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Characteristics and outcomes of intracerebral hemorrhage in a population-based stroke registry

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Summary

Abstract

Background. Intracerebral hemorrhage (ICH) is the most severe stroke type, accounting for 26% of strokes worldwide. Understanding the epidemiology and pathogenesis of ICH is key to design adequate prevention and treatment strategies to improve the dismal prognosis of ICH. In the present study, we aimed to report up-to-date epidemiological data about the incidence and outcome of ICH, investigate its etiologic factors, and assess the role of brain MRI in understanding those factors.

Methods. We performed a prospective population-based study in the district of L'Aquila covering the years 2011-2019. ICH incidence, 30-day and 1-year and case-fatality rates (CFRs) were computed in patients residing in the district and suffering a first-ever ICH over the 2011-2017 period (incidence dataset). All the other assessments were performed in residents of the district reporting either a first-ever ICH or an ICH after a stroke during the 2011-2019 period (full dataset). Cases were actively monitored from multiple sources.

We classified ICH according to the SMASH-U (Structural lesions, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined) system. ICH volumes were calculated using the ABC/2 method. The presence of radiological Edinburgh criteria, including associated subarachnoid hemorrhage (aSAH) and finger-like projections (FLPs) was assessed on the first available brain CT of patients with lobar ICH. The presence of signs of small vessel disease, including cerebral microbleeds (CMBs) and cortical superficial siderosis (CSS) on patients with available brain MRI was also assessed. Radiological assessments were performed by two raters independently.

Crude incidence rates were calculated assuming a Poisson distribution. Incidence rates were also standardized to the Italian and European population using the direct method. Univariate comparisons of categorical variables were performed using the chi-square test. Univariate

comparisons of continuous variables were performed using the t test or ANOVA for normally distributed variables and the Mann-Whitney or Kruskal-Wallis test for non-normally distributed variables. Logistic regression or Cox regression models were used to perform multivariate analyses.

Results. Over the 2011-2019 study period, we identified 645 patients with ICH (full dataset; 58.6% men; mean age 75.3±13.4 years). All patients were hospitalized and had at least one brain CT. The incidence dataset included 514 patients.

The crude ICH incidence rate was 24.6 per 100,000 person-years (95% confidence interval [CI] 22.5-26.8); the corresponding rates were 22.5 per 100,000 person-years (95% CI 21.1-24.0) after standardization to the Italian population and 19.4 per 100,000 person-years (95% CI 17.9-20.9) after standardization to the European population. Case-fatality rates were 36.0% at 30 days and 44.6% a 1-year. At the 1-year follow-up, 11 (2.1%) patients had a recurrent ICH and 7 (1.4%) an ischemic stroke.

Compared with the 567 patients with a first-ever ICH, the 78 patients with ICH after a stroke had a higher pre-stroke disability (median modified Rankin Scale score 2, interquartile range [IQR] 1-3, vs 1, IQR 0-2; P<0.001) and higher ICH volume at onset (median 20 cm^3, IQR 3-53, vs 8, IQR 2-25; P=0.004), but not higher case-fatality rate. Among the 78 patients with ICH after a stroke, the 34 patients with ICH after hemorrhagic stroke had a higher proportion of lobar location compared with the 44 patients with ICH after ischemic stroke (79.4% vs 40.9%; P=0.009).

According to the SMASH-U classification, 39 patients (6.0%) had an ICH attributable to structural lesions, 74 (11.5%) to medication, 41 (6.4%) to systemic or other disease, 217 (33.6%) to amyloid angiopathy, 235 (36.4%) to hypertensive angiopathy, and 39 (6.0%) to undetermined cause. The comparison among those categories revealed differences in the distribution of risk factors, ICH characteristics and case-fatality across the different SMASH-U categories. However, ICH attributable to medication was the only category which independently predicted 30-day (hazard ratio 1.78, 95% CI 1.18-2.67; P=0.006) and 1-year case-fatality (hazard ratio 1.50, 95% CI 1.02-2.19; P=0.038).

We included 259 patients with lobar ICH; 87 (33.6%) had both the Edinburgh CT criteria for the classification of probable amyloid angiopathy, i.e. aSAH+FLPs, while 77 (29.7%) had only one and 95 (25.6%) none of the criteria. Patients with aSAH+FLPs (median age 81 years, IQR 74-85) or one criterion (median 82 years, IQR 73-87) were older than those with none of the criteria (median 78 years, IQR 69-84; P=0.028). Patients with aSAH+FLPs also had more severe ICH at onset, higher 30-day (log rank test P=0.009) and 1-year case-fatality (log rank test P=0.003), and higher mRS scores at discharge (P<0.001) as compared to those fulfilling one or none of the Edinburgh criteria. However, age (P=0.025 at 30 days and P=0.015 at 1 year) and low Glasgow Coma Scale score (P<0.001 at 30 days and at 1 year) were the only independent predictors of case-fatality.
One hundred and seven patients (16.6%) performed a brain MRI for ICH. Lobar ICH (odds ratio [OR] 3.20, 95% CI 1.56-6.58; P=0.002) or ICH in the posterior fossa (OR 3.41, 95% CI 1.30-8.90; P=0.012) and use of statins before ICH (OR 2.34, 95% CI 1.11-4.94; P=0.039) were associated with performing brain MRI, while older age (OR 0.95, 95% CI 0.92-0.97; P<0.001) and intraventricular extension (OR 0.38, 95% CI 0.15-0.95; P=0.038) were associated with less probability of performing brain MRI. Of the 107 patients performing brain MRI, 36 (%) had lobar and 20 (%) deep cerebral microbleeds. Patients with lobar or deep microbleeds had a higher prevalence of hypertension compared with those without (lobar: 80.6% vs 57.7%; P=0.019, deep: 85.0% vs 60.9%; P=0.041); however, ICH location was not associated with the location of microbleeds. The presence of cerebral microbleeds was not associated with that of the Edinburgh CT criteria for probable amyloid angiopathy, namely aSAH or FLPs.

Conclusions. In our population-based study, the incidence and outcomes of first-ever ICH were comparable to those reported in similar studies performed during the last decade. Compared with first-ever ICH cases, those occurring after a stroke and mostly after an ICH had a high prevalence of lobar location, possibly reflecting an underlying amyloid angiopathy. Applying a classification tool to patients with ICH was feasible and identified patient categories with different risk factor profile and different prognosis; however, only ICH attributable to anticoagulant medication was an

independent predictor of ICH case-fatality. Besides, the available classification tools are limited by the coexistence of several etiologic factors in the same patient. Brain MRI could help refining the etiologic diagnosis of ICH; however, we found that brain MRI cannot be applied on a large scale in those patients. Further studies are needed to investigate the multiple etiologic factors of ICH and to design adequate diagnostic protocols that can help the management of this severe stroke type.

1. Background

1.1 Definition of intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is traditionally defined as rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma (R. L. Sacco et al., 2013). In the absence of brain neuroimaging or necropsy examinations and of occlusive peripheral artery disease, a diagnosis of probable ICH can be made in the presence of clinical symptoms reflecting increased intracranial pressure such as headache and vomiting, decreased alertness or coma, and gradual progression to death within 24 hours of onset (Aho et al., 1980).

ICH accounts for approximately 15% of all strokes and 50% of stroke-related mortality, causing approximately 2.8 million deaths worldwide each year (Schrag & Kirshner, 2020). This disproportionate amount of mortality is due to the high severity of the disease, its rapid course, and the relatively few available treatment options.

1.2 Epidemiology

ICH is a major public health problem with an annual incidence of 10–30 per 100 000 population, accounting for 2 million (10–15%) of about 15 million strokes worldwide each year (Qureshi, Mendelow, & Hanley, 2009). According to the Global Burden of Disease 2017, ICH accounts for 26% of strokes worldwide (Krishnamurthi, Ikeda, & Feigin, 2020). The incidence of ICH is substantially variable across countries and ethnicities. The incidence rates of primary ICH in low- and middle-income countries is twice the rates in high-income countries (22 vs. 10 per 100,000 person-years in 2000-2008 (van Asch et al., 2010). ICH incidence also varies across ethnicities, being estimated in 51.8 per 100,00 person-years in Asians, 24.2 in Whites, 22.9 in Blacks, and 19.6 in Hispanics (van Asch et al., 2010). The incidence of ICH is also tightly linked with increasing age., increasing from 0.10 (95% confidence interval [CI] 0.06-0.14) for people aged less than 45 years to 9.6 (6.6-13.9) for people older than 85 years (van Asch et al., 2010). ICHh has a grim

prognosis, with a 30-day case fatality of 40% (van Asch et al., 2010); according to a meta-analysis, the 1-year and 5-year survival of ICH are 46% and 29%, respectively (Poon, Fonville, & Al-Shahi Salman, 2014).

There is uncertainty about the changes of ICH incidence and characteristics over time. Italian population-based data indicate a 48% decrease in ICH incidence from the 1994-1998 to the 2011-2012 period (S. Sacco et al., 2016), similar to the 50% decrease observed in Oxfordshire, UK, from 1981-1986 to 2002-2006 (Lovelock, Molyneux, Rothwell, & Study, 2007). Some studies found a remarkable ICH incidence decrease in subjects aged 75 years or less (Jolink, Klijn, Brouwers, Kappelle, & Vaartjes, 2015; Lovelock et al., 2007), while some others found that the decline was more pronounced in the elderly (Béjot et al., 2013; Zahuranec et al., 2014). Notably, there might have been a change in ICH location over time, with an increase in the relative proportion of lobar over deep ICHs (Béjot et al., 2013; Lovelock et al., 2007; S. Sacco et al., 2016). The trend of ICH mortality over time was stable (Lovelock et al., 2007; van Asch et al., 2010; Zahuranec et al., 2014) or slightly reduced (Meretoja et al., 2011).

1.3 Risk factors

The clinical distinction of ICH by the brain localization is based on the presumed underlying etiology with lobar ICH thought to be caused primarily by cerebral amyloid angiopathy, and deep ICH more related to hypertensive vasculopathy (Ikram, Wieberdink, & Koudstaal, 2012; Qureshi et al., 2001). An ICH is not caused by a single risk factor, but is more likely to be a result of a complex interplay of multiple risk factors—though a single or few risk factors may have a bigger role than others (Ikram et al., 2012). There are two groups of risk factors : modifiable risk factors include hypertension, cigarette smoking, excessive alcohol consumption, decreased low-density lipoprotein cholesterol, low triglycerides, and drugs including anticoagulant, antithrombotic agent, and sympathomimetics; non-modifiable risk factors include old age, male sex, cerebral amyloid angiopathy, and Asian ethnicity (An, Kim, & Yoon, 2017).

Hypertension is the single most important risk factor for intracerebral hemorrhage, as showed from abundant evidence, both from case–control studies and cohort studies (Ikram et al., 2012; O'Donnell et al., 2010). A meta-analysis across 11 case–control studies revealed that hypertensives had an almost 3.5-fold increased risk of intracerebral hemorrhage compared with normotensives (Ariesen, Claus, Rinkel, & Algra, 2003). Improved control of hypertension effectively reduces the risk of ICH (O'Donnell et al., 2010; Qureshi et al., 2009; Qureshi et al., 2001).

Smoking is an important modifiable risk factor for ICH, but its effect is not as large as hypertension effect. Studies have demonstrated a dose–response relationship with the number of cigarettes smoked and risk of intracerebral hemorrhage. Moreover, the effect of smoking extends to former smoking, although the risk is largest for current smokers (Ariesen et al., 2003).

Alcohol abuse is another modifiable risk factor for ICH. Presumed pathways for this association include platelet dysfunction, coagulation disturbances, or endothelial damage. Most literature data suggest that whereas for ischemic stroke moderate alcohol intake has been shown to be protective, the risk of ICH follows a linear dose–response relationship between alcohol intake and ICH risk (Zhang et al., 2011). However, the ERICH study, a multicenter, prospective, case-control study, designed to recruit 1,000 non-Hispanic white patients, 1,000 non-Hispanic black patients, and 1,000 Hispanic patients with ICH, demonstrated an association of effects of rare (<1 drink for month) and moderate (<1 drink and ≤2 drinks per day) alcohol consumption with decreased risk of both lobar and non-lobar ICH, while massive alcohol consumption (>5 per days) was linked with enhanced ICH risk (C. J. Chen et al., 2017).

Obesity is recognized as a modifiable risk factor for cardiovascular disease, particularly ischemic heart disease, while the association between obesity and stroke is less clear. A case-control study separately comparing lobar and deep ICH demonstrated that Body Mass Index values were not associated with lobar ICH risk in either univariate and multivariate analysis, while both low BMI (<18.5 kg/m^2) and very high BMI (>30.0 kg/m^2) were associated with deep hemorrhage (Biffi et al., 2011).

Diabetes mellitus is an interesting risk factor for ICH because of the potential easy intervention and prevention strategies about it (Ikram et al., 2012). A large metanalysis of 102 prospective studies, including 698,782 participants, recently provided convincing evidence for diabetes as risk factor for ICH.; the reported relative risk was 1.6 (95 % confidence interval from 1.2 to 2.1) for persons with diabetes compared to persons without diabetes (Sarwar et al., 2010).

Associations have been reported between ICH and *sympathomimetic drugs* such as cocaine, heroin, amphetamine, and ephedrine, particularly in young patients. Phenylpropanolamine in a relatively high dose was an independent risk factor for ICH, particularly in women (An et al., 2017).

In some prospective studies, ICH occurs more frequently in individuals with low serum cholesterol than in those with higher concentrations (Suh et al., 2001). The use of 3-Hydroxy-3-methylglutaryl coenzyme-A inhibitors (known as statins) has modestly increased over time in ICH patients, despite reports suggesting that statins could increase the risk for ICH. Other studies have, on the contrary, found statins to be associated with reduced disability and mortality after ICH (Mustanoja et al., 2013). Low cholesterol may play a role in promoting arterial medial layer smooth muscle cell necrosis. The impaired endothelium would be more susceptible to microaneurysms, which were the chief pathological finding of ICH. In addition, there is another interesting element to consider: cholesterol levels may reflect the nutritional status of patients with ICH and low cholesterol level may be a surrogate for nutritional deficiencies or a sign of debilitating diseases, thus being predisposed to increased stroke mortality (Wang, Dong, Qi, Huang, & Hou, 2013).

Chronic kidney disease may be a marker of cerebrovascular small vessel disease, which is the major mechanism of hypertensive ICH. Platelet dysfunction in patients with chronic kidney disease might also account for the increased risk of ICH (An et al., 2017).

Anticoagulants are an important modifiable risk factors of ICH (An et al., 2017). However, there are important contributory factors to ICH associated with use of anticoagulants as advancing age of patient and CAA (Qureshi et al., 2009). *Antiplatelet agents* might also increase the risk of ICH by substantially increasing the number of microbleeds at risk for conversion into clinically manifest

macrobleeds (Biffi et al., 2010; Casolla & Cordonnier, 2020). Dual antiplatelet therapy compared to antiplatelet monotherapy is likely to further increase the ICH risk. A study performed in patients with atrial fibrillation showed a twice higher risk of ICH with aspirin plus clopidogrel compared to aspirin alone (Naidech et al., 2009).

Age is the most important non modifiable risk factor for ICH. The available studies demonstrate that there is a direct correlation between age and ICH: the ICH risk increases proportionally with age (Camacho et al., 2015).

Cerebral amyloid angiopathy (CAA) is the second most important single risk factor for ICH, after hypertension. It is more related with lobar ICH. CAA refers to the accumulation of β-amyloid in the media and adventitia of mostly cortical vessels, which can lead to leakage of blood through the vessel wall (Viswanathan & Greenberg, 2011). The frequency of CAA is thought to increase with age, with almost half of all persons older than 90 showing some signs of CAA (Knudsen, Rosand, Karluk, & Greenberg, 2001). Apart from ICH, CAA also increases the risk of Alzheimer's disease, suggesting partly overlapping mechanisms between ICH and Alzheimer's disease (Viswanathan & Greenberg, 2011).

Other causes for ICH are *vascular abnormalities*, including arteriovenous malformations (AVMs), cavernous angioma, and venous malformations. The annual bleeding risk of AVMs amounts 1% to 4% and mostly affects young patients. Outcome after AVM rupture seems to be more favorable in comparison to the outcome after other forms of spontaneous ICH, depending on patient characteristics, bleeding patterns, hemodynamic features, and hemorrhage size (Dinc et al., 2019).

1.4 Pathogenesis

The majority of spontaneous ICHs result from the rupture of damaged small vessels of the brain. The two main forms of cerebral small vessel disease (SVD) are hypertensive SVD that affects mainly the deep perforators that supply the subcortical gray structures, and CAA, which is characterized by the progressive accumulation of beta-amyloid in the leptomeningeal and cortical vessels.

Over 60% of primary bleeds are related to hypertension, and these hematomas are most seen in the posterior fossa, pons, basal ganglia, and thalamus (Ziai & Carhuapoma, 2018) (**Figure 1**). Chronic hypertension can interfere with cerebral autoregulation, the mechanism that maintains stable blood flow despite changes in blood pressure (or, more accurately, cerebral perfusion pressure). Under normal circumstances, cerebral blood flow is regulated through changes in arteriolar diameter. Various processes, including myogenic, neurogenic, endothelial, and metabolic responses, have been implicated in the mediation of cerebral vasomotor reactions. The *myogenic tone* gets produced when arteriole and small artery smooth muscle cells contract in response to increased pressure. In contrast, myogenic tone relaxes in response to decreased pressure. *Neurogenic mediation* of cerebral vasoreactivity involves control of small- and medium-sized vessel diameters. Neurons and other cell types like astrocytes and microglia secrete a variety of neurotransmitters with vasoactive properties. The *metabolic mechanism* subserving autoregulation occurs in smaller vessels that are subject to changes in the local environment. Most notably, carbon dioxide overtly alters vasomotor responses; every 1 mmHg increase in $PaCO_2$ corresponds to a roughly 4% increase in cerebral blood flow. Lastly, *endothelial tissue* products signals that affect vascular tone. The endothelium secretes vasodilators like nitric oxide (NO) and vasoconstrictors like thromboxane A2 and endothelin1 in a paracrine manner ("StatPearls," 2020).

Chronic hypertension damages blood vessels causing their degeneration and rupture. The deposition of fibrillar material on arteriolar wall or on basal membranes causes a reduction of the contractile capability of arterioles. Fibrinoid necrosis of the sub-endothelium with micro-aneurysms and focal dilatations may be seen in some patients. Lipohyalinosis, prominently related to long-standing hypertension, is most often found in non-lobar ICH (Fisher, 1982). Patients with acute and chronic deep hemorrhages not accompanied by bleeds in lobar locations are likely to harbor hypertensive small vessel disease as the principal cause of bleed. By contrast, patients who present with a lobar ICH and multiple strictly lobar bleeds, such as cerebral microbleeds (CMB) or cortical superficial

siderosis (cSS), are likely to have CAA according to the pathologically validated Boston criteria (Knudsen et al., 2001).

CAA involves cerebrovascular amyloid deposition and is classified into several types according to the amyloid protein involved. Of these, sporadic amyloid β-protein (Aβ)-type CAA is most commonly found in older individuals and in patients with Alzheimer's disease (AD). Cerebrovascular Aβ deposits are associated with functional and pathological changes in cerebral blood vessels (CAA-associated vasculopathies). Pathologically, CAA is observed mainly in the leptomeningeal and cortical vessels of the cerebral lobes and cerebellum; the occipital lobe is preferentially affected, whereas CAA is uncommon in the basal ganglia, thalamus, brainstem, and white matter (Yamada, 2015). The CAA-associated vasculopathies consist of aneurysmal vessels with amyloid infiltration, obliterative intimal changes, "double barreling", chronic inflammatory perivascular or transmural infiltrates, hyaline arteriolar degeneration, and fibrinoid necrotizing vascular change (Mandybur, 1986).

CAA-related bleeds include symptomatic lobar macrobleeds, small and typically silent cerebral microbleeds, or superficial cortical hemorrhages that follow the curvilinear shape of the surrounding cerebral gyri. This latter group - designated as convexity subarachnoid hemorrhage when acute and cortical superficial siderosis (cSS) when chronic - has proven particularly relevant to clinical practice. Their proximity to the cortical surface appears to be the trigger for transient focal neurologic symptoms or "amyloid spells" in a substantial proportion of individuals presenting with this syndrome. The other major clinically important role of cSS, particularly when disseminated (affecting more than 3 sulci) or multifocal, appear to have approximately 3 times the hazard ratio for recurrent ICH than those without cSS (Greenberg & Charidimou, 2018) (**Figure 2**). Currently, no disease-modifying therapies are available for CAA. Hypertension control may reduce the progression of brain damage due to CAA (Arima et al., 2010) by controlling the process of fibrinoid necrosis. It is also important to use antithrombotic – and mostly anticoagulant – medications with caution in patients with suspected CAA, due to the increased risk of ICH

(Charidimou, Shakeshaft, & Werring, 2012). Once occurred, ICH can be safely evacuated in selected patients (Yamada, 2015).

Cerebral SVD (cSVD) is a term used to delineate a group of different pathological processes that affect the small vessels of the brain, including small arteries, arterioles, capillaries, and small veins. These vessels are important to maintain the adequate blood flow on the brain surface. The European Small Brain Vascular Disease Expert Group puts forward the classification of cSVD based on cerebrovascular pathologic changes as the following: arteriolosclerosis, sporadic and hereditary CAA, inherited or genetic SVD distinct from CAA, inflammatory and immunologically-mediated SVD, venous collagenosis, and other SVD such as post-radiation angiopathy (Pantoni, 2010). These various pathologic changes result in damage of brain parenchyma including neuronal apoptosis, diffuse axonal injury, demyelination and loss of oligodendrocytes. cSVD is thought to result in reduced cerebral blood flow, impaired cerebral autoregulation and increased blood–brain barrier (BBB) permeability. However, the molecular mechanisms underlying cSVD are incompletely understood (Li et al., 2018). cSVD is categorized in two main forms. The first is the amyloidal form which includes CAA; the second form is characterized as non-amyloidal form of cSVD which is often related to common vascular risk factors, such as older age, hypertension, and diabetes mellitus. The term *hypertensive arteriopathy* is widely used to describe the non-amyloidal form of cSVD.

There are two different causal aspects in cSVD: (1) pathological and (2) genetic. Genetics may play an important role in elucidating the cellular and molecular mechanisms and thus the pathophysiology of hereditary forms of cSVD. Genetic factors and their pathways have been elaborated for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), incontinentia pigmenti, and several other forms of cSVD (Cuadrado-Godia et al., 2018).

Neuroimaging has become an important tool in diagnosing cSVD and the silent neurovascular disease, especially at early stage. The main features visualized are: recent small subcortical infarcts, lacunar infarct, white matter hyperintensities (WMHs), microbleeds, enlarged perivascular spaces, and brain atrophy (Wardlaw, Smith, & Dichgans, 2019) (**Figure 3**).

There are different pathophysiological mechanisms involved in ICH including mechanical trauma, mass effect and ischemia, toxicity of blood components and excitotoxicity. Mass effect and mechanical disruption from extravasated blood, either with initial hemorrhage or with continued hemorrhage and hematoma expansion, causes immediate primary brain injury due to both global increased intracranial pressure and mechanical compression of local structures. The latter can be particularly deadly when bleeds occur in the posterior fossa, where local compression of the aqueduct of Sylvius can lead to obstructive hydrocephalus, or local compression of the brainstem may lead to cardiorespiratory dysfunction. Hematoma expansion is common, occurring in over one-third of patients in the first 24 hours onset (Brott et al., 1997). Global increases in intracranial pressure may lead to herniation syndromes causing arterial compression and resulting ischemia (Orakcioglu et al., 2015). Secondary brain injury is caused by the physiologic response to the hematoma (primarily edema and inflammation) as well as the toxic biochemical and metabolic effects of clot components. The formation of perihematomal edema can occur within hours of ICH and persist for days to weeks, with an average 75% increase in perihematomal edema within the first 24 hours after ICH. A portion of edema develops due to clot retraction and serum protein accumulation around the clot with an initially intact blood-brain barrier. Edema likely contributes to disruptions in cell wall ion processing, including that of K^+, Cl^-, and Na^+, though these damages may persist despite resolution of edema. Inflammatory responses both in the local perihematomal area as well as systemically are noted after experimental ICH and both can have deleterious effects. Locally, diapedesis of neutrophils occurs within days and subsequently, microglial cells are activated. Aside from inflammatory cells themselves, other inflammatory mediators are upregulated with ICH, including tumor necrosis factor, adhesion molecules, and matrix metalloproteinases, all

involved in inflammation-related local brain injury. Another pathological mechanism is the blood products toxicity. Hemoglobin plays a role in injury, as it inhibits the sodium-potassium pump and can cause neuronal depolarization and neuronal cell death in experimental models. Iron is also implicated in ICH, and its chelation with deferoxamine reduced brain injury in animal models. In addition, iron contributes to brain injury with free-radical generation (Wilkinson et al., 2018).

1.5 Classification

ICH is commonly classified according to its location into deep (basal ganglia, thalamus, internal capsule) and lobar (Qureshi et al., 2001). Deep location is also qualified as 'typical' as it is usually associated with hypertensive causes, while the lobar location is qualified as 'atypical' as it is not typically associated with hypertension. To correlate ICH location with its cause, several classification systems have been elaborated.

The *SMASH-U* classification was the first established etiological classification for ICH (Meretoja et al., 2012). It is an acronym of a clinical and practical classification system and represents a method in which ICH are categorized in different ways according to etiology, there are five categories that are: structural (S), Medication (M), Amyloid Angiopathy (A), Systemic/other disease (S), Hypertension (H), Undetermined (U) (**Figure 4**). The SMASH-U classification revealed a strong association with patient outcome. According to the SMASH-U classification, hypertension is defined by the presence of elevated blood pressure (≥160/100 mmHg) before the ICH or by mention of elevated blood pressure by patient, relative, or medical records, associated to left ventricular hypertrophy, or by use of blood pressure medication. For probable CAA, the Boston criteria are used (see below) (Meretoja et al., 2012).

The most important issue raised by the SMASH-U criteria is the sequential attribution of only one cause, which excludes the presence of more than one possible cause. In the original validation cohort, almost 80% of ICH cases had more than one possible cause (Meretoja et al., 2012). To correct for this possible issue, the *H-ATOMIC* classification was introduced (Martí-Fàbregas et al., 2016). This classification includes the following 7 subtypes of ICH: H = arterial Hypertension, A =

CAA, T = Tumour, O = Oral anticoagulants (OA), M = arterio-venous Malformations and cavernoma, I = Infrequent causes associated to ICH, and C = unknown cause or Cryptogenic (by analogy with ischemic stroke classifications, this category is considered an etiologic subtype). Each of the above etiologic categories is scored with a degree of certainty of Definite (1), Probable (2) and Possible (3). This classification is based on three assumptions: 1) The most common etiologies are hypertension (H), CAA (A), tumour (T), OA (O) and vascular malformation (M). There is a long list of infrequent causes (I) that may cause ICH. There is also the possibility of not finding any etiology (C, cryptogenic ICH); 2) It is common to find more than one potential etiology for an individual patient. Thus, in addition to patients with a definite etiology, there are patients who have a combination of probable or possible etiologies; 3) The patient with ICH is often unstable during the first hours after onset and, therefore, a basic study designed to find the cause of the ICH must be rapid and easy to perform. Clinicians use intuitively 4 sources of information to attribute the etiology to a specific disease: Age, location, CT and MRI appearance, and the clinical context (some diseases or risk factors may be typically associated with ICH). However, there is no consensus on the diagnostic strategy to be used and on how to combine all this information to reach a final etiologic classification (Martí-Fàbregas et al., 2016) (**Table 1**).

Referring to the etiologic classification of ICH, the identification of possible CAA-related cases in subjects with lobar ICH was assessed in detail. The *Boston criteria* were first published in 1995 in the Methods section of an analysis of CAA and the apolipoprotein E ε4 allele (Greenberg, Rebeck, Vonsattel, Gomez-Isla, & Hyman, 1995). The "modified Boston Criteria" using brain MRI were proposed and validated in 2010 (Linn et al., 2010). Using the category terminology applied to other brain disorders such as Alzheimer's disease, they defined definite CAA based on full autopsy, probable or possible CAA based on brain imaging plus clinical exclusions, and an additional category of probable CAA with supporting pathology based on clinical scenarios of having limited brain tissue from biopsy or hematoma evacuation. Definite CAA requires high neuropathological severity (including features of advanced vasculopathy such as amyloid replacement and splitting of

the blood vessel wall) to avoid diagnosing the condition when the pathology is only mild and incidental. Lesser histopathological severity is required for probable CAA with supporting pathology to reflect the smaller amount of sampled tissue and consequent lower likelihood of identifying the most advanced foci of disease. Several methodologic issues arise in applying the Boston criteria in practice. One is that all types of hemorrhagic lesions – including ICHs, cerebral microbleeds (CMBs), and (since publication of the modified Boston criteria) acute convexity subarachnoid bleeds or cortical superficial siderosis (cSS) – count towards the multiple lobar hemorrhages required for probable CAA, or alternatively preclude probable CAA if in deep territories. The rationale for counting all types of hemorrhagic lesions is that while different hemorrhage sizes may arise by distinct pathogenic mechanisms, each presumably represents a distinct event of vessel leakage and therefore provides independent evidence for the underlying small vessel condition. Hemorrhagic lesions that may be part of a larger hemorrhage, such as smaller extensions in proximity to a larger hemorrhage or foci of cSS near or directly connected to ICHs that have ruptured into the subarachnoid space, are considered as part of a single bleeding event and so not counted as separate hemorrhages. A second practical issue is that a hemorrhagic lesion in the centrum semiovale can appear a long distance from the outer surface of the brain and still be quite close to the cortico-subcortical junction because of the undulating curves of the cortical gyri. Hemorrhages are considered deep hemispheric only when clearly involving the basal ganglia, thalamus, or internal capsule (Greenberg & Charidimou, 2018).

Although the MRI-based Boston criteria have good and excellent specificity and sensitivity respectively for detecting CAA-related lobar ICH, they cannot be used in an acute setting and patients with contraindications to brain MRI. Under these circumstances, a new simple, three variable model, under the name of *Edinburgh Criteria*, using three CT features (lobar hemorrhage, finger-like projections [FLPs] from the main hemorrhagic spot, associated subarachnoid hemorrhage [aSAH]) and the genetic E4 possession has been proposed (Rodrigues et al., 2018) (**Figure 5**). When the genetic analysis is not available, simplified criteria based on the CT imaging

were proposed. The full Edinburgh criteria comprise of CT features combined with apolipoprotein E (APOE) genotype, and are divided into 3 levels: (1) high probability CAA o lobar intracerebral hemorrhage showing aSAH on CT and either FLPs from the ICH on CT, or possession of at least one APOE ε4 allele; (2) intermediate probability CAA o lobar ICH showing either aSAH on CT, or possession of at least one APOE ε4 allele; (3) low probability CAA or lobar ICH showing neither aSAH nor possession of at least one APOE ε4 allele. The presence of aSAH or APOE ε4 possession had 100% sensitivity for moderate/severe CAA in the development setting (95% CI 88 to 100). Therefore, the absence of these predictors (low probability CAA group) can rule-out CAA-associated lobar ICH. The presence of aSAH and FLPs or APOE ε4 allele possession had 96% specificity (95% CI 78 to 100). Therefore, the presence of these predictors (high probability CAA group) can effectively rule-in CAA-associated lobar ICH (Rodrigues et al., 2018).

1.6 Clinical presentation

Although some individuals develop ICH during exertion or sudden emotional stress, most ICHs occur during routine activity. The neurologic symptoms usually aggravate over minutes or a few hours. Common ICH symptoms are headache, nausea, and vomiting. Headache is more common in patients with large hematomas, and is attributed to traction on meningeal pain fibers, increased intracranial pressure, or blood in the cerebrospinal fluid. Small, deep hematomas are rarely associated with headache. Vomiting is reported in about 50% of patients with hemispheric ICH, and more common in patients with cerebellar hemorrhages. Patients with large ICH often have a decreased level of consciousness due to increased intracranial pressure and compression of the thalamus and brainstem. Stupor or coma indicates large ICHs that involve the brainstem reticular activating formation. Neurological deterioration is common before and during hospital admission and may indicate early hematoma enlargement or worsening of edema. Patients with a supratentorial ICH involving the basal ganglia or thalamus have contralateral sensorimotor deficits. Lobar hemorrhages may present with symptoms of a higher cortical dysfunction such as aphasia, neglect, gaze deviation, and hemianopia. In patients with an infratentorial ICH, signs of brainstem

dysfunction occur such as ocular motor or other cranial nerve abnormalities, and contralateral motor deficits. More than 40% of patients with CAA-associated ICH have some degree of cognitive dysfunction, and the cognitive changes may precede the ICH in some cases (An et al., 2017).

1.7 Diagnosis

Diagnosis of ICH is suggested by sudden onset of headache, focal neurologic deficits, and impaired consciousness, particularly in patients with risk factors. ICH must be distinguished from ischemic stroke, subarachnoid hemorrhage, and other causes of acute neurologic deficits, including seizure and hypoglycemia. Neuroimaging is usually diagnostic.

Noncontrast computerized tomography (NCCT) is a fast technique with excellent sensitivity for identifying acute ICH, and given its wide availability is considered the gold standard for the diagnosis of ICH. NCCT can provide useful elements such as ICH location, intraventricular extension, hydrocephalus, presence and degree of edema, and midline shift or brainstem compression secondary to the mass effect from the hematoma. On CT examination, an acute ICH is clearly hyperdense compared to the normal brain parenchyma; the attenuation coefficient of non-coagulated extravasated blood, in fact, is about 50 Hounsfield Units, while that of gray matter is about 35-40 Hounsfield Units. The formation of the clot and its subsequent retraction lead to a further increase in hyperdensity, which can reach values between 80 and 90 Hounsfield Units. Blood hyperdensity is basically linked to hemoglobin (for more than 90%) and only minimally (8%) to the iron concentration. The appearance of ICH on brain CT changes over time.

Hyperacute and acute phase (0-12 hours up to the 7th day): the hemorrhagic extravasation leads to the formation and retraction of the clot and exudation of serum with simultaneous edematous reaction of the surrounding brain parenchyma. On CT examination, from the early hours of the hemorrhagic event, this situation translates back into the presence of an area of net hyperdensity, with a mass effect on the adjacent ventricular structures. In the days immediately following the insult, a hypodense peripheral halo forms partly secondary to the silky exudation and partly to the tissue edema reaction, with an increase in the mass effect.

Subacute phase (2nd-4th week): the lysis of the clot begins; the focus is surrounded by a predominantly mononuclear cell infiltrate that provides for the phagocytosis of the erythrocytes, the enzymatic digestion of the molecular components and the accumulation of the degradation products of hemoglobin. On CT examination, in repeated checks over time, there is a progressive and centripetal reduction of the hyperdensity area; the hemorrhagic collection takes on a characteristic appearance, in which a hyperdense central portion (consisting of a blood clot not yet lysed) and a hypodense peripheral portion (consisting of cellular debris, serum with low hemoglobin concentration and edema) is distinguished. All this does not involve an effective volumetric reduction of intraparenchymal blood collection and therefore the mass effect is little modified. In this phase, the intravenous administration of contrast allows to appreciate the appearance of a hyperdense labrum (barrier damage) in the hypodense peripheral portion with the creation of a "cockade" image of the pathological area. Between the end of the third and fourth week, the hemorrhagic focus becomes all hypodense and is gradually reabsorbed, with the disappearance of the edema.

Outcome phase (beyond the 4th week): after phagocytosis of tissue debris, a poroencephalic cavity or cicatricial gliosis is formed, although in most cases these two aspects coexist. On a CT skull examination in this phase, the hemorrhagic focus appears as an area of hypodensity (liquor-like in the poroencephalic cavities formed) with associated "ex vacuo" dilation of the adjacent ventricular-cisternal system. If the CT examination is carried out in the period between the subacute phase and the outcome phase, the hemorrhagic lesion may not be detectable as it is isodense to the surrounding parenchyma; after contrast, a ring-like impregnation may appear.

Magnetic resonance imaging (MRI) sensitivity for the diagnosis of ICH is equivalent to NCCT. MRI can be a useful technique to detect underlying secondary causes of ICH such as neoplastic lesions or hemorrhagic transformation of ischemic stroke. Finally, in patients with poor kidney function, contrast allergies or other contraindication to computed tomography angiography, brain vessel imaging can be achieved without contrast through magnetic resonance angiography (Morotti

& Goldstein, 2016). The manifestations of hemorrhage in MRI are related to the formation of products with magnetic properties resulting from the degradation of oxyhemoglobin: these products include deoxyhemoglobin, methemoglobin, ferritin and hemosiderin. As a consequence of the magnetic properties of these products, the appearance of a hemorrhage in MR images varies according to various factors: the pulsed sequence, the intensity of the static magnetic field, the formation and retraction of the clot, the time of hemorrhage, the state of oxygenation of the hemorrhage that is relative to its location. The appearance of an ICH follows a well-defined course and is strongly linked to the intensity of the static magnetic field and the type of pulsed sequence used (Fast or Turbo Spin Echo, Spin Echo, Inversion Recovery or Gradient Echo). Hyperacute hematoma (from the first five minutes to a few hours). Immediately after an intracerebral hemorrhage, a liquefied mass is formed in the brain that contains oxyhemoglobin, but not yet as a paramagnetic substance. The appearance of this mass is like that of any other type of proteinaceous collection, from dark to slightly hyperintense in T1-weighted images and from dark to bright in T2-weighted images. Typically, this mass is circumscribed by a hypointense margin in both T1-weighted and T2-weighted images, but much more marked in T2, due to their longer relaxing time. The more the images are weighted to highlight the phenomena of magnetic susceptibility, the more this hypointense rhyme will be clearly visible.

Acute phase. In this period, the reduction of oxygen tension inside the hematoma determines the formation of intracellular deoxyhemoglobin and methemoglobin in intact red blood cells; given their distribution, these paramagnetic substances produce T2 shortening, so the hematoma will appear dark. The loss of signal is roughly proportional to the square of the intensity of the static magnetic field and is by far more pronounced in long relaxing time images. As on brain CT, fluid-fluid levels can be observed, in which the lower compartment initially contains sedimented red blood cells and will appear dark in T2-weighted images, due to the effect of intracellular paramagnetic substances and the clot. The upper compartment contains fluid-rich plasma and appears bright on T2-weighted images. Furthermore, generally around the area of signal loss

corresponding to the hematoma there is a subtle edge of hyperintensity, which circumscribes it, representing edema.

Subacute phase. During this period there is lysis of the red blood cells. The redistribution of methemoglobin in the extracellular space modifies the effect of this paramagnetic substance on the signal intensity. At this point the predominant effect is that of T1 shortening, which determines an increase in the signal in the T1-weighted images, and to a lesser extent, also in the T2-weighted ones, which begins as a margin at the periphery of the hematoma, extending over time to its central portions. There are three reasons for the increase in signal in T2-weighted images: lysis of red blood cells and therefore disappearance of the T2 shortening; liquid osmosis is drained into the hematoma; and finally the relaxing time generally used for T2 weighted images is not long enough to eliminate the T1 contrast effect in the image. The result of the combination of these effects lies in the hematoma becoming bright in T2-weighted images. At this point, vasogenic edema caused by the loss of proteinaceous fluid in the brain tissue is seen to circumscribe the hematoma. This fluid spreads along the fibrous tracts, giving the edema the appearance of fingers ("fingers of edema") which are deepening in the brain. Sometimes dark areas persist in the hematoma, even when it is expected that the lysis of red blood cells is complete. If of a certain extent, this can be due to the persistence in hematoma portions of hyperconcentrated paramagnetic substances, such as methemoglobin. However, similar significant signal changes are likely to be caused by physical alterations in the structure of the hematoma such as clot retraction.

Outcome phase. During this variable period, the phagocytic cells invade the hemorrhage from the periphery towards the center. These cells metabolize the breakdown products of hemoglobin and store iron in the form of particulate ferritin and hemosiderin. In this form, iron is superparamagnetic and produces T2 shortening. Which produces signal loss along the edge of the hematoma, which is most pronounced in T2-weighted images, but observable to a lesser extent in T1-weighted images. Signal loss can be seen in old hematomas for years and is due to the deposition of hemosiderin (hemosiderin tattoo).

Figure 6 shows the appearance of ICH over time at brain CT and MRI.

A clinical decision rule incorporating three simple patient characteristics- 55years of age or less, no history of hypertension, presence of lobar hemorrhage-appears useful for reducing the number of unnecessary MRI studies while reliably identifying patients who require MRI after ICH (Kamel, Navi, & Hemphill, 2013).

ICH volume is a strong predictor of ICH outcome and can be rapidly estimated with the ABC/2 method (**Figure 7**) (Kothari et al., 1996; Morotti & Goldstein, 2016). According to this method, the CT slice with the largest area of hemorrhage is identified. The largest diameter (A) of the hemorrhage on this slice is measured. The largest diameter 90° to A on the same slice is measured next (B). Finally, the approximate number of 10-mm slices on which the ICH is seen is calculated (C). C is calculated by a comparison of each CT slice with hemorrhage to the CT slice with the largest hemorrhage on that scan. If the hemorrhage area for a particular slice is greater than 75% of the area seen on the slice where the hemorrhage is largest, the slice is considered 1 hemorrhage slice for determining C. If the area is approximately 25% to 75% of the area, the slice was considered half a hemorrhage slice; and if the area was less than 25% of the largest hemorrhage, the slice is not considered a hemorrhage slice. These CT hemorrhage slice values are then added to determine the value for C. All measurements for A and B are made with the use of the centimeter scale on the CT scan to the nearest 0.5 cm. A, B, and C are then multiplied and the product divided by 2, which yielded the volume of hemorrhage in cubic centimeters (Kothari et al., 1996).

CT Angiography (CTA) is a useful diagnostic tool in the acute setting of ICH. It is the most widely available, non-invasive technique for the detection of vascular abnormalities as secondary causes of ICH. The presence of lobar ICH, young age and absence of traditional cerebrovascular risk factors should trigger the suspicion of ICH secondary to vascular malformation or other intracranial pathology (Morotti & Goldstein, 2016). The “spot sign”, described as a 1-2mm sized foci of contrast enhancement or the presence of high density material on CTA within an acute primary

hematoma no matter its shape, has been demonstrated to predict hematoma expansion following acute ICH (Brouwers et al., 2014; Morotti & Goldstein, 2016) (**Figure 8**).

Initial hematoma expansion following spontaneous acute ICH is an important marker of poor prognosis, increased mortality, and longer hospital stay. The spot sign was defined using the following criteria: (1) ≥1 focus of contrast pooling within the ICH; (2) an attenuation ≥120 Hounsfield units (approximately double the background hematoma density); (3) being discontinuous from normal or abnormal blood vessels adjacent to the ICH; and (4) blood vessels of any size and morphology, which can be easily identified by non-radiologists. Those vessels entering the hematoma from the periphery and connecting with the region of contrast extravasation should not be confused with the hematoma. Apart from the site of active extravasation, a locus of arrested hemorrhage forming fibrin globules or associated epiphenomena such as hypertensive microaneurysms from a microvascular lesion also present as a "spot sign" on CTA (Peng, Reis, Reis, Zhang, & Yang, 2017).

1.8 Management

ICH is a medical emergency that needs urgent therapy to prevent mortality and disability. Fifty-eight percent of ICH patients die within 1 year, and 2/3 of survivors remain moderately or even severely disabled. About one-third of ICH patients presenting within the first 3–6 h after symptom onset will have hematoma growth which worsens outcome. Hence, prevention of hematoma growth has become a key target of early ICH management. Another important, but more delayed process is the development of perihematomal edema which contributes substantially to the space-occupying effect of the hematoma (Veltkamp & Purrucker, 2017). The main goal of prehospital management of ICH is to provide airway and cardiovascular support to unstable patients, along with careful reconstruction of symptom onset timing, medical history and current medications. Patients with ICH are often unable to protect the airway because of reduced consciousness. Endotracheal intubation may be therefore necessary, but this decision should be balanced against the risk of losing the neurologic examination. Rapid sequence intubation is typically the preferred approach in

the acute setting. Pretreatment with lidocaine may be preferred as it may blunt a rise in intracranial pressure (ICP) associated with intubation (Morotti & Goldstein, 2016). The mainstays of ICH care in the acute phase include the management of high blood pressure, anticoagulation reversal in case of anticoagulant-related ICH, and neurosurgical referral in patients potentially eligible to ICH evacuation (Parry-Jones et al., 2019). Within the setting of an active quality improvement program to improve acute care for patients with ICH, implementation of the an acute ICH care bundle based on those three elements is associated with improved delivery of intensive BP lowering, better access to neurosurgery, improved supportive care, and a relative reduction in 30-day and 1-year case fatality of more than one-third (Parry-Jones et al., 2019).

Blood pressure management. Most patients present elevated blood pressure in acute phase of ICH and it is associated with higher risk of hematoma expansion. The current American Heart Association (AHA) guidelines indicate that intensive BP treatment is safe and might be associated with better outcome in patients presenting with systolic BP between 150–220 mmHg. Elevated BP should be treated with short half-life agents such as labetalol or nicardipine to avoid overshoot hypotension. Hydralazine and nitroprusside should be avoided given their possible association with increased ICP (Morotti & Goldstein, 2016). An international clinical trial (INTERACT2) of 2829 patients with generally mild to moderately severe ICH showed that early intensive lowering of blood pressure to a systolic target of less than 140 mm Hg led to modest improvements in functional outcomes and health-related quality of life without substantial harms, compared with the contemporaneous standard (systolic target <180 mm Hg) within several hours of onset (Qureshi et al., 2014). However, a second trial (ATACH-II) involving 1000 patients of similar demographic and clinical parameters did not show any benefits of a more intensive blood pressure lowering regimen and raised concerns over an increase in renal adverse events of such treatment (Qureshi et al., 2018).

These discordant results might be largely explained by differences in the manner in which blood pressure was managed. INTERACT2 took a pragmatic approach and allowed various drugs, on the

basis of local availability and familiarity, to be used to lower blood pressure over several hours, whereas ATACH-II had a more intensive blood pressure lowering protocol based on a single intravenous agent (nicardipine) and the investigators, probably influenced by the updating of guidelines, also intensively managed the blood pressure of control patients. Systematic reviews and meta-analyses of these and other, much smaller, clinical trials have not shown any effect of early intensive blood pressure lowering on clinical outcomes, despite there being a modest attenuation of hematoma growth overall and no clear effect on hematoma growth in either INTERACT2 or ATACH-II. However, these studies were unable to account for differences in blood pressure management (Cordonnier, Demchuk, Ziai, & Anderson, 2018).

Hemostatic treatment. Coagulopathy correction is aimed at preventing continued bleeding. Warfarin discontinuation and IV administration of vitamin K are the first therapeutic steps (Aguilar & Freeman, 2010). Vitamin K should be infused slowly (over 10 minutes), at the dose of 10 mg with close monitoring of vital signs given the rare but not negligible risk of anaphylaxis (1/10.000). Given its slow onset of action (6 to 24 h), emergent factor repletion is typically provided in addition. Fresh Frozen Plasma (FFP) and Prothrombin Complex Concentrates (PCCs) are commonly used. According to the AHA/ASA guidelines PCCs may be preferred over FFP because of more rapid action. Two randomized controlled trials of PCC vs. FFP showed that PCCs restore coagulation factors and reverse the International Normalized Ratio (INR) more rapidly than FFP, with no clear difference in thromboembolic risk. The Neurocritical Care Society recommends warfarin reversal with either PCCs or FFP with a target INR<1.5 (Morotti & Goldstein, 2016). Direct oral anticoagulants carry about a 50% lower risk of intracranial hemorrhage compared to vitamin K inhibitors. Nevertheless, if direct oral anticoagulant-related ICH occurs, the outcome including mortality is similar to ICH associated with VKA. Reversal agents specific to dabigatran and the factor Xa inhibitors, respectively, have been developed. The only currently licensed specific reversal agent is idarucizumab (Tsivgoulis et al., 2017).

A relevant number of patients with ICH are taking antiplatelet medication at the time of the event. Cyclooxygenase inhibitors such as aspirin and the P2Y2G inhibitors clopidogrel, prasugrel, and ticagrelor irreversibly block their targets in platelets and thereby attenuate platelet aggregation. The randomized PATCH trial surprisingly revealed that platelet transfusions increased mortality or dependence at 3 months. Hence, platelet transfusion should not be performed in ICH patients taking antiplatelet medication (Veltkamp & Purrucker, 2017). In the TICH-2 trial, functional status 90 days after ICH did not differ significantly between patients who received tranexamic acid and those who received placebo, despite a reduction in early deaths and serious adverse events (Sprigg et al., 2018).

Intraventricular hemorrhage and hydrocephalus management. Intraventricular hemorrhage (IVH) and hydrocephalus are independent predictors of poor outcome in ICH as impaired flow of cerebrospinal fluid and direct mass-effects of ventricular blood lead to obstructive hydrocephalus (Qureshi et al., 2009). Mass effect from the hematoma and surrounding edema and IVH with secondary hydrocephalus are common causes of elevated intracranial pressure (ICP). Current AHA/ASA guidelines suggest ICP monitoring in patients with coma, significant IVH with hydrocephalus and evidence of transtentorial herniation, with a cerebral perfusion pressure (CPP) target of 50 to 70 mmHg (Hemphill et al., 2015). ICP can be measured with parenchymal or ventricular devices.

Hyperosmolar therapy with mannitol or hypertonic saline can be considered in patients at risk of transtentorial herniation (Morotti & Goldstein, 2016). Clots in the catheter and infections prevent sustained beneficial effects on hydrocephalus and neurological status in many patients. Shortening the length of external ventricular drainage with early ventriculoperitoneal shunt placement or lumbar drainage for communicating hydrocephalus might lower the rate of infections. Substitution of lumbar drainage for external ventricular drainage in patients with communicating hydrocephalus might also lessen the need to change temporary ventricular catheters and to use ventriculoperitoneal shunts. To facilitate early and effective clearance of blood in the ventricles, recent efforts have

focused on intraventricular use of thrombolytic drugs in patients who have IVH in association with spontaneous ICH (Qureshi et al., 2009), with encouraging but still unclear results. According to the CLEAR-III trial, patients with primary IVH have a favorable outcome compared with those with secondary IVH (Nelson et al., 2020).

Seizures and antiepileptic treatment. Up to 14% of patients with ICH experience seizures in the early course of the disease (De Herdt et al., 2011). The main risk factors for development of early seizures are cortical location of the ICH and occurrence of medical complications. However, it is not clear that prophylactic antiepileptic (AED) therapy provides benefit to patients, and some data suggests phenytoin may worsen outcome in this population. Therefore, prophylactic administration of AED therapy is not recommended and only subjects with clinical or electroencephalographic (EEG) evidence of seizures should receive antiepileptic drugs. Continuous EEG monitoring should be considered in patients with impaired mental status that is disproportionate to the degree of brain damage (Morotti & Goldstein, 2016).

Surgical treatment. Surgical evacuation may prevent expansion, decrease mass-effects, block the release of neuropathic products from hematomas, and thus prevent initiation of pathological processes. The Surgical Trial in Intracerebral Hemorrhage (STICH) trial compared early surgery (median time of 20 h from presentation to surgery) with medical treatment. At 6 months, early surgery had no benefit compared with initial conservative treatment: 24% versus 26% of patients had good recovery or moderate disability after treatment. The benefits of surgery vs open craniotomy can be outweighed by neural damage incurred and recurrence of bleeding, especially in deep lesions. According to the STICH trial, surgical treatment of lobar hematomas and hematomas within 1 cm of the cortical surface were most likely to benefit (Mendelow et al., 2013). Another potential indication for surgery is acute neurological worsening. One report suggested that emergent surgical evacuation could result in functional independence in a quarter of patients if they had not lost upper brainstem reflexes and did not show extensor posturing (Mendelow et al., 2013). Randomized data suggest that the benefit of early surgery is limited to patients presenting with

initial Glasgow coma scale scores of 8 or more or ICH volumes of 80 mL or less (Mendelow et al., 2013). To limit neural damage and the risk of recurrent bleeding associated with open craniotomy, studies are now focusing on less invasive stereotactic and endoscopic evacuation with the use of thrombolytic drugs. The ASA Stroke Council guidelines do not recommend routine evacuation of supratentorial ICH by standard craniotomy within 96 hours from symptom onset; however, they recommend surgery for patients presenting with lobar ICH within 1 cm of the surface, particularly for those with good neurological status who are deteriorating clinically (Hemphill et al., 2015). The same guidelines recommend urgent surgery for patients with cerebellar hemorrhages with a relatively good neurological status or hematoma larger than 3 cm who are deteriorating clinically, or who have brainstem compression or hydrocephalus from ventricular obstruction (Hemphill et al., 2015). MISTIE III was an open-label, blinded endpoint, phase 3 trial done at 78 hospitals in the USA, Canada, Europe, Australia, and Asia (Hanley et al., 2019). In the MISTIE III trial, aspiration and thrombolytic irrigation of the ICH with alteplase via an image-guided catheter did not improve functional outcomes compared with standard medical care in patients with large ICH. However, mortality at 365 days seemed to be lower in the MISTIE group than the standard medical care group, without a net increase in the proportion of patients with severe disability. Besides, exploratory analyses of clot removal showed an association between extent of removal and lower mRS scores (0–3). MISTIE cannot currently be recommended as an intervention to improve functional outcome for all patients with ICH until the desired reduction in ICH size is uniformly achieved (Ziai et al., 2019).

Medical complications treatment. About 30% of patients with ICH have gastric hemorrhages. Prophylactic H2 blockers or drugs that can protect the mucosa lower the numbers of such events (Misra, Kalita, Pandey, Mandal, & Srivastava, 2005). In the first 2 weeks, deep venous thrombosis can be detected by ultrasonography in 40% of patients. Patients with severe neurological deficits and high d-dimer concentrations are at highest risk. A low-dose regimen of subcutaneous heparin or low-molecular-weight heparin can be started on the second day after onset of ICH in neurologically

stable patients; once a deep-venous thromboembolism develops, treatment should be given to patients at high risk of pulmonary embolism (Qureshi et al., 2009).

2. Aim of the study

Our study aimed to:

1) Provide up-to-date population-based data on the incidence, characteristics, and case-fatality of patients with ICH, together with factors associated with ICH outcome;
2) Investigate the characteristics and outcome of ICH after a first-ever stroke as compared with those of first-ever ICH;
3) Investigate the etiologic factors of ICH, the strengths and limitations of current classification criteria, and their ability in predicting ICH outcome;
4) Assess the clinical applicability and the validity of the classification criteria of lobar ICH;
5) Assess the applicability and the role of brain MRI in the diagnosis of ICH etiological factors.

3. Methods

3.1 Study design and population

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) to report the results of the present study (von Elm et al., 2007). The present study is part of a prospective population-based registry including patients with stroke and transient ischemic attack in the population of 298,343 inhabitants (ISTAT, 2011) of the district of L'Aquila, central Italy. The study was approved by the Internal Review Board of the University of L'Aquila with the registration numbers 13/2018 and 57/2019. Every effort was made to obtain informed consent from the study participants.

We included patients residing in the district of L'Aquila and hospitalized for an ICH from January 1, 2011 to December 31, 2019. The district of L'Aquila is a mountainous area of 5034.46 km^2 with 108 towns and a continental weather pattern. The population is served by four public hospitals, all of which have 24/7 availability of brain CT, 5 private hospitals, general practitioners, and the emergency medical service (EMS). Two hospitals have neurology wards, one a neurosurgical ward, all have intensive care units and general medicine wards.

ICH diagnoses were validated according to the definition of neurological deficits documented by neuroimaging indicating the presence of an intraparenchymal hemorrhage (WHO, 1977; Mohr et al., 1978). Patients with hemorrhagic transformation of cerebral infarction or history of previous stroke were excluded. As the study was observational, patients were treated according to routine clinical practice and following national and international guidelines.

3.2 Case-finding procedures

All the events were identified by active monitoring of all inpatient and outpatient health services. In each clinical ward, all patients admitted for an ICH were identified and examined within 7 days from onset by a senior physician; thereafter all patients were seen by a consulting neurologist to validate the event. To verify all admissions, two consultant neurologists screened the admission and

discharge lists on a daily basis. The EMS, emergency rooms, neuroradiology, neurophysiology, and neurosonology services were systematically checked. Regular contacts were also maintained with rehabilitation and long-term care services. Nearby hospitals were regularly monitored to identify those residents who had cross-boundary medical care. The study purpose was explained in advance to all general practitioners who were asked to refer all stroke cases or give information about patients evaluated at home. Death certificates were checked monthly and clinical data of all patients who died with a diagnosis of stroke, not otherwise included in the registry, were reviewed. Hot pursuit (active identification of all events as they occurred) and cold pursuit (retrospective identification of the same events) were combined in the ascertainment of cases to ensure their most complete identification (V. Feigin & Hoorn, 2004).

3.3 Data collection and follow-up

Clinical data were recorded on standardized forms and stored in a computerized database. Basic information included medical history, routine laboratory and instrumental tests. The National Institutes of Health Stroke Scale (NIHSS) score (Brott et al., 1989) on admission and the modified Rankin Scale (mRS) score (Farrell, Godwin, Richards, & Warlow, 1991) at discharge were also recorded. Extended follow-up of the cohort is still ongoing to record long-term outcome events and mortality.

3.4 Radiological assessments

All the assessments were performed retrospectively on the first available brain CTs and on the first brain MRI available within 30 days from ICH onset. Assessments were performed by two independent raters. Disagreements were resolved by consensus. Primary analyses were performed on the assessments after consensus resolution.

ICH volumes were estimated by a single operator according to the ABC/2 method (Kothari et al., 1996). CT-confirmed cases of ICH were assessed independently by a neurologist and a radiologist trained in the assessment of the Edinburgh criteria by an online tool ("Edinburgh Criteria for CAA-associated ICH Training (ECCITING),"). CT assessments were performed on tridimensional

images of the first brain CT performed by the patients, obtained with multiplanar reformatting. Lobar, non-lobar, or uncertain location was adjudicated according to the Cerebral Haemorrhage Anatomical RaTing InStrument (CHARTS) (Charidimou, Schmitt, et al., 2017). For lobar ICH, the presence of aSAH and FLPs was assessed according to the Edinburgh criteria definition (Rodrigues et al., 2018). The presence of lobar and deep CMBs and cSS on brain MRI was assessed according to the modified Boston criteria (Linn et al., 2010).

3.5 Statistical analysis

ICH incidence, 30-day and 1-year and case-fatality rates (CFRs) were computed in patients residing in the district and suffering a first-ever ICH over the 2011-2017 period (incidence dataset). All the other assessments were performed in residents of the district reporting either a first-ever ICH or an ICH after a stroke during the 2011-2019 period (full dataset).

Descriptive statistics are reported as absolute numbers with percentages, mean ± standard deviation (SD), or median with interquartile range (IQR). Groups were compared using the Student's t-test or the Pearson χ^2 test, and with the Mann-Whitney U test for non-normally distributed variables. Between-operator agreement on ICH classification and neuroimaging findings was assessed using Cohen's kappa. To assess the factors associated to ICH case-fatality, multivariate logistic analyses were performed with the Edinburgh criteria and the variables commonly included in ICH prognostic scores (Zyck et al., 2020), including age, NIHSS and Glasgow Coma Scale scores, systolic blood pressure, antiplatelet treatment, ICH volume and intraventricular extension. Two-sided statistical significance was set at a P level <0.05.

Crude incidence rates were calculated with data from the 2011 census ((ISTAT), 2011). Standardized rates were obtained by the direct method with 10-year age grouping of the Italian and European populations (Statistic & (EUROSTAT), 2011) as standard. Confidence intervals (CIs) for incidence rates were calculated assuming a Poisson distribution for the number of cases. Missing values were not entered when assessing baseline variables. Cumulative incidence and survival

analyses were performed using the Kaplan–Meier method. Comparisons among survival curves were performed by the log-rank test.

Statistical analyses were performed with SPSS Statistics version 20.0 and R statistical software.

4. Incidence and outcomes of intracerebral hemorrhage

Over the 2011-2017 study period, we identified 514 patients with first-ever ICH (incidence dataset): 673 were women and 607 men. **Table 2** reports the baseline characteristics of the included patients. The mean ± SD age was 74.8±13.4 years, with an age range of 18 to 99 years. Women were significantly older than men (79.0±12.0 versus 71.9±13.5 years; P<0.001).

All patients were hospitalized. Median length of hospital stay was 9 days (interquartile range [IQR], 5-17) and it was similar in women and in men (median 9 days vs 9 days; P=0.111). Median NIHSS score was 7 (IQR 4-14) on admission and 6 (IQR 2-11) at discharge; median mRS score was 1 (IQR 0-2) on admission and 3 (IQR 2-4) at discharge.

The crude annual incidence rate of FES was 24.6 per 100,000 person-years (95% CI, 22.5 to 26.8). Incidence steeply raised in patients older than 65 years and was higher in men than in women with the only exception of patients over 85 years of age (**Figure 9** and **Table 3**). The incidence rate, standardized by age and sex to the 2011 Italian population, was 22.5 per 100,000 person-years (95% CI, 21.1 to 24.0); the corresponding rate, standardized to the 2011 European population, was 19.4 per 100,000 person-years (95% CI, 17.9 to 20.9).

As reported in **Table 4**, 185 patients, 97 men and 88 women, died within 30 days from ICH onset (CFR 36.0%; 95% CI, 31.8% to 40.1%); 44 additional patients, 22 men and 22 women, died within 1 year (CFR 44.6%; 95% CI, 40.3% to 48.9%). Causes of death at different time points are reported in **Table 4**. The Kaplan-Meier curve of 1-year survival is reported in **Figure 10-A**.

At the 1-year follow-up, 11 (2.1%) patients had a recurrent ICH (1 fatal) and 7 (1.4%) an ischemic stroke (3 fatal); 8 (1.6%) patients had a TIA, while 3 (0.6%) had a nonfatal myocardial infarction. The cumulative incidence of cerebrovascular events in patients with first-ever ICH is reported in **Figure 10-B**.

5. Comparison between first-ever intracerebral hemorrhage and intracerebral hemorrhage after stroke

For the present study, we used the full dataset, consisting of 645 patients with ICH residing in the district of L'Aquila during the 2011-2019 period. Out of those patients, 378 (58.6%) were men, while the median age was 79 years (IQR 68-85). All patients were hospitalized and had at least a brain CT.

Out of the total, 567 patients (87.9%) had a first-ever ICH, while the remaining 78 (12.1%) had an ICH after stroke, either ischemic or hemorrhagic. Patients with ICH after stroke were older (median age 82 years, IQR 76-87, vs 78, IQR 67-85; P=0.018) and had a higher disability before admission for stroke (median mRS score 2, IQR 1-3, vs 1, IQR 0-2; P<0.001) compared with patients with first-ever ICH (**Table 5**). Patients with ICH after stroke also had a higher use of statins (28.2% vs 14.3%; P=0.003), antiplatelets (41.0% vs 30.9%; P=0.031), and anticoagulants (20.5% vs 14.8%; P=0.031) compared with those with first-ever ICH (**Table 5**). ICHs after stroke were larger than first-ever ICHs (median volume at onset 20 cm^3, IQR 3-53, vs 8 cm^3, IQR 2-25; P=0.007), although having a lower proportion of intraventricular extension (19.2% vs 31.6%; P=0.024) (**Table 5**). ICHs after stroke were more frequently lobar (57.57% vs 37.7%) and less frequently deep (28.2% vs 37.2%) compared with first-ever ICHs (P=0.019; **Table 5**). Multivariate analyses showed that higher mRS scores before admission (OR 1.58 per point, 95% CI 1.27-1.97; P<0.001) and higher ICH volume at onset (OR 1.01 per cm^3, 95% CI 1.00-1.02; P=0.004) were the only factors independently associated with ICH after stroke (**Table 5**).

Among the 78 patients with ICH after stroke, 44 (56.4%) had an ICH after ischemic and 34 (43.6%) after hemorrhagic stroke. Patients with ICH after hemorrhagic stroke had a higher prevalence of atrial fibrillation (34.1% vs 11.8%; P=0.023), use of antiplatelets (47.7% vs 32.4%; P=0.017) and anticoagulants (27.3% vs 11.8%, P=0.017) (**Table 6**). ICH location was also different between patients with ICH after hemorrhagic stroke and after ischemic stroke (P=0.009); the high majority

(79.4%) of patients with ICH after hemorrhagic stroke had a lobar location, while the most frequent location in those with ICH after ischemic stroke was deep (40.9%) (**Table 6**). Multivariate analyses showed that the only significant difference between patients with ICH after hemorrhagic stroke and those with ICH after ischemic stroke was the higher probability of lobar location (OR 7.97; 95% CI 1.95-32.61; P=0.004) (**Table 6**).

Out of the 34 patients with ICH after hemorrhagic stroke, we could retrieve the neuroimaging of the first-ever event in 20 patients; in 15 (75%) of them, first-ever ICH had a lobar location.

6. Etiologic classification of intracerebral hemorrhage

The present analyses were performed on the full dataset of 645 patients with ICH. According to the SMASH-U classification, 39 ICHs were due to structural lesions (6.0%, 95% CI 4.2% to 7.9%), 41 to systemic/other diseases (6.4%, 95% CI 4.5% to 8.2%), 74 to medication (11.5%, 95% CI 9.0% to 13.9%), 217 to amyloid angiopathy (33.6%, 95% CI 30.0% to 37.3%), 235 to hypertensive angiopathy (36.4%, 95% CI 32.7% to 40.1%), and 39 were of undetermined cause (6.0%, 95% CI 4.2% to 7.9%). Interrater reliability for the application of the SMASH-U classification was excellent with a kappa value of 0.82 (95% CI, 0.75 to 0.89; P<0.001).

As expected, arterial hypertension and diabetes mellitus were more prevalent in ICH attributable to hypertensive angiopathy compared with other subtypes; nevertheless, it atrial fibrillation was more prevalent in ICH attributable to medication than in the other subtypes, due to the higher use of anticoagulants, while alcohol abuse was more prevalent in patients with ICH attributable to systemic/other disease as it is a cause of liver failure (**Table 7**). Due to the classification rules, the great majority (86.6%) of patients with ICH attributable to amyloid angiopathy had a lobar location, while the great majority (70.6%) of patients with ICH attributable to hypertensive angiopathy had a deep location; lobar was the most frequent location in ICH attributable to structural lesions, medication, or systemic/other disease, while deep was the most frequent location in ICH due to undetermined cause (**Table 7**).

CFRs were high (>50% at 1 year) for ICH attributable to medication or systemic/other disease, intermediate (40%-50% at 1 year) for ICH attributable to amyloid angiopathy or hypertensive angiopathy, and lower (<30% at 1 year) for ICH attributable to structural lesions or undetermined cause (**Table 8**). Multivariate Cox regression analyses showed that ICH due to medication, together with age, low GCS score on admission, and ICH volume, were independent predictors of mortality at 30 days and at 1 year (**Table 9**).

7. Clinical usefulness of Edinburgh CT criteria in patients with lobar intracerebral hemorrhage

The present analyses were performed on the full dataset of 645 patients with ICH. ICH location was lobar in 259 patients (40.2%), non-lobar in 327 (50.7%), and uncertain in the remaining 59 (9.1%). Among the 259 patients with lobar ICH, 87 patients (33.5%) had aSAH+FLPs, 75 (29.0%) had aSAH only, 2 (0.8%) FLPs only, and 95 (36.7%) none. Interrater agreement was almost perfect for both aSAH (k=0.860; P<0.001) and FLPs (k=0.905; P<0.001).

Patients with aSAH+FLPs had a different median age (81 years, IQR 74-85) than those with only one criterion (82 years, IQR 73-87) or none (78 years, IQR 69-84; P=0.028; **Table 10**). The relative proportion of patients with aSAH+FLPs was highest (42.1%) in patients aged 55-64 years and lowest (14.3%) in those aged <55 years, whereas the relative proportion of patients with none of the criteria was highest in patients aged <55 years (52.4%) and lowest in those aged ≥85 years (20.3%; P=0.005; **Figure 11**). Sex distribution was similar across groups as well as distribution of risk factors and treatments; the only exception was alcohol abuse, that was more frequent in patients with one Edinburgh criteria than in the other two groups (P=0.030; **Table 10**). Intraventricular extension of ICH was more prevalent in patients with aSAH+FLPs (32.2%) as compared with those with one (22.1%) or none of them (9.5%; P=0.001; **Table 10**).

ICH was more severe at onset in patients with aSAH+FLPs compared with those fulfilling one or none of the Edinburgh criteria, as shown by a higher NIHSS score (P=0.003; **Figure 12**-A) and by higher median ICH volumes (P<0.001; **Figure 13**). Those same patients also had worse outcomes as shown by higher mRS scores at discharge (P<0.001; **Figure 12**-B) and lower survival (log rank test P<0.001; **Figure 14**).

The Cox regression analysis performed on age, Edinburgh CT criteria, Glasgow Coma Scale score on admission, and ICH volume showed that older age and low Glasgow Coma Scale score were the

only independent predictors of 30-day and 1-year case-fatality; ICH volume was an independent predictor of 1-year case-fatality (**Table 11**).

8. Diagnostic contribution of brain MRI in intracerebral hemorrhage

The present analyses were performed on the full dataset of 645 patients with ICH. Out of them, 107 (16.6%) performed a brain MRI within 30 days from onset, while 399 (61.9%) performed more than one brain CTs and 139 (21.5%) performed only one brain CT due to early death.

Patients with available brain MRI were younger (median age 68 years vs 81 years; P<0.001), had a lower median mRS score before admission (0 vs 1; P<0.001), a lower median NIHSS score on admission (5 vs 12; P<0.001), and lower ICH volume (median 3 cm^3 vs 11 cm^3; P<0.001) compared with patients without brain MRI (**Table 12**). Those patients also had a lower prevalence of arterial hypertension (65.4% vs 75.5%; P=0.009), diabetes mellitus (15.0% vs 24.3%; P=0.026) and a higher prevalence of cigarette smoking (21.5% vs 7.1%; P<0.001) compared with patients without brain MRI; the use of antithrombotics was less frequent in patients with available brain MRI compared with those without (P=0.005; **Table 12**). Patients with available brain MRI had a higher prevalence of lobar location (51.4% vs 37.9%) and a lower prevalence of deep location (29.9% vs 37.4%) compared with those without (P=0.003); intraventricular extension of ICH (11.2% vs 32.9%; P<0.001) and in-hospital death (7.5% vs 40.9%; P<0.001) were also lower in patients with available brain MRI compared with those without (**Table 12**). The multivariate logistic regression analysis showed that previous use of statins (OR 2.34, 95% CI 1.11-4.94; P=0.039), lobar location (OR 3.20, 95% CI 1.56-6.58; P=0.002), and ICH in the posterior fossa (OR 3.41, 95% CI 1.30-8.90; P=0.012) were independently associated with performing a brain MRI, while age (OR 0.95 per year, 95% CI 0.92-0.97; P<0.001) and intraventricular extension (OR 0.38, 95% CI 0.15-0.95; P=0.038) were independently associated with not performing brain MRI (**Table 12**).

Among the 107 patients performing brain MRI, 36 (33.6%) had lobar CMBs, 20 (18.7%) deep CMBs, and 9 (8.4%) cSS. Patients with lobar or deep CMBs had higher prevalence of arterial hypertension compared with those without (80.6% vs 57.7%, P=0.019, and 85.0% vs 60.9%,

P=0.041, respectively; **Table 13**). Notably, ICH location did not differ according to the presence of CMBs (**Table 13**). The presence of aSAH and/or FLPs on brain CT was not associated with that of CMBs on brain MRI (**Table 14**).

9. Discussion

9.1 Epidemiology of first-ever ICH

ICH is the most severe form of stroke. In our study, we aimed to report up-to-date data on the epidemiology of ICH in the context of the most recent advances in the field.

The reported incidence rate of first-ever ICH of 24.6 per 100,000 person-years is in line with International data (van Asch et al., 2010) and lower than the incidence rate of 36.9 per 100,000 previously reported in the district of L'Aquila (S. Sacco, Marini, Toni, Olivieri, & Carolei, 2009). Our data regarding ICH incidence and 30-day and 1-year case-fatality are within the range of what reported by population-based studies overlapping with the 2011-2017 study period (**Table 15**). In detail, our incidence rate was higher than that found in Nigeria (Okon et al., 2015), Argentina (Bahit et al., 2016), New Zealand (Krishnamurthi et al., 2018), and France (Guéniat et al., 2018), while it was lower than that found in Japan (Takashima et al., 2017) and Greece (Stranjalis et al., 2014; Tsivgoulis, Patousi, et al., 2018). Those differences can be explained by the different structure of populations; Asian populations, including Japanese, have an increased susceptibility to ICH, while the Greek populations reporting a high ICH incidence have a high prevalence of elderly people, like our population. The high case-fatality of ICH found in our study, as well as in the Greek studies (Stranjalis et al., 2014; Tsivgoulis, Patousi, et al., 2018), can also be explained by the high prevalence of elderly people in those populations. Most ICH deaths in our study had a cerebral cause, in line with what reported by an Argentinian study (Bahit et al., 2016); patients with ICH usually face early death, which explains the high proportion of cerebral deaths.

In our population the proportion of patients with ischemic events (ischemic stroke and TIA) after a first-ever ICH was much higher than that of ICH recurrence. None of the comparable population-based studies reported the proportion of patients with recurrent cerebrovascular events after a first-ever ICH. However, our finding is in line with previous cohort studies (Flynn, MacDonald, Murray, MacWalter, & Doney, 2010; Pennlert, Eriksson, Carlberg, & Wiklund, 2014) which also showed

that the risk of ischemic events is higher than that of recurrent ICH after a first-ever ICH. Thus, ICH survivors should be assessed and treated not only for ICH recurrence, but also for the potential risk of ischemic cerebrovascular events.

9.2 ICH after stroke

Together with first-ever ICH, our study also assessed ICH after stroke. In our study, patients with an ICH after stroke had a higher pre-stroke use of statins and antithrombotics. However, the only factors independently associated with ICH after stroke were higher pre-stroke disability and ICH volume (**Table 5**). We found a higher prevalence of lobar location in patients with ICH after first-ever ICH compared with those with ICH after ischemic stroke. This result can be explained by the type of SVD underlying ICH. Previous studies showed that most recurrent ICHs are lobar due to possible underlying CAA (Charidimou, Imaizumi, et al., 2017). Therefore, we also expected that most cases of recurrent ICH would be lobar. In line with previous literature, the most frequent pattern of recurrence was that of a lobar ICH following a lobar ICH (Neau et al., 1997). After ischemic stroke, CAA is a risk factor for ICH mostly in patients treated with anticoagulants (Casolla & Cordonnier, 2020), which can explain the lobar ICH cases following ischemic stroke in our study. However, hypertensive angiopathy might also be an important cause of deep ICH after ischemic stroke. Further studies are needed to test the SVD underlying recurrent ICH. Unfortunately, the research in the field is limited by the fact that recurrent ICH is a rare event.

9.3 Etiology of ICH

One of the aims of our study was to investigate the etiology of ICH in our population. Commonly accepted criteria to diagnose etiologic subtypes of ICH are still lacking, while several etiologic classifications have been proposed for ischemic stroke (Adams et al., 1993; Amarenco et al., 2013). The SMASH-U etiologic classification provides useful criteria to easily and reliably classify ICH. Proportions of ICH subtypes were different from those reported by other studies using the same classification (Meretoja et al., 2012; Mosconi et al., 2020; Yeh, Tang, Tsai, & Jeng, 2014). These differences may be in part explained by different ethnicity and access to medical care.

ICH attributable to hypertensive angiopathy was the leading subtype of ICH followed by ICH attributable to amyloid angiopathy and by ICH attributable to medication. CFRs were high for ICH attributable to medication and systemic/other disease. Most of the deaths occurred within 30 days after the event while only a few additional deaths occurred later. CFRs were intermediate for ICH attributable to amyloid angiopathy and hypertensive angiopathy with unevenly distributed deaths after the event whereas CFRs were low for ICH attributable to structural lesions or undetermined cause. We did not find significant differences in CFRs among etiological subtypes because of the low number of included patients with the less common subtypes of ICH. According to the multivariate analysis, ICH attributable to medication was the only etiologic subtype independently associated with an increased risk of mortality, together with the hematoma volume and low GCS score. In a previous study, in line with our results, ICH attributable to medication was also independently associated with in-hospital case-fatality, together with ICH attributable to systemic/other disease (Mosconi et al., 2020).

Investigating ICH etiology is a poorly considered research question, despite the potential advantages in terms of early management and prognosis prediction. The SMASH-U classification system was easily applicable to our population and might represent an easy-to-use tool for common clinical practice. However, an important limit of that system is the potential overlap of different ICH causes. In our population, arterial hypertension was the most frequent risk factor in all ICH etiologic subtypes, while a relevant proportion of patients was treated with antithrombotics and even anticoagulants in all the etiologic subtypes (Table 7). The original SMASH-U classification paper found a potential overlap among subtypes of 80% (Meretoja et al., 2012). In ICH, there are likely not single causes but etiologic factors with different quantitative contributions to ICH etiology. The H-ATOMIC classification system takes into account the contribution of each etiologic factor to ICH (Martí-Fàbregas et al., 2016); however, this classification is difficult to apply in common clinical practice. A head-to-head comparison between the SMASH-U and H-ATOMIC classifications showed high interrater agreement and reliability of both classifications, despite

discrepancies in about one third of cases (Martí-Fàbregas et al., 2018). Further studies are needed to reliably identify ICH causes in common clinical settings.

9.4 Lobar ICH and its classification

An important field in the investigation of ICH etiology is the classification of lobar ICH. Our study showed that the CT-based radiological Edinburgh criteria are fully applicable in the routine clinical setting in patients who have lobar ICH even in the absence of specifically designed neuroimaging studies. The application of those criteria allows identifying a subgroup of patients with a poor short-term outcome. The higher case-fatality of lobar ICH in the presence of the Edinburgh criteria is interesting as it might provide an easy tool for prognostication.

We found a substantial overlap between the presence of FLPs and aSAH; in detail, all but two patients with FLPs also had aSAH, while one third of patients with lobar ICH had aSAH only. The presence of aSAH+FLPs was associated with higher age and a higher prevalence of antiplatelet treatment, in line with CAA-related lobar ICH, which is usually age-dependent, non-hypertensive in nature, and associated with antithrombotic medication (Charidimou, Gang, & Werring, 2012). By consequence, our findings indirectly support the reliability of the Edinburgh CT criteria. Compared with the presence of aSAH+FLPs and none of the criteria, the presence of aSAH only was associated with intermediate clinical severity, median volume, and case-fatality. Those clinical and radiological characteristics are consistent with the medium probability of moderate or severe CAA associated with aSAH only as compared with the high probability associated with aSAH+FLPs. The higher severity and volume of lobar ICH in patients with aSAH+FLPs compared with those without are in line with previous findings (G. Chen et al., 2014; Raposo et al., 2020). Notably, aSAH and FLPs might be more easily detectable in larger than in smaller lobar ICHs, which provides a further link between the presence of those criteria and ICH prognosis.

The presence of aSAH+FLPs was not independently associated to lobar ICH case-fatality. However, as ICH volume is a continuous variable it is not easily manageable in routine clinical practice, while the application of yes/no criteria such as the Edinburgh CT criteria may easily allow

to predict prognosis even in the emergency room. Currently available prognostic scores for ICH mostly include age, ICH volume, and Glasgow Coma Scale score at onset (Zyck et al., 2020). aSAH+FLPs, which are easily identified on brain CT, are present in a subgroup of patients with old age and high ICH volume and might therefore be considered as indirect markers of poor prognosis, even if only in patients with lobar ICH.

Our study may give some insight on the yield of implementation of ApoE testing. The predicted probability of moderate or severe CAA according to CT findings, without ApoE genotyping, was 97% according to the original study (Rodrigues et al., 2018) (**Table 17**) and would change little with positive or negative ApoE testing. Positive ApoE testing would have significantly increased the probability of moderate or severe CAA in the 29.8% of patients fulfilling only one of the Edinburgh radiological criteria, while negative testing would have ruled out CAA in the 36.7% of patients not fulfilling the radiological criteria (**Table 17**). In summary, our results suggest that ApoE testing would be useful in two thirds of patients with lobar ICH.

9.5 Contribution of brain MRI to the diagnosis of ICH

Brain CT is the current standard to diagnose ICH; however, brain MRI can provide important information regarding ICH etiology and be used to complement diagnosis (Cordonnier et al., 2018). For example, the modified Boston criteria for the diagnosis of CAA-related ICH include neuroimaging findings such as CMBs and cSS that are only found on brain MRI (Linn et al., 2010). On the other hand, brain MRI is of limited applicability in common clinical practice, due to its costs and potential contraindications. Besides, many patients with ICH have consciousness alterations, require immediate intensive care, or face early death, thus limiting the possibility of performing brain MRI. MRI can have little clinical meaning in the presence of clear causes, for example in hypertensive elderly with deep ICH after a hypertensive crisis. Therefore, a rule of thumb to assess which patients should perform brain MRI suggests considering patients aged 50 years or less, without a history of hypertension, and with lobar ICH (Kamel et al., 2013). In our study, those suggestions were followed, as patients performing brain MRI were younger, had a lower prevalence

of arterial hypertension and lobar ICH compared with those not performing brain MRI. Intraventricular extension of ICH was associated with a lower probability of performing brain MRI; that feature of ICH is usually an index of severe ICH (Witsch et al., 2015) requiring intensive treatment and therefore less likely to perform advanced brain imaging.

Overall, only one sixth of patients with ICH performed brain MRI. Nevertheless, performing those exams helped diagnosing small vessel disease in about one third of patients by the detection of CMBs. Interestingly, the presence of CMBs was not associated with lobar location; on the contrary, it was associated with a higher prevalence of arterial hypertension (**Table 13**). This result is potentially biased by patient selection, given the low proportion of patients with available brain MRI; nevertheless, it might suggest that uncontrolled arterial hypertension can lead to CMBs and accelerated amyloid pathology, as reported by the literature (Biffi et al., 2015). It is important to note that lobar CMBs, one of the additional diagnostic criteria for CAA as per the modified Boston criteria, were not associated with the Edinburgh CT criteria for the diagnosis of CAA. This result might also be due to patient selection; patients with aSAH and FLPs on brain CT usually had severe ICH, preventing them from performing brain MRI.

9.6 Strengths and limitations

The present study has several strengths. The "incidence dataset" complies with the available recommendations to study stroke incidence (V. Feigin & Hoorn, 2004; V. Feigin, Norrving, Sudlow, & Sacco, 2018). We provided data without age restrictions, including a high number of patients with all relevant information on clinical and functional status, that were all followed up to one year. We adopted standard definitions making our data comparable to those from other studies. Besides, the 100% hospitalization rate and 100% availability of brain neuroimaging studies increased the quality of the data set. Study population was stable over time ((ISTAT), 2011). Using multiple overlapping methods of case ascertainment and monitoring cross-boundary care, completeness of cases was likely. However, we duly recognize that some limitations exist. We cannot exclude having missed cases not seeking medical attention because of subclinical

manifestations or very early death. Besides, the old age of our population and the 1.7% of non-Caucasian patients ((ISTAT), 2011) limit the generalizability of our results.

To determine ICH etiology, the SMASH-U classification was retrospectively applied, therefore limiting the reliability of our results. Another possible limitation of our study is represented by the relatively small number of included patients with the less common ICH subtypes.

Referring to the potential role of the Edinburgh CT criteria, the main strength of our study is the inclusion of a large series of patients with ICH confirmed by neuroimaging in a multicenter, real-life setting, allowing generalization to common clinical practice. However, the lack of necropsy examinations did not allow assessing whether the Edinburgh CT criteria really reflect CAA pathology in our patients. Besides, we did not perform ApoE testing, impairing the confirmation of our assumptions about the diagnostic yield of genetic testing. Moreover, we based our assessments on the first available brain CT for each patient; the assessment of follow-up imaging would have likely improved the prognostic evaluation of ICH (Lun et al., 2020) and might have disclosed further CAA-related characteristics in some patients. Lastly, we limited our observations to the in-hospital outcomes, not including long-term follow-up for case-fatality and ICH recurrence.

Our study did not give insights on the potential added value of brain MRI over brain CT in the etiologic investigation of lobar ICH. In fact, it is desirable that patients with ICH are investigated with brain MRI in order to better characterize the underlying mechanisms of the hemorrhage.22, 23 The use of brain MRI would have allowed the assessment of CAA markers such as cortical superficial siderosis and cerebral microbleeds,24 as well as other signs of microangiopathy25, 26 and potential secondary causes of ICH. However, further studies are warranted to test the validity of the Edinburgh criteria in different settings.

10. Conclusions

In relation to the aims of our study, we can trace the following conclusions:

1) In our population-based study, the incidence and outcomes of first-ever ICH were comparable to those reported in similar studies performed during the last decade. Our data confirm that ICH is a public health concern worldwide, for which primary preventive measures should be enhanced.
2) Compared with first-ever ICH cases, those occurring after a stroke and mostly after an ICH had a high prevalence of lobar location, possibly reflecting an underlying amyloid angiopathy. The prevalence of CAA-related ICH is still unclear in the population and should be further investigated to improve its prevention and thus decreasing the burden of ICH in the population.
3) Applying a classification tool to patients with ICH was feasible and identified patient categories with different risk factor profile and different prognosis; however, only ICH attributable to anticoagulant medication was an independent predictor of ICH case-fatality. Besides, the available classification tools are limited by the coexistence of several etiologic factors in the same patient. Future research should overcome the limitations of current ICH classification schemes maintaining their applicability in common clinical settings.
4) The Edinburgh CT criteria for the diagnosis of probable CAA-related ICH are easily applicable in routine clinical practice and may help refining their diagnosis and guiding the choice of treatments. Furthermore, the Edinburgh CT criteria reflect the clinical severity of ICH and are markers of in-hospital unfavorable outcomes. However, those criteria need extensive application in several different settings before entering routine clinical care.
5) Brain MRI could help refining the etiologic diagnosis of ICH; however, we found that brain MRI cannot be applied on a large scale in those patients. Establishing rules to perform brain

MRI in selected ICH patients could add to the diagnostic yield of the examination by identifying patients in whom that exam can provide the most relevant information.

Our study shows that the outcomes of ICH are severe, even in recent times. Refining the etiologic diagnosis of ICH can significantly improve its management; however, further studies are needed to investigate the contribution of multiple etiologic factors of ICH and to design adequate diagnostic protocols.

Tables and Figures

Table 1. The H-ATOMIC classification of intracerebral hemorrhage (Martí-Fàbregas et al., 2016)

H score	Prior Arterial Hypertension	Evidence of Arterial Hypertension	Admission Blood Pressure >140/90 mmHg	Deep location	Alternative cause
H_1	+	+/-	+	+	-
H_1	-	+	+	+	-
H_2	+	+/-	+	+	+
H_2	+	+/-	-	+	-
H_2	+	+/-	+	-	-
H_2	-	+	+	+	+
H_2	-	+	-	+	-
H_2	-	+	+	-	-
H_3	+	+/-	+	-	+
H_3	+	+/-	-	+	+
H_3	+	+/-	-	-	-
H_3	-	+	+	-	+
H_3	-	+	-	+	+
H_3	-	+	-	-	-
H_3	-	-	+	+	-
H_3	-	-	+	+	+

CAA score	Postmortem examination[a]	Pathologic tissue (evacuated hematoma or cortical biopsy)	Lobar, cortical, or subcortical hemorrhage	Age ≥ 55y	Other diagnostic lesion (A_1, A_{2a}) Other cause of hemorrhage or siderosis (A_{2b}, A_3)[b]
A_1	+	+/-	+	+	-
A_{2A} with supporting pathology	-	+	+	+	-
A_{2B}	-	-	+[c or d]	+	-
A_3	-	-	+[e or f]	+	-

Primary tumour score	Suspicious lesion	Positive biopsy	Alternative cause
T_1	+	+	-
T_2	+	-	-
T_3	+	-	+

Metastatic tumour score	Known primary solid cancer	Number of lesions	Positive biopsy	Alternative cause
T_1	+	>1	-	-
T_1	+	1	+	-
T_2	+	1	-	-
T_2	+	>1	-	+
T_3	-	>1	-	-
T_3	+	1	-	+

AVK	The patients is receiving AVK	INR	Alternative cause
O_1	+	≥2	-
O_2	+	≥2	+
O_2	+	<2	-
O_3	+	<2	+

NOAC	The patients is receiving NOAC	Blood coagulation test altered	Alternative cause
O_1	+	+	-
O_2	+	+	+
O_2	+	-	-
O_3	+	-	+

Table 1. (continued)

Arteriovenous Malformation score	Angiographic demonstration	Indirect evidence (neuroimaging)	Alternative probable/possible diagnosis
AVM			
M_1	+	+/-	-
M_2	+	+/-	+
M_3	-	+	+/-
Cavernoma	MRI suggestive	MRI non conclusive or not done (but cavernoma is suspected)	Alternative probable/possible diagnosis
M_1	+	-	-
M_2	+	-	+
M_3	-	+	+/-

Infrequent cause score	Infrequent cause	Alternative cause
I_1	+	-
I_2	+	+ (alternative is possible)
I_3	+	+ (alternative is probable)

Table 2. Baseline characteristics of the 514 included patients with a first-ever intracerebral hbemorrhage in the 2011-2017 period.

Characteristic	Value
Age, years	
Mean±SD	74.8±13.4
Range	18-99
Male sex, no. (%)	300 (58.4)
Risk factors, no./total no. (%)	
Arterial hypertension	384 (74.7)
Atrial fibrillation	78 (15.2)
Diabetes mellitus	122 (23.7)
Hypercholesterolemia	90 (17.5)
Coronary heart disease	102 (19.8)
Cigarette smoking	45 (8.8)
Blood pressure, mmHg	
Systolic, mean±SD	164±33
Diastolic, mean±SD	90±18
Glucose, mg/dL	
Median	128
IQR	104-162
Cholesterol, mg/dL	
Total, mean±SD	178±49
LDL, mean±SD	110±40

Table 3. Incidence rates (per 100,000) of first-ever intracerebral hemorrhage according to sex and age.

	No. of patients	Person-years	Rate	95% CI
Men				
0-14	-	131,250	-	-
15-24	2	107,632	1.9	0.2-6.7
25-34	2	134,757	1.5	0.2-5.4
35-44	12	153,293	7.8	4.0-13.7
45-54	16	157,066	10.2	5.8-16.5
55-64	45	140,469	32.0	23.4-42.9
65-74	71	98,658	72.0	56.2-90.8
75-84	102	70,994	143.7	117.2-174.4
≥85	50	23,261	215.0	159.6-283.3
Total	300	1,017,380	29.5	26.2-33.0
Standardized (Italy)		201,218,549	27.5	25.2-29.9
Standardized (Europe)		1,710,118,039	23.6	21.4-26.0
Women				
0-14	-	123,396	-	-
15-24	-	102,088	-	-
25-34	2	128,646	1.6	0.2-5.6
35-44	1	152,565	0.7	0.02-3.7
45-54	10	160,076	6.2	3.0-11.5
55-64	13	142,065	9.2	4.9-15.6
65-74	28	108,045	25.9	17.2-37.5
75-84	87	103,418	84.1	67.4-103.8
≥85	73	50,722	143.9	112.8-180.9
Total	214	1,071,021	20.0	17.4-22.8
Standardized (Italy)		214,817,659	17.9	16.2-19.8
Standardized (Europe)		1,794,787,232	15.3	13.6-17.2
Both				
0-14	-	254,646	-	-
15-24	2	209,720	1.0	0.1-3.4
25-34	4	263,403	1.5	0.4-3.9
35-44	13	305,858	4.3	2.3-7.3
45-54	26	317,142	8.2	5.4-12.0
55-64	58	282,534	20.5	15.6-26.5
65-74	99	206,703	47.9	38.9-58.3
75-84	189	174,412	108.4	93.5-125.0
≥85	123	73,983	166.3	138.2-198.3
Total	514	2,088,401	24.6	22.5-26.8
Standardized (Italy)		416,036,208	22.5	21.1-24.0
Standardized (Europe)		3,504,905,271	19.4	17.9-20.9

Table 4. Causes of death in patients with first-ever intracerebral hemorrhage at different time points.

	30 days		31 days to 1 year		Overall	
Cause of death	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**
Cerebral	158	85.4 (80.3-90.5)	20	45.5 (30.7-60.2)	178	77.7 (72.3-83.1)
Cardiovascular	21	11.4 (6.8-15.9)	13	29.5 (16.1-43.0)	34	14.8 (10.2-19.5)
Nonvascular	6	3.2 (0.7-5.8)	11	25.0 (12.2-37.8)	17	7.4 (4.0-10.8)
Total	185	100	44	100	229	100

Table 5. Comparison between intracerebral hemorrhage after a stroke and first-ever intracerebral hemorrhage.

	All (n=645)	**After stroke (n=78)**	**First-ever (n=567)**	**P value (univariate)**	**Odds ratio (95% CI)**	**P value (multivariate)**
N (%)						
Male	378 (58.6)	44 (56.4)	334 (58.9)	0.675	-	-
Arterial hypertension	483 (74.9)	64 (82.1)	419 (73.9)	0.125	-	-
Diabetes mellitus	150 (23.3)	20 (25.6)	130 (22.9)	0.595	-	-
Hypercholesterolemia	121 (18.8)	21 (26.9)	100 (17.6)	0.050	1.47 (0.43-2.68)	0.538
Cigarette smoking	61 (9.5)	8 (10.3)	53 (9.3)	0.635	-	-
Coronary heart disease	119 (18.4)	11 (14.1)	108 (19.0)	0.325	-	-
Atrial fibrillation	106 (16.4)	19 (24.4)	87 (15.3)	0.211	-	-
Peripheral arterial disease	34 (5.3)	7 (9.0)	27 (4.8)	0.099	0.92 (0.28-2.11)	0.888
Statin use	103 (16.0)	22 (28.2)	81 (14.3)	0.003	1.27 (0.37-2.50)	0.710
Previous antithrombotic use				0.031		
None	338 (52.4)	30 (38.5)	308 (54.3)		1 (Ref.)	-
Antiplatelets	207 (32.1)	32 (41.0)	175 (30.9)		1.28 (0.63-2.60)	0.489
Anticoagulants	100 (15.5)	16 (20.5)	84 (14.8)		2.03 (0.95-4.35)	0.067
ICH location				0.019		
Deep	233 (36.1)	22 (28.2)	211 (37.2)		1 (Ref.)	-
Lobar	259 (40.2)	45 (57.7)	214 (37.7)		1.50 (0.75-3.00)	0.256
Posterior fossa	69 (10.7)	5 (6.4)	64 (11.3)		0.83 (0.25-2.70)	0.750
Intraventricular or multiple	25 (3.9)	2 (2.6)	23 (4.1)		0.58 (0.09-3.90)	0.572
Uncertain	59 (9.1)	4 (5.1)	55 (9.7)		0.37 (0.09-1.47)	0.156
Intraventricular extension of ICH	194 (30.1)	15 (19.2)	179 (31.6)	0.024		
In-hospital death	235 (36.4)	33 (42.3)	202 (35.6)	0.250	-	-
Median (IQR)						
Age	79 (68-85)	82 (76-87)	78 (67-85)	0.018	1.02 (0.99-1.05)	0.243
mRS score before admission	1 (0-2)	2 (1-3)	1 (0-2)	<0.001	1.58 (1.27-1.97)	<0.001
NIHSS score on admission	10 (5-19)	10 (5-21)	10 (5-18)	0.574	-	-
ICH volume (cm^3)	9 (2-28)	20 (3-53)	8 (2-25)	0.007	1.01 (1.00-1.02)	0.004

ICH indicates intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale

Table 6. Comparison between intracerebral hemorrhage after ischemic and after hemorrhagic stroke.

	After ischemic (n=44)	After hemorrhagic (n=34)	P value (univariate)	Odds ratio* (95% CI)	P value (multivariate)
N (%)					
Male	22 (50.0)	22 (64.7)	0.194	-	-
Arterial hypertension	37 (84.1)	27 (79.4)	0.593	-	-
Diabetes mellitus	14 (31.8)	6 (17.6)	0.155	-	-
Hypercholesterolemia	15 (34.1)	6 (17.6)	0.104	-	-
Cigarette smoking	5 (11.4)	3 (8.8)	0.999	-	-
Coronary heart disease	5 (11.4)	6 (17.6)	0.517	-	-
Atrial fibrillation	15 (34.1)	4 (11.8)	0.023	0.41 (0.07-2.17)	0.320
Peripheral arterial disease	6 (13.6)	1 (2.9)	0.111	-	-
Statin use	15 (34.1)	7 (20.6)	0.113	-	-
Previous antithrombotic use			0.017		
None	11 (25.0)	19 (55.9)		1 (Ref)	-
Antiplatelets	21 (47.7)	11 (32.4)		0.37 (0.05-2.58)	0.316
Anticoagulants	12 (27.3)	4 (11.8)		0.36 (0.11-1.14)	0.081
ICH location			0.009		
Deep	19 (43.2)	3 (8.8)		1 (Ref.)	-
Lobar	18 (40.9)	27 (79.4)		7.97 (1.95-32.61)	0.004
Posterior fossa	3 (6.8)	2 (5.9)		4.49 (0.43-46.78)	0.209
Intraventricular or multiple	1 (2.3)	1 (2.9)		11.14 (0.47-263.80)	0.136
Uncertain	3 (6.8)	1 (2.9)		2.08 (0.14-30.31)	0.591
Intraventricular extension of ICH	10 (22.7)	5 (14.7)	0.564	-	-
In-hospital death	19 (43.2)	14 (41.2)	0.859	-	-
Median (IQR)					
Age	84 (77-90)	81 (75-84)	0.105	-	-
mRS score before admission	2 (1-4)	2 (1-3)	0.383	-	-
NIHSS score on admission	12 (7-23)	9 (4-18)	0.218	-	-
ICH volume (cm^3)	9 (2-46)	21 (3-71)	0.404	-	-

*after hemorrhagic vs after ischemic stroke

ICH indicates intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale

Table 7. Characteristics of intracerebral hemorrhages by etiologic subtype.

	SL (n=39)	M (n=74)	SOD (n=41)	AA (n=217)	HA (n=235)	U (n=39)	All (n=645)	P Value
Median (IQR) age, years	55 (44-69)	81 (73-86)	74 (61-82)	81 (74-85)	79 (67-85)	73 (51-82)	79 (68-85)	<0.001
Men, n (%)	22 (56.4)	47 (63.5)	32 (78.0)	110 (50.7)	151 (64.3)	16 (41.0)	378 (58.6)	0.001
Median (IQR) hematoma volume, cm^3	2 (1-19)	8 (2-27)	13 (2-33)	21 (6-45)	5 (2-19)	8 (1-23)	9 (2-29)	<0.001
Median (IQR) NIHSS score	6 (3-13)	12 (5-21)	17 (5-25)	11 (5-20)	12 (6-18)	7 (2-19)	11 (5-20)	0.036
Risk factors, n (%)								
Arterial hypertension	17 (43.6)	56 (75.7)	26 (63.4)	170 (78.3)	204 (86.8)	10 (25.6)	483 (74.9)	<0.001
Diabetes mellitus	3 (7.7)	14 (18.9)	8 (19.5)	41 (18.9)	78 (33.2)	6 (15.4)	150 (23.3)	<0.001
Atrial fibrillation	-	48 (64.9)	24 (58.5)	3 (1.4)	26 (11.1)	5 (12.8)	106 (16.4)	<0.001
Hypercholesterolemia	2 (5.1)	13 (17.6)	7 (17.1)	48 (22.1)	48 (20.4)	3 (7.7)	121 (18.8)	0.074
Smoking	15 (38.5)	-	6 (14.6)	17 (7.8)	21 (8.9)	2 (5.1)	61 (9.5)	<0.001
Alcohol abuse	2 (5.1)	1 (1.4)	7 (17.1)	4 (1.8)	15 (6.4)	2 (5.1)	31 (4.8)	0.001
Coronary heart disease	11 (28.2)	17 (23.0)	8 (19.5)	38 (17.5)	41 (17.4)	4 (10.3)	119 (18.4)	0.371
Ongoing antithrombotics, n (%)								<0.001
None	37 (94.9)	-	32 (78.0)	104 (47.9)	125 (53.2)	31 (79.4)	338 (52.4)	
Antiplatelets	1 (2.6)	-	7 (17.1)	93 (42.9)	99 (42.1)	5 (12.8)	207 (32.1)	
Anticoagulants	1 (2.6)	74 (100.0)	2 (4.9)	20 (9.2)	11 (4.7)	3 (7.7)	100 (15.5)	
Location, n (%)								<0.001
Deep	10 (25.6)	27 (36.5)	12 (29.3)	-	166 (70.6)	16 (41.0)	233 (36.1)	
Lobar	15 (38.5)	28 (37.8)	17 (41.5)	188 (86.6)	5 (2.1)	8 (20.5)	259 (40.2)	
Posterior fossa	8 (20.5)	9 (12.2)	2 (4.9)	-	44 (18.7)	6 (15.4)	69 (10.7)	
Intraventricular/multiple location	2 (5.1)	1 (1.4)	5 (12.2)	10 (4.6)	6 (2.6)	1 (2.6)	25 (3.9)	
Uncertain	4 (10.3)	9 (12.2)	5 (12.2)	19 (8.8)	14 (6.0)	8 (20.5)	59 (9.1)	

SL indicates structural lesion; M medication; SOD systemic/other diseases; AA, amyloid angiopathy; HA, hypertensive angiopathy; U undetermined.

Table 8. Case-fatality rates of intracerebral hemorrhage by etiologic subtypes.

	30-day			1-year		
	n	%	95% CI	n	%	95% CI
Structural lesion (n=39)	6	15.4	4.0-26.7	8	20.5	7.8-33.2
Medication (n=74)	38	51.4	40.0-62.7	41	55.4	44.1-66.7
Systemic/other disease (n=41)	18	43.9	28.7-59.1	24	58.5	43.4-73.6
Amyloid angiopathy (n=217)	89	41.0	34.5-47.6	106	48.8	42.2-55.5
Hypertensive angiopathy (n=235)	78	33.2	27.2-39.2	101	43.0	36.6-49.3
Undetermined (n=39)	9	23.7	10.2-37.2	11	28.9	14.5-43.3
All intracerebral hemorrhages (n=645)	238	36.9	33.2-40.6	291	45.1	41.3-49.0

Table 9. Predictors of mortality in patients with intracerebral hemorrhage at the multivariate Cox regression analysis.

	30-day			1-year		
Predictors	HR	95% CI	P	HR	95% CI	P
Age, per year	1.02	1.00-1.03	0.009	1.02	1.01-1.03	0.003
GCS score on admission per point	0.85	0.82-0.88	<0.001	0.86	0.83-0.89	<0.001
Hematoma volume, per cm^3	1.01	1.00-1.01	0.039	1.01	1.01-1.01	<0.001
Intraventricular extension	1.09	0.82-1.45	0.542	1.17	0.90-1.50	0.255
Infratentorial origin	1.13	0.72-1.76	0.601	1.22	0.80-1.85	0.351
SMASH-U						
Hypertensive angiopathy	1	Ref.	-	1	Ref.	-
Structural lesion	0.46	0.16-1.31	0.146	0.55	0.23-1.32	0.181
Medication	1.78	1.18-2.67	0.006	1.50	1.02-2.19	0.038
Amyloid angiopathy	1.10	0.78-1.54	0.587	0.97	0.71-1.32	0.841
Systemic/other disease	0.94	0.54-1.64	0.832	0.88	0.54-1.42	0.591
Undetermined	1.13	0.56-2.28	0.730	0.88	0.44-1.76	0.716

Table 10. Characteristics of the included patients with lobar intracerebral hemorrhage in the present study.

	All lobar ICHs (n=259)	**aSAH+FLPs (n=87)**	**aSAH or FLPs only (n=77)**	**No aSAH or FLPs (n=95)**	**P value**
Male, n (%)	133 (51.4)	38 (43.7)	39 (50.6)	56 (58.9)	0.119
Age, median (IQR)	81 (72-85)	81 (74-85)	82 (73-87)	78 (69-84)	0.028
Systolic blood pressure at onset, median (IQR)	150 (140-180)	150 (133-173)	150 (130-180)	153 (140-180)	0.357
Intraventricular extension of ICH, n (%)	54 (20.8)	28 (32.2)	17 (22.1)	9 (9.5)	0.001
Risk factors, n (%)					
Arterial hypertension	194 (74.9)	60 (69.0)	57 (74.0)	77 (81.1)	0.167
Hypercholesterolemia	47 (18.1)	18 (20.7)	10 (13.0)	19 (20.0)	0.364
Diabetes mellitus	47 (18.1)	17 (19.5)	11 (14.3)	19 (20.0)	0.575
Atrial fibrillation	39 (15.1)	11 (12.6)	13 (16.9)	15 (15.8)	0.727
Coronary heart disease	49 (18.9)	17 (19.5)	12 (15.6)	20 (21.1)	0.628
Cigarette smoking	21 (8.1)	8 (9.2)	7 (9.1)	6 (6.3)	0.743
Alcohol abuse	7 (2.7)	-	5 (6.5)	2 (2.1)	0.030
Antithrombotic treatment at onset, n (%)					0.229
None	126 (48.6)	38 (43.7)	38 (49.4)	50 (52.6)	
Antiplatelets	89 (34.4)	38 (43.7)	24 (31.2)	27 (28.4)	
Anticoagulants	44 (17.0)	11 (12.6)	15 (19.5)	18 (18.9)	

aSAH indicates associated subarachnoid hemorrhage; FLPs, finger-like projections; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation

Table 11. Cox regression analysis of predictors of case-fatality in patients with lobar intracerebral hemorrhage.

	30-day			1-year		
Predictors	HR	95% CI	P	HR	95% CI	P
Age, per year	1.03	1.00-1.05	0.025	1.03	1.01-1.05	0.014
GCS score on admission per point	0.83	0.78-0.88	<0.001	0.85	0.80-0.90	<0.001
ICH volume, per cm^3	1.00	1.00-1.01	0.070	1.01	1.00-1.01	0.042
Intraventricular extension	0.89	0.56-1.42	0.627	0.97	0.64-1.48	0.888
Edinburgh criteria						
aSAH+FLPs	1.17	0.55-2.47	0.687	1.22	0.69-2.54	0.556
aSAH or FLPs	1.15	0.54-2.45	0.709	1.32	0.69-2.54	0.403
None	1	Ref.	-	1	Ref.	-

aSAH indicates associated subarachnoid hemorrhage; CI, confidence interval; FLPs, finger-like projections; GCS, Glasgow Coma Scale; HR, hazard ratio; ICH, intracerebral hemorrhage

Table 12. Comparison between patients with and without brain magnetic resonance imaging among those with intracerebral hemorrhage.

	MRI (n=107)	No MRI (n=538)	P value (univariate)	Odds ratio (95% CI)	P value (multivariate)
N (%)					
Male	70 (65.4)	301 (55.9)	0.117	-	-
Arterial hypertension	70 (65.4)	406 (75.5)	0.009	0.52 (0.26-1.04)	0.065
Diabetes mellitus	16 (15.0)	131 (24.3)	0.026	0.65 (0.30-1.37)	0.256
Hypercholesterolemia	26 (24.3)	93 (17.3)	0.112	-	-
Cigarette smoking	23 (21.5)	38 (7.1)	<0.001	1.56 (0.67-3.63)	0.325
Coronary heart disease	23 (21.5)	95 (17.7)	0.432	-	-
Atrial fibrillation	12 (11.2)	91 (16.9)	0.120	-	-
Peripheral arterial disease	5 (4.7)	28 (5.2)	0.782	-	-
Previous stroke	16 (15.0)	62 (11.5)	0.435	-	-
Statin use	24 (22.4)	78 (14.5)	0.063	2.34 (1.11-4.94)	0.039
Previous antithrombotic use			0.005		
None	71 (66.4)	267 (49.6)		1 (Ref.)	-
Antiplatelets	24 (22.4)	183 (34.0)		1.45 (0.54-3.88)	0.457
Anticoagulants	12 (11.2)	88 (16.4)		1.31 (0.62-2.77)	0.473
ICH location			0.003		
Deep	32 (29.9)	201 (37.4)		1 (Ref.)	-
Lobar	55 (51.4)	204 (37.9)		3.20 (1.56-6.58)	0.002
Posterior fossa	16 (15.0)	53 (9.9)		3.41 (1.30-8.90)	0.012
Intraventricular or multiple	2 (1.9)	23 (4.3)		2.25 (0.37-13.52)	0.375
Uncertain	2 (1.9)	57 (10.6)		0.56 (0.06-5.11)	0.609
Intraventricular extension of ICH	12 (11.2)	177 (32.9)	<0.001	0.38 (0.15-0.95)	0.038
In-hospital death	8 (7.5)	220 (40.9)	<0.001	0.35 (0.12-1.05)	0.064
Median (IQR)					
Age	68 (52-76)	81 (73-86)	<0.001	0.95 (0.92-0.97)	<0.001
mRS score before admission	0 (0-1)	1 (0-2)	<0.001	0.82 (0.61-1.09)	0.170
NIHSS score on admission	5 (2-10)	12 (6-20)	<0.001	0.98 (0.94-1.02)	0.327
ICH volume (cm^3)	3 (1-18)	11 (3-33)	<0.001	0.98 (0.97-1.00)	0.070

ICH indicates intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale

Table 13. Characteristics of patients with deep (A) or lobar (B) cerebral microbleeds at brain magnetic resonance imaging compared with those without.

(A)

	Lobar CMBs (n=36)	**No lobar CMBs (n=71)**	**P value**
Arterial hypertension (n, %)	29 (80.6)	41 (57.7)	0.019
Age (median, IQR)	69 (57-77)	67 (51-74)	0.777
NIHSS score (median, IQR)	6 (3-9)	5 (2-12)	0.399
ICH volume (cm^3)	4 (1-20)	2 (1-18)	0.230
Previous antithrombotic use			0.694
None	22 (61.1)	49 (69.0)	
Antiplatelets	5 (13.9)	7 (9.9)	
Anticoagulants	9 (25.0)	15 (21.1)	
ICH location			0.380
Deep	0	2 (2.8)	
Lobar	22 (61.1)	33 (46.5)	
Posterior fossa	6 (16.7)	10 (14.1)	
Intraventricular or multiple	0	2 (2.8)	
Uncertain	8 (22.2)	24 (33.8)	

(B)

	Deep CMBs (n=20)	**No deep CMBs (n=87)**	**P value**
Arterial hypertension (n, %)	17 (85.0)	53 (60.9)	0.041
Age (median, IQR)	67 (51-69)	68 (52-77)	0.373
NIHSS score (median, IQR)	5 (3-6)	5 (2-12)	0.682
ICH volume (cm^3)	2 (1-6)	3 (1-19)	0.477
Previous antithrombotic use			0.667
None	12 (60.0)	59 (67.8)	
Antiplatelets	2 (10.0)	10 (11.5)	
Anticoagulants	6 (30.0)	18 (20.7)	
ICH location			0.283
Deep	0	2 (2.3)	
Lobar	9 (45.0)	46 (52.9)	
Posterior fossa	6 (30.0)	10 (11.5)	
Intraventricular or multiple	0	2 (2.3)	
Uncertain	5 (25.0)	27 (31.0)	

ICH indicates intracerebral hemorrhage; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale

Table 14. Association between the Edinburgh CT criteria and the presence of cerebral microbleeds.

(A)

	Lobar CMBs (n=36)	**No lobar CMBs (n=71)**	**P value**
Associated subarachnoid hemorrhage	9 (25.0)	20 (28.2)	0.999
Finger-like projections	3 (8.3)	9 (12.7)	0.747

(B)

	Deep CMBs (n=20)	**No deep CMBs (n=87)**	**P value**
Associated subarachnoid hemorrhage	3 (15.0)	26 (29.9)	0.383
Finger-like projections	10 (50.0)	2 (2.3)	0.999

Table 15. Incidence rates per 100,000 person-years of intracerebral hemorrhage in International population-based stroke registries overlapping with the 2011-2017 study period.

	Men (rate, 95% CI)		Women (rate, 95% CI)		Total (rate, 95% CI)	
	Crude	**Standardized***	**Crude**	**Standardized***	**Crude**	**Standardized***
Akure, Nigeria (Okon et al., 2015)	12, 8-17	11, 10-13	10, 6-15	14, 12-15	11, 8-14	12, 11-13
Auckland, New Zealand (Krishnamurthi et al., 2018)	18, 15-22	22, 20-24	19, 16-23	26, 24-28	19, 16-21	24, 23-25
Dijon, France** (Guéniat et al., 2018)	15, 13-16	-	9, 8-10	-	11, 10-12	-
Evros, Greece (Tsivgoulis, Patousi, et al., 2018)	99, 70-126	80, 57-103	60, 41-80	45, 30-59	69, 54-84	63, 50-77
Lesvos, Greece (Stranjalis et al., 2014)	NR	-	NR	-	29, 18-40	15, 9-22
Shiga, Japan (Takashima et al., 2017)	40, 36-46	36, 33-38	38, 34-43	33, 31.35	39, 36-43	34, 33-36
Tandil, Argentina (Bahit et al., 2016)	21, 13-30	28, 26-30	21, 14-30	20, 18-21	21, 16-27	24, 22-25
Present study	30, 26-33	24, 21-26	20, 17-23	15, 14-17	25, 23-27	19, 18-21

*Data are standardized to the 2011 European population; **Includes first-ever and recurrent strokes; NR: not reported

Table 16. Thirty-day and one-year case-fatality rates in International population-based stroke registries overlapping with the 2011-2017 study period.

	%	**95% CI**
30-day		
Akure, Nigeria (Okon et al., 2015)	NR	-
Auckland, New Zealand* (V. L. Feigin et al., 2015)	NR	-
Dijon, France** (Guéniat et al., 2018)	[32.6]	[26.4-38.8]
Evros, Greece* (Tsivgoulis, Patousi, et al., 2018)	40.4***	31.3-49.4
Lesvos, Greece (Stranjalis et al., 2014)	26.7***	14.0-45.0
Shiga, Japan* (Takashima et al., 2017)	18.9	[15.6-22.2]
Tandil, Argentina (Bahit et al., 2016)	24.1	14.2-36.6
Present study	36.0	31.8-40.1
1-year		
Evros, Greece (Tsivgoulis, Katsanos, et al., 2018)	47.0	36.6-57.6
Present study	44.6	40.3-48.9

*28-day case-fatality rate. **Includes first-ever and recurrent strokes; ***Intracerebral and subarachnoid hemorrhages reported together. CI: confidence interval; NR: not reported. Numbers in square brackets indicate the Authors' imputations from data reported in the studies.

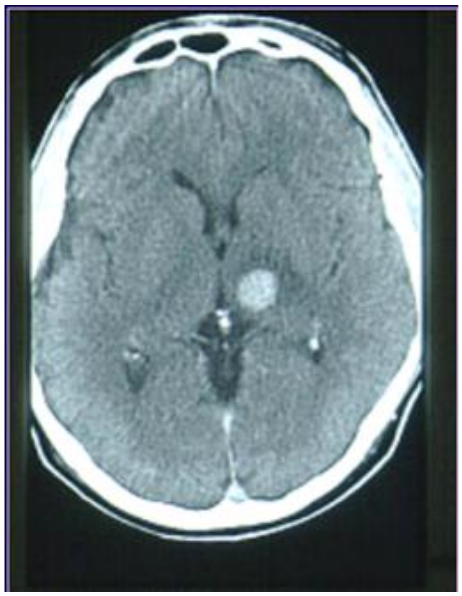
Table 17. Predicted probability of moderate or severe cerebral amyloid angiopathy in patients with lobar intracerebral hemorrhage in the present study.

Characteristic	N (%)	No ApoE testing (present study)	ApoE ε4-	ApoE ε4+
aSAH+FLPs	87 (33.5)	97%	95%	99%
aSAH only	75 (29.0)	62%	44%	95%
FLPs only	2 (0.8)	84%	66%	98%
None	95 (36.7)	22%	7%	64%

ApoE indicates apolipoprotein; aSAH, associated subarachnoid hemorrhage; FLPs, finger-like projections; PPV, positive predictive value

Figure 1. Deep (A) and lobar (B) location of intracerebral hemorrhage. The first one is commonly attributed to hypertension, while the second one is commonly attributed to cerebral amyloid angiopathy (Qureshi et al., 2001).

(A)



(B)

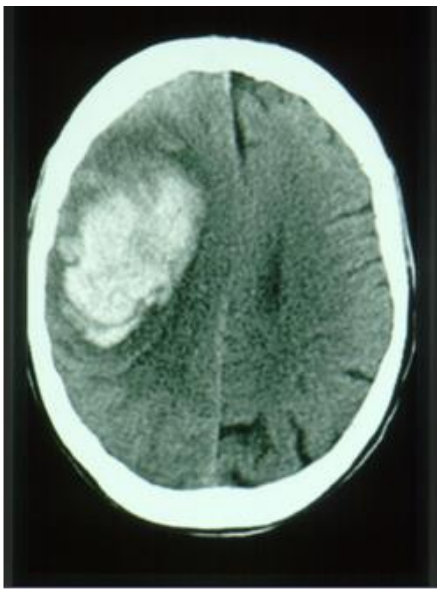
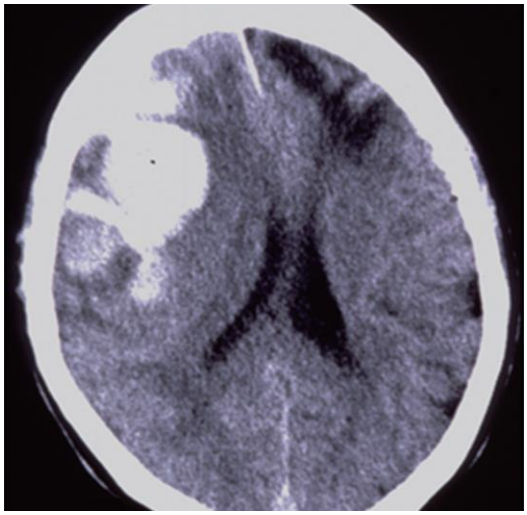
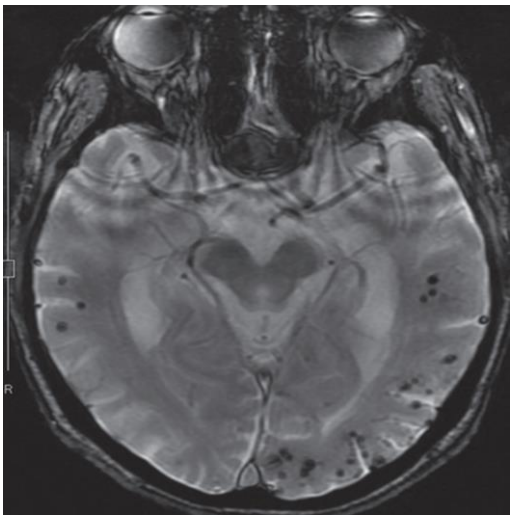


Figure 2. Typical neuroimaging findings of cerebral amyloid angiopathy. (A) Recent and old lobar macrohemorrhages in the frontal lobes on brain computed tomography. (B) Cortical microhemorrhages with lobar distribution and (C) focal subarachnoid hemorrhages (superficial siderosis) on gradient echo T2*-weighted brain magnetic resonance imaging. (D) Posterior distribution of white matter hyperintensities (arrows) on T2-weighted brain magnetic resonance imaging (Yamada, 2015).

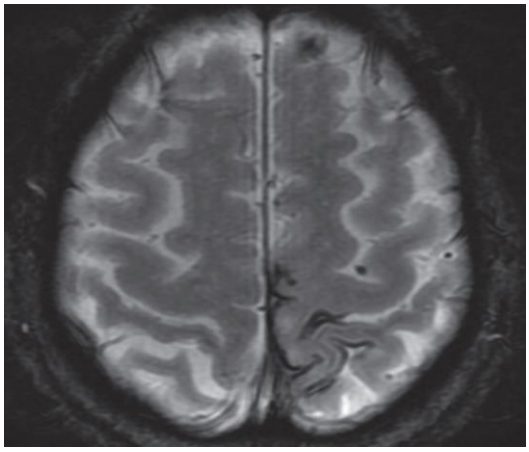
(A)



(B)



(C)



(D)

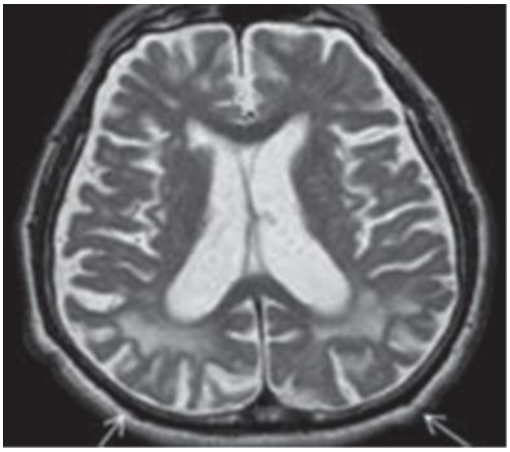


Figure 3. Brain magnetic resonance imaging appearance of cerebral small vessel disease (Wardlaw et al., 2013).

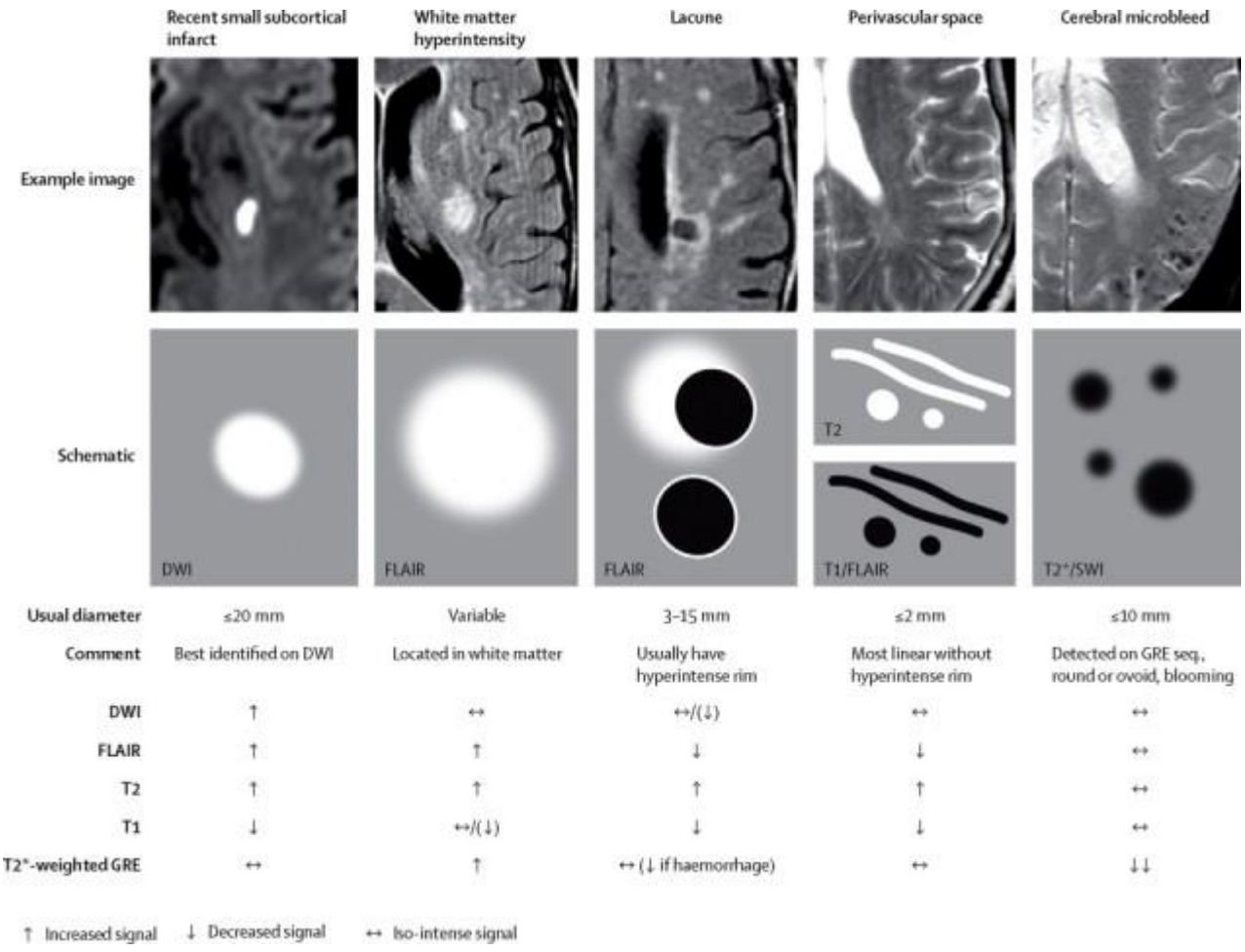


Figure 4. Scheme of the SMASH-U classification of intracerebral hemorrhage (Meretoja et al., 2012).

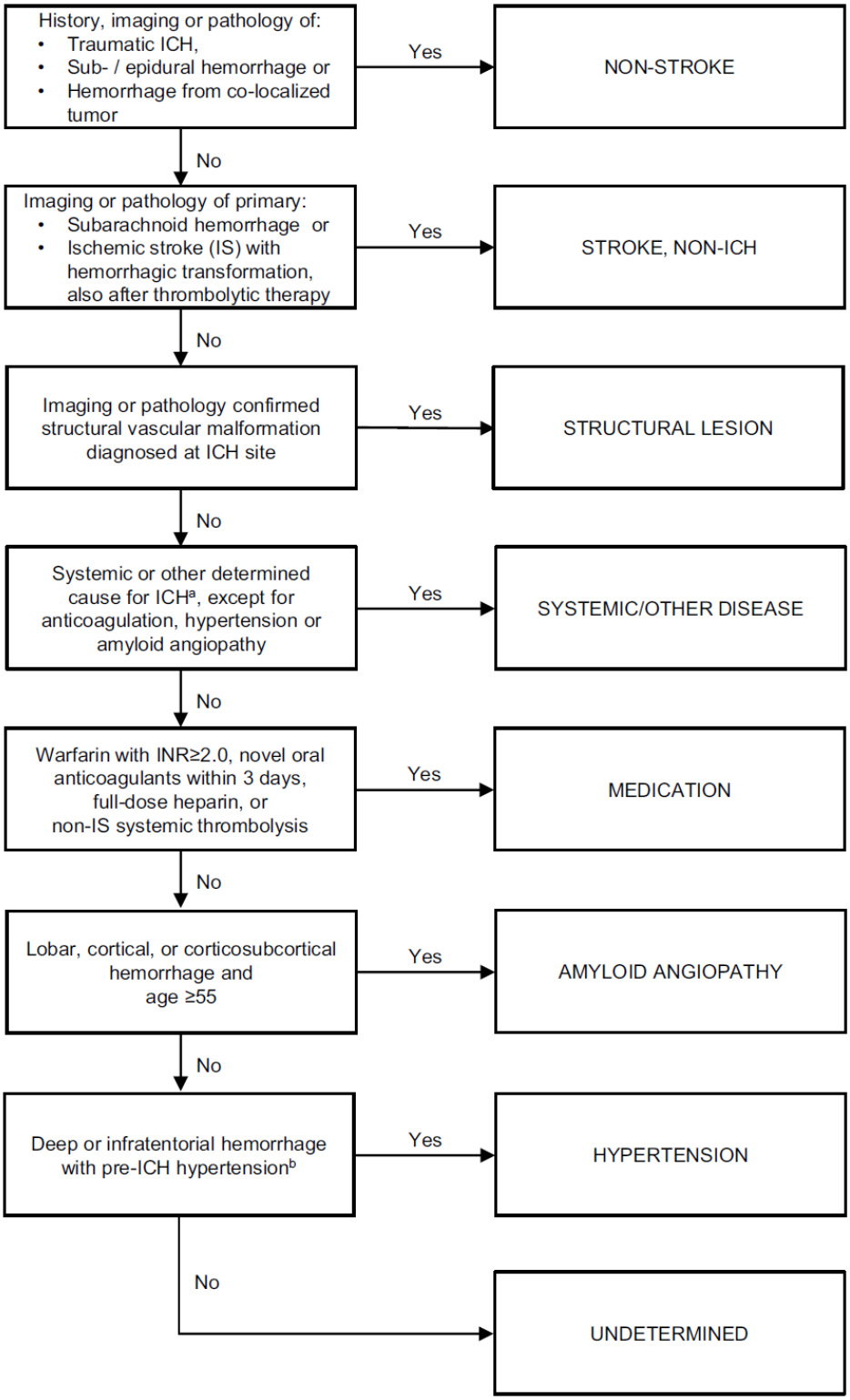


Figure 5. Probability of cerebral amyloid angiopathy-related intracerebral hemorrhage according to three predictor variables (Subarachnoid hemorrhage, APOE ε4 allele, and finger-like projections) ("Edinburgh Criteria for CAA-associated ICH Training (ECCITING)," ; Rodrigues et al., 2018).

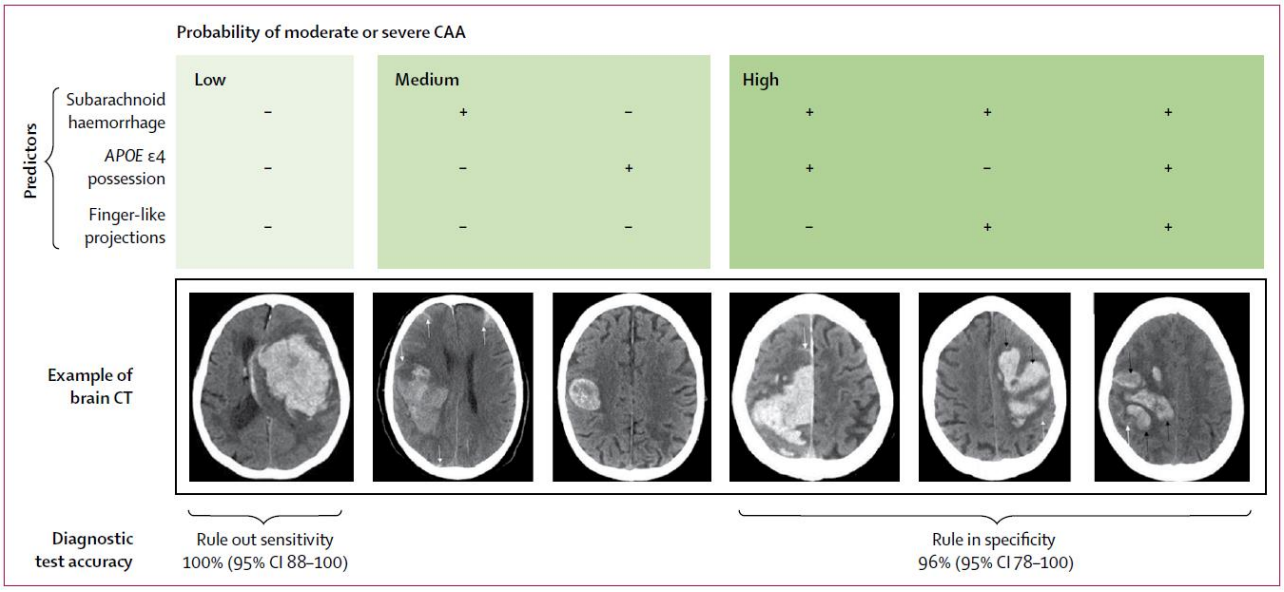
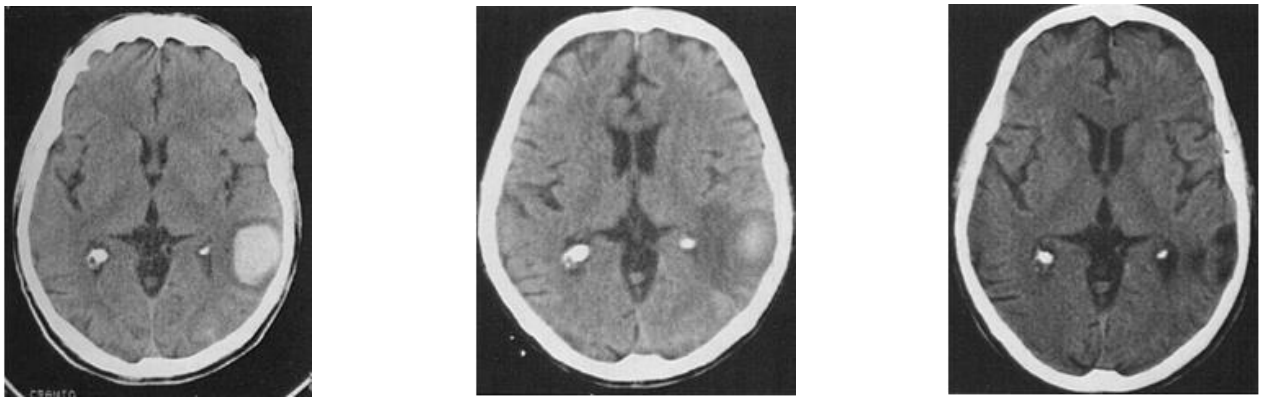


Figure 6. Evolution of intracerebral hemorrhage over time on brain computed tomography (A: acute phase; B: subacute phase; C: outcome phase) and magnetic resonance imaging (T2* sequences; D: acute phase; E: subacute phase; F: outcome phase). Images from Radiopedia: .

(A) (B) (C)



(D) (E) (F)

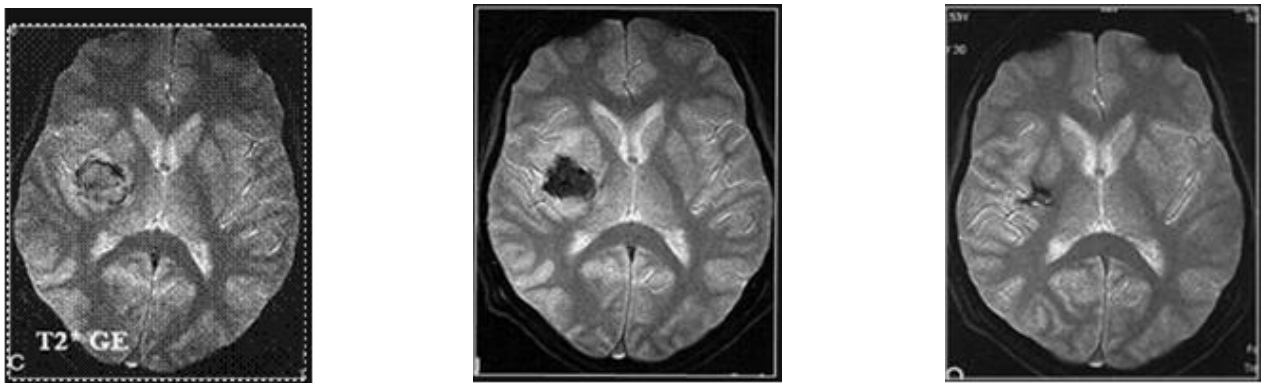


Figure 7. The ABC/2 method for ICH volume estimation (Kothari et al., 1996; Morotti & Goldstein, 2016)

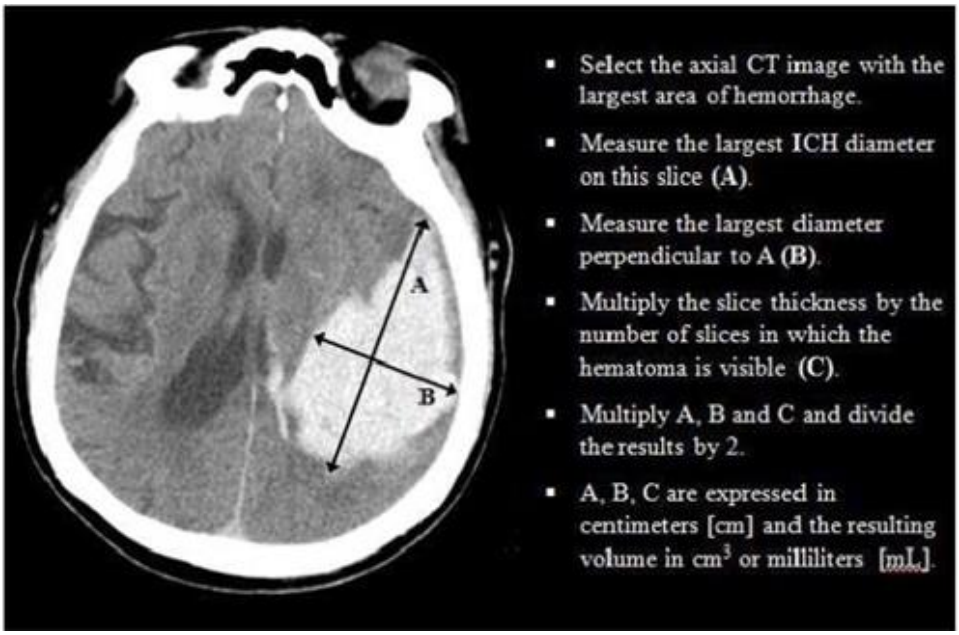


Figure 8. "Spot sign" and hematoma expansion of intracerebral hemorrhage (Morotti & Goldstein, 2016). A) Left deep intracerebral hemorrhage on noncontrast brain computed tomography (volume: 45 mL); B) brain computed tomography angiography showing the presence of spot sign (arrow); C) follow-up noncontrast brain computed tomography 19 hours after symptom onset, demonstrating significant hematoma growth (volume 192 mL) with severe midline shift and massive intraventricular extension.

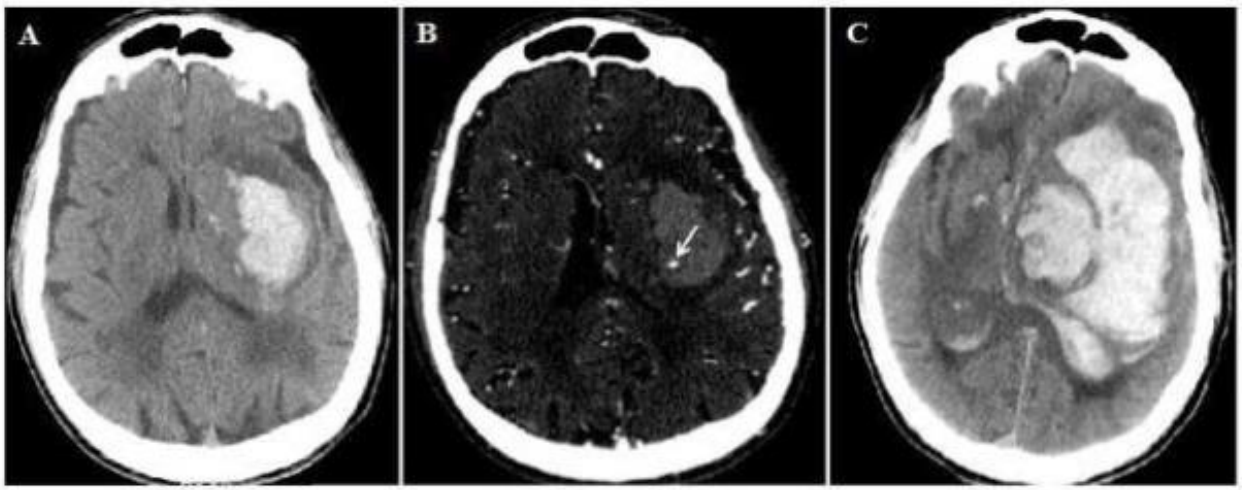


Figure 9. Age- and sex-specific incidence rates for first-ever intracerebral hemorrhage.

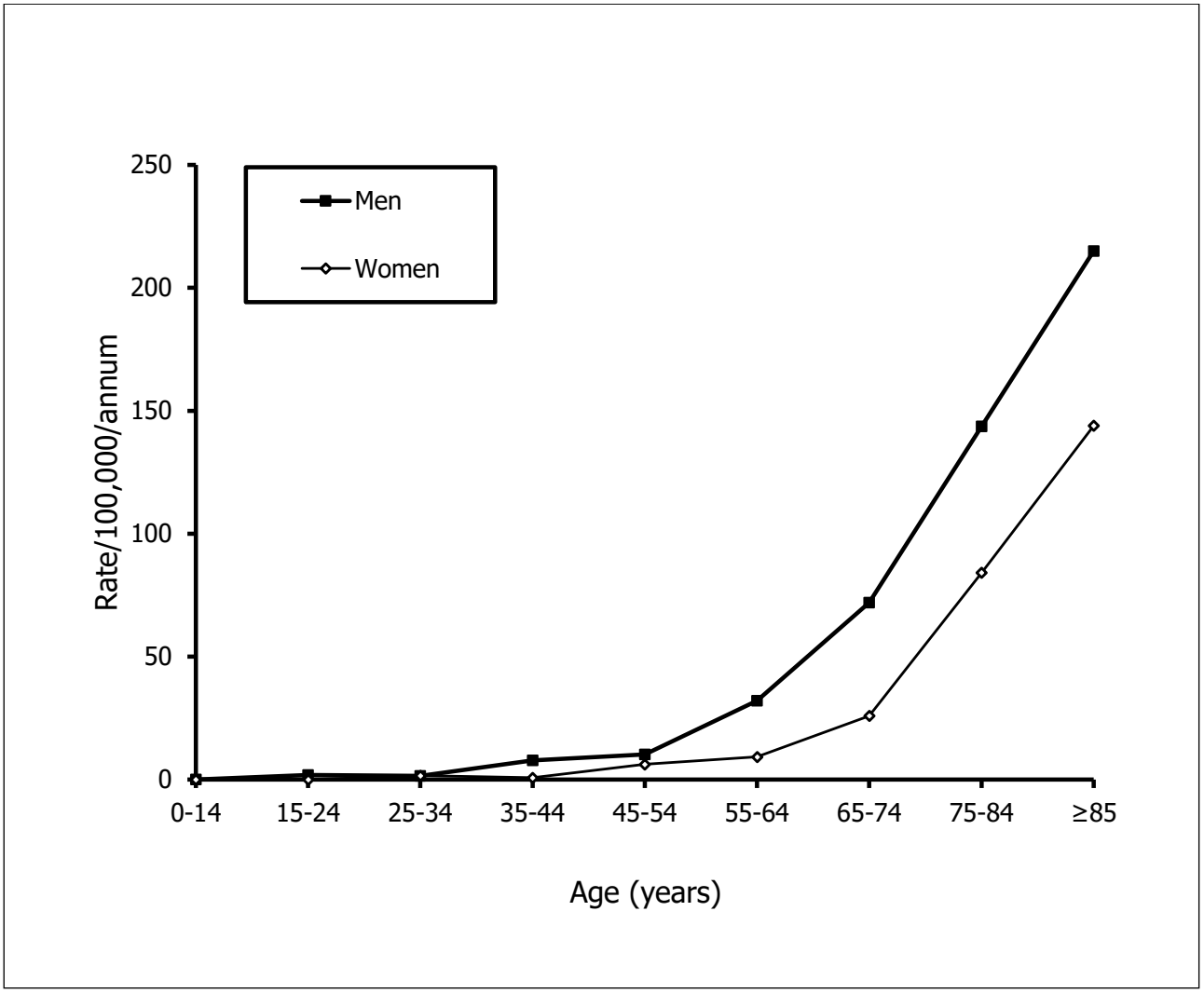
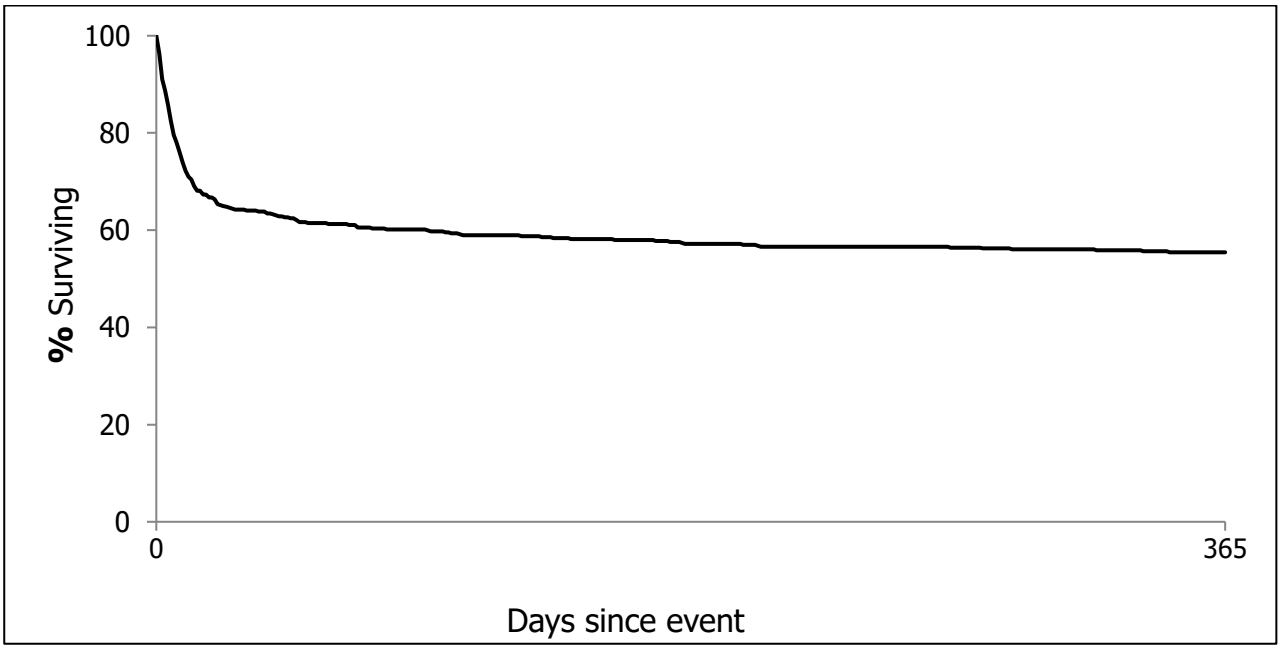


Figure 10. One-year survival (A) and cumulative incidence of cerebrovascular events (B) in patients with a first-ever intracerebral hemorrhage.

(A)



(B)

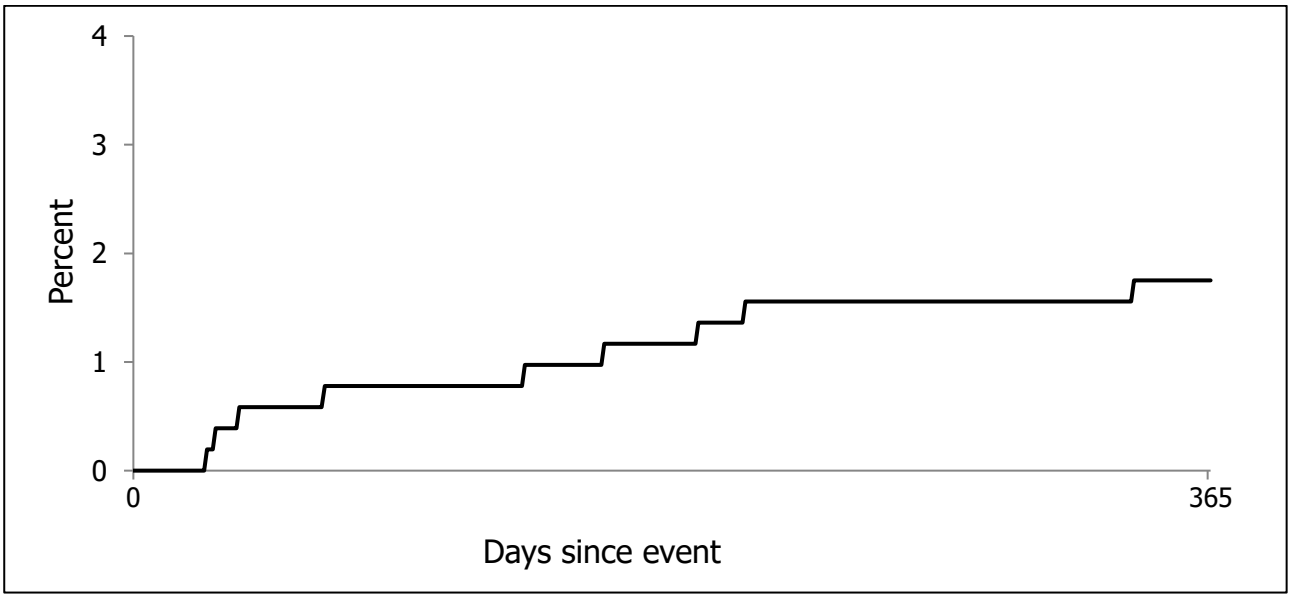
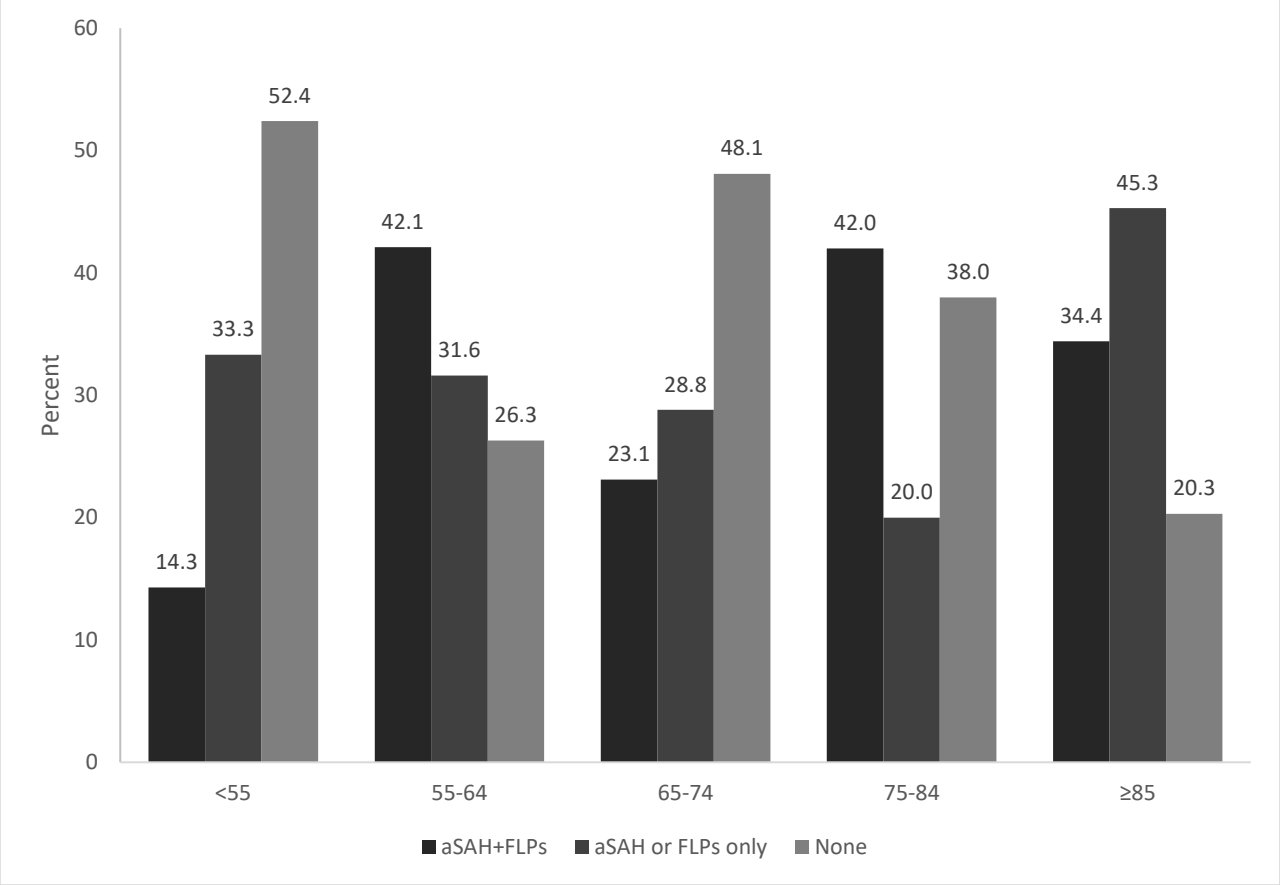


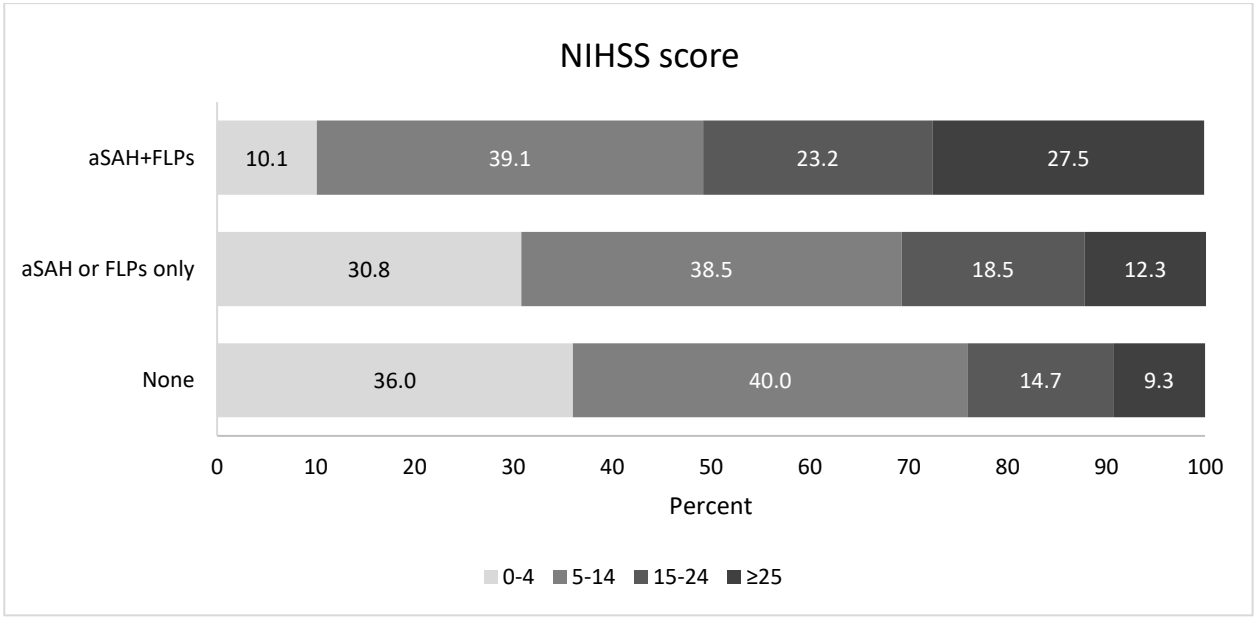
Figure 11. Relative prevalence of the Edinburgh criteria for probable cerebral amyloid angiopathy in patients with lobar intracerebral hemorrhage according to age groups.



aSAH indicates associated subarachnoid hemorrhage; FLPs, finger-like projections

Figure 12. Distribution of (A) National Institutes of Health Stroke Scale score categories on hospital admission and (B) modified Rankin Scale scores at hospital discharge according to the presence of Edinburgh criteria for probable cerebral amyloid angiopathy.

(A)



(B)

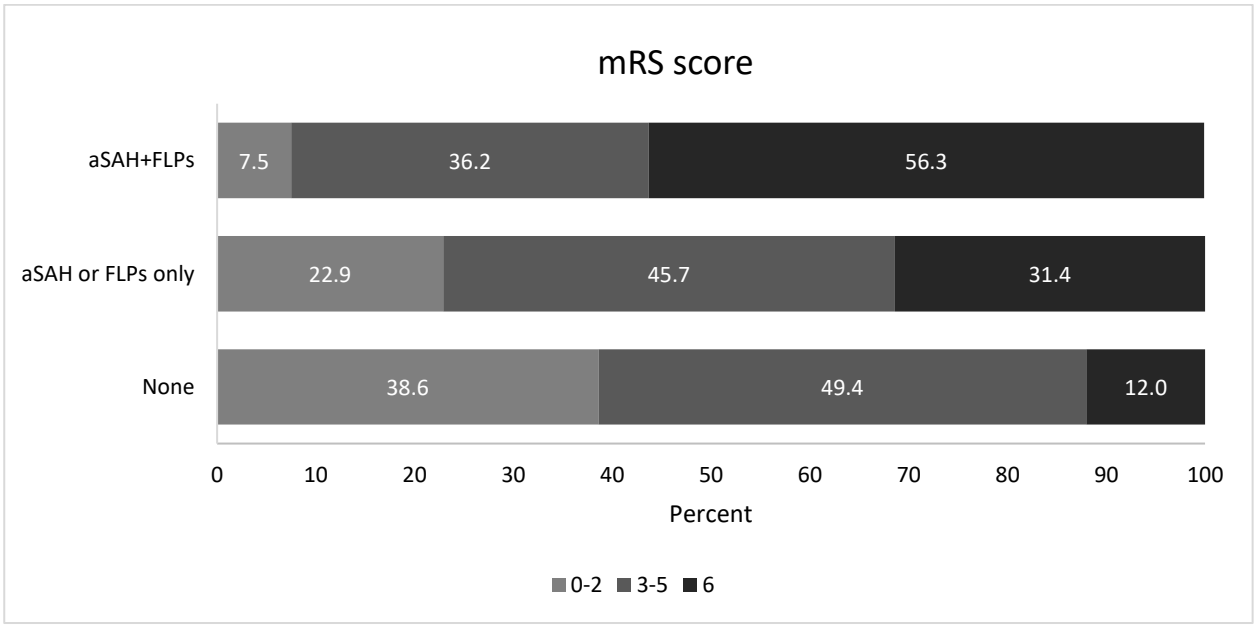


Figure 13. Box plot of intracerebral hemorrhage volume according to the presence of Edinburgh criteria for probable cerebral amyloid angiopathy in patients with lobar intracerebral hemorrhage. Boxes indicate interquartile ranges.

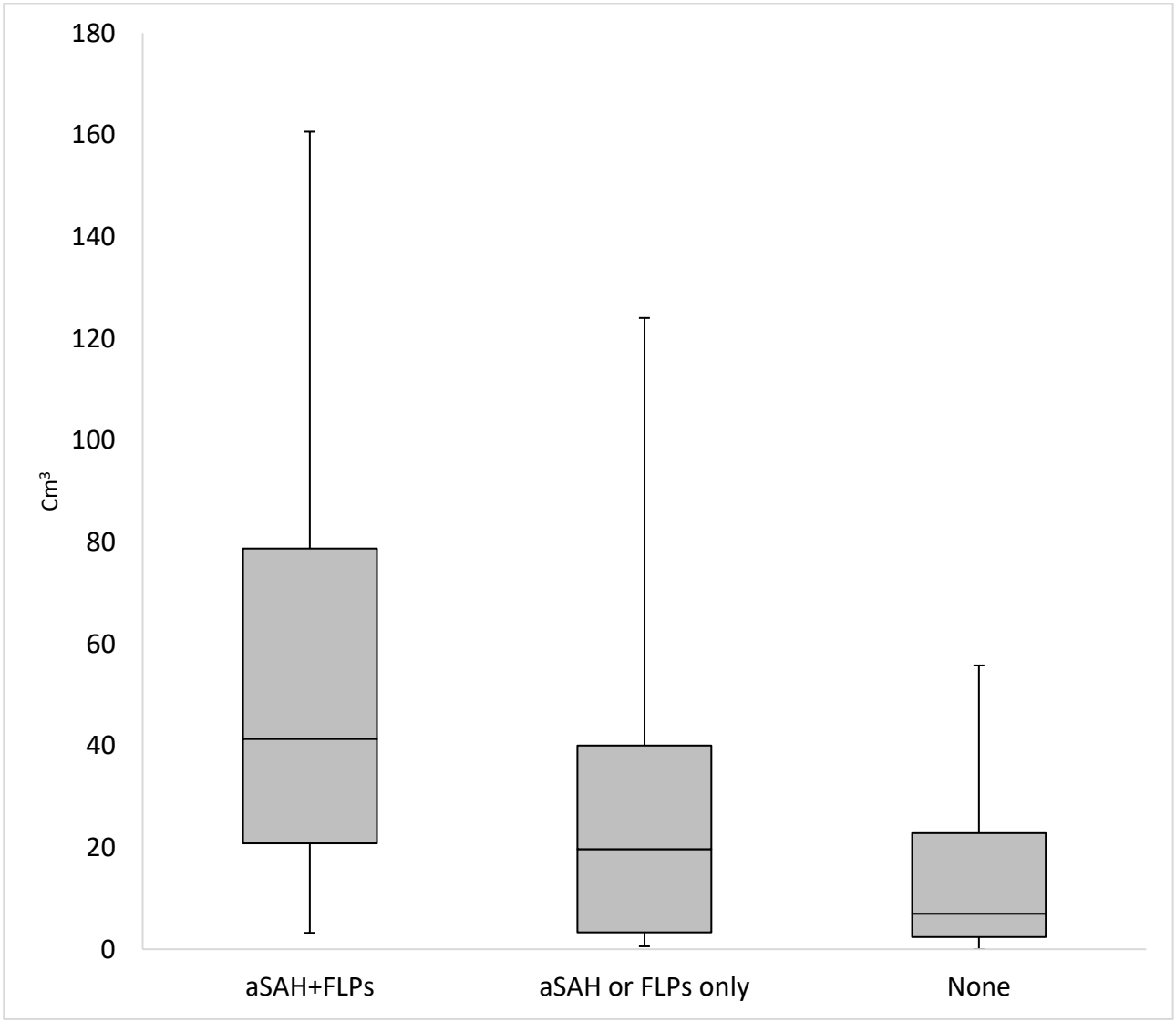
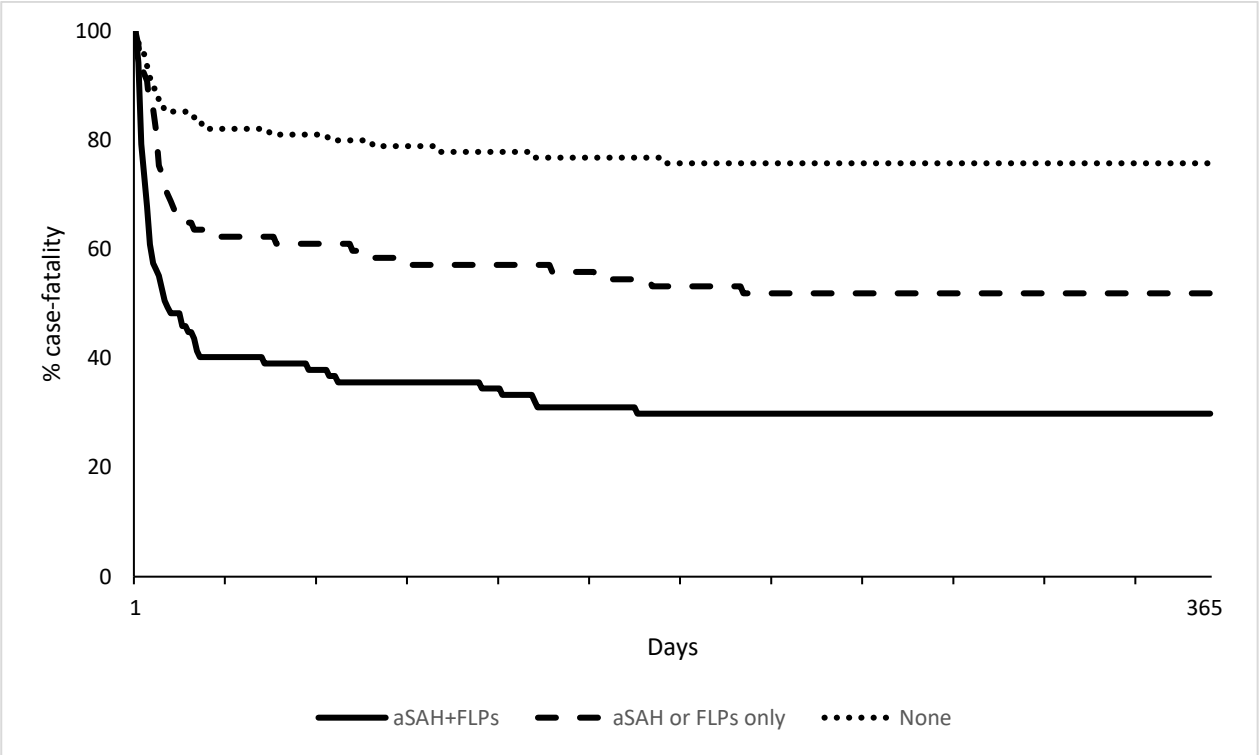


Figure 14. Kaplan-Meier curves of survival according to the presence of Edinburgh criteria for probable cerebral amyloid angiopathy in patients with lobar intracerebral hemorrhage.



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