# Cognitive impairment before and after intracerebral haemorrhage: a systematic review

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**Conflict of interest**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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## Abstract

**Introduction:** There is increasing interest in understanding cognitive dysfunction before and after Intracerebral haemorrhage (ICH), given the higher prevalence of dementia reported (ranging from 5% to 44%) for this stroke type. Evidence to date examining cognitive impairment associated with cerebrovascular disease has tended to focus more on ischaemic stroke. The aim of this review was to identify and quantify studies that focused on cognitive dysfunction pre and post ICH.

**Methods:** We conducted a systematic search using databases PubMed, Science Direct, Scopus and PsycINFO to identify studies that exclusively assessed cognitive function pre and post ICH. Studies were included in the review if used a measure of global cognition and/or a neuropsychological battery to assess cognitive function. Nineteen studies were deemed relevant for inclusion, where n=8 studies examined cognitive impairment pre ICH and n=11 post ICH.

**Results:** Prevalence of cognitive impairment ranged between 9%-29% for pre ICH and 37%-88% for post ICH. Predictive factors identified for pre and post ICH were previous stroke, ICH volume and location, and markers of cerebral amyloid angiopathy (CAA). Most common cognitive domains affected post ICH were information processing speed, executive function, memory, language and visuo-spatial abilities. Most common cognitive assessments tools were the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) for preexisting cognitive impairment and the Mini-Mental State Examination for global cognition post ICH and the Trail Making Test for neuropsychological testing.

**Conclusion:** Cognitive impairment and dementia affected almost one-third of patients examined, whether assessing cognitive functioning either pre or post ICH.

# 1. Introduction

Spontaneous, non-traumatic intracerebral haemorrhage (ICH) is defined as bleeding within the brain parenchyma and occurs without trauma or known bleeding causes such as an arteriovenous malformation, cerebral aneurysm or tumour [1]. ICH accounts for 10-15% of all strokes worldwide. The overall incidence of ICH is reported to range between 15 to 40 cases per 100,000, but might be higher in Asian populations, and has increased in individuals over 75 years [14]. ICH can be classified by its location and is referred to as lobar (15%-30%), deep (35%-70%) or infratentorial (10%-20%) [1, 10]. Lobar ICH are located in cortical-subcortical areas, while deep ICH are located within the basal ganglia; infratentorial ICH (sometimes classified under deep ICH) involves the brainstem and cerebellum. Regarding aetiology, the most frequent cause of lobar ICH in older people is cerebral amyloid angiopathy (CAA) [14], which refers to abnormal aggregations of beta amyloid deposits that form in the walls of cerebral arteries, arterioles and capillaries, causing an increased risk of intracerebral bleeding and cognitive impairment [13]. By contrast, the commonest cause of deep ICH is deep perforating vasculopathy [37] or "hypertensive arteriopathy" and has range of different pathological features including arteriolosclerosis, fibrinoid necrosis and mural thickening or damage [9]; hypertension is an important (but not necessary) risk factor.

### 1.1 Post stroke cognitive impairment and/or dementia

Historically, much attention regarding cognitive impairment as a result of stroke has tended to focus on ischaemic stroke subtype because it is more common than ICH, with lower mortality. In contrast, ICH have been considered methodologically more challenging to include in studies due to their higher mortality rates and greater stroke severity. However, regardless of stroke subtype cognitive impairment has greatest impact on individuals' lives [20] in terms of coping strategies and adjustment after stroke [16]. Preexisting and new dementia has been reported to be frequent in stroke patients with 10% of patients having dementia before first stroke, 10% developing new dementia soon after first stroke, and more than a third having dementia after recurrent stroke [42].

Cognitive impairment is one of the most common sequelae following stroke with 40%-75% of stroke survivors experiencing some degree of cognitive deficit [11, 15, 56]. For the majority of patients, some degree of cognitive impairment will be evident in the acute phase post stroke where associated predictors include type of stroke, recurrent stroke episodes, site and laterality of the lesion(s), volume of cerebral infarction, medial temporal lobe atrophy, and coexistent neurodegenerative pathology. Other biological factors known to exacerbate cognitive impairment further are aphasia, diabetes mellitus, atrial fibrillation, and depression [15, 28]. Many of the cognitive problems resolve over time, but approximately 35% of individuals will be left with some residual cognitive impairment and poor long-term outcomes, including survival and disability, up to four years after stroke [15]. Definitions for post stroke cognitive impairment and post stroke dementia are sometimes used interchangeably within studies due to the variety of classifications and diagnostic criteria for describing post stroke cognitive problems [25, 34]. Cognitive assessment after stroke is further complicated by the varying measures used, lack of measurement of cognition before stroke and the diversity and variation of measures used post stroke. Vascular cognitive impairment, inclusive of vascular dementia [54], in ischaemic and ICH refers to cognitive deficits that result from a range of vascular lesions and pathologies [63]. However, within the last decade, there has been an increasing focus on understanding cognitive dysfunctions in patients after ICH given the high prevalence of dementia, ranging from 5% to 44% reported for this stroke subtype [63].

**1.2 Cognitive impairment and ICH**

Understanding the underlying mechanisms for cognitive impairment following ICH is important to improve knowledge of prognosis and clinical management. The underlying pathologies associated with ICH are also potential mechanisms determining cognitive impairment [39], in addition to direct tissue injury from ICH. Small vessel diseases (SVD; CAA and deep perforating arteriopathy), the common underlying pathologies in patients with ICH, are considered to be the underlying determinant for pre-existing cognitive impairment before ICH, and might also influence the severity and location of the Index ICH and cognitive deficits observed in the acute phase [63]. The underlying SVD and/or neuropathology might also contribute, in the chronic phase, for cognitive decline. There has been extensive evidence

linking SVD disease, in particular cerebral microbleeds (CMBs) [32] and CAA [57], to vascular cognitive impairment in the aged brain [8]; there are ongoing efforts to understand the precise nature of these underlying mechanisms [51]. Although previous reviews have aimed to understand the relationship between ICH and dementia [39, 44], there is growing evidence to suggest that pre-existing cognitive impairment and dementia are common in patients with ICH [63] and that cognitive decline after ICH is part of an ongoing progressive process rather than being triggered by the ICH event itself [61]. More recent reviews have highlighted the lack of studies determining pre-existing cognitive deficits [20, 54] and that studies in community or hospital settings should identify those patients who have suffered the cognitive decline before the stroke in terms of analysis to understand predisposing associated risk factors better. The aim of this systematic review is to identify and quantify studies that have focused exclusively on evaluating cognitive function pre or post ICH. The review objectives are to identify the prevalence of cognitive impairment, methods of cognitive assessment used, and to determine specific cognitive domains affected pre or post ICH.

_____TABLE 1 ABOUT HERE_____

# 2. Method

### 2.1 Search strategy

We conducted a systematic review for studies examining the assessment of cognitive function pre or post intracerebral haemorrhage. The computer search was performed on databases PubMed, Science Direct, Scopus and PsycINFO up to January 30, 2019. Initial searches were carried out to examine variation in phraseology relating to the research topic. Key search terms were refined on the basis of MeSH results. These included “intracerebral haemorrhage”, “cognitive impairment” and “neuropsychological assessment”, and were combined using Boolean operators (see Table 1 for search syntax). In addition to the databases’ searches, reference lists of selected articles were checked for their included relevant research papers.

_____FIGURE 1 HERE_____

### 2.2 Selection and categorisation of articles

The following inclusion and exclusion criteria were used:

(a) Inclusion criteria:

- Studies that focused exclusively on spontaneous intracerebral haemorrhage.
- Descriptive and observational studies that included cognitive assessment pre or post ICH as the primary study aim.
- Peer-reviewed empirical studies.
- Written in English.

(b) Exclusion criteria:

- Study cohorts were traumatic ICH or subarachnoid or other haemorrhage types.
- Study cohorts that were ischaemic stroke, TIA and mixed stroke cohorts (cognitive assessment not stratified by stroke type).
- Animal studies.
- Research articles describing research proposals, reviews or commentaries.
- Study cohorts with age < 18 years (childhood stroke).
- Single individual case studies.

The publication selection process adhered to the PRISMA guidelines [35]. Studies that met the inclusion criteria were then assessed against indicators for methodological quality in terms of study design and statistical methods employed. The quality of the included studies in the review were critically appraised, using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [59] as a checklist of what must be reported and in what part of a publication, and the Consensus-based Standards for the selection of health status Measurement Instruments (COSMIN) methodology [36] as an evaluation tool for publication quality assessment. The lead author (CD) screened all records identified from the database computer search. Two independent raters (CD and DW) evaluated the studies at the eligibility and inclusion phases of the review where there was full agreement for publication selection.

# 3. Results

From using the extensive search syntax in Table 1, n=1715 articles were identified through the database computer search. Following removal of duplicates and records meeting the exclusion criteria, n=47 abstracts were then screened for eligibility (see Figure 1). A further n=24 records were excluded at this stage of screening due to articles: only relevant to ischaemic stroke (n=2), were a protocol, review article or correction (n=3), no cognitive assessment included (n=5), assessed risk of stroke (n=1), not in English (n=1), were mixed stroke cohort and did not report cognitive function stratified by stroke type (n=10) or were case studies (n=2).

Twenty-three full-text articles were then assessed for eligibility to be included in the review. Twelve of these articles were excluded at this eligibility stage as they did not meet the inclusion criteria of focusing exclusively on ICH cohorts. Excluded articles included studies focusing on cognitive assessment in mixed stroke cohorts (ischaemic and haemorrhagic strokes) where cognitive assessment results were described or reported by stroke type. A further n=8 studies were identified for inclusion from the reference lists of the identified articles from the initial computer search. Finally, n=19 studies were selected to be eligible to be included in the review (see figure 1). All studies scored adequate to very good for methodological quality by COSMIN indicating a lower risk of bias assessment. These studies were organised into 2 categories for summarizing main neuropsychological assessment, studies' findings and critical appraisal of each category. The studies reviewed related to assessment of cognitive function 1. Pre ICH (n=8) or 2. Post ICH (n=11). Table 2 presents a summary of the studies reviewed.

_____TABLE 2 HERE_____

### 3.1 Characteristics of included studies

Overall, all studies (n=19) included in this review aimed to identify factors associated with cognitive impairment either pre or post ICH in order to understand the impact on patients' outcome (see Table 2). There was wide variation across all studies regarding cohort sizes, ICH

location ratio, neuropsychological and/or cognitive assessment in terms of measures or tools used, heterogeneous timing of assessment post ICH and type of study design e.g. prospective or retrospective studies. The average age range of cohorts was between 52 and greater than 80 years of age and no apparent gender or other socio-demographic differences were identified with the exception of one study that aimed to examine ethnic-origin differences [41]. All studies used CT and/or MRI for assessing volume and location of ICH. The proportion of deep ICH compared to lobar and infratentorial was generally higher in all studies that reported this. The majority of studies reported using the ABC/2 method [30] for determining haemorrhage volume calculation and the Boston Criteria [29] for studies identifying probable and possible CAA as an associated variable with cognitive impairment. However, in some studies haematoma volume was determined [5, 48, 53] by other methods such as computerized volumetric analysis [18]. Five studies [5, 6, 19, 26, 45] quantified the amount of white matter hyperintensity, attributed to small vessel disease, using the Fazekas Scale [17]. Two studies reported using other methods for determining WMH such as the Age-Related White Matter Changes (ARWMC) Rating Scale [31] and WMH volume determined on a fluid attenuated Recovery sequence [58]. Neuroimaging markers of cerebral small vessel disease were defined using the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria [60] in 4 studies [4, 5, 45, 62]. One study included neuropathology in addition to radiological assessment of ICH [12]. However, other studies used less precise imaging methods for describing anatomical atrophy from the resulting ICH and associated pathology [40, 53].

### 3.2 Cognitive assessment pre ICH and associated factors

The Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) was the most commonly used measure for assessing preexisting cognitive impairment and dementia [5, 12, 31, 48, 52, 58] pre ICH. The IQCODE is a 26-item and a shortened version 16-item validated questionnaire administered to a patient's family member or caregiver to assess pre morbid cognitive function in the past 10 years [27]. Other approaches to assess pre-existing dementia or cognitive impairment were by patients' physicians before hospitalization through formal clinical evaluation [41] and also via medical records [26, 48, 58]. Prevalence of pre morbid cognitive impairment varied between 9.3% [41] and 29% [12] and for reported dementia

between 9.3% [41] and 16% [12]. The main factors associated with pre morbid cognitive impairment were neuroimaging markers of CAA [5], prior stroke or TIA [31], haematoma volume [31, 48], ICH location, functional independence, age and Glasgow Coma Scale score [48].

For studies that reported results by ICH classification, for lobar ICH, factors associated with pre morbid cognitive impairment were mortality [26], increasing age, education [12], degree of tissue microstructural alteration [58], severe white matter damage and advanced periventricular hyperintensities [52]. While some studies reported pre ICH cognitive impairment was not associated with WMH volume, number of microbleeds, visible cerebral atrophy [58] and functional outcome [41]. For deep ICH, factors associated with pre morbid cognitive impairment were presence of old territorial vascular lesions and increasing severity of leucoaraiosis [12] but not mortality [26].

**3.3 Cognitive assessment post ICH and associated factors**

The majority of studies reviewed post ICH included a measure of global cognition (n=8) [6, 7, 19, 38, 45, 53, 55, 62] while some studies included more extensive neuropsychological assessments of cognitive function (n=6) [4, 19, 38, 45, 53, 62] (see Table 2). Some studies included both a global cognition and neuropsychological assessments [19, 38, 45, 53, 62] while others only included a measure of global cognition [6, 7, 55]. One study used a tailored neuropsychological assessment but did not specify the names of the tests [4] and another study assessed cognitive status by asking informants to compare the subject's ability to perform a list of daily cognitive tasks involving memory, praxis, calculation or reasoning with his or her baseline 5 to 10 years previous to the Index event [21]. There was one study that specifically assessed delirium within the acute period post ICH using a symptoms measure only [40]. The most commonly used global cognition measure was the Mini-Mental State Examination (MMSE) [6, 19, 38, 45, 62] followed by the Montreal Cognitive Assessment (MoCA) [19, 55]. In studies with more detailed neuropsychological assessment, the main cognitive domains assessed included memory, processing speed, executive function, language, visuo-spatial perception and praxis. Neuropsychological assessment measures used were very varied across studies making further analysis regarding their psychometric

properties beyond the scope of this review. The only neuropsychological measures used in more than one study were the Trial Making Test (TMT) [38, 45, 62], the Digit Span Test [45, 62] and the Hopkins Verbal Learning Test (HVLT) [38, 62]. There were 3 studies [19, 38, 45] that adhered to and included a neuropsychological protocol and/or criteria [22, 47, 49]. Five of the studies did not exclude pre-existing dementia and/or cognitive impairment [4, 19, 21, 40, 55].

Rates of cognitive impairment reported post ICH ranged from 37% after 6 months follow-up [6] to 88% after 3 months follow-up [45]. The prevalence for dementia was reported to be as high as 39% [7] with 19% developing early onset dementia within 6 months [7] and 28% at 4 years post ICH [38]. There was a trend towards a higher prevalence range of 36-84% reported for cognitive impairment in studies that did not exclude preexisting cognitive decline [4, 19, 21, 55] and for ICH survivors developing dementia where only a global measure of cognition was used [7].

For all ICH types, the most common cognitive domain deficits were reported for non-verbal IQ [4], information processing speed [4, 19] executive function [4, 19] episodic memory, language and visuo-constructive abilities [19]. For lobar ICH, cognitive deficits reported were naming [4, 45], processing speed [45, 62], executive function [45, 62], memory [45, 62], attention [45, 62], visual perception [4] and semantic fluency [62]. The incidence of new onset dementia was twice as high for patients with lobar ICH compared to non-lobar ICH [38]. One study reported lobar ICH patients to have more deficits in naming and visual perception compared to non-lobar [4] whereas another study reported no differences in cognitive functioning between lobar and deep ICH patients [45]. For studies that compared ICH patients to heathy controls, ICH patients performed worse in all cognitive domains [45, 53, 62].

Prognostic factors for cognitive decline after ICH were previous stroke or TIA, pre-existing cognitive impairment, severity of cortical atrophy [6], age, lobar ICH location [55] and higher number of haemorrhages at baseline [21]. Prognostic factors for new onset dementia were disseminated superficial siderosis, cortical atrophy, a higher number of CMBs, underlying CAA [38], age [7, 38], ICH location and volume, and ApoE $\varepsilon 2$ variant [7]. Predictors of long-term

dementia were haemorrhage volume and functional dependency at discharge [19] and age, educational level, ethnicity, previous mood disorder, increasing white matter disease severity and burden of lobar CMBs and ApoE ε4 variant [7]. Haematoma volume was associated with delirium symptoms but not ICH location [40].

## 4. Discussion

In this review, we aimed to identify studies that exclusively evaluated cognitive function pre or post ICH and were inclusive of neuropsychological assessment in addition to global cognition measures where possible. We included 19 studies: 8 that assessed cognitive function pre ICH and 11 post ICH. These studies provide supportive evidence for increasing interest in the cognitive status of patients before and after ICH as a separate pathology from ischaemic stroke types [63]. The prevalence of cognitive impairment whether it was existing impairment prior to ICH or as a direct result of the brain injury caused by ICH, was common and affected at least one-third of cohorts examined from reviewing all studies. There was a broad age-range for cohorts included; increasing age was associated with both pre and post ICH cognitive impairment. All studies that classified ICH according to location had greater patient numbers with deep ICH in comparison to lobar and infratentorial ICH. However, some studies specifically focused on and recruited CAA-related (lobar) ICH patients only and findings reported indicated cognitive function to be significantly impaired in patients with lobar ICH compared to healthy controls of similar age. There were mixed findings from studies that compared cognitive deficits between lobar and deep ICH patients in that some studies indicated lobar ICH patients to perform worse in some cognitive domains compared to deep ICH whereas other studies reported no differences by ICH location.

### 4.1 Cognitive assessment pre ICH and associated factors

There was a wide prevalence range reported from the various studies that assessed pre morbid ICH cognitive impairment with the rate as high as 30% in one study. Key predictors of pre ICH cognitive impairment were neuroimaging markers of CAA, previous stroke or TIA, and haemorrhage volume and location. These findings are in keeping with a previous review that highlighted the differences in underlying pathology between CAA versus deep perforating vasculopathy [63] and also a previous study that has reported CAA as an important

determinant of cognitive decline in the brains of older persons [8]. There were differences between lobar and deep ICH in relation to factors associated with pre morbid cognitive impairment with mortality been the main factor for lobar ICH but not deep ICH. The pathological explanations for lobar ICH is that these patients are reported to have more underlying neurodegenerative disease (e.g. AD pathology) compared to those with deep ICH, who have mainly deep perforator SVD pathology [63]. Consistent with this idea, we found that for deep ICH patients, old territorial vascular lesions and increasing severity of leucoaraiosis were associated with pre ICH cognitive impairment. All findings reported for pre morbid ICH cognitive impairment were based on the use on one assessment measure the IQCODE. For stroke studies, the IQCODE has been reported to have good specificity but modest sensitivity and has been reviewed in terms of diagnosing dementia post stroke and other available informant measures for cognition have not been validated or specifically designed for use in stroke [33].

**4.2 Cognitive assessment post ICH and associated factors**

The prevalence rates for reported cognitive impairment and/or dementia whether early or late onset were high. However, prevalence rates tended to be higher for cognitive impairment in studies that did not control for preexisting cognitive deficits, or used only a global measure of cognitive function rather than a more detailed neuropsychological battery. The specific cognitive domains affected post ICH were reported to be varied, possibly as a result of the diversity of assessment batteries used. The common cognitive domains that were reported to be affected irrespective of ICH location were executive function, processing speed, memory, attention and language. However, none of the studies reported associations between specific cognitive domains affected and ICH volume. There were mixed findings regarding the specific cognitive domains affected for lobar versus deep ICH in that one study reported greater deficits in naming and visual perception for lobar compared to non-lobar whereas another study reported no differences between the ICH location types. However lobar ICH location was reported as one of the main prognostic factors for cognitive decline after ICH in addition to cortical atrophy, age and higher number of macrohaemorrhages at baseline. Underlying pathology such as superficial siderosis, cortical atrophy, a higher number of CMBs, underlying CAA and ApoE e2 variant were all reported as prognostics factors for

early onset dementia in addition to acute factors such as ICH location and volume. Prognostic factors for later onset dementia also were inclusive of underlying pathology such as increasing white matter disease, burden of lobar CMBs and ApoE e4 variant in addition to acute factors and other socio-demographical factors i.e. age, education and ethnicity.

**4.3 Comparing cognitive impairment between ICH and ischaemic stroke**

It is important to establish whether the cognitive trajectory might be different for ICH compared with ischemic stroke. The most comprehensive review of the prevalence and associated factors of pre and post stroke dementia to date is a systematic review and meta-analysis by Pendlebury et al (2009) [42]. Findings from their review reported that prevalence of pre stroke dementia ranged between 10%-14% and between 10%-30% for post stroke dementia. These figures are similar to those reported here in the current review exclusively on dementia for pre (9%-16%) but are lower for post (37%-88%) ICH. The factors reported to be associated with pre stroke dementia were medial temporal lobe atrophy, female gender and a family history of dementia whereas factors associated with post stroke dementia were previous and recurrent stroke, several stroke lesions, aphasia, stroke severity, "haemorrhagic stroke", volume of the infarct and location of stroke (increased with left hemisphere and decrease with brainstem) [42]. Although we found that previous stroke, ICH volume and location were reported to be prognostic factors for new onset dementia post ICH, so too were other pathological causes such as disseminated superficial siderosis, cortical atrophy, a higher number of CMBs and underlying CAA. Identifying more pathological prognostic factors in ICH exclusive stroke studies is possible as a result of more detailed CT and MRI acquisitions and analysis compared to previous stroke studies that included less neuroimaging data.

Despite our findings of very high rates of both pre and post ICH cognitive impairment, international stroke consortia continue to have a greater focus on ischaemic stroke [50]. A more recent consortium to examine the epidemiology, diagnosis and treatment of neurocognitive disorders in relation to cerebrovascular disease predominantly identified previous strokes from members' own research centres and as a result more representative of more westernized regions [50]. Few of these studies included comprehensive neuropsychological or neuroimaging assessment and analysis. This consortium and a more

recent review on the psychometric properties of cognition measures used in all stroke types [46] acknowledge the challenges in harmonizing neuropsychological data where the criteria for defining cognitive impairment and assessment measures used remains heterogeneous. Addressing the differences in cognitive impairment profiles between ischaemic and haemorrhagic stroke is beyond the scope of this review. However, understanding comparing the differences in cognitive deficits for the presenting pathologies and location distributions for stroke subtypes (ischaemic and ICH) will be of great importance for further reviews and empirical studies and also to facilitate health care professionals to have a comprehensive and updated perspective on ICH outcome in acute and chronic phases [43].

**4.4 Main limitations in studies reviewed**

The prevalence rate of cognitive impairment and/or dementia pre and post ICH was very varied across the studies that reported these figures. The methodological issues included limited consistency across neuropsychological measures used in studies in addition to the timing of assessments. For the studies that focused on post ICH cognitive impairment, almost half of the studies did not exclude pre-existing dementia and/or cognitive impairment, included modest samples sizes and some studies were of retrospective design. Although a larger number of the studies reviewed were longitudinal, the timing and number of follow-up assessments also varied widely across studies from in the immediate period post ICH to 3, 6, 12 months and up to 4 years post ICH. Therefore, determining and defining acute, subacute and chronic phases following ICH was not consistent across studies. Due to the heterogeneity of the neuropsychological measures used across the different studies, it was not possible to conclude or analyse the psychometric properties for each respective measure used for the various cognitive domains assessed. Hence, the requirement for greater use of working group collaborations that have devised specific protocols for the assessment of vascular cognitive impairment to facilitate greater clarity of comparisons between assessment measures between studies [22]. There was also variation in studies in terms of whether global cognition or more comprehensive neuropsychological cognitive assessments were used and therefore, interpreting studies' results based on global cognition scores versus more detailed neuropsychological assessment may result in issues concerning prevalence rates, definition and consistency of cognitive deficits. In addition to the various study design and

methodological issues outlined above, there was also great diversity in the use of statistical tests and analysis approaches. A number of studies were underpowered in terms of drawing conclusions based on the sample sizes recruited. For example, some studies used parametric statistics where sample sizes were modest and where there was no reporting regarding the normality of the data distribution. In other studies, there was elaborate uses of statistical analyses such the use of the General Linear Model (GLM) and Structured Equation Modelling where sample sizes were not deemed large enough for these modelling approaches. The majority of studies did not correct for multiple comparisons either apriori or post hoc were conducted e.g. the use of Bonferroni's or Tukey's.

## 5. Future research, recommendations and conclusions

This systematic review identified studies that assessed cognitive function pre or post ICH and as a result of the wide variation in the assessment measures employed, there were a number of gaps or limitations identified in drawing conclusions.

- For future studies, methodological approaches may be required to extend beyond using generic measures of cognition and to assess specific cognitive domains known to be affected from resulting pathological stroke type and region involved.
- When assessing cognition following ICH it is important to assess the pre-existing cognitive function prior to ICH, allow immediate delirium to subside and to assess cognitive functions frequently and consistently within the acute and subacute time periods. Standardization of timing of assessment post ICH would facilitate determining the differences in specific cognitive domains affected at early and late onset of cognitive impairment.
- Further studies are warranted that compared cohorts with pre-existing cognitive impairment with those with no pre-existing impairment when determining cognitive status and deficits post ICH and not only exclude patients with pre-existing cognitive impairment in order to determine severity of post ICH cognitive impairment.
- More extensive neuroimaging methods and acquisitions using recommended protocols and criteria for imaging analysis are warranted for all stroke type studies and not only exclusively for ICH studies to facilitate comparisons of cognitive deficits between different stroke types. Consistent and standardized neuroimaging methods

will also facilitate comparisons between ICH location and volume with specific cognitive domains affected, and allow better understanding of the contribution of different arteriopathies including CAA.

- Global cognition measures are red flag warnings for underlying cognitive impairments and are mainly highlighting concerns and issues regarding cognitive function. In order to preplan and advance rehabilitative interventions, cognitive assessments following ICH must include measures that will detect cognitive dysfunctions allowing tailored intervention programmes to address and manage areas of concern. Cognitive assessment in ICH patients may need to extend measurement beyond global and other neuropsychological objective testing and to be inclusive of disease classifying criteria [3]. In addition, assessing subjective cognitive complaints may facilitate rehabilitation [2]. Greater assessment and awareness of cognitive impairments by health professionals, especially the allied health groups, is also warranted given the interdisciplinary nature of stroke management and rehabilitative strategic interventions [23, 24].
- A validated cognitive screening protocol for patients at risk for and who have diagnosed SVD causing spontaneous ICH, would allow greater consistency of cognitive assessment across these patient groups.

This article presented a systematic review of studies that assessed and evaluated cognitive function either pre or post ICH and aimed to identify the assessment methods employed. As a result of reviewing assessment methods for evaluating cognitive function in studies exclusive to ICH, it was possible to make some estimations regarding current prevalence rates for cognitive impairments and/or dementia, the most common assessment measures used and the cognitive domains affected as a result of spontaneous ICH.

Table 1: Initial Key Search terms and associated words

| Main Search Terms | Relevant associated words |
|---|---|
| Intracerebral haemorrhage | *"cerebral amyloid angiopathy" OR "microbleed" OR "microbleeds" OR "small vessel disease" OR "intracerebral hemorrhage" OR "intracerebral haemorrhage" OR "cerebral hemorrhage" OR "cerebral haemorrhage" OR "brain hemorrhage" OR "brain haemorrhage" OR "microhemorrhage" OR "microhaemorrhage" OR "hemorrhagic stroke" OR "haemorrhagic stroke"* |
| | **AND** |
| Cognitive impairment | *(cognitive OR cognition) AND (dysfunction* OR deficit* OR impairment*) OR dementia OR delirium* |
| | **AND** |
| Neuropsychological assessment | *assessment OR tool OR tools OR measure OR measurement OR scale OR scales OR criteria OR screen OR screens OR screening OR test OR tests* |

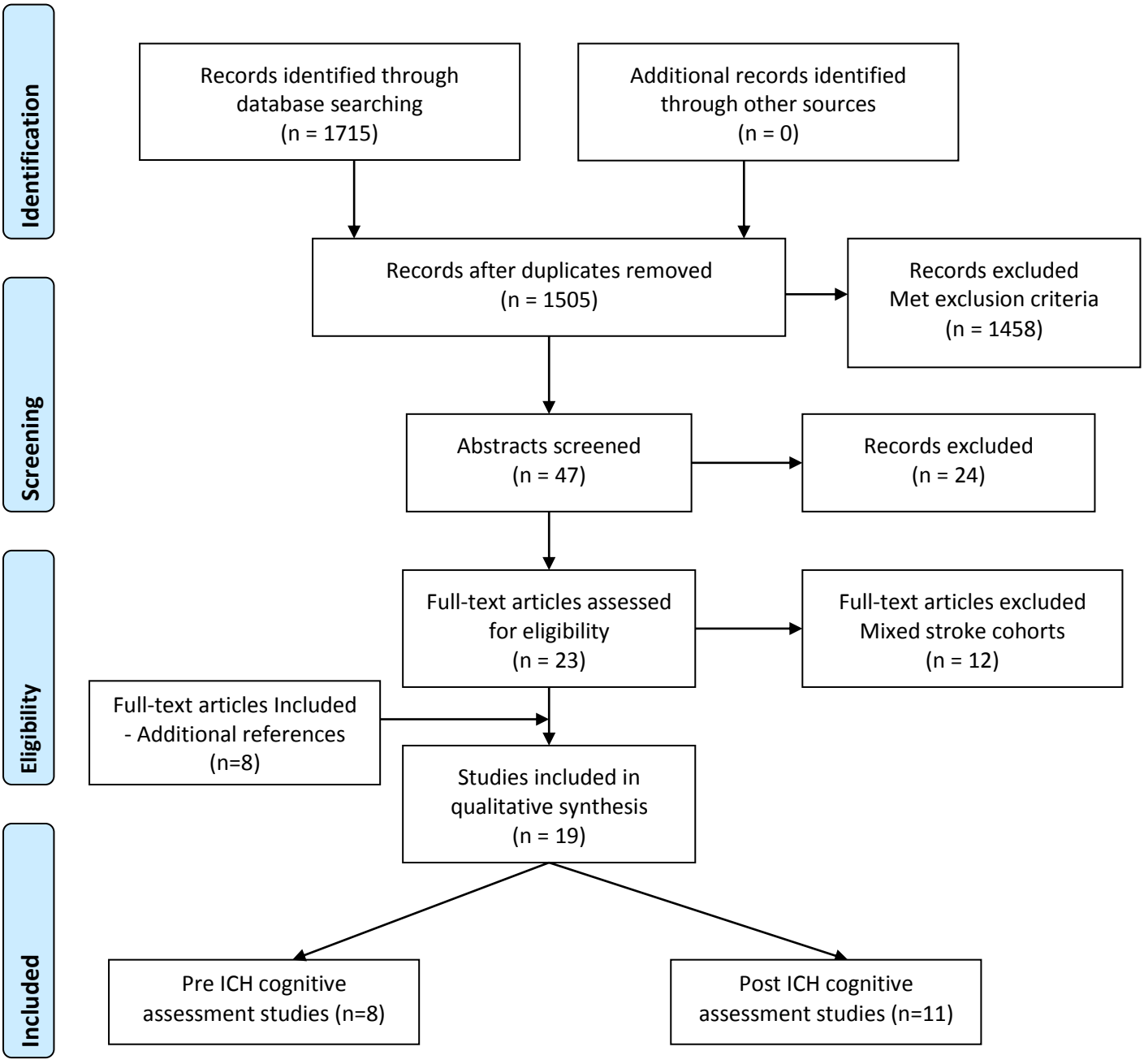


**Fig. 1. Workflow diagram of publication selection process using PRISMA guidelines. "n" is the number of articles after each screening stage.**

Table 2: Neuropsychological (cognitive) assessment pre or post spontaneous intracerebral haemorrhage **(n=19)**

| **Author and Year** | **Study aim** | **Method**<br>a. Study design<br>b. Sample/cohort (n)<br>c. Timing post ICH/neuropsychological assessment<br>d. Include/exclude pre-existing cognitive decline | **Neuropsychological Assessments**<br>a. Cognition domains (assessment tools)<br>b. Other cognitive impairment or dementia diagnosis criteria | **Other assessment**<br>a. Imaging modality<br>b. ICH assessment<br>c. Other variables | **Results and reported findings**<br>a. Prevalence of cognitive impairment and/or dementia<br>b. Other reported findings |
|---|---|---|---|---|---|
| | | | **Pre ICH cognitive impairment (n=8)** | | |
| Banerjee et al. (2018)[5] | Investigate if neuroimaging evidence of CAA and SVD at presentation were associated with cognitive impairment before ICH | a. Prospective cross-sectional<br>b. n= 166 (63% male, mean age 69 years)<br>c. From time of hospital admission for ICH | a. Pre morbid cognitive function in the past 10 years (IQCODE) | a. CT or MRI<br>b. Probable or non-probable CAA – Boston criteria, SVD – STRIVE criteria, ICH volume – semi-automated volumetric assessment, WMH – Fazekas Scale | a. 25% pre ICH cognitive impairment.<br>b. Pre ICH cognitive impairment was independently associated with neuroimaging markers of CAA, cortical superficial siderosis, lobar microbleeds and lobar ICH location. |

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| Nakagawa et al. (2018) [41] | Compare functional outcome in after ICH between Asians and native Hawaiians and other Pacific Islanders (NHOPI). | a. Prospective observational longitudinal study.<br>b. n=220 acute ICH (n=105 deep, n=65 lobar and n=50 infratentorial), (n= 161 Asians (mean age 65 years), n= 59 NHOPI (mean age 52)).<br>c. Patients enrolled between July 2011 and June 2015 after hospitalisation and followed up by telephone at 3 months. | a. Pre-existing dementia or cognitive impairment (made by patients' respective physicians before hospitalisation through formal clinical evaluation). | a. CT<br>b. Haemorrhage volume calculation (ABC/2 method), ICH score calculation (based on age, CT findings and GCS on arrival)<br>c. Functional ability (modified Ranking Scale) | a. 9.3% Asians and 0% NHOPI pre ICH cognitive impairment/dementia.<br>b. NHOPI had better functional outcome. Pre-existing cognitive impairment/dementia was not a predictor of functional outcome in the multivariate analysis but ICH score was. |
| Laible et al. (2016) [31] | Determine prevalence of premorbid cognitive impairment in patients with ICH. | a. Prospective observational cross-sectional study.<br>b. n= 89 acute ICH (n=51 deep, n=23 lobar, n= 11 infratentorial and n=4 intraventricular) (median age 70 years).<br>c. Patients enrolled between March 2011 and September 2012 and timing of assessment within the first 2 days after the ICH. | a. Pre-existing cognitive impairment or dementia (IQCODE). | a. CT or MRI<br>b. Haemorrhage volume calculation (ABC/2 or ABC/3 methods), white matter lesions (ARWMC Rating Scale)<br>c. Functional dependency (modified ranking scale. Activities of Daily Living). | a. 18% pre ICH cognitive impairment, 17% lobar ICH and 20% deep ICH had some form of pre ICH cognitive impairment.<br>b. Factors associated with pre ICH cognitive impairment were prior stroke or TIA and haematoma volume. |
| Jamieson et al. (2012) [26] | Investigate role of dementia and cognitive impairment prior to ICH as a risk factor and mortality predictor in lobar and non-lobar ICH | a. Prospective observational longitudinal study.<br>b. n=136 ICH patients (n=53 lobar) (mean age 77 years).<br>c. Patients enrolled from January 2003 to March 2004 and assessed at 7 days post ICH and at 1, 2 and 3 months. | a. History of vascular disease, AD, mixed dementia or cognitive impairment (obtained from medical record and coded as dementia/cognitive impairment). | a. CT or MRI<br>b. Haemorrhage volume calculation (ABC/2 method), cerebral vascular disease (Fazekas Scale). | a. 12% pre ICH cognitive impairment or dementia.<br>b. In lobar ICH, prevalence of history of cognitive impairment or dementia, confusion at presentation, previous ICH, multiple haemorrhages and initial haematoma volume were significantly higher compared to non-lobar ICH. Predictors of mortality in lobar ICH were |

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| | | | | | history of cognitive impairment or dementia (at 3 months), initial haematoma volume (at 2 months), prior antiplatelet use (at 2 and 3 months), age (at 1,2 and 3 months), male gender (at 1 and 2 months) and low GCS (at 7 days and at 1 month). Predictors of mortality in non-lobar ICH were initial haematoma volume, prior antiplatelet use, age and low GCS. |
| Cordonnier et al. (2010) [12] | Determine prevalence and mechanisms of pre-existing dementia in patients with ICH. | a. Prospective observational cross-sectional study.<br>b. n= 417 acute ICH (n=207 deep, n= 138 lobar, n=53 infratentorial) (median age 72 years).<br>c. Patients enrolled from the PITCH cohort from November 2004 to April 2009 and timing of assessment was within 48 hours of stroke onset. | a. Pre-existing cognitive decline and dementia (IQCODE). | a. CT<br>b. Haemorrhage volume calculation (ABC/2 method)<br>c. Neuropathology on patients who died | a. 29% pre ICH cognitive impairment, 14% had cognitive impairment with no dementia and 16% pre ICH dementia. 19% in the lobar group, 13% in the deep group and 9% in the posterior fossa group cognitive impairment with no dementia.<br>b. In lobar ICH group, factors associated with pre-existing dementia were increasing age, having < 8 years of education and increasing cortical atrophy. In deep ICH group, factors associated with pre-existing dementia were presence of old territorial vascular lesions and increasing severity of leucoaraiosis. |
| Rost et al. (2008) [48] | Develop a clinical score, assessed on admission to predict patients' likelihood of reaching | a. Prospective observational longitudinal study.<br>b. n=629 patients with ICH (42% lobar, 47% deep and 11% infratentorial). | a. Pre ICH cognitive impairment (IQCODE and medical record review). | a. CT and MRI<br>b. ICH volume – computerised volumetric analysis | a. 16% pre ICH cognitive impairment.<br>b. Pre ICH cognitive impairment, age, GCS, ICH location and volume were independently |

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| | functional independence following ICH | c. Patients enrolled between January 1998 to August 2005 and assessed following hospital presentation for ICH. | | c. Functional independence (Glasgow Outcome Scale). | associated with functional independence. |
| Viswanathan et al. (2008) [58] | Determine whether higher global mean apparent diffusion coefficient would be associated with chronic cognitive impairment in CAA | a. Prospective longitudinal study<br>b. n=49 patients with lobar ICH (n= 10 with pre ICH cognitive impairment, mean age 76 years and n=39 with no pre ICH cognitive impairment, mean age 73 years).<br>c. Patients enrolled between August 2001 to August 2005 and assessed shortly after the index event during hospitalisation for ICH. | a. Pre ICH cognitive impairment (IQCODE and medical records). | a. CT and MRI with diffusion weighted sequences<br>b. CAA diagnosis (Boston criteria, chronic tissue disruption (mean ADC)), ICH volume (segmentation on baseline CT at time of haemorrhagic stroke). WMH volume (FLAIR sequence), degree of tissue microstructural alteration (mean ADC). | a. 20% pre ICH cognitive impairment.<br>b. Degree of tissue microstructural alteration was associated with pre ICH cognitive impairment independent of age, clinical variables, amount of visible cerebral atrophy and other MRI markers. Pre ICH cognitive impairment was not associated with WMH volume, number of micro bleeds or visible cerebral atrophy. |
| Smith et al. (2004) [52] | Investigate relationships between WMLs, cognitive impairment and risk of recurrent haemorrhage in lobar ICH. | a. Prospective longitudinal study<br>b. n= 182 ICH (n=41 with no WMH and mean age 71 years ; n=82 mild WMH and mean age 76 years; n=59 severe WMH and mean age 80 years).<br>c. Patients were enrolled between July 1994 to July 2001 and assessed at baseline and 1 month, 3 months and every 6 months thereafter of the index ICH event. | a. Pre ICH cognitive impairment (IQCODE). | a. CT (at baseline to determine eligibility into the study) and MRI (at 3 months follow-up).<br>b. Cortical atrophy (graded on CT), WMH (FLAIR sequence)<br>c. Functional dependency (modified Ranking Scale), ApoE genotype. | a. 23% pre ICH cognitive impairment.<br>b. Patients with pre ICH cognitive impairment were more likely to have severe white matter damage and have advanced periventricular hyperintensities. The relationship between pre ICH cognitive impairment and WMH was similar in the subset of patients with possible and probable CAA. |

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| **Post ICH cognitive impairment (n=11)** | | | | | |
| Banerjee et al. (2018)[4] | Describe cognitive profile following acute ICH & explore how CAA may impact performance. | a. Retrospective cross-sectional<br>b. n= 187 (56% male, mean age 59 years, lobar ICH n=92)<br>c. Median 12 days post stroke<br>d. Pre-existing cognitive impairment not excluded | a. Pre morbid intellectual functioning, current intellectual functioning, verbal and visual memory, naming, visuo-spatial perception, information processing speed and executive function (Tailored neuropsychological assessment) | a. CT or MRI.<br>b. Probable or non-probable CAA – Boston criteria, SVD – STRIVE criteria. | a. 84% of patients were impaired in one cognitive domain and 65% in 2 or more domains.<br>b. Most common deficits were in non-verbal IQ, information processing speed and executive functions. More deficits in naming and visual perception in lobar ICH compared to non-lobar ICH. Probable CAA, predicted impairment in verbal IQ and executive function. |
| Planton et al. (2017) [45] | Estimate frequency of vascular cognitive disorders (VCD) in ICH groups and to compare CAA-related ICH group cognitive profile with deep ICH, MCI-AD and HC groups. | a. Prospective, observational longitudinal study<br>b. n= 20 CAA-ICH (mean age 71 years), n=20 deep ICH (mean age 66 years), n=20 MCI-AD (mean age 72 years) and n=17 healthy controls (mean age 70 years).<br>c. After 3 months onset of ICH.<br>d. For ICH patients, excluded pre-existing cognitive decline | a. Global cognition (MMSE), memory (FCSRT, Delayed Matched Sample test, Digit Span test), executive function (FAB, TMT, Stroop test), attention and information processing speed (Stroop test, TMTA), language (picture naming test) and praxis (Mahieux's test).<br>b. VASCOG criteria. | a. MRI.<br>b. Probable or non-probable CAA – Boston criteria, WMH -Fazekas score, neuroimaging markers of SVD – STRIVE criteria. | a. 88% mild and 2.5% major vascular cognitive disorders.<br>b. No significant difference in cognitive functioning between CAA-related and deep ICH patients. Most impaired cognitive process in the CAA group was naming, followed by processing speed, executive functioning, memory and attention. The cognitive pattern different from MCI-AD only in gestural praxis and by construction in memory processes. |
| Xiong et al. (2016)[62] | Investigate neuropsychological features of non-demented patients with CAA and to analyse the association between CAA related | a. Part of a longitudinal cohort study.<br>b. n=58 non demented CAA (mean age 70 years), n=138 cognitively normal subjects.<br>c. Patients presenting to a stroke unit from March 2006 to July | a. Global cognition (MMSE), executive function (TMT, FAS, Digit Span Backward), processing speed (TMTA), attention (Digit Span Forward), semantic fluency (Animal Naming), episodic | a. MRI.<br>b. Diagnosis of CAA – Boston criteria, neuroimaging markers of SVD – STRIVE criteria. | a. No prevalence reported.<br>b. Patients with CAA had significantly worse performance on all neuropsychological domains tested compared to the cognitive normal group. Cognitive decline was for processing speed, |

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| | neuroimaging markers and cognitive domains. | 2015 with symptomatic and non-symptomatic ICH indicated and timing post ICH not indicated.<br>d. Excluded pre-existing cognitive decline | memory (HVLT-R Delayed Recall). | | followed by executive function, episodic memory, semantic fluency and attention. Total brain volume (lower) of CAA patients correlated with processing speed and executive function. |
| Biffi et al. (2016)[7] | Determine extent of central nervous system injury associated with acute haematoma formation would be strongly associated with early post-ICH dementia (EPID) and limited risk of delayed post-ICH dementia (DPID). | a. Prospective longitudinal study.<br>b. n=738 ICH survivors (mean age 74 years)<br>c. Enrolled ICH survivors from January 2006 to December 2013 and interviewed at 3 and 6 months after Index ICH, and every 6 months thereafter.<br>d. Excluded pre-existing cognitive decline | a. Pre ICH dementia (IQCODE), global cognition (Modified Telephone Interview for Cognitive Status test). | a. CT and MRI.<br>b. Haematoma location and size (CT-defined), WMH and CMBs burden and location (lobar vs. non-lobar) (MRI defined).<br>c. APOE genotype. | a. 39% of ICH survivors developed dementia and 19% developed incident dementia within 6 months.<br>b. Early incident dementia after ICH was associated with age at Index ICH, ICH location, ICH volume and ApoE ε2 variant. Delayed incident dementia was associated with age, educational level, ethnicity, previous mood disorder, increasing CT-WMD severity, increasing burden of lobar CMBs and ApoE ε4. |
| Moulin et al. (2016) [38] | Determine incidence and risk factors after ICH. | a. Prospective observational study.<br>b. n=218 ICH patients (median age 67 years) (n=77 lobar ICH)<br>c. Enrolled from the PITCH cohort and cognitive assessment at 6, 12 and 48 months post ICH.<br>d. Excluded pre-existing dementia | a. Pre-existing dementia (IQCODE), Subjective cognitive complaint (Face to face interview on cognitive complaint), global cognition (French Greco version of MMSE), neuropsychological battery<br>b. NINDS- Canadian Stroke Network Vascular Cognitive Impairment Harmonisation Standards. | a. CT and MRI<br>b. Haemorrhage volume calculated using ABC/2 method. | a. 14% developed new onset dementia at 1 year and 28% at 4 years.<br>b. Risk factors of new onset dementia were disseminated superficial siderosis, cortical atrophy score, a higher number of CMBs and older age. Findings indicate that underlying CAA is a contributing factor to new onset dementia. Incidence of new onset dementia was twice as high for patients with lobar ICH compared to non-lobar ICH. |

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| Benedictus et al. (2015) [6] | Determine prognostic factors for cognitive decline in ICH patients. | a. Prospective observational study – longitudinal study.<br>b. n=167 patients (median age 64 years) (n=55 lobar ICH)<br>c. Enrolled from the PITCH cohort and cognitive assessment at 6, and 12 months and annually thereafter.<br>d. Excluded pre-existing dementia or cognitive impairment | a. Pre ICH dementia (IQCODE), global cognition (MMSE) | a. CT and MRI<br>b. Haemorrhage volume calculated using ABC/2 method, WMH – (Fazekas scale)<br>c. Depression – (MADRS) | a. 37% reported cognitive decline during follow up.<br>b. Previous stroke or TIA, pre-existing cognitive impairment, severity of cortical atrophy were prognostic factors for cognitive decline after ICH. Severity of cortical atrophy was the only prognostic factor in patients without pre-existing cognitive impairment. No difference in prognostic factors for patients with lobar or non lobar ICH. |
| Tveiten et al. (2014) [55] | Assess clinical functioning including cognition in long-term survivors of ICH. | a. Retrospective observational study – cross sectional<br>b. n=50 first-ever ICH (mean age 71 years)<br>c. Enrolled patients between August and November in 2011 that were first ever ICH in 2005-2009 (median follow-up time was 4 years)<br>d. Did not exclude pre-existing dementia or cognitive impairment | a. Global cognition (MoCA). | a. CT<br>b. Haemorrhage volume calculated using ABC/2 method.<br>c. Functional outcome (Modified Ranking Scale). | a. 61% had cognitive impairment.<br>b. Factors associated with cognitive impairment were age and lobar ICH location. 32% of patients were dependent and factors associated with dependency were leukaraiosis. No association reported between cognitive impairment and functional dependency. |

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| Garcia et al. (2013) [19] | Determine frequencies of cognitive impairment and dementia in a cohort of patients that were hospitalised for acute spontaneous ICH. | a. Retrospective observational study – cross sectional.<br>b. n=78 ICH patients (n=26 lobar ICH) (n= 30 assessed by telephone interview and n=48 assessed with neuropsychological tests).<br>c. Patients admitted with acute spontaneous ICH between December 2002 and December 2006 were enrolled in the study in 2008 (mean time post stroke 3.4 years).<br>d. Did not exclude pre-existing dementia or cognitive impairment | a. Telephone interview of cognitive assessment (IQCODE), premorbid intellectual efficiency (National Adult Reading Test), current general intellectual efficiency (MMSE, MoCA and Mattis Dementia Rating Scale), language abilities (Token Test), visuospatial and constructive abilities (test not specified), short-term and episodic memory (test not specified), executive functions (test not specified), and behavioural executive disorders. Aphasia (Boston Diagnostic Aphasia Examination).<br>b. Dementia diagnosis using DSM-IV, vascular dementia and Alzheimer's disease diagnosis (NINDS-AIREN and NINCDS-ADRDA). | a. CT or MRI.<br>b. Haemorrhage volume calculated using ABC/2 method, Fazekas scale – WMH.<br>c. Anxiety (Goldberg Anxiety Scale and Hamilton Rating Scale for Anxiety) and depression (MADRS). | a. 77% cognitive impairment without dementia, 23% dementia.<br>b. Cognitive disorders included episodic memory (52%), psychomotor speed (44%), executive function (37%), followed by language and visuo-constructive abilities. Haemorrhage volume and functional dependency at discharge were the predictors of long-term dementia. |
| Naidech et al. (2013)[40] | Understand prognostic significance of delirium symptoms, functional outcome and quality of life after ICH | a. Prospective observational study – cross-sectional.<br>b. n=114 ICH (n=16 persistent coma and n=98 assessed for delirium) (mean age 63 years).<br>c. Patients enrolled from December 2009 to April 2013 and assessed within 4 weeks of ICH. | a. Delirium (CAM-ICU) | a. CT.<br>b. Not reported.<br>c. Level of arousal (Agitation-Sedation Scale), functional dependency (modified Ranking Scale), quality of life (Neuro-QOL and PROMIS). | a. 27% delirium symptoms, 59% had no symptoms and 14% had persistent coma.<br>b. Delirium symptoms were hypoactive, first detected on average within 6 days after ICH symptom onset, associated with poorer functional outcome and worse quality of life in the domains of applied cognition-executive function and fatigue. There was a significant difference between patients with delirium |

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| | | | | | symptoms and those without or in a coma and haematoma volume but there was no difference for ICH location. |
| Su et al. (2007) [53] | Examine frequency and pattern of cognitive deficits in patients with basal ganglia haemorrhage and to identify clinical correlates of cognitive dysfunction | a. Prospective observational cross-sectional study.<br>b. n=30 basal ganglia haemorrhage (mean age 54 years) and n=37 healthy controls (mean age 57 years).<br>c. Patients were enrolled between August 1999 and July 2000 and were assessed between 1 to 6 months post stroke.<br>d. Excluded pre-existing dementia or cognitive impairment | a. Attention (Digital Span, Visual Memory Span, MMSE, Wechsler Memory Scale Revised), memory (orientation to time, person and place from the MMSE, Form D of the Benton Visual Retention Test, verbal memory Scale from the Chinese version of the Luria-Nebraska Neuropsychological Battery(LNNB)), visuospatial function (Block Design from the Wechsler Adult Intelligence Scale-Revised, Hooper Organisation Test, Test of Visual Perception Skills), language (the Chinese version of the Luria-Nebraska Neuropsychological Battery(LNNB)) and executive function (Winconsin Card Sorting Test). | a. CT or MRI.<br>b. Basal Ganglia haemorrhage confirmed by neurosurgeon from brain imaging. | a. 70% cognitive impairment<br>b. Patients with basal haemorrhage performed worse in all cognitive domains compared to healthy controls. 97% of patients performed poorly on at least 3 cognitive domains. |
| Greenberg et al. (2004) [21] | Address whether microhaemorrhages and larger symptomatic ICHs share a similar distribution in the brain or risk factors such as ApoE genotype and whether the number of | a. Prospective observational longitudinal study<br>b. n=94 lobar ICH patients (mean age 55 years).<br>c. Patients enrolled from July 1994 to March 2002 and were assessed over 33 months (at baseline, 12 and 18 months). | a. Cognitive impairment defined as the presence of deficits in memory or other cognitive area sufficient to affect performance of activities of daily living (cognitive status assessed by asking informants to compare | a. MRI with axial gradient-echo.<br>b. ApoE genotype | a. 36% developed cognitive impairment as well as functional dependency or death at mean time of 28 months.<br>b. Higher numbers of haemorrhages at baseline predicted increased risk for subsequent cognitive |

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| | old haemorrhages predict future events such as recurrent symptomatic ICH, cognitive impairment or functional decline. | d. Pre-existing dementia or cognitive impairment not excluded. | the subject's ability to perform a list of daily cognitive tasks involving memory, praxis, calculation or reasoning with his or her baseline 5 to 10 years previous to the Index event). | impairment. Individuals with cognitive impairment prior to their Index ICH showed a trend towards more haemorrhages at baseline than those without prior cognitive impairment. |

ADC – apparent diffusion coefficient, ApoE – apolipoprotein, ARWMC - Age-Related White Matter Changes, CAA – cerebral amyloid angiopathy, CMBs – cerebral microbleeds, CT – computerized tomography, FAB – Frontal Assessment Battery, FAS – F-A-S Phonemic Verbal Fluency Test, FCSRT – Free and Cued Selective Reminding Test, HVLT-R – Hopkins Verbal Learning Test – Revised, MRI – magnetic resonance imaging, PITCH – Prognosis of intracerebral haemorrhage, SVD – small vessel disease, STRIVE - Standards for Reporting Vascular Changes on Neuroimaging Consensus Criteria, TMT – Trail Making Test, VASCOG – Diagnostic Criteria for vascular cognitive disorders, WMH – white matter hyperintensities.

## Supplement 1 PRISMA checklist

| Section/topic | # | Checklist item | |
|---|---|---|---|
| TITLE | | | |
| **Title** | 1 | Identify the report as a systematic review, meta-analysis, or both. | |
| ABSTRACT | | | |
| **Structured summary** | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | |
| INTRODUCTION | | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of what is already known. | |
| **Objectives** | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |
| METHODS | | | |
| **Protocol and registration** | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | |
| **Eligibility criteria** | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | |
| **Information sources** | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | |
| **Search** | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | |
| **Study selection** | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | |
| **Data collection process** | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | |
| **Data items** | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | |
| **Risk of bias in individual studies** | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | |
| **Summary measures** | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | |
| **Synthesis of results** | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | |

| Section/topic | # | Checklist item | |
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| **Risk of bias across studies** | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | |
| **Additional analyses** | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | |
| RESULTS | | | |
| **Study selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | |
| **Study characteristics** | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | |
| **Risk of bias within studies** | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | |
| **Results of individual studies** | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | |
| **Synthesis of results** | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | |
| **Risk of bias across studies** | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| **Additional analysis** | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| DISCUSSION | | | |
| **Summary of evidence** | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | |
| **Limitations** | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | |
| FUNDING | | | |
| **Funding** | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | |

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For more information, visit: **www.prisma-statement.org**.

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