrhage (IVH) and ICH volume. We defined short-term mortality as occurrence of ICH-related mortality among patients within 3-months of stroke onset. Similarly, IVH was defined as the presence of concomitant hemorrhage within the ventricular cisterns.

Secondary analyses

Subgroup analyses were conducted to assess the prevalence rates based on different etiology-oriented ICH classifications and use of detailed neuroimaging. We also assessed the rates of CAA-related ICH based on the use of Boston criteria[15] among the included studies.

Statistical approach

All statistical analyses were conducted using Comprehensive Meta-Analysis software, Version 2.23. We calculated prevalence rates and their corresponding 95% confidence intervals to measure the effect size. For the qualitative interpretation of heterogeneity, $I^2 > 50\%$ and $I^2 > 75\%$ indicated substantial and considerable heterogeneity, respectively.[16] Publication bias across individual studies was graphically evaluated using a funnel plot,[17] while funnel plot asymmetry was assessed using Egger's linear regression test with $P<0.10$ significance level. A random-effects model (DerSimonian Laird)[18] was used to calculate the pooled prevalence rates in both the overall and subgroup analyses. Random effects model was chosen due to the presumed disparity between studies in both the population and study design levels, and thus the expected between study variability in effect estimates. We performed equivalent z test for each pooled OR, and a two-tailed p value <0.05 was considered statistically significant.

Additionally, we used random effects model (Methods of Moments) to perform meta-regression analyses which were conducted when 10 or more studies were available to assess the association of age with the prevalence rates of various ICH types.

Data availability statement

The study design (systematic review and meta-analysis) was exempt for approval from the Institutional Review Board. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Results

Study selection and study characteristics

We screened 1062 titles and abstracts from which 34 eligible studies were retained for full-text evaluation. After careful evaluation and no disagreements among the two reviewers, 10 studies were excluded (Supplemental Table I) resulting in selection of 24 studies that met inclusion criteria (Figure 1).

We included 24 studies that recruited a total of 15,828 spontaneous ICH patients (mean age: 64.8 years, men: 60.8%). Our systematic review and meta-analysis involved six prospective[8, 12, 19-22] and 18 retrospective[5, 9-11, 23-36] observational studies. The study design and patient characteristics of included studies are shown in Supplemental Table II and Table III. More specifically, prior history of ICH was documented in 6 studies and the prevalence ranged between 0% and 7.3%. Prior alcohol consumption was recorded in 13 studies and the prevalence ranged between 2.0% and 50.6%. Statin pretreatment was available in 4 studies with a prevalence ranging between

18.8% and 25.8%. Pretreatment with antiplatelets was documented in 10 studies with a prevalence ranging between 2.1% and 42%. Finally, pretreatment with anticoagulants was available in 15 studies with a prevalence ranging between 0% and 43.2%.

Supplemental Table IV describes the definitions of various ICH etiologies among the studies that did not use etiology-oriented classification. The studies were conducted in United States (n=4), Taiwan (n=3), Australia (n=2), Germany (n=2), Netherlands (n=2), France (n=1), Japan (n=1), China (n=1), Italy (n=1), Spain (n=1), Mexico (n=1), Finland (n=1), Nigeria (n=1), Saudi Arabia (n=1), Ecuador (n=1), and Canada (n=1). The corresponding authors from included studies were contacted to obtain necessary unpublished data and this was provided in two studies.[24, 27]

Study Quality and Publication Bias

Risk of bias amongst the cohort studies was assessed using Newcastle-Ottawa scale (Supplemental Table V). The risk of outcome bias was considered moderate mainly due to studies that failed to report missing data or data on losses to follow-up. The risk of comparability bias was also moderate as only half of the studies compared their cohorts based on the analysis. The overall score of Newcastle-Ottawa scale was 136/216 (63%), which is considered to represent an overall moderate quality of included studies.

We inspected funnel plot symmetry and Egger's statistical test for outcomes involving ≥10 studies.[17] Funnel plot inspection revealed no evidence of asymmetry in studies reporting the prevalence (p=0.59; Supplemental Figure I) and mortality (p=0.24; Supplemental Figure II) rates among ICH patients of undetermined etiology.

Overall Analysis

The prevalence rates (Figure 2) of undetermined cause of ICH was 18% (24 studies; 95%CI: 13-23%) with evidence of a high-level of heterogeneity (p for Cochran Q statistic<0.001, I^2=98.3%). Similarly, the prevalence of HTN-A ICH and CAA were 50% (22 studies; 95%CI; 43-58%; p for Cochran Q statistic<0.001, I^2=98.6%) and 12% (15 studies; 95%CI: 7-17%; p for Cochran Q statistic<0.001, I^2=98.7%), respectively. The difference in the prevalence rates between the three ICH subgroups was significant (p<0.001).

The rates of short-term mortality (Figure 3) were observed to be highest among the patients with undetermined ICH at 33% (10 studies; 95% CI, 25-42%; p for Cochran Q statistic<0.001, I^2=93.1%) followed by CAA-ICH at 24% (8 studies; 95% CI, 20-28%; p for Cochran Q statistic<0.001, I^2=67.6%) and HTN-A ICH at 22% (9 studies; 95% CI, 16-27%; p for Cochran Q statistic<0.001, I^2=94.1%). The difference in the short-term mortality rates among the three ICH subgroups was non-significant (p=0.079).

The rates of IVH (Figure 4) were noted to be 40% in HTN-A ICH (8 studies; 95% CI, 27-53%; p for Cochran Q statistic<0.001, I^2=94.1%), 38% in undetermined cause of ICH (8 studies; 95% CI, 28-48%; p for Cochran Q statistic<0.001, I^2=94.1%) and 28% in CAA-ICH patients (7 studies; 95% CI, 23-33%; p for Cochran Q statistic<0.001, I^2=74.7%). The difference in the IVH rates among the three ICH subgroups was not significant (p=0.084).

The volume of ICH (Supplemental Figure III) was observed to be largest in CAA-ICH at 24.7 mL (3 studies; 95% CI, 19.7-29.8 mL; p for Cochran Q statistic<0.001, I^2=81.8%), followed by HTN-A ICH at 16.2 mL (3 studies; 95% CI, 10.9-21.5 mL; p for Cochran Q statistic<0.001,

I^2=95.0%) and undetermined cause of ICH at 15.4 mL (3 studies; 95% CI, 6.2-24.5 mL; p for Cochran Q statistic<0.001, I^2=96.7%). The difference in the ICH volume among the three ICH subgroups was significant (p<0.001).

Subgroup analyses

We performed subgroup analyses of studies that used a) an etiology-oriented ICH classification, b) detailed neuroimaging studies, and c) Boston criteria to define CAA-ICH.

Based on the etiology-oriented classification, we evaluated for any moderating effect on the prevalence rates of different ICH etiologies. SMASH-U classification was used in nine studies and H-ATOMIC classification was used in one study, whereas the rest of the studies (n=14) did not use any specific etiology-oriented classification for ICH. The prevalence rates of undetermined ICH (Supplemental Figure IV) were 22% (14 studies; 95% CI, 15-29%; p for Cochran Q statistic<0.001, I^2=96.1%) for studies that did not use an etiology-oriented classification and 13% (10 studies; 95% CI, 7-20%; p for Cochran Q statistic<0.001; I^2=99.1%) for studies with the use of etiology-oriented classification. The subgroup difference was not significant (p=0.08).

No significant subgroup difference (p=0.79) was observed between the prevalence rates of HTN-A ICH (Supplemental Figure V) as 49% (12 studies; 95% CI, 37-62%; p for Cochran Q statistic<0.001, I^2=97.8%) for studies without the use of etiology-oriented classification and 52% (10 studies; 95% CI, 41-62%; p for Cochran Q statistic<0.001; I^2=99.2%) for studies with the use of etiology-oriented classification. Similarly, the prevalence rates of CAA-related ICH (Supplemental Figure VI) were 8% (5 studies; 95% CI, 0-23%; p for Cochran Q statistic<0.001, I^2=98.0%) for studies without the use of etiology-oriented classification and 14% (10 studies; 95%

CI, 9-19%; p for Cochran Q statistic<0.001; I^2=98.3%) for studies with the use of etiology-oriented classification; subgroup difference p=0.46.

We assessed the studies that performed detailed neuroimaging and evaluated the prevalence rates of different ICH etiologies. No subgroup difference was observed among the studies that did or did not perform detailed neuroimaging to assess the prevalence rates of undetermined cause of ICH (p=0.62; Supplemental figure VII), HTN-A ICH (p=0.79; Supplemental figure VIII), and CAA-ICH (p=0.61; Supplemental figure IX). Similarly, no difference (p=0.08; Supplemental figure X) was noted among the studies that did or did not use Boston Criteria to evaluate the prevalence of CAA-ICH.

Meta-regression analyses

We additionally performed meta-regression analysis to assess the potential association of age with the prevalence of various ICH subtypes. A linear positive association was documented between age and CAA-ICH [regression coefficient: 0.007 (95%CI: 0.002-0.011, p=0.005; Supplemental Figure XI], however no significant association was noted between age and ICH of undetermined etiology (p=0.85; Supplemental Figure XII) as well as HTN-A ICH (p=0.73; Supplemental Figure XIII).

Discussion

Our systematic review and meta-analysis involving 15,828 spontaneous ICH patients demonstrates that approximately 18% of these patients were classified as undetermined etiology. Patients with undetermined ICH and HTN-A were observed to have similar rates of IVH and

comparable ICH volumes. CAA-related ICH patients had significantly higher ICH volumes compared to HTN-A and undetermined ICH patients. In comparison to HTN-A ICH and CAA ICH, patients with undetermined ICH etiology were observed to have a trend towards a higher rate of short-term mortality. Subgroup analysis of the studies that used an etiology-oriented ICH classification demonstrated a lower rate of undetermined etiology of ICH. Finally, in our meta-regression analysis, age was associated with CAA-ICH, whereas no such association was noted for the prevalence rates of HTN-A ICH or ICH with undetermined etiology.

The incidence of spontaneous ICH has not decreased over time.[37] Rapid ascertainment of risk factors and determination of ICH etiology remains paramount. Various risk factors such as advanced age, Asian ethnicity, vascular malformations, history of HTN, CAA, smoking, excessive use of alcohol or other illicit drugs are prevalent among spontaneous ICH patients.[9, 37, 38] However, the etiology of acute ICH remains elusive in many of these patients. Prior studies have provided a broad range of 10-35% prevalence rate for undetermined etiology among spontaneous ICH patients.[8-11] Our systemic review and meta-analysis involving 24 studies reports a pooled prevalence rate of 18% for undetermined etiology among ICH patients.

There are few well established predictors of mortality among ICH patients including advanced age, lower GCS score on arrival, large ICH volume, infratentorial location and IVH extension.[39] In line with a previous meta-analysis,[37] a recent population-based registry of spontaneous ICH patients observed no improvement in early case-fatality rates of ICH from 1985 to 2011.[40] Evaluation of various ICH etiologies is warranted to effectively reduce mortality rates

associated with specific ICH etiology. Among patients with undetermined ICH etiology, studies have reported a wide range of mortality rates ranging between less than 3 months and up to 5 years from the index event.[8, 9, 11] In our study, we observed that the short-term mortality rates tended to be higher among ICH patients with undetermined etiology. This likely relates to a circular reasoning concept as these patients are considered too critical to undergo detailed etiological evaluation suggesting a self-fulfilling prophecy from the treating clinicians. These results reinforce a need for rapid etiological diagnosis among spontaneous ICH patients to improve the overall management and clinical outcomes.

Incomplete diagnostic evaluations of patients with ICH could result in misclassification of ICH etiology. Various etiology-oriented classifications, based on the systematic stratification of underlying vascular pathologies, have emerged with a goal of early diagnosis and rapid treatment of ICH patients. SMASH-U classification defines ICH etiologies secondary to structural lesion, medication, amyloid angiopathy, systemic/other disease, hypertension, or undetermined.[9] To avoid oversimplification of SMASH-U classification, authors maintained strict definitions for HTN-A and CAA-related etiologies and opted for a definite demonstration of risk factors directly related to the acute ICH. Similarly, the H-ATOMIC classification, [12] refers to hypertension, cerebral amyloid angiopathy, tumor, oral anticoagulants, vascular malformation, infrequent causes and cryptogenic etiologies. SMASH-U classification is the most commonly used etiology-oriented ICH classification and has been recently demonstrated to significantly predict in-hospital mortality among ICH patients.[5] Although we presume that routine ICH etiologies such as HTN-A, medications or CAA contribute to the majority of the ICH cases with undetermined etiology, these

etiology-based classifications remain important guide to clinicians for assessment and goal-directed management of ICH patients.

Neuroimaging remains important for the diagnostic evaluation of spontaneous ICH patients. Initial diagnostic evaluation includes computed tomography (CT) or magnetic resonance imaging (MRI) with gradient recalled echo (GRE) sequence to assess the ICH characteristics, followed by CT or MR angiography to evaluate for hematoma expansion or other etiologies such as vascular malformations. Structural and rare causes tend to be more prevalent among younger patients, whereas only 15% of ICH patients with mean age of 65 years have been noted to have significant findings on angiography.[41] This is likely due to the increase in comorbidities with age that may suggest that vascular imaging would render a lower yield in older ICH patients. In addition to the futile attempt as a part of circular reasoning concept, the lower yield of neuroimaging further reassures treating clinicians to avoid detailed neuroimaging in elderly ICH patients.

Recent AHA/ASA guidelines recommend rapid neuroimaging with either CT or MRI as reasonable initial options (Class I; LOE A) and suggest CTA or MRA, contrast-enhanced CT or MRI, and CT or MR venography for clinical or radiological suspicion of underlying vascular malformations (Class IIa; LOE B).[1] However, these guidelines lack recommendations for a systematic evaluation of ICH patients based on etiology-oriented ICH classifications. Decision-making clinicians must be cautious to segregate multiple etiologies in a particular ICH patient, and correctly diagnose ICH mechanism using etiology-oriented classification. Accordingly, we

propose an algorithm (Figure 5) for diagnostic evaluation of ICH patients with undetermined etiology underscoring that ICH cases need to be classified as undetermined etiology only if a detailed diagnostic workup using former ICH classifications remain inconclusive. Thus, these classifications may assist in homogenizing and harmonizing the classification of undetermined ICH subgroup among patients with spontaneous ICH. This, in turn may have implications for the design of future randomized-controlled clinical trials similar to the Embolic Stroke of Undetermined Source paradigm in cryptogenic stroke.[42]

Our study has certain limitations that warrant further consideration. First, the majority of our included studies were observational with retrospective design that predisposes to inherent biases, especially selection bias. To counteract these inherent biases, we performed further subgroup analyses to account for the moderating effect via use of etiology-oriented classifications and detailed neuroimaging in these studies. Although we performed subgroup and meta-regression analyses that highlight the robustness of our findings, our study is unable to exclude any residual confounding due to lack of individual study patient data. Second, majority of the studies using etiology-oriented classification preferred the use of SMASH-U classification whereas one study used H-ATOMIC classification for ICH etiology. Accordingly, we performed a subgroup analysis to compare the studies that did and did not use the etiology-oriented classification. Additionally, only few studies relied on autopsy confirmation for diagnosis of CAA-related ICH, whereas the remaining studies either used Boston criteria or failed to clarify the method used to diagnose CAA. Third, use of neuroimaging varied among the included studies as only few studies clarified the use of MRI with GRE sequence to diagnose CAA-related ICH and use of CTA or MRA for assessment

of vascular malformations. Accordingly, we subdivided the studies based on the use of detailed neuroimaging involving vascular imaging and MRI with GRE sequence. Fourth, our results may be confounded due to lack of consensus in stroke care among spontaneous ICH patients: use of interchangeable terminologies for ICH patients with undetermined etiology, lack of knowledge and routine use of etiology-oriented classification, inadvertent use of circular reasoning concept by avoiding detailed neuroimaging for concerns of futility, and lack of availability of data on location of ICH for patients with undetermined ICH and their post-mortem data. In particular, given the need for resource and cost savings, many providers may not feel the need to perform additional testing if the overall exam, neuroimaging, and clinical history fits a certain diagnosis. Fifth, crucial information pertaining to the use of anticoagulants, type of anticoagulant and whether the patients were subtherapeutic, therapeutic or above therapeutic range when ICH occurred were unavailable in the included studies. Last, there was substantial heterogeneity of the included studies across all the three ICH subgroups with regard to the year study was conducted, prevalence, clinical and radiographic outcomes. This heterogeneity lends support to a cautious interpretation of the study findings and may be related to differences in study design, neuroimaging modalities and studied population.

In conclusion, the reported etiology of spontaneous ICH remains undetermined among 18% of spontaneous ICH patients and is probably much higher in routine stroke care. These prevalence rates were noted to be higher among studies that did not use an etiology-oriented classification for ICH patients. Patients with HTN-A ICH and undetermined ICH etiology were observed to have a similar rate of IVH and ICH volumes. ICH volume was significantly greater in

CAA-related ICH compared to undetermined or HTN-A ICH. In comparison to HTN-A and CAA related-ICH, patients with undetermined ICH etiology were observed to have a trend towards a higher rate of short-term mortality. Future population-based studies are warranted to assess the use of etiology-oriented classification and evaluate their use in different ethnic cohorts.

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Supplemental Materials

Expanded Materials and Methods

References [16-18, 43-53]

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Figure Legends

Figure 1. Flow-chart Diagram Presenting the Selection of Eligible Trials.

Figure 2. Pooled prevalence rates of Undetermined, Hypertensive Arteriopathy and Cerebral Amyloid Angiopathy related etiologies among spontaneous intracerebral hemorrhage patients.

Figure 3. Pooled mortality rates of Undetermined, Hypertensive Arteriopathy and Cerebral Amyloid Angiopathy related etiologies among spontaneous intracerebral hemorrhage patients.

Figure 4. Pooled intraventricular hemorrhage rates of Undetermined, Hypertensive Arteriopathy and Cerebral Amyloid Angiopathy related etiologies among spontaneous intracerebral hemorrhage patients.

Figure 5. Algorithm for the Diagnostic Evaluation of Patients with intracerebral hemorrhage

Table 1. Overview of the primary analyses

Etiology / Rates	Hypertensive arteriopathy; 95% CI	N	I^2, p for Cochran Q	CAA; 95% CI	N	I^2, p for Cochran Q	Undetermined; 95% CI	N	I^2, p for Cochran Q	P for subgroup difference
Prevalence	50% (43-58%)	22	98.7%, p<0.001	12% (7-17%)	15	98.7%, p<0.001	18% (13-23%)	24	98.3%, p<0.001	p<0.001
Mortality	22% (16-27%)	9	94.1%, p<0.001	24% (20-28%)	8	67.6%, p<0.001	33% (25-42%)	10	93.1%, p<0.001	p=0.079
IVH	40% (27-53%)	8	94.1%, p<0.001	28% (23-33%)	7	74.7%, p<0.001	38% (28-48%)	8	94.1%, p<0.001	p=0.084
ICH volume, ml	16.2 (10.9-21.5)	3	95.0%, p<0.001	24.7 (19.7-29.8)	3	81.8%, p<0.001	15.4 (6.2-24.5)	3	96.7%, p<0.001	p<0.001

CI indicates confidence interval; N, number of studies; CAA, cerebral amyloid angiopathy; IVH, intraventricular hemorrhage;

ICH, intracerebral hemorrhage

SUPPLEMENTAL MATERIAL

TITLE: Prevalence and Characteristics of Intracerebral Hemorrhage of Undetermined Etiology: A Systematic Review and Meta-Analysis

Supplemental Methods

Complete search algorithm used in MEDLINE search

((((((("intracerebral haemorrhage"[All Fields] OR "cerebral hemorrhage"[MeSH Terms]) OR ("cerebral"[All Fields] AND "hemorrhage"[All Fields])) OR "cerebral hemorrhage"[All Fields]) OR ("intracerebral"[All Fields] AND "hemorrhage"[All Fields])) OR "intracerebral hemorrhage"[All Fields]) OR (("intraparenchymal"[All Fields] OR "intraparenchymally"[All Fields]) AND ((((((((((((((((((((("blood"[MeSH Subheading] OR "blood"[All Fields]) OR "blood"[MeSH Terms]) OR "bloods"[All Fields]) OR "haematology"[All Fields]) OR "hematology"[MeSH Terms]) OR "hematology"[All Fields]) OR "haematoma"[All Fields]) OR "hematoma"[MeSH Terms]) OR "hematoma"[All Fields]) OR "haemorrhage"[All Fields]) OR "hemorrhage"[MeSH Terms]) OR "hemorrhage"[All Fields]) OR "haemorrhages"[All Fields]) OR "hemorrhages"[All Fields]) OR "haemorrhagic"[All Fields]) OR "haemorrhaging"[All Fields]) OR "hematologies"[All Fields]) OR "haematomas"[All Fields]) OR "hematomas"[All Fields]) OR "hematoma s"[All Fields]) OR "hematomae"[All Fields]) OR "hemorrhaged"[All Fields]) OR "hemorrhagic"[All Fields]) OR "hemorrhagical"[All Fields]) OR "hemorrhaging"[All Fields])))) OR (((((("intracranial haemorrhage"[All Fields] OR "intracranial hemorrhages"[MeSH Terms]) OR ("intracranial"[All Fields] AND "hemorrhages"[All Fields])) OR "intracranial hemorrhages"[All Fields]) OR ("intracranial"[All Fields] AND "hemorrhage"[All Fields])) OR "intracranial hemorrhage"[All Fields])) AND ((((("undeterminated"[All Fields] OR "undetermined"[All Fields]) OR "undefined"[All Fields]) OR "cryptogenic"[All Fields]) OR ((((((("classification"[MeSH Terms] OR "classification"[All Fields]) OR "classifications"[All Fields]) OR "classification"[MeSH Subheading]) OR "classification s"[All Fields]) OR "classificator"[All Fields]) OR "classificators"[All Fields]))) AND ((((((((((("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields]) OR "prevalence"[All Fields]) OR "prevalence"[MeSH Terms]) OR "prevalance"[All Fields]) OR "prevalences"[All Fields]) OR "prevalence s"[All Fields]) OR "prevalent"[All Fields]) OR "prevalently"[All Fields]) OR "prevalents"[All Fields]) OR ((((((("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields]) OR "incidence"[All Fields]) OR "incidence"[MeSH Terms]) OR "incidences"[All Fields]) OR "incident"[All Fields]) OR "incidents"[All Fields])) OR ("j rehabil assist technol eng"[Journal] OR "rate"[All Fields])) OR ("proportion"[All Fields] OR "proportions"[All Fields]))

Data Sources and Database Searches

The study included publicly available published studies and was exempt for approval from the Institutional Review Board. The study protocol for inclusion and exclusion criteria was designed *a priori* and was not registered. There were no restrictions performed during the literature search. Keywords used to query all of the databases included: “intracerebral hemorrhage”, “undetermined”, “undefined”, “cryptogenic”, “classification” and “prevalence”. For any missing or unpublished data, corresponding authors were contacted, and individual patient-level data was obtained. Additional manual search included conference abstracts and bibliographies of candidate studies and recent systematic reviews for a comprehensive literature search.

Data extraction

Three authors (KM, AT & CZ) independently reviewed the retrieved articles as summarized in the supplemental methods section of online supplement. In case of disagreements regarding the literature search results, the senior author (GT) was consulted to formulate a mutual consensus. The following information was extracted: name of study, first author and year of publication, mean age, sex distribution, total number of study participants, and clinical outcomes.

Study quality and assessment of publication bias

We used the Newcastle–Ottawa Scale as previously described to assess the quality of cohort studies included in our meta-analysis. Quality control and bias identification were performed independently by two authors (KM, AHK), and potential disagreements were resolved by a third tie-breaking evaluator (GT).

Publication bias across individual studies was graphically evaluated using a funnel plot, while funnel plot asymmetry was assessed using the Egger's linear regression test with $P<0.10$ significance level. For all other outcomes of interest, we performed equivalent z test for each pooled estimate, and a two-tailed P levels <0.05 was considered statistically significant.

Supplemental Tables

Supplemental Table I: Excluded Studies with Reasons for Exclusion

Study name	**Reason for exclusion**
Gedansky et al	Prevalence of ICH classification unavailable
Guidoux et al	Etiology-related prevalence rates unavailable
Liu et al	Prevalence of ICH classification unavailable
Jolink et al	Prevalence of ICH classification unavailable
Rincon et al	Prevalence of ICH classification unavailable
Bejot et al	Prevalence of ICH classification unavailable
Tveiten et al	Prevalence of ICH classification unavailable
Lavados et al	Prevalence of ICH classification unavailable
Obajimi et al	Prevalence of ICH classification unavailable
Qureshi et al	Excluded due to mutual patient cohort

Supplemental Table II. Study design and characteristics of included studies in our meta-analysis

First author, Year	Country, Design	ICH classification	Total patients, n	Men, %	Mean age, years	Initial NIHSS (median)	Detailed Neuroimaging; MRI with GRE, Angiography
Awada, 1996	Saudi Arabia, Retrospective	None	243	73.2	56.9±18.2	NA	No*, Yes
Chang, 2018	United States, Retrospective	SMASH-U	803	68	63±14	9 (3-18)	Yes, Yes #
Del Brutto, 1999	Ecuador, Retrospective	None	151	61	33.6±8.5	NA	No*, Yes
Forman, 2020	United States, Retrospective	None	220	31.8	85.6	NA	Yes, Yes
Gupta, 2019	Canada, Retrospective	SMASH-U	162	61	72.2±12.6	5 (2-15)	Yes, Yes
Koivunen, 2015	Australia, Retrospective	None	336	59.5	42 (34-47)	8 (2-19)	Yes, Yes
Lai, 2005	Taiwan, Retrospective	None	296	75.6	37±7.7	NA	No*, Yes
Lei, 2016	China, Retrospective	SMASH-U	3475	64.5	59.1	NA	Yes, Yes #
Marti-Fabregas, 2016	Spain, Prospective	H-ATOMIC	439	61.3	70.8±14.5	8 (3-19)	Yes, Yes
Meretoja, 2012	Australia, Retrospective	SMASH-U	1013	57	68	11 (4-20)	Yes, Yes
Mosconi, 2020	Italy, Retrospective	SMASH-U	726	55.7	72±13.9	NA	Yes, Yes
Ohtani, 2003	Japan, Retrospective	None	81	69.13	63.5±13.5	NA	No*, Yes

Palm, 2013	Germany, Prospective	SMASH-U	152	50.7	71.3±13.5	NA	Yes, Yes
Qureshi, 1997	United States, Retrospective	None	403	56.6	56.4±14.3	NA	No*, Yes
Qureshi, 2015	United States, Retrospective	None	50	NA	70.1±14.9	NA	No*, Yes
Rosenow, 1997	Germany, Retrospective	None	896	53	57	NA	No*, Yes
Ruiz-Sandoval, 1999	Mexico, Retrospective	None	200	53	27±6.7	NA	No*, Yes
Rutten-Jacobs, 2014	Netherlands, Prospective	None	98	50	38	12 (4-16)	No, No
Sarfo, 2018	Nigeria, Retrospective	SMASH-U	270	59.4	40.95±6.58	NA	Yes, Yes
van Asch, 2015	Netherlands, Prospective	None	298	23.1	53±11.5	NA	Yes, Yes
Wu, 2017	Finland, Retrospective	SMASH-U	1452	57	70	NA	Yes, No [#]
Y Chen, 2016	France, Prospective	None	32	53.1	67	31 (11-38)	Yes, No
YC Chen, 2006	Taiwan, Retrospective	None	247	77.7	39.3±5.8	NA	No*, Yes

Yeh, 2014	Taiwan, Prospective	SMASH-U	3785	63.3	59	12 (5-22)	Yes, Yes

ICH indicates intracerebral hemorrhage; MRI, Magnetic resonance imaging; GRE, Gradient-recalled echo sequence, NIHSS, National Institutes of Health Stroke Scale; and SMASH-U, structural vascular lesions, medication, cerebral amyloid angiopathy, systemic disease, hypertension, or undetermined; H-ATOMIC, Hypertension, cerebral Amyloid angiopathy, Tumor, Oral anticoagulants, vascular Malformation, Infrequent causes and Cryptogenic; NA: not available. Data are expressed as mean ± SD, median [interquartile range], or no. (%) as provided in selected studies.

* Only MRI brain was performed without reference of GRE or SWI sequence.

[#] Not all patients underwent detailed neuroimaging

Supplemental Table III. Patient characteristics regarding risk factors for intracerebral hemorrhage of included studies in our meta-analysis

First author, Year	Prior ICH (%)	History of alcohol consumption (%)	Prior treatment with statins (%)	Prior treatment with anticoagulant (%)	Prior treatment with antiplatelets (%)
Awada, 1996	NA	NA	NA	2.1	NA
Chang, 2018	NA	4.0	25.8	3.8	32.1
Del Brutto, 1999	NA	NA	NA	1.3	NA
Forman, 2020	NA	NA	NA	NA	NA
Gupta, 2019	NA	NA	NA	43.2	42
Koivunen, 2015	NA	14.6	NA	0.6	NA
Lai, 2005	NA	6.3	NA	NA	NA
Lei, 2016	NA	20.1	NA	3.0	2.1
Marti-Fabregas, 2016	7.3	NA	NA	17.4	26.7
Meretoja, 2012	5	NA	19	13	26
Mosconi, 2020	7.2	NA	NA	14.5	25.1
Ohtani, 2003	NA	50.6	NA	NA	NA
Palm, 2013	NA	NA	NA	15.8	23
Qureshi, 1997	NA	40.4	NA	NA	NA
Qureshi, 2015	NA	NA	NA	NA	NA
Rosenow, 1997	NA	10.7	NA	12.3	NA
Ruiz-Sandoval, 1999	NA	9.5	NA	NA	NA
Rutten-Jacobs, 2014	0	NA	NA	5.2	NA
Sarfo, 2018	NA	2.0	NA	NA	NA
van Asch, 2015	NA	11.1	NA	0	9.7
Wu, 2017	5	NA	22	14	30

Y Chen, 2016	3.2	26.7	18.8	NA	NA
YC Chen, 2006	NA	42.6	NA	NA	NA
Yeh, 2014	NA	18.4	NA	3.2	5.2

NA: not available. Data are expressed as percentages (%) as provided in selected studies

Supplemental Table IV: Definitions of various etiologies of ICH among studies without use of etiology-oriented classification

Authors, Year	Definition of undetermined ICH	Definition of HTN-A ICH	Definition of CAA ICH
Awada, 1996	Using appropriate diagnostic studies	Chronic HTN with LVH on EKG and/or fundoscopic changes and no other cause	Using appropriate diagnostic studies
Del Brutto OH, 1999	NA	NA	NA
Forman, 2020	NA	NA	NA
Koivunen, 2015	NA	Absence of vascular causes or lobar location of ICH	NA
Lai, 2005	Neuroimaging was not performed, or patients died before examination	According to clinical findings and location of ICH	NA
Ohtani, 2003	NA	NA	NA
Qureshi, 1997	ICH without features typical of hypertensive etiology and normal or no angiograms	Presence of established or newly diagnosed HTN with ICH at typical HTN related sites or at sites less likely to be associated with HTN or to have a high frequency of underlying vascular lesions, after neuroimaging ruled out other etiologies	NA
Qureshi, 2015	ICH without features typical of hypertensive etiology and normal or no angiograms	Presence of established or newly diagnosed HTN with ICH at typical HTN related sites or at sites less likely to be associated with HTN or to have a high frequency of underlying vascular lesions, after neuroimaging ruled out other etiologies	NA
Rosenow, 1997	NA	History of HTN, antihypertensive medication at discharge or prior to the ICH, or elevated BP >160/100 later than 6 days after ICH or signs of LVH on EKG or at autopsy	NA
Ruíz-Sandoval JL, 1999	patients without risk factors or predisposing conditions, no structural	ICH located in typical hypertensive related ICH, or white matter (including lobar) and documentation 3 different readings of HTN with	NA

	abnormalities on MRI or angiograms to explain ICH and with follow-up for 6 months with control neuroimaging	BP readings >160/95 mm Hg or actual treatment, and exclusion of other potential cause of ICH	
Rutten-Jacobs, 2014	NA	ICH in locations of hypertensive cause, in patients without a known history of HTN, and no evidence of a vascular malformation or other etiology	NA
van Asch, 2015	NA	ICH in locations of hypertensive cause in presence of HTN	According to the Boston criteria
Y Chen, 2016	Unable to fulfill criteria for CAA or deep perforating vasculopathy	ICH in locations of hypertensive cause without any acute or old bleed in lobar location	According to the Boston criteria
YC Chen, 2006	No vascular abnormalities on neuroimaging of patients without risk factors	HTN diagnosed by a clinician or SBP>140 mm Hg and/or DBP >90 mm Hg for 6 months after the acute ICH with prescription of antihypertensive medication	NA

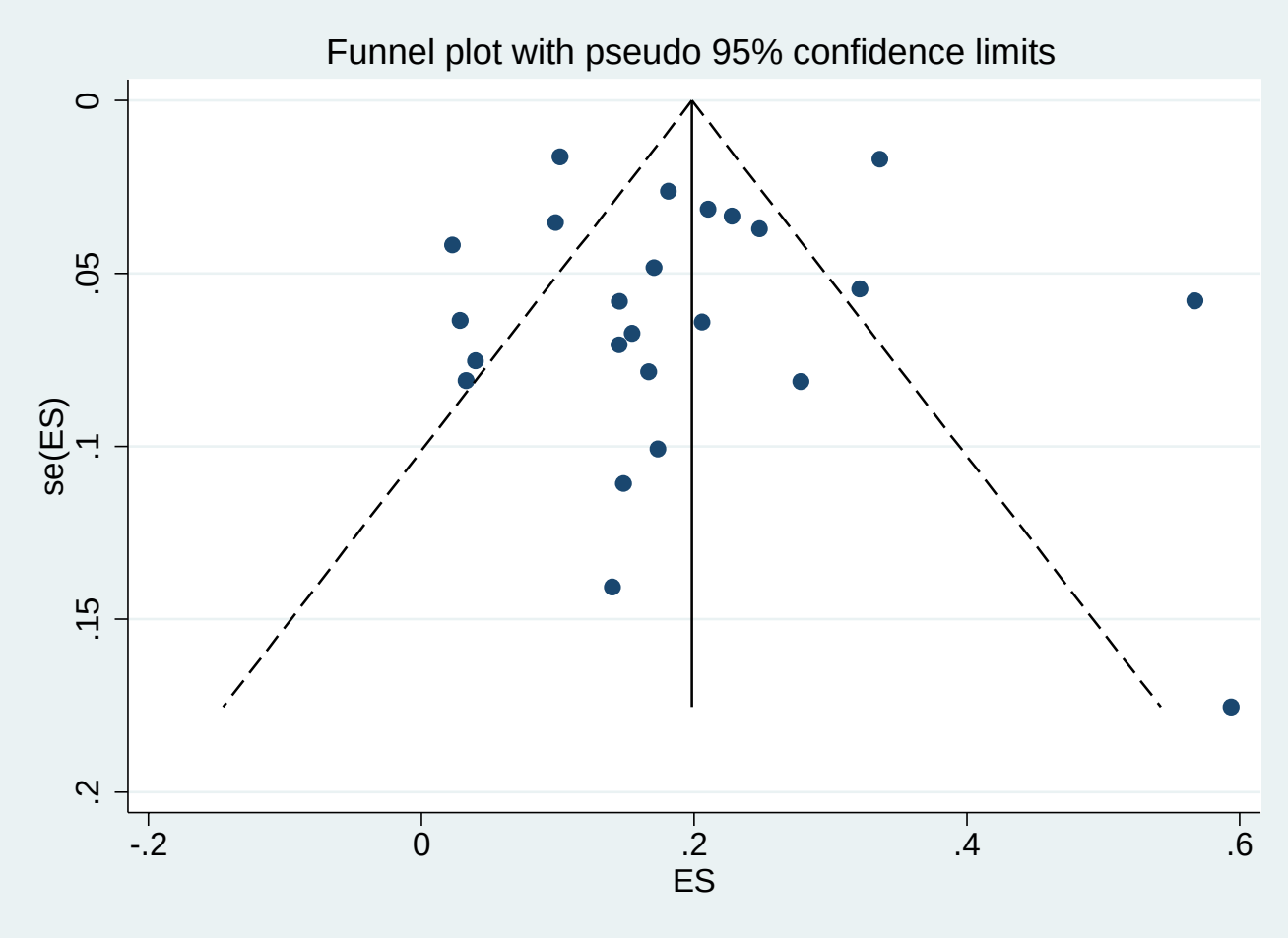
HTN indicates hypertension; LVH, left ventricular hypertrophy; HTN-A, hypertensive arteriopathy; CAA, cerebral amyloid angiopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; EKG, electrocardiography; NA, not available

Supplemental Table V: Quality assessment of included studies with the Newcastle–Ottawa Scale

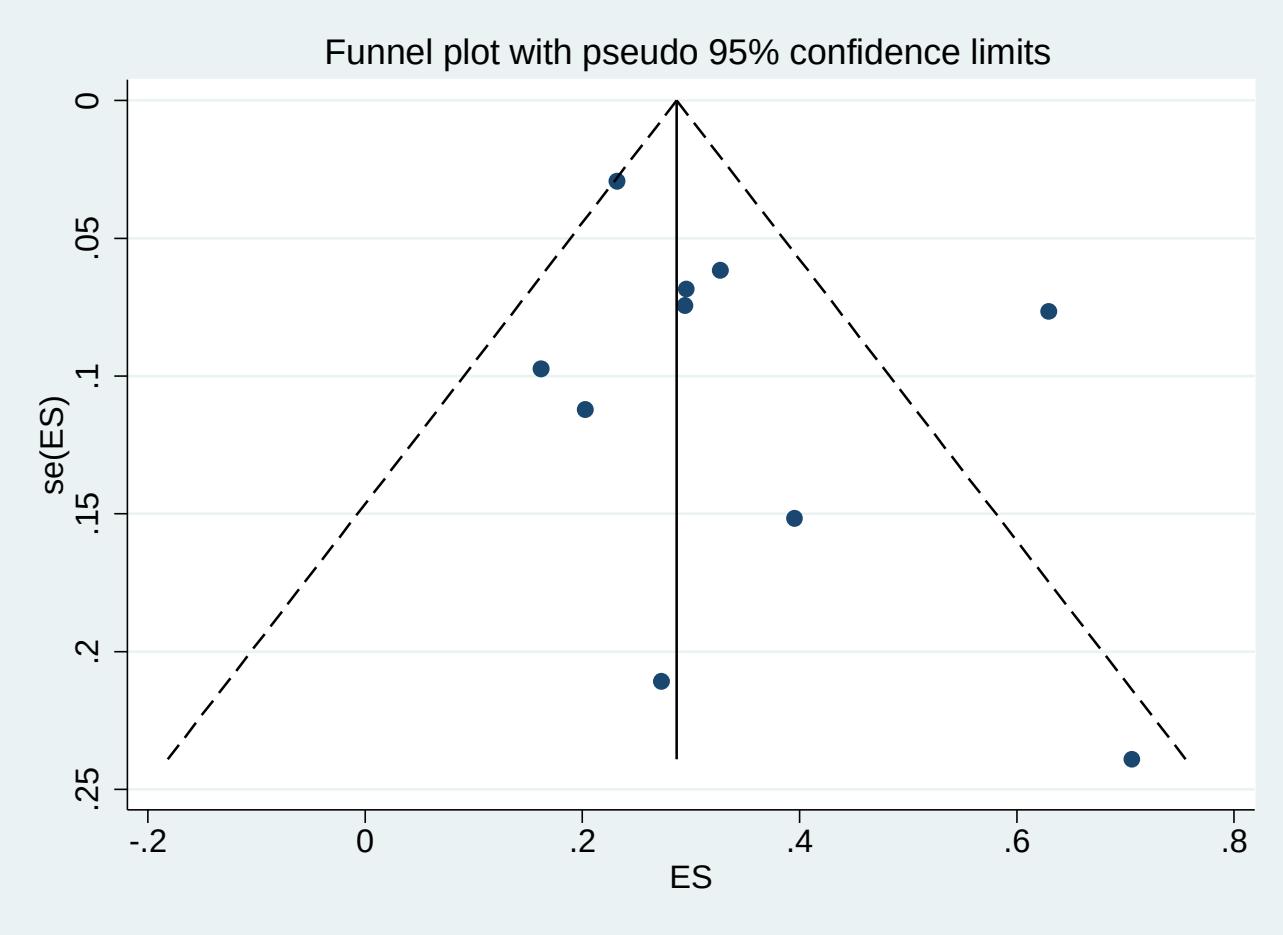
First author, Year	Selection	Comparability	Outcome	Overall score
Awada, 1996	***		*	4/9
Chang, 2018	***	**	**	7/9
Del Brutto, 1999	***		*	4/9
Forman, 2020	***	**	*	6/9
Gupta, 2019	***		*	4/9
Koivunen, 2015	***		**	5/9
Lai, 2005	***	**	**	7/9
Lei, 2016	***	**	**	7/9
Marti-Fabregas, 2016	***		*	4/9
Meretoja, 2012	***	**	***	8/9
Mosconi, 2020	***		*	4/9
Ohtani, 2003	**		*	3/9
Palm, 2013	***	**	**	7/9
Qureshi, 1997	***		*	4/9
Qureshi, 2015	***	**	*	6/9
Rosenow, 1997	***		*	4/9
Ruiz-Sandoval, 1999	***		**	5/9
Rutten-Jacobs, 2014	***		***	6/9
Sarfo, 2018	****	**	*	7/9
van Asch, 2015	****		**	6/9
Wu, 2017	***	**	***	8/9
Y Chen, 2016	***		**	5/9
YC Chen, 2006	***	**	***	8/9
Yeh, 2014	***	**	**	7/9
Total	73/96	22/48	41/72	136/216

Supplemental Figures

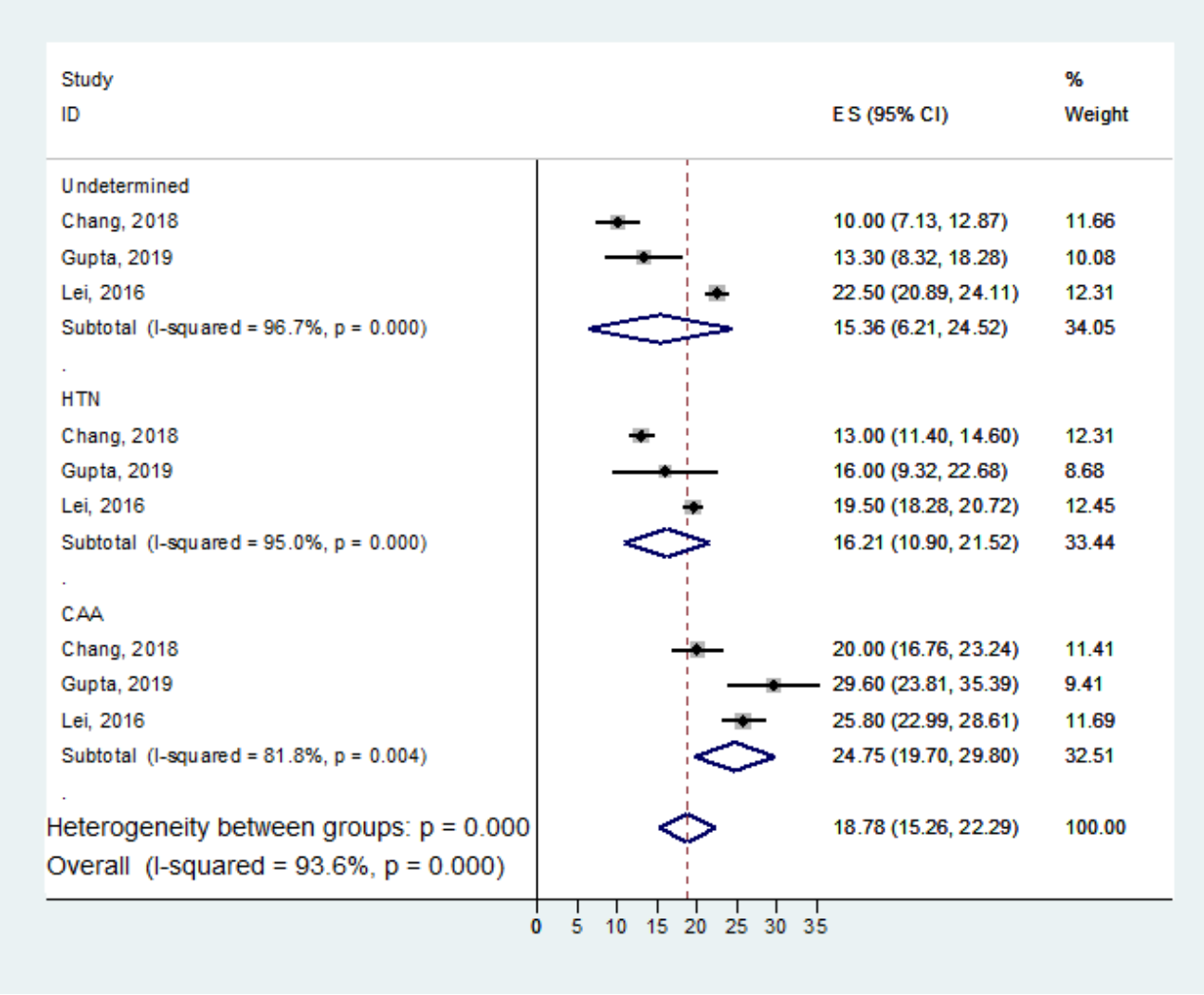
Supplemental Figure I: Funnel Plot with pseudo 95% confidence interval demonstrating the effect sizes derived from each study (logit event rate) against their corresponding standard errors reporting prevalence rates among spontaneous intracerebral hemorrhage patients of unknown etiology.



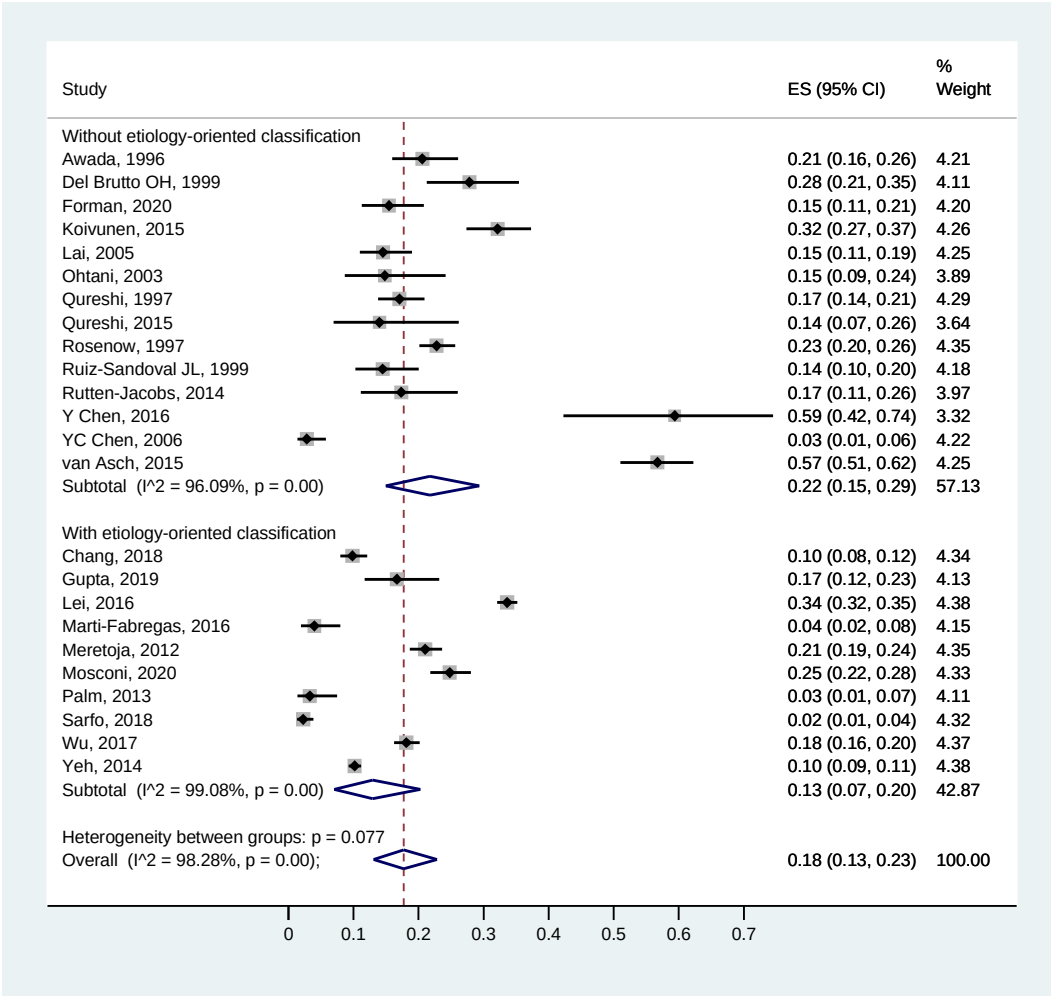
Supplemental Figure II: Funnel Plot with pseudo 95% confidence interval demonstrating the effect sizes derived from each study (logit event rate) against their corresponding standard errors reporting mortality rates among spontaneous intracerebral hemorrhage patients of unknown etiology.



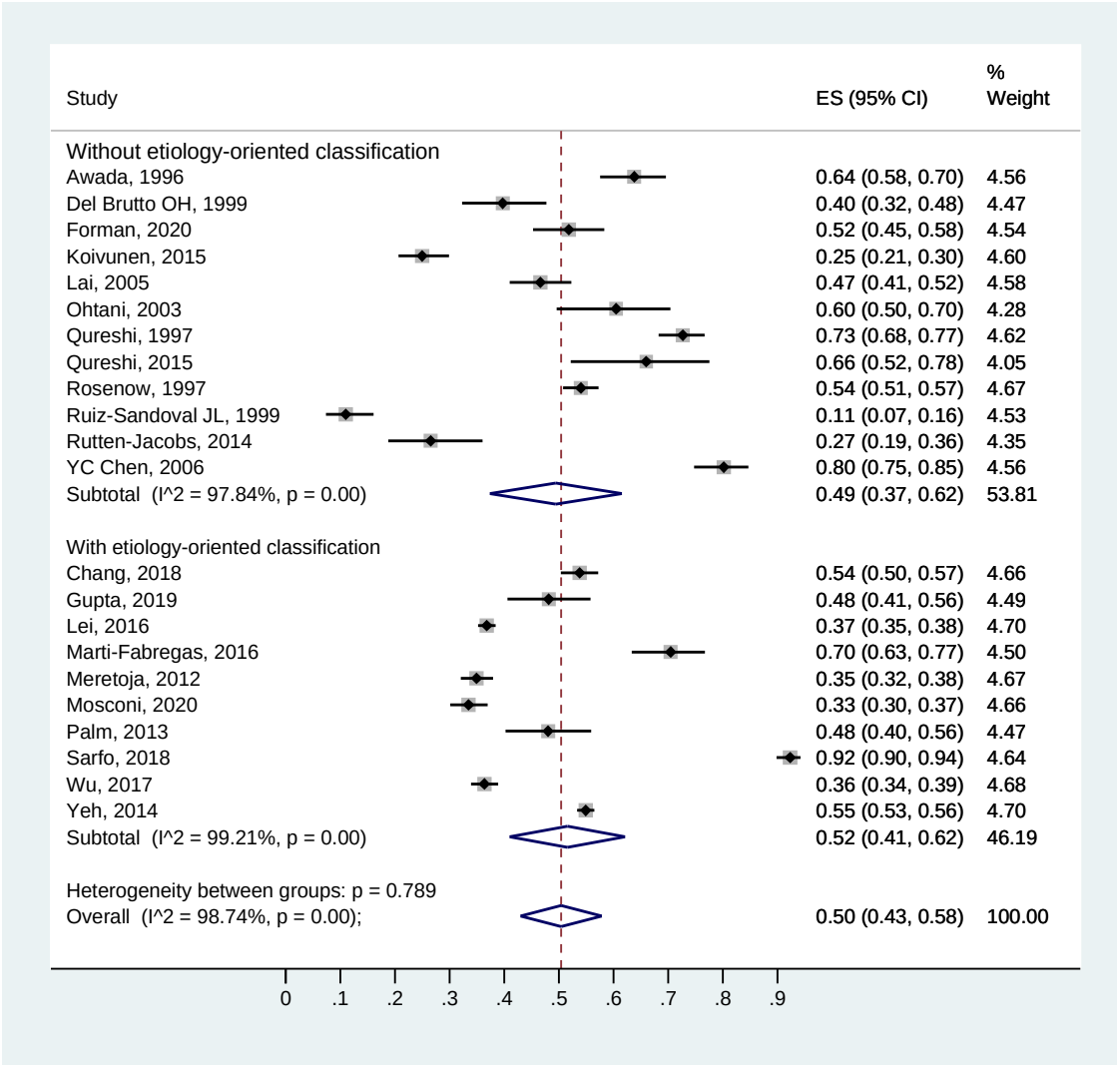
Supplemental Figure III: Pooled intracerebral hemorrhage volumes rates of undetermined, hypertensive arteriopathy and cerebral amyloid angiopathy related etiologies among spontaneous intracerebral hemorrhage patients.



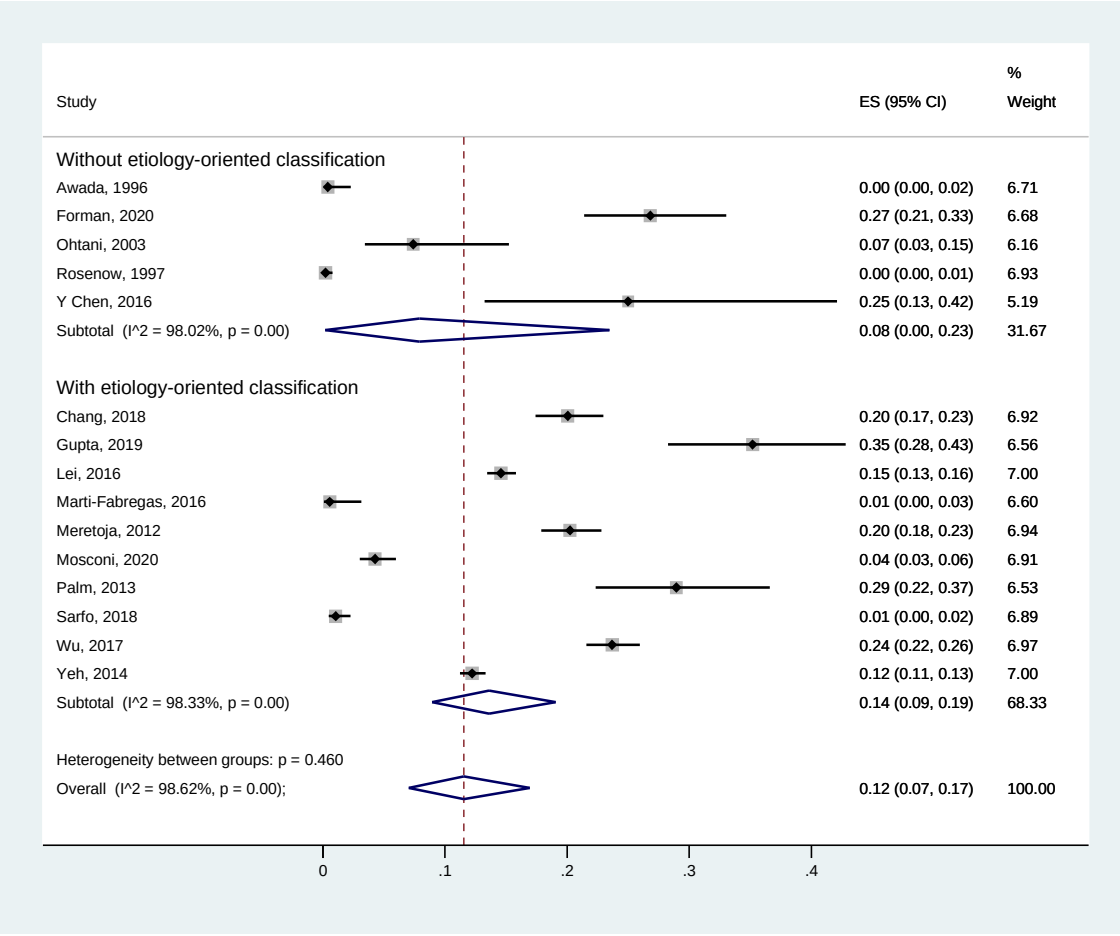
Supplemental Figure IV: Subgroup analysis according to etiology-oriented classification comparing the prevalence rates of undetermined etiology among spontaneous intracerebral hemorrhage patients



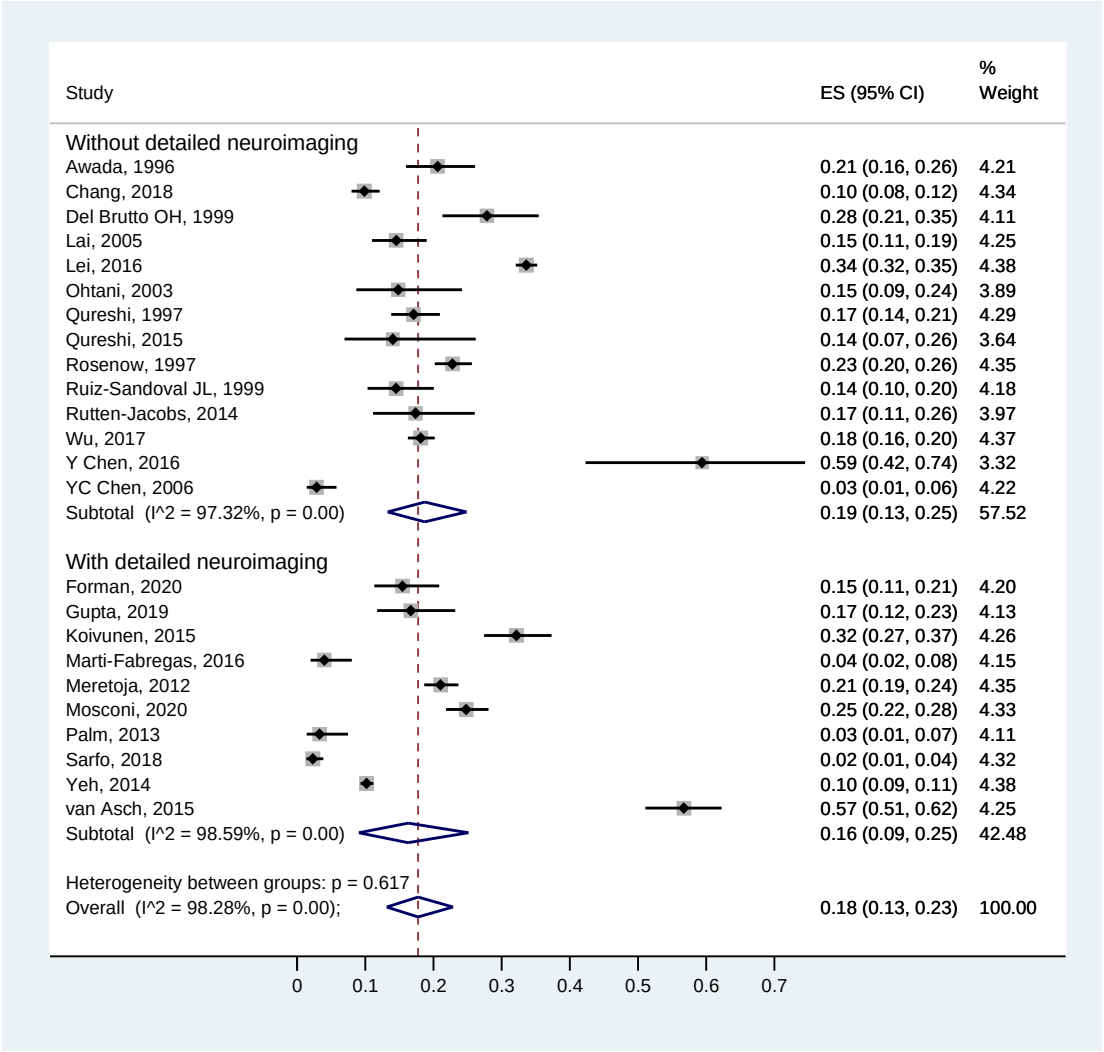
Supplemental Figure V: Subgroup analysis according to etiology-oriented classification comparing the prevalence rates of hypertensive arteriopathy-related etiology among spontaneous intracerebral hemorrhage patients



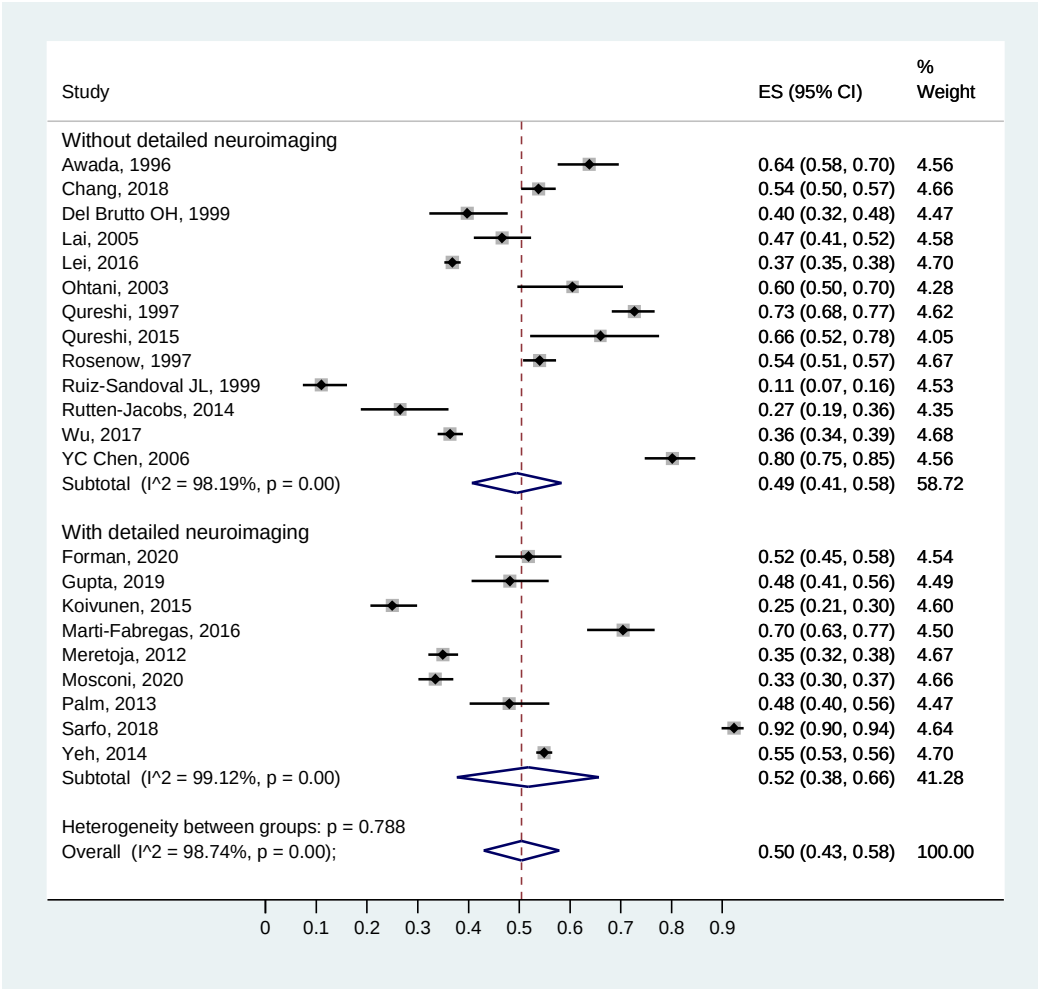
Supplemental Figure VI: Subgroup analysis according to etiology-oriented classification comparing the prevalence rates of cerebral amyloid angiopathy-related etiology among spontaneous intracerebral hemorrhage patients.



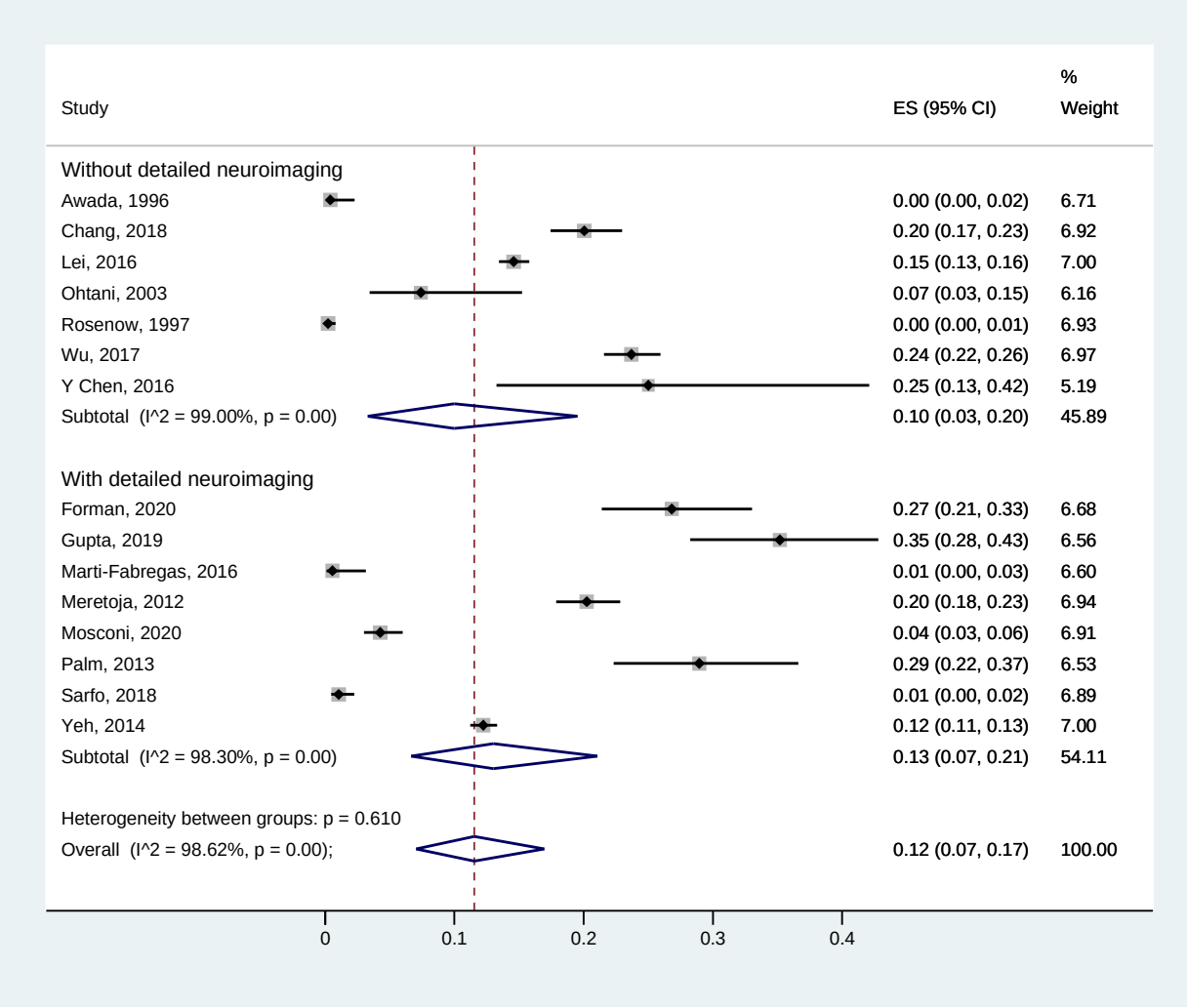
Supplemental Figure VII: Subgroup analysis of studies with and without detailed neuroimaging comparing the prevalence rates of undetermined etiology among spontaneous intracerebral hemorrhage patients.



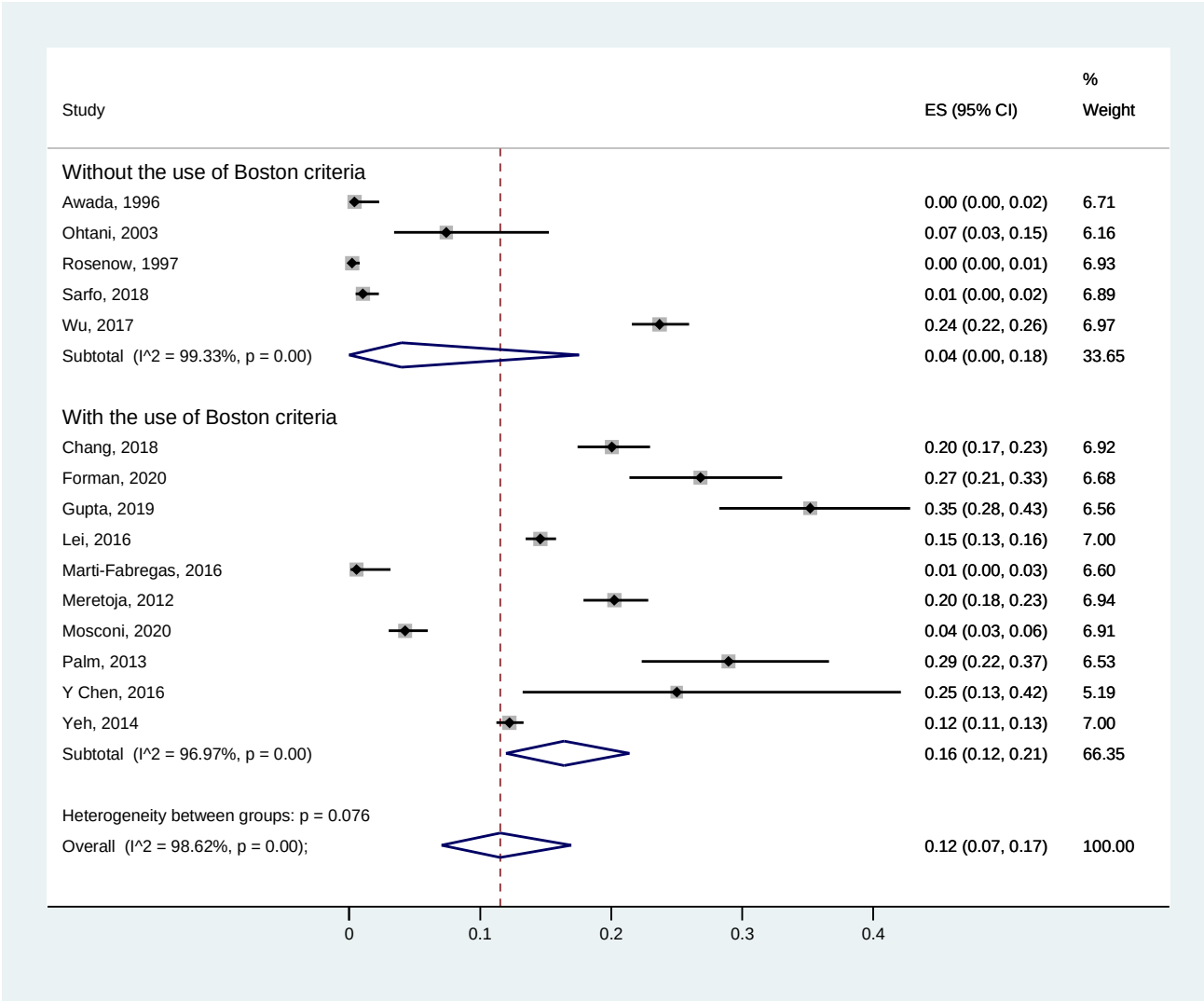
Supplemental Figure VIII: Subgroup analysis of studies with and without detailed neuroimaging comparing the prevalence rates of hypertensive arteriopathy-related etiology among spontaneous intracerebral hemorrhage patients.



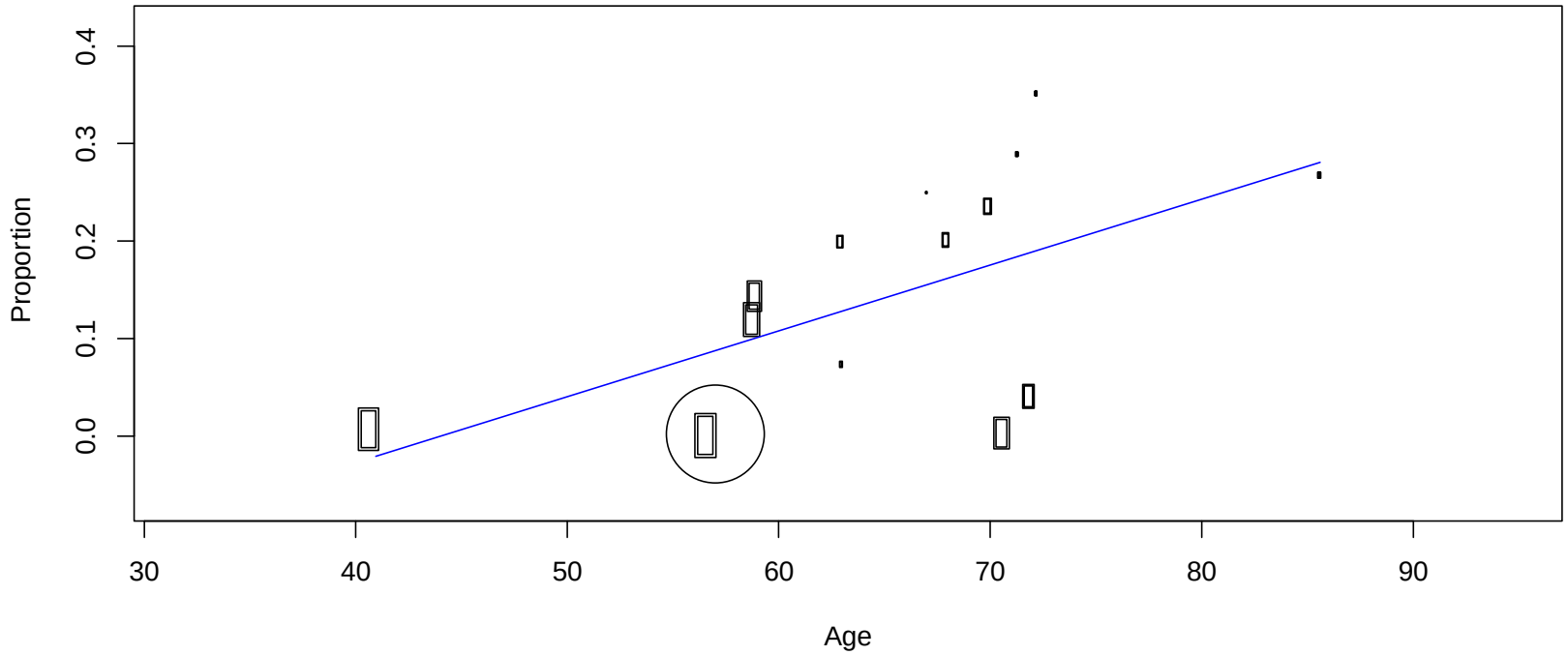
Supplemental Figure IX: Subgroup analysis of studies with and without detailed neuroimaging comparing the prevalence rates of cerebral amyloid angiopathy-related etiology among spontaneous intracerebral hemorrhage patients.



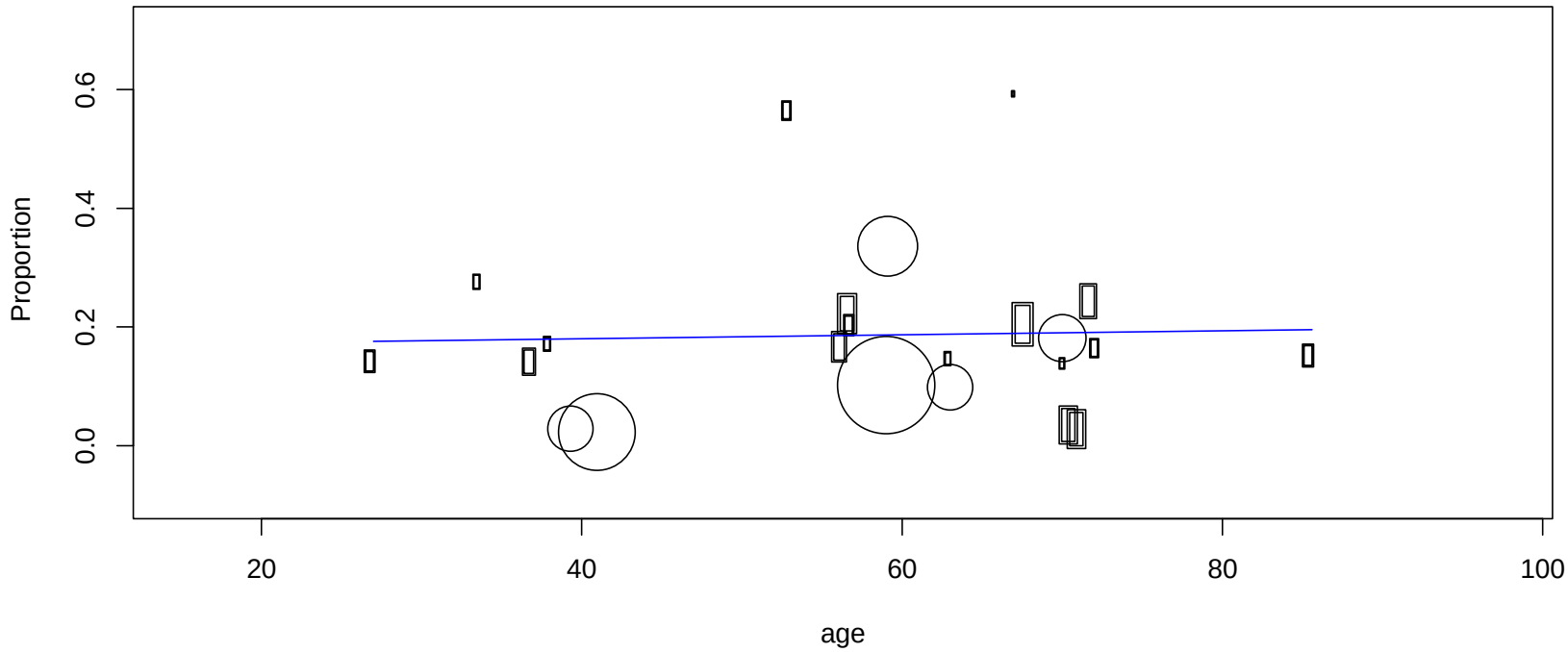
Supplemental Figure X: Subgroup analysis of studies based on the use of Boston Criteria to assess the prevalence rates of cerebral amyloid angiopathy-related etiology among spontaneous intracerebral hemorrhage patients.



Supplemental Figure XI: Meta-regression analysis of studies on the association of age with prevalence of cerebral amyloid angiopathy-related etiology among spontaneous intracerebral hemorrhage patients.



Supplemental Figure XII: Meta-regression analysis of studies on the association of age with prevalence of undetermined etiology among spontaneous intracerebral hemorrhage patients.



Supplemental Figure XIII: Meta-regression analysis of studies on the association of age with prevalence of hypertensive arteriopathy-related etiology among spontaneous intracerebral hemorrhage patients.