



Review Article

Intracerebral hemorrhage outcome: A comprehensive update

 João Pinho^{a,*}, Ana Sofia Costa^{b,c}, José Manuel Araújo^a, José Manuel Amorim^d, Carla Ferreira^a
^a Neurology Department, Hospital de Braga, Portugal^b Department of Neurology, RWTH Aachen University Hospital, Germany^c JARA-BRAIN Institute Molecular Neuroscience and Neuroimaging, Forschungszentrum Jülich GmbH and RWTH Aachen University, Germany^d Neuroradiology Department, Hospital de Braga, Portugal

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ABSTRACT

Non-traumatic intracerebral hemorrhage (ICH) is associated with a significant global burden of disease, and despite being proportionally less frequent than ischemic stroke, in 2010 it was associated with greater worldwide disability-adjusted life years lost. The focus of outcome assessment after ICH has been mortality in most studies, because of the high early case fatality which reaches 40% in some population-based studies. The most robust and consistent predictors of early mortality include age, severity of neurological impairment, hemorrhage volume and antithrombotic therapy at the time of the event. Long-term outcome assessment is multifaceted and includes not only mortality and functional outcome, but also patient self-assessment of the health-related quality of life, occurrence of cognitive impairment, psychiatric disorders, epileptic seizures, recurrent ICH and subsequent thromboembolic events. Several scores which predict mortality and functional outcome after ICH have been validated and are useful in the daily clinical practice, however they must be used in combination with the clinical judgment for individualized patients. Management of patients with ICH both in the acute and chronic phases, requires health care professionals to have a comprehensive and updated perspective on outcome, which informs decisions that are needed to be taken together with the patient and next of kin.

1. Introduction

Even though spontaneous, non-traumatic, intracerebral hemorrhage (ICH) is responsible for only 10–20% of all acute strokes [1], the global burden of hemorrhagic stroke in 2010, expressed in disability-adjusted life years lost, was greater than the burden of ischemic stroke [2]. The global incidence of hemorrhagic stroke has increased in the past decades, for which the major contribution was a 22% increase of its incidence in low- and middle-income countries from 1990 to 2010, whereas it has slightly decreased in high-income countries [2]. At the same time, the age-adjusted mortality has decreased in the past decades, both in high-income countries and in low- and middle-income countries [2,3]. Despite the lack of a specific disease-modifying treatment, there is some evidence showing a trend for decrease in early case-fatality rates in the past 30 years [4,5], which may be related to improved general early acute management. It is not without reason that most of the discussion concerning ICH outcome is dedicated to mortality, because short-term case fatality may reach 50% [6]. Most of the therapeutic trials in early ICH have mortality as their primary endpoint [7–10], however, outcome after ICH is a complex subject and may be evaluated in multiple domains, through different perspectives, and at

different time-points (Fig. 1). The severity of ICH, defined by the neurological status and hemorrhage volume at presentation, is one of the most robust mortality and functional outcome predictors, but other markers are also important for the prediction of other complications after ICH.

We aim to update the current knowledge on ICH outcome, by analyzing recent studies in this field. Despite being predominantly a narrative review, it includes a systematic review and meta-analysis of population-based studies reporting mortality after ICH. This review focuses on non-traumatic, often called “primary”, ICH, with no underlying vascular malformation nor structural cause such as brain tumor, ischemic infarct or venous thrombosis. Different outcome domains and prognostic factors are reviewed.

2. Mortality

2.1. Population-based studies

A systematic revision of all population-based studies reporting mortality data after non-traumatic ICH in cohorts of ≥ 50 cases was carried out, methodology details are provided in the Supplemental

* Corresponding author at: Neurology Department, Hospital de Braga, Sete Fontes, São Victor, Braga 4710-243, Portugal.
 E-mail address: jdpinho@gmail.com (J. Pinho).

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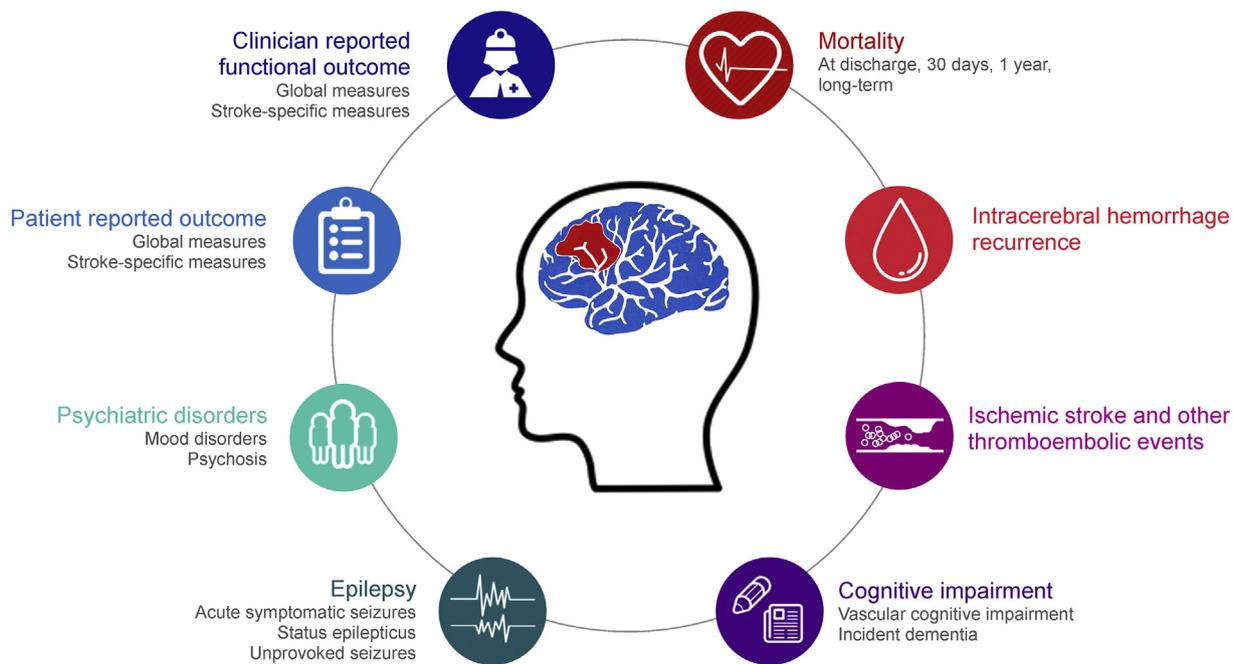


Fig. 1. Domains of outcome assessment in intracerebral hemorrhage.

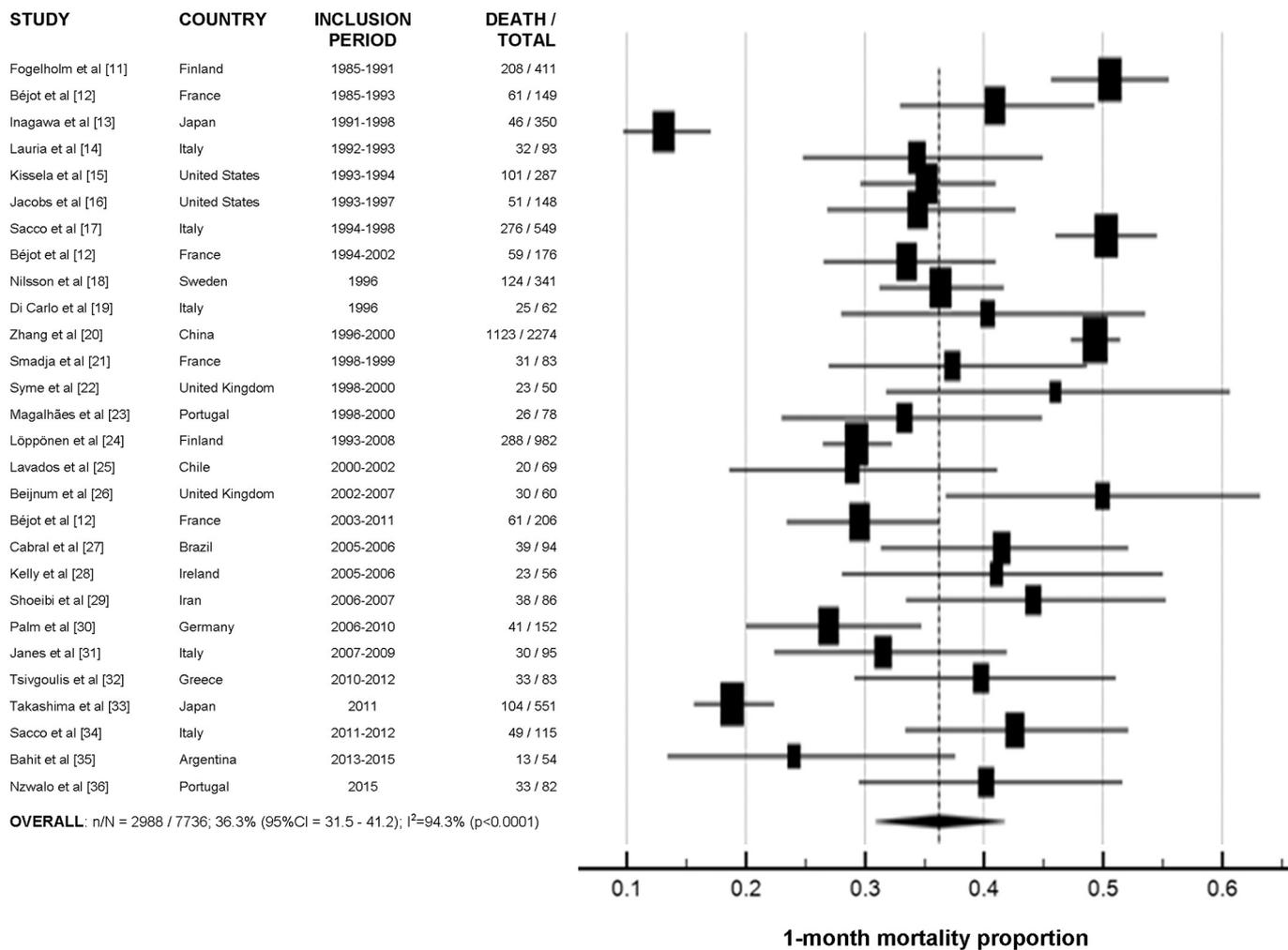


Fig. 2. Proportion of patients who died in the first month after intracranial hemorrhage, in population-based studies, stratified by studies and years of patient inclusion.

STUDY	COUNTRY	INCLUSION PERIOD	DEATH / TOTAL
Fogelholm et al [11]	Finland	1985-1991	238 / 411
Kissela et al [15]	United States	1993-1994	131 / 287
Sacco et al [17]	Italy	1994-1998	324 / 549
Nilsson et al [18]	Sweden	1996	162 / 341
Di Carlo et al [19]	Italy	1996	35 / 62
Syme et al [22]	United Kingdom	1998-2000	28 / 50
McCormick et al [37]	United Kingdom	1995-2011	358 / 782
Vibo et al [38]	Estonia	2001-2003	31 / 57
Beijnum et al [26]	United Kingdom	2002-2007	34 / 56
Shoebi et al [29]	Iran	2006-2007	48 / 86
Palm et al [30]	Germany	2006-2010	67 / 152
Samarasekera et al [39]	United Kingdom	2010-2011	72 / 128
Tsivgoulis et al [32]	Greece	2010-2012	40 / 83
Takashima et al [33]	Japan	2011	161 / 551
Sacco et al [34]	Italy	2011-2012	60 / 115
OVERALL: n/N = 1789 / 3710; 50.7% (95%CI = 45.2 - 56.2); I ² =96.4% (p<0.0001)			

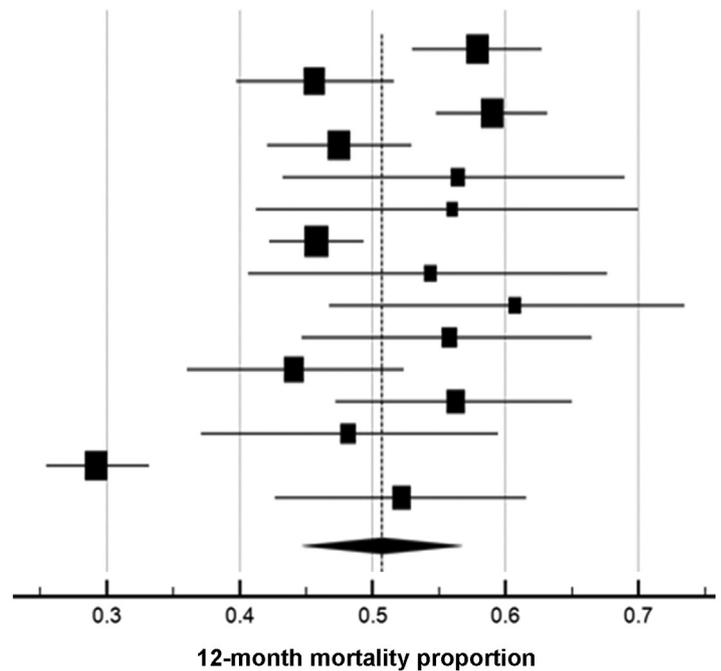


Fig. 3. Proportion of patients who died in the first 12 months after intracranial hemorrhage, in population-based studies, stratified by studies and years of patient inclusion.

Material. A meta-analysis of the case fatality at different time points was performed using a random effects model and thirty studies [11–40] were included in the final analysis. The pooled mortality 1 month after ICH was 36.3% (95% confidence interval [95%CI] = 31.5-41.2; n/N = 2988/7736; I² = 94.3%, p < 0.0001), at 3 months was 35.3% (95%CI = 28.1-42.8; n/N = 821/2648; I² = 92.7%, p < 0.0001), at 12 months was 50.7% (95%CI = 45.2-56.2; n/N = 1789/3710; I² = 90.2%, p < 0.0001), and at 10 years was 69.2% (95%CI = 52.6-83.5; n/N = 726/1105; I² = 96.4%, p < 0.0001). Graphical representation of the meta-analyses can be observed in Figs. 2 and 3, further results can be found in the Supplemental Material. A linear regression model to assess the temporal evolution of mortality according to the years of patient inclusion in the different studies, revealed a significant reduction of mortality at 12 months (-0.8% per year, 95%CI = -1.5 to -0.1, p = 0.038), but no significant reduction of mortality at 1 month (-0.4% per year, 95%CI = -1.0 to 0.2, p = 0.155) (details of the model can be found in the Supplemental Material).

2.2. Mortality predictors

The majority of studies found that the most robust baseline clinical predictors of short and long-term mortality are older age [5,6,41,42], and increased severity of neurological impairment, as measured by the Glasgow Coma Scale (GCS) [41,43–45] or neurological deficits severity scales such as the National Institutes of Health Stroke Scale (NIHSS) [22,46]. Patients who were medicated with antiplatelet therapy at the time of ICH also have a higher risk of early mortality, with an adjusted odds ratio (aOR) of 1.27 (95% confidence interval [95%CI] 1.09-1.53) in a pooled analysis of 21 cohorts [47]. This increased risk associated with antiplatelet therapy was also confirmed in a more recent study which analyzed data from the Get With The Guidelines (GWTG) stroke registry of 82576 ICH patients, with an aOR of 1.05 (95%CI 1.01-1.11) for in-hospital mortality [48]. Oral anticoagulation with vitamin K antagonists (VKA) is a well established risk factor for early mortality after ICH, and this risk increases with higher international normalized ratio values [49]. More recently, a review of 141311 ICH patients included in the GWTG stroke registry found that the prior use of both VKA

and non-vitamin K oral anticoagulants (NOAC) were associated with higher in-hospital mortality, with aOR of 1.62 (95%CI 1.53-1.71) and 1.21 (95%CI 1.11-1.32) respectively [50]. A recent individual patient data meta-analysis of cohort studies comparing case-fatality of ICH in VKA- and NOAC-treated patients revealed smaller baseline hematoma volumes in NOAC-treated patients, however did not demonstrate a difference in case-fatality at 30 days [51]. Another meta-analysis which only included patients from therapeutic trials, also revealed that the case fatality rate was similar in VKA- and NOAC-related ICH patients [52]. Specific antidotes for dabigatran anti FXa inhibitors have shown to be very effective in neutralizing the anticoagulation effect of these NOACs [53,54], and even though recent evidence points that they could be associated with lower case-fatality [52], their clinical benefit in NOAC-related ICH is yet to be established.

The most robust imagiological outcome predictor in ICH is the hematoma volume, making it difficult to analyze other hematoma imaging characteristics independently from volume. Likewise, collinearity between severity of neurological impairment and hematoma volume, must be considered when analyzing predictors of outcome. In 1993, Broderick et al showed that hematoma volume was significantly and independently associated with 30-day mortality, and demonstrated in a cohort of 162 patients that for volumes > 60cm³, mortality ranged from 71-93% according to the hematoma location [43]. The relationship between hematoma volume and 3-month mortality was further clarified in 2006, when it was shown that each mL increase in baseline volume was associated with a 1% increased risk of mortality [55]. The growth of the hematoma volume, either assessed as the ultraearly hematoma growth (volume of the hematoma in the initial imaging / time from symptom onset to imaging) or defined as an increase in the volume in follow-up imaging, has been found to be significantly associated with mortality [50,56]. It is known that clinically significant hematoma growth on follow-up imaging at 24 hours (> 33% of baseline volume), occurs in up to 1/4 of ICH patients [57] and for each 10% increase in hematoma volume growth, the risk of death increases by 5% [55]. As expected, the location of the hemorrhage also predicts mortality, namely the occurrence of infratentorial hemorrhage, has been associated with a 4-fold increased risk of early mortality [44,58].

Box 1

Mortality: key points.

- Mortality after ICH is high, and occurs in 1/3 of patients after 1 month, and 1/2 of patients after 1 year
- A temporal trend for a reduction of mortality 1 year after ICH is apparent in population-based studies.
- There are few population based-studies reporting long-term survival after ICH
- The more robust clinical predictors of mortality are age, level of consciousness, severity of neurological deficits and antithrombotic therapy
- The more robust paraclinical predictors of mortality are baseline hematoma volume, location of the hematoma, and intraventricular extension of the hematoma

Thalamic and lobar ICH involvement was also found to be a predictor of 3-month mortality in the participants of the INTERACT2 trial [59]. Initial and delayed intraventricular hemorrhage has been consistently associated with higher mortality, probably because of the risk of hydrocephalus and severe intracranial pressure increase [60,61]. Computed tomography (CT) angiography in the acute phase, in addition to provide information on ICH etiology, may be used to search the spot sign, which is thought to represent active bleeding within the hematoma, and is associated with an aOR of 2.4 (95%CI 1.4-4.0) for 3-month mortality [62]. Other imaging findings in non-contrast CT found to be predictive of short-term mortality include the black hole sign [63] and the swirl sign [64], sedimentation levels [65], and association with subdural hematoma [66] (Box 1).

Increased blood biomarkers such as C reactive protein [67,68], d-dimer [69,70], glucose levels [71,72], and neutrophil-to-lymphocyte ratio [73,74], have been associated with higher risk of short-term mortality after ICH. However, blood biomarkers are not routinely used in clinical practice to predict ICH outcome, and the majority of studies dedicated to this topic have small size populations which preclude any definite conclusions [75].

3. Clinician reported functional outcome

3.1. Population based studies

Patients who survive ICH frequently have persistent and important neurological deficits which interfere significantly with their daily activities and functioning. The evaluation of functional outcome is less frequently reported in the literature, and most studies used the modified Rankin Scale (mRS) at different timings after ICH, with varying cut-offs used for the definition of favorable outcome (≤ 2 or ≤ 3). Additional selected clinician reported functional outcome measures which are used in stroke patients are described in Table 1. In the L'Aquila registry, outcome was available at discharge, and only 15% of all initial patients were functionally independent [27]. In the Ludwigs-shafen Stroke Study, between 2006-2010, among 129 patients with known functional outcome at 1-year, 36.4% were independent or had moderate disability requiring some help [22]. In the LATCH study, functional independence at 1-year was observed in only 14% of all ICH patients [32]. Recently, functional outcome at the time of the acute ward discharge was reported in the Dijon Stroke Register, where independent walking was 64.1% in 1985-1993 but only 39.6% in 2003-2011, which was accompanied by a decrease in the acute phase mortality [76]. In 2014, a systematic review of the few population-based studies which reported functional outcome after ICH, found that 32.8-42.4% of all patients were independent at 6 months, and that only 16.7-24.6% of all patients were independent at 12 months [41] (Box 2).

3.2. Functional outcome predictors

Many of the previously described mortality predictors are also predictors of functional outcome, and have been included in the multiple ICH prognostic scores available [77]. However, the definition of outcome in most of these studies included mortality in the poor

outcome category, leading to potential bias. Short- and medium-term functional outcome in survivors has been evaluated using the Barthel Index, and lower scores (greater functional dependence) have been associated with age, GCS, baseline hemorrhage volume, change of hemorrhage volume at 24h, and presence of intraventricular hemorrhage [55]. Favorable functional outcome in young ICH survivors was independently associated with younger age, lower NIHSS score, and intraventricular extension of the hemorrhage [78]. Another study on long-term outcome in ICH survivors in Norway found that the only independent predictors of favorable functional outcome were male sex and lower leukoaraiosis burden on baseline CT [79]. Concerning anticoagulation-related ICH, even though NOAC-treated patients appear to have smaller baseline intracerebral hematoma volumes when compared to VKA-treated patients, there was no significant difference in the functional prognosis at hospital discharge, 3 months and 6 months [51]. Hematoma growth in follow-up CT at 24h has also been shown to be strongly associated with dependency alone at 3 months [59]. In a post-hoc analysis of the INTERACT2 study, the occurrence of major disability at 3 months (defined as mRS of 3-5) was associated with hemorrhage involvement of the posterior limb of the internal capsule, with sparing of the caudate head or lobar locations [57]. A systematic review of 37 studies which reported outcome after ICH in relation to hemorrhage location, concluded that patients with lobar hemorrhages had better short- and medium-term outcomes when compared to patients with deep / non-lobar hemorrhages, and suggested no difference in outcome in relation to hematoma laterality [80]. Interestingly, a recent imaging study in patients with basal ganglia hemorrhage with volumes between 20-50 mL, revealed that brain atrophy, measured by the hemi-intercaudate distance and the sylvian fissure ratio, was associated with favorable functional outcome in ICH survivors, probably because of a protective effect against space-occupying lesions [81]. Predictors of motor recovery of the upper limb have been extensively studied in stroke patients, however, little is known of the predictors of motor recovery in ICH patients, because most studies specifically excluded or included only very few patients with hemorrhagic stroke [82]. More recently, the use of diffuse tensor imaging in magnetic resonance has proven valuable for the characterization of the white matter integrity in regions of interest during the acute phase of ICH. Cerebral peduncles fractional anisotropy values have been significantly correlated with both short- and long-term functional and motor outcomes measured by mRS, motor score of NIHSS and Functional Independence Measure scores [83,84].

4. Patient reported outcome

The need for clinical trials to redefine outcomes after stroke, focusing on patient-centered perspectives using patient reported outcomes (Table 1), health-related quality of life measures (HRQoL) and utility-weighted scales, is being increasingly recognized [85,86]. Utility scores express HRQoL as a fraction of what the general population perceives as perfect health (score = 1), death (score = 0) or health states worse than death (negative scores), and average scores of disease-free populations are 0.8-0.9 [87]. In the FAST trial, the 3-month EuroQoL scale was assessed in ICH survivors: only 13% perceived their status as

Table 1
Selected clinician-reported and patient-reported outcome measures in ICH survivors.

	Time to administer	Domains assessed								
		Mobility	Hand function	Self care	ADL	Cognition	Emotion	Fatigue	Pain	Other
Clinician reported functional outcome measures										
Modified Rankin Scale ^a	3-5 min	X		X	X					
Glasgow Outcome Scale ^b	3-5 min	X		X	X					
Barthel Index ^c	10 min	X		X						
Functional Independence Measure	30-40 min	X		X		X				Social interaction
Fugl-Meyer Assessment ^d	45 min	X	X						X	Sensation
Chedoke - McMaster Stroke Assessment ^e	45-60 min	X	X						X	
Patient reported outcome measures										
EQ5D ^f	5 min	X		X	X		X		X	
SF-36 ^g	10 min	X			X		X		X	Social activities
Neuro-QOL ^h	30-45 min	X	X	X	X	X	X	X		Social activities, stigma, sleep, work
SS-QOL ⁱ	10-15 min	X		X		X	X	X		Social activities, family role, vision, work
SA-SIP30 ^j	15-25 min	X		X	X		X			Social activities
SIS ^k	20-30 min	X	X	X	X	X	X			Social activities

^a van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van GJ. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604-607.

^b McMillan M, Wilson L, Ponsford J, Levin H, Teasdale G, Bond M. The Glasgow outcome scale – 40 years of application and refinement. *Nat Rev Neurol* 2016;12:477-485.

^c Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md tate Med J* 1965;14:61-65.

^d Sullivan KJ, Tilson JK, Cen SY, et al. Fugl-Meyer Assessment of sensorimotor function after stroke. Standardized training procedure for clinical practice and clinical trials. *Stroke* 2011;42:427-432.

^e Gowland C, Stratford P, Ward M, et al. Measuring physical impairment and disability with de Chedok-McMaster Assessment. *Stroke* 1993;24:58-63.

^f Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;35:1095-108.

^g McHorney CA, Ware JE, Lu JF, Sherbourne CD. The MOS 36-Item Short Form Health Survey: III. tests of data quality, scaling assumptions and reliability across diverse patient groups. *Med Care* 1994;32:40-66.

^h Gershon RC, Lai JS, Bode R, et al. Neuro-QOL: quality of life item banks for adults with neurological disorders: item development and calibrations based upon clinical and general population testing. *Qual Life Res* 2012;21:475-486.

ⁱ Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a stroke-specific quality of life scale. *Stroke* 1999;30:1362-1369.

^j van Straten A, de Haan RJ, Limburg M, Schuling J, Bossuyt PM, van den Bos GA. A stroke-adapted 30-item version of the Sickness Impact Profile to assess quality of life [SA-SIP30]. *Stroke* 1997;28:2155-2161.

^k Duncan PW, Bode RK, Min Lai S, Perera S. Rasch analysis of a new stroke-specific outcome scale: the Stroke Impact Scale. *Arch Phys Med Rehabil* 2003;84:950-963.

perfect health, and 2% of patients had a negative EuroQoL utility score [88]. In the INTERACT trials the EuroQoL-5D scale, which measures HRQoL in 5 dimensions, was assessed at 3 months after ICH [89], and it was found that 45.4% of the patients had a utility score ≤0.7. In this study, the proportion of patients reporting at least some problem or difficulty in each of the domains was 64% for mobility, 48% for self-care, 61% for usual activities, 42% for pain/discomfort and 32% for anxiety/depression. Both studies [88,89] found that age, greater hemorrhage severity (higher NIHSS, larger hematoma), presence of intraventricular hemorrhage and non-lobar hematoma location were independent predictors of poor quality of life after ICH. Interestingly, among INTERACT2 trial participants, the only hematoma location that was consistently associated with worse EuroQoL-5D scores in every of the five domains was the posterior limb of the internal capsule [57].

Returning to work, in addition to serve as a measure of direct and indirect socioeconomical impact of stroke, may also reflect the patients' self-perception of their own abilities. Even though there are scarce

studies addressing this question in ICH patients, a Danish study reported that among 2272 ICH survivors, aged between 20-57 years, who were gainfully occupied before the event, 43.0% resumed an occupation 2-years after stroke [90]. Using different definitions and methodology, a study in Japan reported that among 119 ICH survivors who had a paid job at the time of stroke, only 12.6% patients had a full return to work 1 year after stroke [91]. In both studies return to work of ICH patients was less frequent than in ischemic stroke patients (Box 3).

5. Intracerebral hemorrhage recurrence

Medium- and long-term mortality and functional outcome after ICH are greatly influenced by the occurrence of major vascular events, namely ICH recurrence. Etiological investigation during the first hemorrhagic event is, therefore, fundamental to identify the cause of ICH and its contributing factors, which may allow interventions to lower the risk of recurrence. In the 2014 systematic review by Poon et al,

Box 2

Clinician reported functional outcome: key points.

- For the definition of favorable functional outcome or functional independence by clinicians, several measures have been used
- The majority of these measures are simple to apply systematically in clinical practice, but do not assess psychological or social domains
- At 1 year, only 1/6 to 1/4 of all patients who suffered an ICH achieve functional independence
- Little is known about the pattern and predictors of motor recovery in ICH patients

Box 3

Patient reported outcome: key points.

- Patient-centered measurements of outcome have been infrequently used in the assessment of outcome after ICH, but provide an essential perspective on the impact in patients' lives and their needs
- It is very frequent that ICH survivors report at least some difficulties in domains other than mobility, such as pain and mood
- Half of ICH survivors evaluate their health status as worse than the evaluation of a disease-free population, and only a minority perceive their health status as perfect at 3 months

spontaneous ICH recurrence in survivors was 1.8-7.4% during the first year, and 2.0-2.4% per year after the first year [41]. The results of a large single-center cohort study of patients with spontaneous ICH, revealed that the recurrence risk was 7.8% per year in patients with lobar ICH, and 3.4% per year in patients with non-lobar ICH [92]. In this study, an independent association between inadequate blood pressure control and ICH recurrence was found both in patients with non-lobar and with lobar ICH. This suggests that causes of lobar ICH (such as cerebral amyloid angiopathy [CAA]) have a higher recurrence risk than causes of non-lobar ICH (such as hypertensive cerebral microangiopathy), but that the risk is modulated by concomitant contributors and precipitators. This was later confirmed in a meta-analysis with pooled data from 10 studies, where CAA-associated ICH had a recurrence risk of 7.4% per year, and CAA-unrelated ICH had a recurrence risk of 1.1% per year [93]. This meta-analysis also demonstrated that a greater cerebral microbleed burden was associated with increased recurrence risk both in CAA-associated and CAA-unrelated ICH. Among ICH survivors with a diagnosis of CAA, additional factors associated with ICH recurrence include older age, frequent centrum semi-ovale perivascular spaces [94], presence of acute convexity subarachnoid hemorrhage and presence of cortical superficial siderosis [95]. When patients with ICH have a concomitant or past illness for which antithrombotic therapy is recommended, physicians are faced with the dilemma to start, restart or continue antiplatelet therapy or anticoagulation, given the perceived increased risk of recurrent ICH [96,97]. Even though the risk of recurrence may be significant in patients who need anticoagulation after ICH [98], this risk needs to be balanced with the risk of ischemic events without antithrombotic therapy [99], and the quality of available evidence to guide this decision is low [100]. A testament to this is that in a study with cohorts of patients from different European countries, only 1/5 of patients with an antithrombotic-associated ICH restarted antithrombotic therapy, with significant variation in clinical practice [101] (Box 4).

6. Ischemic stroke and other thromboembolic events

Because many of the vascular risk factors for ICH are also risk factors for ischemic stroke, ischemic heart disease, atrial fibrillation and systemic embolism, the occurrence of these major vascular events are also important to consider when assessing outcome.

In a population-based study in Sweden, ischemic stroke occurred more frequently than recurrent hemorrhage in patients with an index ICH, during a mean follow-up of 4 years [102]. In another population-based study in Scotland, among 417 ICH survivors, the rate of subsequent events were 2.87% per year for ischemic stroke or myocardial infarction, and 0.97% per year for recurrent ICH [103]. The relative weight of each type of stroke during follow-up after ICH depends on the

Box 4

Intracerebral hemorrhage recurrence: key points.

- Recurrence of spontaneous ICH occurs in up to 7% of patients in the first year, and 2% per year after the first year
- Recurrence is significantly higher in patients with CAA when compared to other causes
- Markers of increased recurrence risk in CAA patients include the burden of microbleeds and cortical superficial siderosis

presence of specific vascular risk factors and cardiac conditions, such as atrial fibrillation (AF), the etiological distribution of ICH, and whether antithrombotic therapy was started or restarted, which was decided by the treating physician according to individualized risk assessment in the majority of studies. These important biases need to be considered when evaluating the results of observational studies which included patients with anticoagulation-associated ICH and AF. The rate of thromboembolic events varied between 12.7% per year and 13.8% at 3 years in patients with AF who did not resume anticoagulation, and between 3.9% per year and 6.3% at 3 years in patients with AF who resumed anticoagulation [104,105]. In the same studies, the rate of ICH recurrence varied between 3.9% per year and 4.4% at 3 years in patients with AF who did not resume anticoagulation, and between 3.9% per year and 6.9% at 3 years in patients who resumed anticoagulation [104,105]. Even though many other issues are involved in the decision of starting antithrombotic therapy in patients who had ICH, namely age, post-stroke functional status, co-morbidities, presence of cerebral amyloid angiopathy and microangiopathy burden, the absolute risk of thromboembolic events also needs to be considered for an accurate prognostication. In the current clinical practice, the CHA2DS2-VASc score for patients with AF who had ICH may be used for an estimation of the occurrence of ischemic events [106], and the HAS-BLED score may be used for estimation of the occurrence of major bleeding, even though it has not been validated specifically for patients who have suffered ICH and there is a discussion of how to count the score in these patients [107]. The decision of restarting anticoagulation should not be based solely on these scores, and there are several trials which in the future may provide valuable evidence for the management of these patients, namely the “Restart or Stop Antithrombotics Randomised Trial”, the “Start or Stop Anticoagulants Randomised Trial” and the APACHE-AF trial. Some case series have also suggested that left atrial appendage closure may be of use in these patients [108,109], even though it also requires transitory anticoagulation and chronic antiplatelet therapy. Its net benefit in ICH patients with atrial fibrillation is yet to be established, especially when compared to restarting a NOAC (Box 5).

7. Cognitive impairment

There are several mechanisms underlying cognitive impairment in ICH patients including: (a) as a direct consequence of the cerebral lesions, (b) related to the underlying cause of ICH, (c) associated with post-ICH psychiatric manifestations, and (d) related to other co-morbidities.

The prevalence of cognitive decline before ICH was 29% in the French PITCH cohort of 417 patients, whereas 16% of patients fulfilled criteria for dementia [110]. In a recent multicentre study cognitive

Box 5

Ischemic stroke and other thromboembolic events: key points.

- Because most of the risk factors for ICH are also risk factors for thromboembolic events, there is an increased risk of such events in this population of patients
- The absolute risk for ischemic events such as ischemic stroke and myocardial infarction after ICH is globally higher than the risk of ICH recurrence
- The high risk of thromboembolic events in ICH survivors who have atrial fibrillation poses complex management problems regarding starting or restarting anticoagulation therapy

impairment before ICH was present in 24.7% of 166 patients [111]. Both studies identified CAA as well as lobar hemorrhage location to be associated with pre-existing dementia. Other variables associated with dementia before ICH included lower education, higher leukoaraiosis burden, and more significant cortical atrophy, as well as cortical siderosis and lobar microbleeds.

Prospective studies also based on the PITCH cohort found a cumulative incidence of dementia after ICH of 14.2% at 1 year and 28.3% to 37% at 4 years follow-up [112,113]. A more recent study reported an incidence of 19% of dementia after ICH at 6 months and 5–8% per year afterwards [114]. Whereas the severity of cortical atrophy was an independent predictive factor for patients with previous cognitive impairment [113], the role of mood disorders and the APOE ϵ 4 variant have also been identified as significant predictors of incident dementia after ICH. Furthermore, predictive factors such as lobar hemorrhage location, disseminated cortical siderosis and a higher burden of cerebral microbleeds [112] demonstrates the importance of the identification of cerebral amyloid angiopathy in predicting long-term outcome in ICH patients (Box 6).

Compared to ischemic stroke, there are fewer studies characterizing the neuropsychological profile of patients with vascular cognitive impairment after ICH. A small single-center study comprehensively assessed neuropsychological performance 4 months after deep ICH in 20 patients compared to CAA-related lobar ICH and identified major and minor deficits in 2.5% and 87.5% of all ICH patients, respectively, according to internationally defined criteria for vascular cognitive disorders, the VASCOG criteria [115]. All CAA patients were cognitively impaired, most frequently exhibiting deficits in naming, but no significant differences existed when compared to deep ICH patients. Even though episodic memory, processing speed and executive function have been reported to be the more frequently involved cognitive domains [116], the profile may depend not only on the strategic dysfunction caused by the location of the hemorrhage, but also on the underlying pathology, namely the occurrence of deep white matter microangiopathic changes or cortical microbleeds and cortical thinning [117,118].

8. Psychiatric disorders

The majority of studies addressing psychiatric disorders in stroke patients have focused on ischemic stroke [119]. There are many psychiatric complications of stroke, which can manifest both in the acute phase and in later chronic phases, and can be disabling and devastating for the patient's quality of life and for the family and caregivers [120]

Box 6

Cognitive impairment: key points.

- Several mechanisms contribute to the occurrence of cognitive impairment in ICH patients, namely those directly related to the cerebral lesion, but also those related to the underlying pathogenesis
- Up to 1/4 of patients with ICH have pre-ICH cognitive decline
- Incident cognitive decline during the first 4 years after ICH occurs in up to 1/3 of survivors
- Impairment of episodic memory, processing speed and executive function are frequently reported, but the pattern of cognitive impairment is not homogeneous and depends on several factors

(Box 7).

Anxiety symptoms in ICH survivors who can communicate have been found to be one of the most common psychiatric manifestations, with a prevalence of 22% at 3 months [121], and 40% at a median follow-up of 10 years [122].

Depressed mood is also another frequent complication of ICH, either occurring in the setting of a major depressive episode, or accompanied by other mood symptoms, such as anhedonia, irritability, apathy, loss of energy, difficulty in sleeping, difficulty in concentrating, but without fulfilling criteria for major depression. In the FAST trial, according to an instrumental assessment of depression symptoms (Hamilton Depression Rating Scale) conducted 3 months after ICH, 20.1% of patients presented depressed mood [121]. Using the same instrument, a substudy of the DASH study found a prevalence of depressed mood at 1-year after ICH of 15% [123]. In another study which evaluated ICH survivors at a median follow-up of 10 years, using the Beck Depression Inventory II and the Hospital Anxiety and Depression Scale, post-stroke depression was present in 23.1% of patients [122].

A recent systematic review of post-stroke psychosis revealed that in the studies which described the subtype of stroke, only a residual proportion of 18.1% of patients [n = 34] with post-stroke psychosis had had ICH [124]. Visual and auditory hallucinations, reduplicative paramnesias, and other delusions were reported mainly in individual case studies [125–128], however there is no data to accurately estimate the proportion of ICH survivors who develop psychosis or to accurately define predictors of its development [129].

9. Epilepsy

The occurrence of epileptic seizures after stroke has been studied according to the timing of occurrence, due to the different prognostic significance carried by the occurrence of early or acute symptomatic seizures (within 7 days of stroke) or late or unprovoked seizures (after 7 days of stroke) [130]. Acute symptomatic seizures, the majority of which are partial seizures, have been demonstrated to occur more frequently in ICH than in ischemic stroke [131,132], and were found in 8.2–16.2% of ICH patients [131,133–135]. In these studies, the occurrence of status epilepticus within 7 days of ICH was 1.0–6.7%. Short- and medium-term mortality was shown not to be associated with the occurrence of acute symptomatic seizures [132–136]. In addition to this, because the prophylactic use of antiepileptic drugs after ICH has no benefit in preventing late seizures, it is not recommended in current guidelines [137]. Unprovoked seizure incidence is higher in the first 2

Box 7

Psychiatric disorders: key points

- Psychiatric complications of ICH can be devastating for the patient's quality of life and for the family and caregivers
- The most frequently reported psychiatric complications of ICH are anxiety symptoms, depressive mood and depression
- Only a minority of patients present post-stroke psychosis

Box 8

Epilepsy: key points.

- Acute symptomatic seizures occur in up to 1/6 of patients after ICH
- Late unprovoked seizures occur more frequently during the first 2 years and new cases are less frequent afterwards
- Factors such as acute symptomatic seizures, lobar hemorrhage, pre-ICH dementia and white matter disease severity have been identified as risk factors for late unprovoked seizures
- There is no established association of post-ICH seizures with mortality or with functional outcome

years after ICH (6.9% at 1 year, 9.1% at 2 years), and fewer new cases were observed afterwards [138]. Other studies found variable incidence of unprovoked seizures, ranging from 7.1-10.8% at 1 year, to 9.1% at a median follow-up of 3.9 years, to 11.8% at 5 years [134,139,140]. The characteristics more consistently associated with increased risk of developing unprovoked epileptic seizures were cortical or lobar involvement of the hemorrhage and occurrence of acute symptomatic seizures [134,138,140]. Younger age was also identified as a risk factor for unprovoked seizures in some studies [78,131,141], which may be due to the fact that younger patients more often are submitted to neurosurgical treatment for ICH, have higher survival, and that seizures may be more difficult to recognize in elderly patients [78,131] (Box 8).

Interestingly, in a large and extensively studied cohort of patients with ICH, Biffi and collaborators found that risk factors for the occurrence of recurrent seizures after an acute symptomatic seizure were different from those associated with the occurrence of inaugural unprovoked seizures during follow-up, the later being associated with markers of cerebrovascular disease, such as pre-ICH dementia, prior lobar hemorrhage, white matter disease severity, exclusively lobar microbleeds and APOE ϵ 4 genotype [139]. This work emphasizes the clinical and biological heterogeneity in post-ICH seizures, suggesting different underlying mechanisms in early and late seizures. The association between post-ICH seizures with worse functional outcome as been suggested by Rossi et al [142], however, this has not been confirmed in other studies [133,139,140].

10. Prediction scores and subjective outcome estimation

Several scores for predicting functional outcome and mortality after ICH have been developed, combining known individual clinical and neuroimaging predictors, with the goal to increase prognostication accuracy [77]. Among the most used and validated scores are the ICH score [44], the Essen ICH score [143], and the FUNC score [144]. The ICH score is determined by the level of consciousness, ICH volume, presence of intraventricular hemorrhage, infratentorial hemorrhage location and age, and each 1-point increase (from 0 to 5) was associated with a higher likelihood of death and worse functional outcome

Box 9

Prediction scores: key points.

- Several scores for predicting functional outcome and mortality after ICH have been developed to increase prognostication accuracy
- The majority of scores include clinical variables such as age and level of consciousness, and neuroimaging variables such as hematoma volume and location
- The use of these scores is recommended and they are very useful for informing the patients and their next-of-kind, and for supporting management decisions

throughout the first year after ICH, with c-statistics between 0.80-0.90 for both outcomes at different times points during the first year [44,145]. The Essen ICH score is determined only by clinical variables (age, severity of neurological deficits and level of consciousness), has the advantage of not requiring the measurement of ICH volume, and it is associated with c-statistics of between 0.80-0.90 for complete recovery determined by the Barthel Index at 100 days and for death at 3 months [143]. The FUNC score is determined by age, level of consciousness, ICH volume, ICH location, and additionally takes into consideration the occurrence of pre-ICH cognitive impairment as determined by an informant interview, which adds a degree of subjectivity to the score. It focuses on predicting functional independence at 3 months, which in the original study was 0% for scores 0-4 and > 80% for a score of 11 [144]. These scores are very useful for informing the patients and their next-of-kind, and for supporting management decisions, even though they only rely on non-modifiable variables. More recently, efforts have been made for identifying predictors of hematoma expansion, which could lead to the identification of ICH patients likely to benefit from anti-expansion therapies in the setting of future trials [146]. The BAT score, which was designed for this purpose, is determined by the presence of any hypodensity, the blend sign, and time from onset to CT, with c-statistics for the occurrence of hematoma expansion between 0.65-0.80 [147]. It has the disadvantage of not including anticoagulation, a known determinant of hematoma expansion, and the fact that the included CT signs may not have an optimal interrater reliability [148] (Box 9).

Even though the use of prognostic scores is recommended in current guidelines [149], other factors must also weigh when evaluating individual patients. This is demonstrated by the observation that early subjective clinical judgment by experienced clinicians is not inferior to the application of formal prognostic scores in predicting outcome 3 months after ICH [150,151].

11. Conclusion

The overall poor prognosis of ICH, namely the high short-term mortality, is a reflection both of the severity of the disease and absence

of disease-modifying treatments in the acute phase. The acute management of patients with ICH should take place in specialized units with experienced professionals within a multidisciplinary team, where accurate prediction of short-term outcome informs the decisions needed to be taken together with the patient, next of kin or caregivers. Long-term outcome in ICH survivors is multifaceted and should be assessed not only in terms of functional outcome, or occurrence of complications such as cognitive impairment, psychiatric disorders and epilepsy, but also from a patient-perspective health-related quality of life. A better understanding of long-term outcome after ICH is needed, namely regarding subsequent hemorrhagic and thromboembolic events, which may allow a better tailoring of prophylactic therapy.

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Appendix A. Supplementary data

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