INTRACEREBRAL HEMORRHAGE IN YOUNG ADULTS

Riku-Jaakko Koivunen

ACADEMIC DISSERTATION
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ABSTRACT

Intracerebral hemorrhage (ICH) is a devastating form of stroke, and a catastrophic medical emergency with high mortality and morbidity. Its common risk factors include hypertension and smoking, but different underlying causes are numerous. Knowledge regarding clinical characteristics and outcome of young ICH patients is limited. The long-term human and economic consequences of ICH in this population, encompassing 10% of all ICH patients, are particularly devastating.

The aims of this study were to define the prevalence of risk factors, etiologic distribution, clinical picture, and early mortality of young patients with ICH, as well as to compare these to older population. The second goal was to investigate medical complications suffered in the acute course of ICH. Third, we defined long-term mortality, functional outcome, and prevalence of post-stroke depression (PSD) among these patients. For this Thesis project, we collected detailed clinical, radiological, mortality and follow-up data on all consecutive patients between 16 and 49 years of age with first-ever ICH treated at the Helsinki University Hospital (HUH) between 2000 and 2010. Results concerning the early course of ICH were compared to a series of ICH patients aged >49 years treated in HUH between 2005 and 2010, the Helsinki ICH Study.

Median age was 42 years (interquartile range 34-47) and males comprised 59.5% of the 336 patients included. Annual incidence of ICH was 4.9 (95% confidence interval 4.5-5.3) per 100,000. The most prevalent risk factors were hypertension (29.8%) and smoking (22.3%). Compared to older ICH patients (n=921) hypertensive microangiopathy was less common (25.0% vs. 34.3%, P=0.002) and structural lesions more common (25.0% vs. 4.9%, P<0.001) assumed etiologies of ICH. The cause remained elusive in 32.1% of all young patients, and in 22.5% of those who underwent MRI and any angiography (n=89, P=0.023).

Three-month mortality rate was lower among young patients compared to older ones, (17.0% vs. 32.7%, p<0.001). Hematoma volumes were similar across all ages (p=0.324) and it independently predicted mortality in older patients, but not in the young. More severe stroke initially, measured by the National Institutes of Health Stroke Scale (NIHSS) score, infratentorial hematoma location, hydrocephalus, herniation, and multiple hemorrhages associated with increased 3-month mortality. When adjusted for these factors as well as demographics, ICH volume, and the underlying cause, we found that surgical evacuation was associated with lower mortality (odds ratio 0.06; 95% confidence interval 0.02-0.21, P<0.001). In propensity-score matched analysis, case-fatality rates were three-fold in those treated conservatively (27.5% vs. 7.8%, P<0.001). The most common medical complications
included hyperglycemia (51%), hyponatremia (45%), hypopotassemia (32%), and infections (28%). Hyperglycemia was the only single complication independently associated with increased mortality (5.90, 2.25-15.48, P<0.001). However, three or more concomitant complications also associated with increased mortality (7.76, 1.42-42.49, P=0.018).

Among the 268 one-month survivors, 1-year survival was 98.1% (95% confidence interval 96.2-100%), 5-year survival 93.2% (89.3-97.1%), and 10-year survival 88.8% (84.9-92.7%), with male gender (3.36, 1.28-8.80, P=0.014) and diabetes (2.64, 1.01-6.89, P=0.047) being associated with mortality. Unfavorable outcome (modified Rankin Scale score 2-5) emerged in 49%, and was independently predicted by higher age (1.09 per one year, 1.03-1.15, P=0.002) stroke severity (1.17 per one NIHSS score point, 1.08-1.27, P<0.001), and intraventricular extension of hemorrhage (3.26, 1.11-9.55, P=0.031). PSD was present among one out of four survivors of ICH at young age. Since only one out of ten currently used antidepressants, treatment of depression appears as an unmet need in young ICH survivors.

In summary, prevention and treatment of cardiovascular risk factors are vital in ICH prevention among young adults. Comprehensive diagnostic work-up and imaging are essential in identifying the underlying cause of ICH. The young seem to survive ICH better than the elderly, particularly if surgical hematoma evacuation is pursued. A holistic approach to prevent and treat associated complications, specifically hyperglycemia, is vital in regard of survival. Only half of the survivors reach favorable functional outcome. Therefore, more effective measures of rehabilitation and mental health must be developed to improve the quality of life of this patient population.
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**LIST OF ORIGINAL PUBLICATIONS**

The thesis is based on the following publications, referred to in the text by their Roman numerals:


In addition, some unpublished data are presented.

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### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AED</td>
<td>Antiepileptic drug</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<td>AVM</td>
<td>Arteriovenous malformation</td>
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<td>BDI-II</td>
<td>Beck Depression Index II</td>
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<td>BP</td>
<td>Blood pressure</td>
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<td>BPI</td>
<td>Brief Pain Inventory</td>
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<tr>
<td>CAA</td>
<td>Cerebral amyloid angiopathy</td>
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<tr>
<td>CPP</td>
<td>Cerebral perfusion pressure</td>
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<tr>
<td>CPSP</td>
<td>Central post-stroke pain</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed tomography angiography</td>
</tr>
<tr>
<td>CVT</td>
<td>Cerebral venous sinus thrombosis</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life year</td>
</tr>
<tr>
<td>DNR</td>
<td>Do-not-resuscitate</td>
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<tr>
<td>DSA</td>
<td>Digital subtraction angiography</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EuroQualityOfHealth-5D-3L</td>
</tr>
<tr>
<td>ESO</td>
<td>European Stroke Organisation</td>
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<tr>
<td>EVD</td>
<td>External ventricular drainage</td>
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<tr>
<td>FFP</td>
<td>Fresh frozen plasma</td>
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<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
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<tr>
<td>HELLP</td>
<td>Syndrome of hemolysis, elevated liver enzymes, and low platelet count</td>
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<tr>
<td>HSP</td>
<td>Hemiplegic shoulder pain</td>
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<tr>
<td>HUH</td>
<td>Helsinki University Hospital</td>
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<tr>
<td>ICH</td>
<td>Intracerebral hemorrhage</td>
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</tbody>
</table>
ICP | Intracranial pressure
ICSU | Intensive care stroke unit
ICU | Intensive care unit
INR | International normalized ratio
IPC | Intermittent pneumatic compression
IVH | Intraventricular hemorrhage
LDL | Low-density lipoprotein
LMWH | Low-molecular-weight heparin
MAP | Mean arterial blood pressure
MI | Myocardial infarction
MIS | Minimally invasive surgery
MISTIE | Minimally Invasive Surgery plus rt-PA for Intracerebral Hemorrhage Evacuation
MoCA | Montreal Cognitive Assessment
MRI | Magnetic resonance imaging
MRA | Magnetic resonance angiography
mRS | Modified Rankin Scale
NIHSS | National Institutes of Health Stroke Scale
NSAID | Non-steroidal anti-inflammatory drug
OAC | Oral anticoagulant
PASS-20 | Pain Anxiety Symptoms Scale
PCC | Prothrombin complex concentrate
PE | Pulmonary embolism
PEG | Percutaneous endogastric tube
PROGRESS | Perindopril Protection Against Recurrent Stroke Study
PSD | Post-stroke depression
RCT | Randomized controlled trial
RCVS | Reversible cerebral vasoconstriction syndrome
SAH | Subarachnoid hemorrhage
SICHPA | Stereotactic treatment of intracerebral hematoma by means of plasminogen activator
STICH | Surgical Trial in Intracerebral hemorrhage
TIA | Transient ischemic attack
UTI | Urinary tract infection
Blood eruption into the brain parenchyma is designated intracerebral hemorrhage (ICH). It is a devastating form of stroke, often being a fatal disturbance in the brain circulation. Stroke accounts for the second highest number of deaths and the third highest number of disability-adjusted life-years (DALYs) worldwide.\textsuperscript{1,2} ICH covers 10 to 30\% of all strokes.\textsuperscript{3-5} ICH is the most devastating of the main stroke subtypes with overall mortality of 40 to 50\%.\textsuperscript{6-15} The overall ICH incidence is an annual 25 cases per 100,000/year, remaining steady during recent decades.\textsuperscript{16}

In contrast to recent success in ischemic stroke prevention and acute treatment, no such significant improvement has occurred in the medical care of ICH.\textsuperscript{16} To limit further brain injury and to prevent and treat associated complications the acute care of ICS has remained mostly supportive.\textsuperscript{17} A proportion of patients receive neurosurgical treatment, but data are insufficient to constitute uniform guidelines. After acute-phase treatment, intensive multiprofessional rehabilitation often follows. Despite this, the independence rate among survivors lies between 12\% and 39\%.\textsuperscript{16} In addition to the prominent physical impact on the patients, substantial consequences for mental health emerge frequently.

ICH has long gone understudied in young adults. Only about a dozen mostly small young ICH cohorts have been published since the 1980s with their upper age limit 35 to 45 years. Regarding the upper age cut-off of ischemic or hemorrhagic stroke studies in the young, the most recent studies have applied 50 or even 55 as the limit – a fact likely resulting from increased longevity in industrialized countries. Patients in this age group suffer about 10\% of all ICHs.\textsuperscript{16}

ICH in the young differs from that in the elderly in several important aspects: Their risk factor and etiological spectrum is different and more diverse. The young have fewer cardiovascular risk factors and preexisting chronic diseases. Importantly, many more quality-weighted life years will be lost in case severe ICH affects a young individual. Since the young patients are at their most productive age, and usually have under-aged children, the disease may result in profound long-term socioeconomic and humane consequences, including long sick leaves, early retirement, prolonged institutional care, and even death.\textsuperscript{18-20}

Further knowledge and accurate up-to-date data on young-adult ICH is vital. In this Thesis project we aimed to describe the incidence, distribution of underlying causes and risk factors, acute-phase course of treatment, associated complications, and short- and long-term outcome of ICH in the young. Further, we sought to identify baseline factors associated with outcome, as well as to analyze differences between the younger and older ICH patients. For these purposes, we designed a comprehensive database comprising detailed clinical, imaging, laboratory, and follow-up data on consecutive patients with first-ever ICH at age of 16 to 49.
2 REVIEW OF THE LITERATURE

2.1 DEFINITION OF INTRACEREBRAL HEMORRHAGE

Non-traumatic ICH (hereafter referred to as “ICH”) is a subtype of stroke, a catastrophic cerebrovascular insult without an underlying head trauma as its cause. Traumatic ICH, therefore, is never considered a stroke subtype. ICH is defined as “extravasation of blood into brain parenchyma”. Outburst of blood is the opposite of ischemic stroke, in which a cerebral artery is occluded. Both induce disturbance of neuronal function through different pathophysiological mechanisms in brain tissue resulting in abrupt onset of neurological symptoms and signs.

2.2 INCIDENCE OF ICH

Of all strokes ICH accounts for 10-30%. In contrast to past advances with ischemic stroke prevention, ICH incidence has remained steady. According to ethnic origin, a fairly recent meta-analysis of 36 studies from 20 countries reported ICH incidence of 24.2 cases per 100,000 population per year in white people, 22.9 in black people, 19.6 in Hispanic people, and 51.8 in Asian people. These changes are only partly explained by differences in educational attainment, socioeconomic status, and prevalence of vascular risk factors, such as hypertension, smoking, and alcohol consumption. Overall ICH incidence is 24.6 (range from 1.8 to 129.6) cases per 100,000 population per year, a discovery by the same meta-analysis, having remained steady since 1980, and having decreased only in few populations with improved access to medical care and blood-pressure control.

Incidence markedly increases with age: from annual 1.9 cases per 100,000 among people aged under 45 to 196.0 cases among those over 84. Studies have shown 44.4% of all ICH occurring at age over 60, median age of ICH patients being 61, and incidence rates doubling every 10 years after age 35. A few studies showed that incidence of ICH was higher in winter than summer. Reason for this has remained unresolved, but climatic conditions acting as synchronizers to endogenous rhythms and thereby influencing periodic occurrence of pathological vascular events has been proposed as explanation. Blood pressure increases during colder months.
Incidence of ICH in Finland has been investigated in only few studies. One reported 31 cases annually per 100,000 on average, with substantial increase with age: incidence rate of 2 in those 30-39 years, and 222 in those over 80 years. These results were later confirmed by another study reporting incidence rate of 27 on average, and the mean age at incident being 70 years. Incidence of ICH has remained steady in Finland. As the proportion of the elderly increases in the future in Finland and other industrialized countries, ICH incidence is also expected to increase.

### 2.3 ECONOMICAL IMPACT OF INTRACEREBRAL HEMORRHAGE

The financial burden of ICH has been investigated in few countries. Because of the need for close monitoring for clinical deterioration or cardiorespiratory support due to impaired consciousness, patients most often need treatment in intensive care stroke unit (ICSU), intensive care unit (ICU), or neurosurgical treatment in the acute phase on the course of ICH. All these are much more expensive in comparison to regular hospital ward. After the patient has been stabilized, neurological hospital ward follows aiming to initiate multi-professional rehabilitation, and – depending on the underlying cause of ICH – commencing secondary prevention of ICH. Average in-hospital treatment of 7.7 days, estimated to cost $15,256, has been reported, with $1,569 for each additional day. Working-aged patients may need long sick-leaves, or even early retirement. Due to the loss of productivity, the financial burden of ICH of $125,000 per patient has been estimated, resulting in an overall cost of $6 billion in the United States alone. Stroke, including hemorrhagic and ischemic stroke, have been estimated to cause annual direct and indirect costs of $816,1 million in Finland.

### 2.4 PATHOPHYSIOLOGY OF INTRACEREBRAL HEMORRHAGE

Instead of a single event, ICH is a dynamic process with three phases: 1) initial blood eruption, 2) hematoma expansion, and 3) development of perihematomal edema. The initial hemorrhage causes prominent amount of parenchymal damage as the hematoma bulk dissect along the white matter tissue planes of the brain, encircling islands of intact neural tissue. Animal models have failed to reveal secondary damage being caused by local mass effect. Expansion of hematoma due to continuing bleeding is usually defined as >12.5 ml or >33% increase in the hematoma volume. Hematoma expansion typically occurs during the few hours following initial hemorrhage and is associated with neurological
deterioration: in 26%, 36%, and 47% of the patients within 1, 3, and 24 hours after ictus, respectively. A more recent study showed that 73% of patients assessed within 3 hours from ictus have some degree of hematoma expansion, and 35% have clinically prominent expansion. Hematoma expansion is highly unlikely to result after 24 hours from ictus, and even 6 hours, if hematoma volume is <25 ml. It is still unclear what the mechanisms of early hematoma growth are, but it is likely related to sudden increases in intracranial pressure (ICP), which causes local tissue distortion and disruption, vascular engorgement secondary to obstructed venous outflow, blood-brain-barrier disruption, and a local coagulopathy secondary to release of tissue thromboplastin. Expansion of the hematoma is a common cause of early neurological deterioration, increased mortality, and poor functional outcome. Higher hematoma volume and IVH on admission associate with neurological deterioration. Diabetes, high systolic blood pressure on hospital arrival, and elevated C-reactive protein associate with hematoma expansion. Mortality increases exponentially when the hematoma volume exceeds 30ml; the 30-day mortality among patients with >60ml hematoma and Glasgow Coma Scale (GCS) score <9 is >90%, whereas only 19% for those with <30ml hematoma and a GCS score ≥9. Hematoma may extend to ventricular system containing cerebrospinal fluid (CSF) in up to 40% of the cases; this condition is defined as intraventricular hemorrhage (IVH), and associates with obstructive hydrocephalus and worsened prognosis.

Perihematomal edema develops over many days and is the primary cause of neurological deterioration after the first day from ictus, by interfering with functioning of nearby brain areas, causing relative ischemia by compressing blood vessels, and by increasing intracranial pressure. It derives from plasma, is caused mainly by the inflammatory response secondary to local release of thrombin and other end products of coagulation from the hematoma, by cytotoxic mediators, by disruption of the blood-brain-barrier, sodium pump, and neurons. Correlating with lysis of red blood cells, edema peaks around 3 to 7 days after onset, but has been observed to last even two weeks in experimental models. The degree of edema correlates with the hematoma volume. It has been implicated that both hemoglobin and its degradation products are directly and indirectly neurotoxic. Retrospective evidence suggest that larger amount of cerebral edema relative to the initial hemorrhage correlates with worse clinical outcomes, but not independently from hematoma volume.

No uniform consensus exists on the issue whether ICH is surrounded by ischemic penumbra, but a recent study found no evidence of potentially salvageable
ischemic penumbra in the acute phase after ICH, suggesting that perihematomal hypoperfusion is a consequence of reduced metabolic demand rather than tissue ischemia.\textsuperscript{94,95} It is more likely that perihemorrhagic tissue damage is primarily related to the inflammatory and cytotoxic response of tissue and vasculature of hemorrhage site, and that the impact of perihematomal ischemia is probably small.

\section*{2.5 Risk Factors of Intracerebral Hemorrhage}

Risk factors for ICH have been reported by multiple studies.\textsuperscript{32,96-98} The most important risk factor for ICH, as well as other stroke subtypes, is hypertension, commonly defined as systolic blood pressure $>160$ mmHg or diastolic blood pressure $>110$ mmHg.\textsuperscript{97,99,100} The severity and duration of hypertension have a clear correlation with the risk of ICH.\textsuperscript{96} Antihypertensive treatment in patients with hypertension decreases risk of stroke, including ICH.\textsuperscript{101,102} Male gender and higher age have also been reported as risk factors for ICH.\textsuperscript{5,96,97,103} Age-related degenerative changes in cerebral arteries increase the risk for rupture, but also for ischemic stroke. Women are protected by estrogen, which reduces the risk of all detrimental cardiovascular insults, such as myocardial infarction and ischemic stroke. One reason for this is, estrogen having a protective effect against atherosclerosis by mediating transportation of cholesterol.\textsuperscript{104-106} In addition, estrogen may have neuroprotective effects and induce recovery after ischemic stroke.\textsuperscript{107,108} The association of dyslipidemias or statin use and ICH has been subject to numerous studies and intensive debate in recent years, but remains conclusively unresolved. Hypocholesterolemia has been reported as risk factor for ICH in few studies.\textsuperscript{109-111} This association was not evident in other cohorts.\textsuperscript{112,113} Two more recent studies reported hypercholesterolemia as a risk factor for ICH.\textsuperscript{114,115} Hyper-LDL cholesterolemia and hypo-HDL cholesterolemia were also identified as possible risk factors, while triglyceridemia was not associated with ICH.\textsuperscript{115} The investigators proposed use of statins for a possible measure of secondary prevention of ICH. Their results, however, are in contrast to a previous study with similar number of ICH patients.\textsuperscript{116} Other previous studies have, however, reported statins as a risk factor for ICH and cerebral microbleeds, asymptomatic intracerebral bleeding seen with T2*-weighted MRI and risk factor for ICH themselves, and suggested avoiding statin use after a patient has suffered an ICH, especially one of lobar location.\textsuperscript{116-122} On the contrary, a recent meta-analysis found no association between statins and increased ICH prevalence, and another meta-analysis found no association between statin use and hematoma volume, mortality, or functional outcome after ICH.\textsuperscript{123,124} Preventative impact of statins on coronary heart event and ischemic stroke are proven, but safety on secondary prevention of ICH is still under debate and uniform guidelines are lacking.\textsuperscript{125}
Smoking is another important risk factor for ICH, ischemic stroke, and SAH, with gradual increase depending on how many cigarettes are smoked.\textsuperscript{109,110,126} This association seems to be independent from hypertension, but most likely also resulting from atherosclerosis and structural damage to the arterial wall.\textsuperscript{127,128} Excessive alcohol use (>60 mg/d) too increases risk of ICH, partially because of alcohol-induced hypertension but also independently, and most likely due to impaired coagulation, thrombocyte dysfunction, and directly affecting the integrity of cerebral vasculature.\textsuperscript{96,129-135} Short-term moderate or heavy alcohol intake within 24 hours or one week (binge drinking) causes higher risk for ICH in comparison to long-term habitual heavy drinking.\textsuperscript{133}

High-dose aspirin use also increases the risk of ICH, with 1300 mg or over daily causing 2-fold risk of ICH, but possible association with dipyridamole or clopidogrel remains unresolved due to contradictory findings.\textsuperscript{133,136-139} Absolute risk increase of 12 events per 10,000 persons associated with aspirin must be put in the context of the benefit of reduced risk of myocardial infarction (MI) and ischemic stroke.\textsuperscript{5,140} One study found no association between antiplatelet therapy and recurrent hemorrhage.\textsuperscript{141} OAC and fibrinolytic agents are a growing precipitant for secondary ICH accounting for nearly 20% of all ICH as long-term use of OAC increases the risk of ICH 7- to 10-fold.\textsuperscript{142-147} The risk of ICH roughly doubles as INR increases by one.\textsuperscript{5,148} OAC use on patients with history of ICH has been widely considered problematic dilemma, due to the risk of recurrent ICH, and high early mortality associated with it – even after reversal of vitamin K antagonist by vitamin K, and clotting factor replacement with prothrombin complex concentrate (PCC), or fresh frozen plasma.\textsuperscript{5,149-151} Some evidence exists that with a certain group of patients, those with deep hemispheric ICH at particularly high risk for thromboembolic insult or low risk of ICH recurrence, the benefit of long-term OAC outweighs the risks.\textsuperscript{152} Another issue is the timing of re-initiation of OAC, which has been instructed to commence earliest between 7 to 14 days after ictus, but not enough data yet exists for strong recommendations.\textsuperscript{153-155} Relationship between both OAC and antiplatelet therapy with cerebral microbleeds has been shown, indicating the need for selecting those patients in lesser risk of recurrent ICH.\textsuperscript{156,157} Due to lack of data from RCTs, no uniform guidelines currently exists addressing antithrombotic or antiplatelet therapy after ICH, and treating physicians are left to make clinical decisions on the basis of indirect and observational evidence.\textsuperscript{150-158} Selective serotonin reuptake inhibitors also predispose ICH. Reports on nonaspirin nonsteroidal anti-inflammatory drugs (NSAID) being a risk factor for hemorrhagic or ischemic stroke have so far been contradictory, and further investigation is needed to draw conclusions.\textsuperscript{159-161}

Genetic risk factors of ICH are still under investigation.\textsuperscript{162} A point mutation in the gene involved in the formation of factor XIII, responsible for fibrin cross-linking, has been reported to increase risk of ICH.\textsuperscript{163} Epistaxis has also been reported as
risk factor for ICH. Diabetes is a well-known risk factor for ischemic stroke. It has been associated with ICH in few cohorts, but a meta-analysis of 8 case-control studies could not confirm that association. More data are needed to draw conclusions whether diabetes is a risk factor for ICH. Prior ischemic stroke is a risk factor for ICH; prevalence of ischemic stroke among ICH patients of 29% has been reported. Chronic kidney disease has been proposed being a risk factor for ischemic stroke, and for ICH after thrombolysis of ischemic stroke, but no evidence has been reported it being a risk factor for spontaneous ICH. Finally, low socioeconomic status and level of education associate with higher incidence of stroke, ICH in particular, most likely resulting from unhealthy lifestyle habits and impaired compliance of treatment of hypertension. Risk factors of ICH are summarized in Table 1.

Table 1. Risk factors of intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Risk factor</th>
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<tbody>
<tr>
<td>Male gender</td>
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<tr>
<td>Age</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Alcohol</td>
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<tr>
<td>Anticoagulant use</td>
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<tr>
<td>Antiplatelet use</td>
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<tr>
<td>Genetic factors</td>
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2.5.1 PREVENTION OF INTRACEREBRAL HEMORRHAGE

Due to its high morbidity, mortality, and lacking proven therapy, primary prevention of ICH is of paramount importance. Treatment of mild to moderate hypertension reduces the risk of stroke, including ICH, in middle-aged and elderly by 36% to 48%. Treatment of chronic hypertension is probably the most effective means of preventing ICH. Results from Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed that perindopril plus optional indapamide significantly lowered the risk of ICH in patients with any cerebrovascular disease. Cessation of smoking and restrained use of alcohol are reasonable recommendations to prevent ischemic and hemorrhagic stroke. Patients for vitamin K antagonist anticoagulation should be carefully selected, and INR values on those selected patients regularly monitored. A recent meta-analysis showed that using novel oral anticoagulants instead of warfarin reduces incidence of ICH caused by anticoagulation by half. Patients for thrombolysis for myocardial infarction and
acute ischemic stroke should also be carefully selected. Physical activity reduces the risk of stroke. Increased daily consumption of fruits and vegetables may as well decrease the risk of stroke, including ICH.

2.6 CAUSES OF INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage can be caused by numerous factors, classified in two groups – primary and secondary. Primary ICH, accounting for 78 to 88% of all cases, occurs without any underlying congenital or acquired brain lesion or abnormality, whereas secondary ICH is directly related to a pre-existing intracranial abnormality or condition. High-quality studies defining the most likely cause for an ICH and including autopsy verification are scarce, and developing a comprehensive classification has been fairly recently acknowledged as a research priority.

2.6.1 PRIMARY INTRACEREBRAL HEMORRHAGE

Rupture of small penetrating arteries damaged by chronic hypertension is regarded responsible for approximately 70% of primary ICH, making hypertensive microangiopathy the most important cause. Approximately half of hypertension-related ICH locates deep, in the basal ganglia, thalamus, periventricular gray matter, or brain stem, 30% in superficial areas, and rest in cerebellum (Figure 1). These areas are perfused by the thin perforating arteries that rise directly from the large basal cerebral arteries, and are directly exposed to the harmful effects of hypertension because they lack the protection of preceding gradual decrease in vessel caliber. This induces pathological changes such as degeneration in the vessel wall smooth muscle, which is replaced by collagen and intimal hyalinization, and development of small miliary aneurysms associated with thrombosis leading to microhemorrhages. The atherosclerotic changes, or “lipohyalinosis”, result in development of noncompliant narrowed vessels that are susceptible to both sudden occlusion (lacunar infarction) and rupture (ICH). Evidence with electron microscopy has shown that degeneration and bleeding occurs at or near the bifurcation of affected arteries.

Cerebral amyloid angiopathy (CAA), estimated to account for more than 20% of all ICH in patients older than 70 years, causes mainly lobar and subcortical hematomas (Figure 2). Distinct of systemic amyloidosis, it is characterized by accumulation of β-amyloid protein and degenerative changes in the media and adventitia of blood vessels of cerebral cortex and leptomeninges. CAA is highly
associated with age, because over 60% of autopsy samples from patients older than 90 years exhibit some degree of amyloid deposition. Genetic variations of apolipoprotein Ee2 and Ee4 seem to associate with CAA. The Boston criteria, combining clinical, radiologic, and pathologic data, have been developed between 1995 and 1996 to classify lobar ICH into categories of possible, probable, or definite likelihood of underlying CAA, and have since been validated. CAA is definitely evident only after pathological analysis revealing deposition of vascular amyloid, and probably evident in patients older than 55 years with multiple hemorrhages without other explanation. CAA is possible cause of ICH in patients older than 55 years with single cortical or subcortical hemorrhage without another cause, multiple hemorrhages with a possible but not a definite cause, or some hemorrhage in an atypical location.

Figure 1. A deep-located ICH.
2.6.2 SECONDARY INTRACEREBRAL HEMORRHAGE

Due to their risk of bleeding, vascular structural anomalies are important causes of secondary ICH. Including arteriovenous malformation (AVM), cavernous hemangioma, intracranial aneurysms, and Moyamoya disease, they constitute approximately 5% of all ICH.\textsuperscript{23,219} Rupture of aneurysm causes 85% of SAHs, and also ICH may occur—mostly in cases with middle cerebral or distal anterior cerebral artery aneurysm.\textsuperscript{220} AVMs are vascular lesions, in which blood flows from arteries to veins without capillaries (Figures 3A and 3B.). They are most likely congenital but not hereditary, and their most common clinical presentation is ICH.\textsuperscript{221} The estimated annual rate of bleeding is between 2 to 3%.\textsuperscript{222} Cavernous hemangiomas, another type of vascular malformation, have less blood flow, and usually cause epilepsy. They carry, however, annual risk of ICH of 1 to 2%.\textsuperscript{223} Epithelioid hemangioendotheliomas and capillary telangiectasies are rare structural causes of ICH. Primary or metastatic intracranial neoplastic tumor may also bleed into brain parenchyma.\textsuperscript{5}

Oral anticoagulation (OAC) associates nearly 20% of all ICHs, having markedly increased since 1990s as a result of increasing use of OAC to prevent ischemic events in patients with atrial fibrillation.\textsuperscript{7,143,144,187,224} Annual risk for ICH is between 0.3
Figures 3A and 3B. Left temporal ICH with intraventricular extension in a 22-year old woman seen in CT (3A) and the underlying AV-malformation seen in CT-angiography (3B).
and 1.0% among patients under OAC.\textsuperscript{143} Most episodes of OAC-caused ICH often occur during international normalized ratio (INR) being between 2.0 and 3.5.\textsuperscript{225,226} OAC use is associated with larger initial hematomas, hematoma expansion, and neurological deterioration in the first 24 to 48 hours.\textsuperscript{227,228} Recent evidence shows that OAC-related ICH is more often lobar than deep.\textsuperscript{229} Novel oral anticoagulants have substantially lower risk of ICH in comparison to traditional OAC.\textsuperscript{189} Other acquired coagulopathies include those related to liver diseases, such as liver cirrhosis, due to the decreased production of clotting factors I (fibrinogen), II (prothrombin), V, VII, VIII, IX, X, and XI. Rarely ICH may also be caused by hereditary coagulopathies, such as von Willebrand’s disease, or malignant hematological diseases, such as leukemia or polycythemia vera. Iatrogenic etiologies include carotid endarterectomy and heparin. Thrombolysis of myocardial infarction poses a risk of 1% for ICH.

Hemorrhagic transformation of ischemic stroke, the most feared complication of ischemic stroke and thrombolysis treatment, cerebral venous thrombosis (CVT), and intracranial vasculitis are also possible, but rare causes of ICH.\textsuperscript{190,191,230} National Institute of Neurological Disorders and Stroke has reported that the overall risk of ICH after use of tissue plasminogen activator for ischemic stroke is 6.4%.\textsuperscript{191,234,235} Eclampsia acutely raises blood pressure, and by the same mechanism, or by reversible cerebral vasoconstriction syndrome (RCVS), pheochromocytoma, glomerulonephritis, and strenuous physical activity, may also cause ICH.\textsuperscript{236-242} In all of these cases, hemorrhage is caused by pathologic circumstances in brain circulation and parenchyma. Finally, illicit drugs, such as amphetamine or cocaine, may also cause ICH by RVCS or necrotizing angiitis. One case has also been reported of ICH associated with ephedrine abuse.\textsuperscript{243} Causes of ICH are summarized in Table 2. If no cause of ICH is evident, it is considered cryptogenic.

2.6.3 CAUSES OF INTRACEREBRAL HEMORRHAGE IN THE YOUNG

ICH among young people has been studied in single-center studies (total n=1890) with the largest series including 404 patients (Table 3).\textsuperscript{110,244-254} Reflecting the different numbers of patients, geographic settings, and patients' ethnic backgrounds, as well as the upper age cut-off chosen, the proportions of ICH etiologies have varied largely among these studies (Table 3). The proportion of ICHs caused by hypertensive microangiopathy has been from 11 to 79%, while structural causes have accounted from 17 to 65%. Previous reports suggest the young adults have a wide range of causes underlying ICH.\textsuperscript{245,247,249}
Table 2. Primary and secondary causes of intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive microangiopathy</td>
<td>Vascular malformations</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>Medication</td>
</tr>
<tr>
<td></td>
<td>Coagulopathy</td>
</tr>
<tr>
<td></td>
<td>Hematologic disorders</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
</tr>
<tr>
<td></td>
<td>Moyamoya disease</td>
</tr>
<tr>
<td></td>
<td>Cerebral venous thrombosis</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic transformation of cerebral infarct</td>
</tr>
<tr>
<td></td>
<td>Aneurysms</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
</tr>
<tr>
<td></td>
<td>Reperfusion after carotid endarterectomy</td>
</tr>
<tr>
<td></td>
<td>Thrombolysis</td>
</tr>
<tr>
<td></td>
<td>Illicit drugs</td>
</tr>
<tr>
<td></td>
<td>Reversible cerebral vasoconstriction syndrome</td>
</tr>
<tr>
<td></td>
<td>Other rare causes</td>
</tr>
</tbody>
</table>

2.7 CLINICAL PRESENTATION AND EVALUATION OF INTRACEREBRAL HEMORRHAGE

2.7.1 CLINICAL PICTURE OF INTRACEREBRAL HEMORRHAGE

The clinical presentation of ICH depends on its size and location as well as presence of IVH. The classic presentation of ICH is sudden onset of a focal neurological deficit that – in contrast to other stroke subtypes – progresses gradually over minutes to hours, with accompanying headache, nausea, vomiting, decreased consciousness, and elevated blood pressure.\textsuperscript{180,256} Gradual progression most likely relates to ongoing bleeding. Only 15% present symptoms at awakening.\textsuperscript{180} The most common symptom is headache of variable intensity and the most common focal neurological deficits include hemiparesis, dysarthria, and aphasia.\textsuperscript{23} Headache is present in about 40%.\textsuperscript{257} Prevalence of vomiting has been reported 49% for ICH patients, but it is common in all stroke subtypes located in the posterior fossa (Figure 4).\textsuperscript{180} Clinical signs of increased ICP, such as early impaired consciousness, nausea, and vomiting are suggestive of ICH. Seizures appear in approximately 10% of all patients with ICH and in almost one half of patients with lobar hemorrhage. Nearly all seizures occur at the onset of bleeding or within the first days of ictus and are not strongly predictive of the
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
<th>Age (Sex distribution)</th>
<th>Comorbidities</th>
<th>Etiology</th>
<th>Early death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toffol et al. (Arch Neurol. 1987)</td>
<td>United States</td>
<td>72</td>
<td>15-45</td>
<td>-</td>
<td>AVM 29%, hypertension 15%, aneurysm 10%, sympathomimetic drugs 7%, undetermined 24%</td>
<td>13% (in-hospital)</td>
</tr>
<tr>
<td>Bevan et al (Stroke 1990)</td>
<td>United States</td>
<td>46</td>
<td>15-45</td>
<td>-</td>
<td>hypertension 15%, vessel anomaly 65%, coagulopathy 4%, tumor 11%, other 9%</td>
<td>26% (in-hospital)</td>
</tr>
<tr>
<td>Fuh et al (J Stroke Cerebrovasc Dis 1994)</td>
<td>Taiwan</td>
<td>170</td>
<td>15-45</td>
<td>-</td>
<td>Hypertension 38%, AVM 20%, blood dyscrasia 8%, acute alcohol intoxication 2%, aneurysm 2%, sympathomimetic drugs 2%, moyamoya 1%, endocarditis 1%, preeclampsia/eclampsia 1%, glioblastoma 1%, SLE 1%, undetermined 25%</td>
<td>34% (in-hospital)</td>
</tr>
<tr>
<td>Lin et al. (Kaohsiung J Med Sci. 1997)</td>
<td>Taiwan</td>
<td>91†</td>
<td>15-40</td>
<td>-</td>
<td>hypertension 30%, undetermined 25%</td>
<td>18% (1-month)</td>
</tr>
<tr>
<td>Awada et al. (J Stroke Cerebrovasc Dis. 1998)</td>
<td>Saudi Arabia</td>
<td>107</td>
<td>0-45</td>
<td>-</td>
<td>AVM 23%, hypertension 20%, blood dyscrasia 16%, aneurysm 8%, other causes 7%, undetermined 26%</td>
<td>27% (in-hospital)</td>
</tr>
<tr>
<td>Ruiz-Sandoval et al. (Stroke 1999)</td>
<td>Mexico</td>
<td>200</td>
<td>15-40</td>
<td>hypocholesterolemia 35%, smoking 20%, hypertension 13%, excess alcohol 10%</td>
<td>AVM 33%, cavernoma 16%, hypertension 11%, CVT 5%, sympathomimetic drugs 4%, toxemia of pregnancy 4%, undetermined 15%</td>
<td>8% (in-hospital)</td>
</tr>
<tr>
<td>Del Brutto et al. (Funct Neurol 1999)</td>
<td>Ecuador</td>
<td>151</td>
<td>15-44</td>
<td>-</td>
<td>hypertension 40%, AVM 22%, other 11%, undetermined 28%</td>
<td>23% (in-hospital)</td>
</tr>
<tr>
<td>Lai et al (European Journal of Neurology 2005)</td>
<td>Taiwan</td>
<td>296</td>
<td>15-45</td>
<td>hypertension 49%, diabetes 8%, smoking 38%, excess alcohol use 6%, drug use 2%, hyperlipidemia 36%, hypocholesterolemia 28%, family history of stroke 7%</td>
<td>hypertension 47%, vessel anomaly 17%, coagulopathy 5%, tumor 6%, undetermined 10%</td>
<td>24% (in-hospital)</td>
</tr>
<tr>
<td>Chen et al (Cerebrovascular diseases 2006)</td>
<td>Switzerland</td>
<td>247†</td>
<td>-</td>
<td>hypertension 80%, excess alcohol use/smoking 5%</td>
<td>hypertension 80%, vascular anomaly 5%, medical problems 9%, cryptogenic 5%</td>
<td>-</td>
</tr>
<tr>
<td>Roditis et al (Romanian Neurosurgery 2011)</td>
<td>Romania</td>
<td>8</td>
<td>27-35</td>
<td>-</td>
<td>hypertension 63%, AVM 13%, undetermined 25%</td>
<td>-</td>
</tr>
<tr>
<td>Kalita et al. (J Neu Sci 2014)</td>
<td>India</td>
<td>404</td>
<td>16-50</td>
<td>hypertension 57%, hypocholesterolemia 34%, excess alcohol use 16%, anticoagulant 4%</td>
<td>hypertension 79%, vascular malformation 4%, coagulopathy 4%, CVT 2%, thrombocytopenia 1%, vasculitis 1%, cryptogenic 9%</td>
<td>25% (1-month)</td>
</tr>
<tr>
<td>Rutten-Jacobs et al (J Neurol 2014)</td>
<td>Netherlands</td>
<td>98</td>
<td>18-50</td>
<td>hypertension 24%, diabetes 2%, smoking 35%, excess alcohol use 7%, history of TIA 7%</td>
<td>hypertension 27%, AVM 22%, cavernous angioma 5%, medication 5%, bleeding disorder 3%, substance abuse 2%, septic embolism 1%, cryptogenic 17%, multiple causes 3%, incomplete evaluation 14%</td>
<td>20% (1-month)</td>
</tr>
</tbody>
</table>

* This study included subarachnoid hemorrhage patients.
† Sex distribution not reported.
AVM, arteriovenous malformation; CVT, cerebral venous thrombosis; SLE, systemic lupus erythematosus
development of delayed epilepsy. More than 90% patients present with elevated blood pressure (>160/100 mmHg), and symptoms caused by dysautonomia, such as hyperventilation, tachycardia, bradycardia, central fever, and hyperglycemia are also frequent.

**Figure 4.** ICH of infratentorial location (posterior fossa).

Large hemorrhages may cause coma due to increased ICP leading to decreased cerebral perfusion or due to direct infiltration or distortion of diencephalic or brainstem structures (Figure 5). Putaminal hemorrhages present with contralateral motor deficits, gaze paresis, aphasia, or hemineglect (Figure 6). Thalamic hemorrhages present with contralateral sensory loss; pupillary and oculomotor abnormalities are possible, especially if the thalamic hemorrhage extends into the rostral brainstem (Figure 7). Cerebellar hemorrhages present with nausea, vomiting, ataxia, nystagmus, decreased level of consciousness, and ipsilateral gaze palsies or facial paralysis (Figure 8). Pontine hemorrhages present with coma, pinpoint pupils, disturbed respiratory patterns, autonomic instability, quadriplegia, and gaze paralysis, and are commonly fatal. The presentation of lobar hemorrhages depends on the exact location of the hemorrhage. Blood extending into the ventricular system causes reduced level of alertness due to ventricular ependymal irritation or the development of hydrocephalus. Clinical deterioration develops in 30% to 50% of patients, usually within 24 hours following ictus, and most often due to hematoma expansion. Deterioration occurring over 24 hours more often results due to increased edema surrounding ICH.
Figure 5.  A massive ICH compressing brain structures.

Figure 6.  A putaminal ICH.
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Figure 7. A thalamic ICH with IVH.

Figure 8. A cerebellar ICH.
2.7.2 EARLY MORTALITY AFTER INTRACEREBRAL HEMORRHAGE

ICH is the most catastrophic subtype of strokes with high mortality and morbidity. Early mortality after ICH has been studied in multiple cohorts. A fairly recent meta-analysis concluded that case-fatality at 1 month was 40%, increasing to 54% at one-year. Investigators of individual cohorts have reported early mortality rates between 40% and 50%, with half of deaths occurring within the first 2 days. In Finland 3-month mortality after ICH is 35%. In young adults in-hospital or 1-month mortality after ICH was between 8% and 34% (Table 3). Factors predicting early mortality or poor functional outcome have been also investigated in several studies. Radiological and clinical characteristics indicating the severity of hemorrhage have been repeatedly reported to associate with the outcome. Daverat et al. found 30-day mortality being increased by higher hematoma volume, lateral shift of cerebral midline structures, and intraventricular hemorrhage (IVH). These findings, in addition to impaired consciousness upon arrival to emergency department, measured by GCS, and infratentorial hematoma location are the most important factors associated with increased early mortality, with hematoma volume being the most powerful individual predictor. Using National Institutes of Health Stroke Scale (NIHSS) score instead of GCS predicts mortality equally well. At simplest, the volume can be estimated on the initial CT by measuring the length, width, and depth of the hematoma and then dividing by 2. OAC-associated ICH have been reported being irregularly shaped and using division of 3, therefore, predicts the volume more accurately. Higher volume of IVH also independently associates with poor outcome, as well as early growth of IVH (Figure 9). Infratentorial ICH may damage brainstem, important brain structure where centers regulating many vital functions are located, if occurring in brainstem, or by pressure caused by transtentorial herniation, displacement of brain parenchyma behind tentorium. Cingulate herniation, resulting from large hemispheric ICH causing mass-effect, also predicts poor outcome. Higher age has also been reported to predict poor outcome in some studies. In 2001 Hemphill et al. presented a scoring system with these factors, the ICH score, to forecast patient’s odds for survival at 1 month. This, fairly easy-to-use tool for clinicians, has since been widely accepted, and also validated to prognose functional outcome at 6 months and 1 year. Instead of admission, the score seems to be more accurate, when measured at 24 hours. Recently, a new scoring system for predicting outcome after IVH, the Modified Graeb Score, has been introduced, but not yet commonly accepted. Midline-shift, lateral displacement of brain parenchyma, caused by mass-effect of hematoma or edema, also predicts increased mortality.
also cause obstructive hydrocephalus by tempering with circulation of cerebrospinal fluid, another predictor of poor prognosis.\textsuperscript{279} Edema is not independently associated with outcome, but rather affects through large hematoma volume (Figure 9).\textsuperscript{89,93} Investigators have recently reported a method to measure perihematomal edema with excellent reliability at baseline and 24 hours post-ICH.\textsuperscript{296}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{A large ICH with IVH and severe brain edema.}
\end{figure}

OAC use associates with rapid clinical deterioration, as well as increased short-term mortality, up to 67%, and poor functional outcome.\textsuperscript{71,143,144,146,147,187,224,227,228,297} This results due to the larger hematoma volumes and hematoma expansion.\textsuperscript{298-303} Preceding antiplatelet therapy also associates with increased mortality.\textsuperscript{136,304-306} High mean arterial blood pressure (MAP), hypothesized to be caused by “Cushing reflex” mechanism to maintain sufficient blood perfusion in the brain, but consequently causing ICP to increase, associates with early death and poor functional outcome, which may relate to higher hematoma volumes.\textsuperscript{307-311} Several other factors besides directly related to hematoma or pathological intracranial mechanisms have also been reported. Few studies have noted high plasma glucose on admission to associate with poor outcome, but the mechanism for this is unclear.\textsuperscript{11,312,313} The underlying etiology behind ICH may also contribute to the prognosis: ICH caused by hypertensive microangiopathy associates with poor outcome.\textsuperscript{109} Hypertensive ICH has been regarded different in clinical characteristics and outcome between the young and the elderly with the young having decreased mortality at the expense of more incapacitating disabilities suggesting age-related differences in
disease pathogenesis. This may be associated with subcortical hematoma location being also associated with poor outcome, since hypertensive ICH more often occurs in deep location. In addition, cardiovascular comorbidities associate with poor outcome: Ischemic heart disease and atrial fibrillation both associate with increased 3-month mortality after ICH. Diabetes and hypertension also emerge as factors predicting increased early mortality. Reasons for this remain yet unresolved, but increase in in-hospital complications has been proposed. On the contrary, pre-ICH statin use is not associated with increased mortality, poor functional outcome or higher hematoma volumes. Need of mechanical ventilation signals for poor outcome. Interestingly, preceding infections have also been identified to predict poor outcome in one study. Chronic kidney disease and renal failure have been identified to predict increased mortality and disability after ischemic stroke, as well as after ICH. Factors associated with poor outcome after ICH are summarized in Table 4.

Important finding is that early care limitations independently predict mortality. Do-not-resuscitate order being associated with less active treatment and poor prognosis has been revealed by several studies. Clinicians should, therefore, avoid therapeutic nihilism and limiting treatment in the first few days that may cause self-fulfilling prophecies.

Table 4. Summary of factors associated with poor outcome after intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Factor</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma volume &gt; 30 mL</td>
<td>266,275</td>
</tr>
<tr>
<td>Arrival GCS &lt; 13</td>
<td>275</td>
</tr>
<tr>
<td>Presence and volume of IVH</td>
<td>275,290</td>
</tr>
<tr>
<td>Infratentorial hematoma location</td>
<td>275</td>
</tr>
<tr>
<td>Age &gt; 80</td>
<td>275</td>
</tr>
<tr>
<td>Imminent herniation</td>
<td>292</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>279</td>
</tr>
<tr>
<td>OAC use</td>
<td>297</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>136,304-306</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>11,312,313</td>
</tr>
<tr>
<td>Hypertension</td>
<td>109,318</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>315,316</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>275</td>
</tr>
<tr>
<td>Diabetes</td>
<td>284,312,318-320</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>173,324-338</td>
</tr>
</tbody>
</table>
2.7.3 DIAGNOSIS AND INITIAL ASSESSMENT OF INTRACEREBRAL HEMORRHAGE

Clinical evaluation alone is insufficient to differentiate ICH from other stroke subtypes, and to determine the characteristics and possible cause of ICH. Thus imaging of the brain is needed, and the diagnostic study of choice in ICH at first place is usually non-contrast brain computed tomography (CT). It provides a significant amount of information about the size and location of the hemorrhage, presence of intraventricular, subarachnoid, or subdural blood, and about the presence of mass-effect with threatening herniation or hydrocephalus.\textsuperscript{279,292} CT differentiates ICH from cerebral infarction with high sensitivity – an imperative matter in the management of acute stroke, given the availability of thrombolytic therapy. Hemoglobin displays bright on non-contrast head CT.\textsuperscript{21} CT may also enable the prediction of hematoma expansion based on pattern of bleeding.

Magnetic resonance imaging (MRI) is as sensitive in detecting ICH as is CT, but superior in identifying perihematomal edema, arteriovenous malformation (AVM), amyloid angiopathy, or underlying neoplasm.\textsuperscript{345,346} MRI may provide important hints regarding underlying pathology, such as microbleeds, lacunar infarcts, and chronic white-matter change, which all suggest microangiopathy.\textsuperscript{120,121} It can also provide information about the time course of ICH.\textsuperscript{180} Compared to CT, shortcomings of MRI include longer scanning time, and limited possibilities to monitor and treat critically ill patient while in scanner. CT remains, therefore, as the gold standard, but MRI is the first-line imaging method for all younger ICH patients.\textsuperscript{200}

Location of a hemorrhage may provide information about the etiology. Deep subcortical structures (putamen, caudate, thalamus),pons, cerebellum, and periventricular deep white matter are typical locations for hypertensive small-vessel disease, whereas single or multiple lobar hemorrhages in the cortical surface are often caused by CAA. These assumptions may, however, be incorrect: majority of patients with lobar ICH have a history of hypertension, and vascular malformations may also be the cause of deep or lobar hemorrhages.\textsuperscript{180,347} According to one study, in 48% of normotensive patients younger than 45 years, in 49% of patients with lobar hemorrhage, and 65% of cases with isolated intraventricular hemorrhage, there are abnormalities on angiography, such as aneurysm or AVM.\textsuperscript{144}

CT-angiography (CTA), MR-angiography (MRA), or digital subtraction angiography (DSA) should be performed in all young patients due to the high likelihood of underlying vascular abnormality. Angiography should also be performed in other patients without obvious risk factors or cause of ICH, if intraventricular, subarachnoid, perisylvian, or interhemispheric fissural blood is present, if abnormal calcification or prominent draining vein is present, if hematoma shape is unusual (noncircular), if edema is out of proportion to the early time the ICH is first imaged, if location of ICH is unusual, and if abnormal structure in the brain is visible.\textsuperscript{9,348,349} Need of angiography also depends on whether patient is candidate...
for neurosurgery, and angiography timing depends on urgency of surgery. If a suspicion of a structural abnormality remains after a negative CTA or MRA, an adjunct DSA is highly recommended after two to four weeks after the resolution of the hematoma, when vascular anomalies may become visible. In contrast to younger individuals, elderly patients with a history of hypertension and a thalamic, putaminal, or posterior fossa ICH are less likely to benefit from angiography.

Both contrast extravasation into the hematoma and presence of tiny enhancing foci, “spot sign” predict hematoma expansion and poor outcome. MRI with gadolinium as a contrast medium also gives insight to structural causes underlying ICH, such as a tumor. In general, an angiographic study is strongly recommended in ICH cases except in patients who are not candidates for active surgery or active treatment.

A detailed patient history and clinical examination are necessary in every ICH patient. A thorough examination should be conducted to detect signs of external trauma, pressure sores, and rhabdomyolysis, particularly in patients with depressed level of consciousness. A comprehensive laboratory evaluation covering a complete blood cell count, prothrombin time, activated partial thromboplastin time, serum electrolytes, liver function tests, glucose, glycosylated hemoglobin, C-reactive protein, creatinine, creatinine kinase, troponin-T, and coagulation profile, urea, nitrogen, and INR, is needed to detect underlying or complicating pathologies, such as infection, electrolyte disturbance, renal failure, rhabdomyolysis, or myocardial ischemia that are frequently treatable. Urine analysis, urine culture, and pregnancy test should be conducted in a woman of childbearing age, and toxicology screening should be executed in young and middle-aged patients to detect illicit drug use. Routine electrocardiography is also needed, for it may reveal prior cardiac injury indicating poor cardiac function, or left ventricular hypertrophy, an evidence of chronic hypertension, and chest radiograph, for it may reveal aspiration or other pulmonary process suffered, or an enlarged heart.

2.8 TREATMENT OF INTRACEREBRAL HEMORRHAGE

Acute treatment of ICH in intensive care stroke unit (ISCU) instead of general intensive care unit (ICU) or general ward has been consistently proved to reduce death and dependency, and is therefore strongly recommended. The reasons for this are most likely multifactorial, and include unified treatment strategies, dedicated multiprofessional teams familiar with the interactions between the injured brain and internal organ systems, and early access to stroke rehabilitation services. Substantial resources needed to treat patients with ICH include neurology, neurosurgery, neuroradiology, and critical care facilities. Medical complications, such as infections and venous thrombotic events are largely
preventable, and often serve as a measure of quality of standards in institutions with a stroke center designation.\textsuperscript{360} Having multiple complications strongly increase the risk of death.\textsuperscript{361} Combined treatment in ICSU and short-term ward with supported early discharge has been proposed to reduce mortality and complications in comparison to general medical ward.\textsuperscript{362} Unfortunately, some patients require being transferred back to the primary referring physician.\textsuperscript{363,364} A pro-active approach in order to prevent, identify, and treat any complications early in all stroke patients to improve outcome and reduce costs, therefore, is imperative.\textsuperscript{363,365,366}

\subsection*{2.8.1 PREHOSPITAL MANAGEMENT}

ICH is a medical emergency and therefore any delays in treatment may result in worse outcomes. Initial prehospital care should focus on ventilatory and cardiovascular management by maintaining airways, breathing, and circulation to prevent hypoxia and limit hematoma growth while maintaining cerebral perfusion.\textsuperscript{200} Quick delivery to the nearest emergency department (ED) is imperative in patients with abrupt neurological focal deficit, such as hemiparesis, impaired consciousness, or severe headache, which is presumed to be of vascular origin until proven otherwise.\textsuperscript{9,180} Finally, an advance notice to the ED of the forthcoming potential stroke patient by emergency medical service providers is of great value, since it shortens the time to CT in the ED.\textsuperscript{367}

\subsection*{2.8.2 INITIAL MANAGEMENT IN THE EMERGENCY DEPARTMENT}

It is of utmost importance that ED is prepared to treat patients with ICH or has a plan for swift transfer to a tertiary center.\textsuperscript{9} Majority of ICH patients are instable in the acute phase and require close monitoring, particularly on cardiovascular, respiratory, and neurologic status. Respiratory and hemodynamics may be compromised in patients with impaired consciousness. Cardiovascular instability associated with increased ICP needs immediate attention to avoid the damage caused by hypertension or hypotension in a patient with limited autoregulation.\textsuperscript{47} Initial management should focus on stabilization of cardiorespiratory function and treatment of intracranial complications. Intubation is needed, if other measures are insufficient to protect airways and sustain adequate ventilation in patients with decreasing consciousness (GCS$\leq$8) or impairment of reflexes protecting the airways. Approximately 30\% of patients with supratentorial ICH and majority of patients with infratentorial ICH require intubation.\textsuperscript{322} Low GCS has been identified as a factor predicting a need for tracheostomy in two studies.\textsuperscript{368,369} One of them also described hydrocephalus, midline-shift, thalamic location of hematoma, large hematoma...
volume, and intraventricular hemorrhage factors to associate with tracheostomy.\textsuperscript{368} Initiation of tracheostomy early could reduce the length of stay in hospital.\textsuperscript{369} Elective tracheostomy should be performed after intubation of 2 weeks at the latest.

Urgent brain CT scanning upon arrival to the ED is vital to differentiate between ischemic stroke, subarachnoid hemorrhage, and intracerebral hemorrhage, and to evaluate the characteristics of hemorrhage, such as location and volume, as well as to detect presence of IVH, edema, increased ICP, obstructive hydrocephalus, and imminent brain herniation.

\subsection*{2.8.3 REVERSAL OF ANTICOAGULATION}

Effects of vitamin K antagonists must be reversed in the ED.\textsuperscript{200,370-374} Due to the lack of data on RCTs investigating OAC reversal on ICH patients no uniform guidelines to treat these patients currently exist, but clinical observational and pharmacological data have led to infusion of vitamin K and fresh frozen plasma (FFP) for patients on vitamin K antagonists and intravenous protamine sulfate for patients on heparin, until INR of 1.2 has been reached.\textsuperscript{154,155,375-377} Vitamin K has a long-lasting effect by promoting endogenous clotting factor synthesis, but as it takes 6 hours to take effect, immediate use of fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) should as well be executed for vitamin K antagonist reversal. FFP contains factors II, VII, IX and X. It has short duration of action, and therefore large volumes may be required. If the patient’s cardiac reserve or intracranial compliance is limited, a sufficient amount of FFP cannot be given fast enough due to the risk of heart failure or increased ICP.\textsuperscript{373,376} FFP also has the general risks and disadvantages of blood transfusion.

PCCs are plasma products containing high concentrations of factors II, IX, and X, with or without factor VII.\textsuperscript{378-381} PCC can correct INR faster than FFP, and more effectively reduce hematoma growth, as well as to improve outcome in observational studies.\textsuperscript{71,301,382} Although dose related, PCCs are also associated with higher risk of thromboembolic complications than FFP.\textsuperscript{383} Recombinant factor VIIa is a new candidate for rapid reversal of vitamin K antagonist anticoagulation, but further randomized trials are needed to support its use in this indication.\textsuperscript{384-388} According to the recommendations of AHA and ESO, anticoagulation can be resumed between 7 and 14 days after the ICH in patients with high risk for thrombotic events (e.g. in patients with prosthetic valve).\textsuperscript{152,158,374,389-391}

No specific antidote yet exists for novel oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban), nor has there been RCTs investigating the treatment of ICH associated with them. Antidotes are expected to be available in the near future. Our knowledge regarding the treatment of ICH caused by thrombolytic therapy is limited also, but PCC, antifibrinolytics, cryoprecipitate, FFP, Vitamin K, aminocaproic acid
and platelets have been used. Antidotes are under development and currently some are already under investigation in clinical trials.

2.8.4 HEMOSTATIC TREATMENT

Halting the ongoing bleeding and hematoma expansion is crucial and should improve the outcome. Recombinant factor VIIa (rFVIIa) was originally developed as a treatment for hemophilic patients, and has since been investigated as a treatment to control bleeding in major trauma and surgical catastrophes. It was, therefore, proposed and later confirmed that early hemostatic therapy with rFVIIa prevents further hematoma expansion in patients with ICH. Freeman et al. demonstrated that rFVIIa rapidly lowers INR and appears safe to use in patients with OAC-associated ICH. Mayer et al. published promising results from a phase II trial, in which 399 patients with spontaneous ICH were randomized to receive placebo or 1 of 3 doses of rFVIIa within 3 hours after ictus. Those who received rFVIIa had less hematoma expansion, less edema, and smaller lesion total volume, in addition to 38% relative reduction in mortality and a dose-related trend toward less morbidity. Unfortunately, when rFVIIa was tested in a phase III trial (the FAST-trial) involving 821 patients from 22 countries with spontaneous ICH without coagulopathy, the treated group had less hematoma growth and improved outcome at 15 days, but the mortality and disability at 90 days were indifferent. Those treated had adversely more thrombotic events, such as myocardial infarction and cerebral infarction, which most likely resulted in increased mortality and morbidity at 90 days. RFVIIa also increases risk for deep vein thrombosis, a complication of ICH, associated with hospitalization and immobility. A fairly recent meta-analysis confirmed these findings. Routine use of rFVIIa, therefore, is not currently recommended for treatment of ICH. A post-hoc analysis of data from FAST-trial suggested that those under 70 years of age with hematoma volume less than 60ml might benefit from rFVIIa administered within 2.5 hours from symptom onset. More data are needed to confirm this, and to identify other patient subgroups which would benefit from rFVIIa. Efficacy of tranexamic acid for treatment for ICH is also being investigated by RCTs currently.

Platelet transfusion has been proposed for treatment of ICH in those receiving antiplatelet drugs. Replacing the non-functional thrombocytes with functional ones might increase the chance of hemostasis. Only one study, however, has so far investigated the use of thrombocytes for ICH, and the patient sample was rather small. In this study, platelet transfusion had no effect on platelet function or ICH progression. Two RCTs investigating platelet transfusion for ICH are currently ongoing.
Increased ICP may result after mass-effect caused by hematoma or surrounding edema, inflammation and destruction process caused by bleeding, or obstructive hydrocephalus from IVH or hematoma pressing CSF circulation system. Our knowledge regarding the frequency and optimal management of increased ICP in patients with ICH is, however, limited due to the lack of data. It is considered to be a major contributor to mortality and poor functional outcome after ICH, and detection and treatment of it, thus, is essential. ICP monitoring should be considered for all patients with large hemorrhage, IVH, GCS score of 8 or less, those patients whose condition is thought to be deteriorating due to elevated ICP, and those who need to be sedated or pharmacologically restrained and that way have compromised clinical monitoring, those with external ventricular drainage (EVD), and, obviously, those who are treated for increased ICP. Patients with small hematomas and limited IVH usually do not require treatment to lower ICP. According to one study preoperative monitoring of ICP associated with delayed neurological deterioration, decreased early mortality, and improved functional outcome at discharge, but no association was found with 6-month outcome.

Treatment of increased ICP should be directed at the underlying cause, particularly if caused by hydrocephalus or mass effect from the hematoma (see later section regarding these). We are still lacking evidence from RCTs to make strong recommendations on measures to lower ICP in adults with ICH. Hyperventilation is commonly used to treat ICP. In case of impending transtentorial herniation, a combination of hyperventilation and osmotherapy is frequently used, though data from RCTs is lacking.

Osmotherapy is the first-line medical treatment for increased ICP by reduction of perihematomal edema. It has been proved promising in animal models, and two nonrandomized clinical trials. Mannitol can be used, for it is believed to extract water from the cerebral extracellular space of both normal and edematous brain into the intravascular compartment. It should not be, however, used prophylactically or more than five days. Glycerol has been tested in one RCT on 107 ICH patients over four hours for six consecutive days, but no differences emerged at 6-month mortality or disability in comparison to placebo.

Neuromuscular paralysis combined with adequate sedation, as well as optimal head positioning can reduce elevated ICP. General anesthesia by barbiturares and induced hypothermia should only be used if other methods are ineffective. Pilot data indicated mild hypothermia (35°C) started within 12 hours from onset for 10 days reduced perihematomal edema and resulted in relatively high survival and functional outcome at 12 months. Several studies have investigated corticosteroid treatment in patients with ICH. A recent meta-analysis of these studies found
no beneficial effect of dexamethasone on 6-month case fatality.\textsuperscript{155} Corticosteroids are, therefore, not currently recommended for treatment of ICH.\textsuperscript{155}

2.8.6 TREATMENT OF INTRAVENTRICULAR HEMORRHAGE AND HYDROCEPHALUS

If ICH extends near to ventricles, i.e. originating from basal ganglia or being lobar with large volume, it may spread to CSF circulation (IVH).\textsuperscript{291,430} It has been reported being present among 40\% to 60\% of all ICH patients, but, interestingly, among only 3\% to 4\% of young patients.\textsuperscript{109,110,266,290,404,431-435} Delayed IVH seems to be less common and more benign than one discovered on admission.\textsuperscript{436}

The adverse effect may be related to IVH interfering with normal functions of CSF by causing localized lactic acidosis, and causing mass-effect on periventricular structures, which is associated with global hypoperfusion of overlying cortex.\textsuperscript{47,290,437} IVH blood clot may also cause obstruction of the CSF flow resulting in obstructive hydrocephalus, and even subsequent herniation, another predictor of poor outcome after ICH, usually manifesting with unconsciousness (Figure 10).\textsuperscript{279,291,404,405,434-436,438-442} In addition, it may cause inflammation of the choroid plexus leading to increased CSF production and that way worsening hydrocephalus, as well as cerebral vasospasm.\textsuperscript{439} Delayed communicating hydrocephalus may also follow IVH, when the degradation products of the blood clot generate an inflammatory response that gradually occludes the arachnoid granulations where CSF is absorbed.\textsuperscript{434}

![Figure 10. ICH and IVH causing obstructive hydrocephalus.](image)
Hydrocephalus (Figure 10) is a life-threatening condition, and should be treated with EVD of CSF through an intraventricular catheter, as an emergency measure, if necessary. EVD reduces ICP, but also carries a risk of clotting and infection. Intrathecal thrombolysis with urokinase is used to prevent and treat hydrocephalus, since it has been reported to reduce mortality and it seems acceptably safe. In accordance, a recent meta-analysis concluded intraventricular fibrinolysis being safe, and possibly reducing mortality, improving functional outcome, and diminishing the need for permanent shunting without increasing the risk of infection or rebleeding. The Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR) III RCT is still ongoing. Dutch Intraventricular Thrombolysis after Cerebral Hemorrhage study (DITCH) is also ongoing. ESO guidelines currently recommend considering the use of EVD combined with fibrinolytic agent in patients with spontaneous ICH with IVH and clinical and/or neuroradiological signs of hydrocephalus. Neuroendoscopic removal of blood clot in IVH has shown promising results, but no conclusive evidence yet exists regarding the preference between that and EVD. Too few data also exist to support open surgical evacuation, or lumbar drainage of IVH. Clot-removal techniques may improve in the future, as our knowledge on pathophysiological mechanisms associated with clot progression ameliorates, and minimally invasive surgical methods combined with atraumatic catheter-based clot removal are developed.

2.8.7 NEUROSURGICAL TREATMENT

Controversy has dominated the debate of neurosurgical evacuation of hematoma from the brain parenchyma, and the feasibility of surgical intervention still remains unanswered. Only with infratentorial hematomas, due to the risk of obstructive hydrocephalus, brainstem compression, and neurological deterioration, advantage of immediate surgical evacuation over EVD alone, particularly if ICH width is >3 cm, has been approved. Although reported evidence includes only few patient samples, a RCT to test this now would be unethical.

A meta-analysis of seven trials failed to show clear benefit of surgery for ICH. The results from the International Surgical Trial in Intracerebral Hemorrhage (STICH), showed no overall benefit or disadvantage from early surgery over initial conservative treatment. A post-hoc analysis of the STICH trial showed that patients with superficial hematomas and IVH absent benefit from surgery. A Cochrane review from 2008 including ten RCTs with 2059 patients concluded that surgical evacuation added to best medical management reduces mortality and disability. A meta-analysis on 12 studies published one year before that reported similar results. Later on, STICH II investigated whether surgical evacuation would
reduce mortality or disability at 6 months in patients with lobar ICH without IVH. The results, unfortunately, did not show significant difference in this RCT either.\textsuperscript{432} No significant benefit for survival or functional outcome was also reported by another recent study including ICH in other locations besides lobar ones.\textsuperscript{481} As a rule, young and middle-aged patients have been excluded from all these RCTs, as well as those with imminent herniation, and therefore recommendations for these patients remain uncertain.\textsuperscript{154} The role of decompressive hemicraniectomy in treatment of ICH is not established.\textsuperscript{482} Another unanswered issue is the optimal timing for surgery.\textsuperscript{433,483-489}

Minimally invasive surgery (MIS) is another option and offers some advantages over conventional craniotomy, including the possibility for local anesthesia, reduced operating time, and reduced tissue trauma.\textsuperscript{5,200,470} Studies on endoscopic clot evacuation have reported decreased mortality, but results concerning functional outcome have been contradictory.\textsuperscript{486,490-491} Stereotactic aspiration and thrombolysis of hematoma by image guidance is the second main type of MIS.\textsuperscript{489-498} Preliminary results from “Minimally Invasive Surgery Thrombolysis Plus Recombinant Tissue-type Plasminogen Activator for ICH Evacuation” (MISTIE) and results from “Stereotactic treatment of intracerebral hematoma by means of plasminogen activator” (SICHPA), showed greater clot resolution and decreased perihematomal edema with MIS and rtPA than with traditional medical management.\textsuperscript{485,499,500} According to a recent meta-analysis of 12 RCTs with 1955 patients, those with supratentorial ICH may benefit from MIS in comparison to conservative medical treatment and conventional craniotomy, particularly those of age between 30 and 80, those with superficial hematoma, GCS score ≥9, hematoma volume between 25 and 40 mL, and intervention performed within 72 hours after onset of symptoms.\textsuperscript{501} These findings are supported by another recent meta-analysis comparing stereotactic aspiration and craniotomy.\textsuperscript{502}

According to AHA guidelines, last released in 2010, before above-mentioned meta-analyses, the effectiveness of minimally invasive clot evacuation utilizing either endoscopic or stereotactic aspiration with or without thrombolytic usage is uncertain due to greatly depending on the accurate catheter placement and, therefore, considered investigational.\textsuperscript{154} The MISTICH and ICES trials are RCTs currently in progress to define whether MIS could improve the prognosis of ICH in comparison to craniotomy, and ECMOH is a RCT investigating whether endoscopic surgery is better than conservative treatment for patients with moderate-volume hematomas in the basal ganglia.\textsuperscript{503,504}

Surgical intervention may be needed in case the underlying etiology of ICH is structural, such as AVM or cavernous hemangioma, visualized by CT angiography or MRI. Ruptured AVMs can be treated with microsurgery, endovascular treatment, stereotactic irradiation, or by observation with medical management, according to the commonly accepted Spetzler-Martin classification.\textsuperscript{505-511} The optimal strategy for
management is still under debate. With hemorrhagic cavernomas, microsurgery has been declared as the only healing therapy.\textsuperscript{512-515}

Current practice favors surgical intervention in case of ICH being superficial, clot volume being between 20 and 80 ml, worsening neurological status, patient being of young age, and if ICH is causing midline shift or increased ICP. Opposing factors include hematoma being small (<2 cm) in an alert patient, and hematoma being extensive in a moribund patient, often causing coma with poor motor responses and unreactive pupils.\textsuperscript{466} Individualized decisions account also age, site of hematoma, underlying etiology and the presence of accompanying systemic complications.\textsuperscript{466} Brainstem or thalamic hemorrhages are usually not evacuated, due to the poor consequences.\textsuperscript{180} While the decision to operate a supratentorial ICH is currently based on local traditions, the need for clear and strong international guidelines is obvious.

### 2.8.8 Blood Pressure Management

High BP commonly occurs with ICH and usually persists for few days before returning to baseline.\textsuperscript{23} At presentation, 75% of ICH patients have systolic blood pressure (BP) >140 mmHg, and 20% have >180 mmHg.\textsuperscript{259} High BP is caused by the activation of a combination of neuroendocrine system (catecholamines), renin-angiotensin axis, and glucocorticoid system involved in a nonspecific response to stress, and further worsened by the patients’ chronic hypertension.\textsuperscript{9,309,516} Brainstem-mediated release of catecholamines may be induced by increased ICP. This hypothesized “Cushing reflex” is a protective response aiming to preserve cerebral perfusion.\textsuperscript{516} However, high BP on admission is associated with hematoma expansion and poor outcome.\textsuperscript{64,68,69,517-523} It may also worsen cerebral edema. The rationale for lowering BP, therefore, is to decrease ongoing bleeding and reduce hematoma expansion. It has been suggested that overaggressive treatment of BP may, however, decrease CPP and worsen brain injury, particularly if increased ICP is present, for it may hamper autoregulation.\textsuperscript{524,525} The absence of ischemic penumbra around a small-volume ICH means that sudden therapeutic reduction of BP does not necessarily involve the same risks that are well known with ischemic stroke. Studies on autoregulation, cerebral perfusion, and one randomized study showed no significant reduction in cerebral blood flow if the pressure is lowered 20% or less in the acute phase.\textsuperscript{6,526-528}

One observational study reported better outcomes in ICH patients whose BP was maintained below mean arterial pressure (MAP) of 125 mmHg.\textsuperscript{308} Another observational study reported hematoma expansion in 9% of patients when systolic BP was maintained <150 mmHg, and 30% of patients with BP maintained <160 mmHg or a higher threshold.\textsuperscript{523} Two pilot RCTs and one large RCT have investigated BP management on outcome after ICH.\textsuperscript{65,529-531} The investigators from ATACH study
and INTERACT study both reported early BP-lowering treatment being clinically feasible and well tolerated. Results also inferred it may reduce hematoma growth. These results were only recently confirmed in a large RCT (INTERACT2) concluding that intensive lowering of BP, with a target systolic level of <140 mmHg within 1 hour did not increase mortality. Unfortunately, treatment of BP did not either reduce mortality or severe disability at 90 days, but indicated improved functional outcomes. Candesartan at one to seven days following stroke did not improve outcome after ischemic stroke or ICH. More evidence is needed regarding the utility of hyperacute BP reduction after ICH, and therefore ATACH-2, ENOS, and PATICH are RCTs currently investigating BP treatment on ICH.

In 2014 updated guidelines based on meta-analysis of RCTs ESO concludes that intensive BP reduction with target systolic BP <140 mmHg is safe and may be superior to a target of < 180 mmHg. The AHA guidelines state that the management of hypertension with continuous infusion of antihypertensive drugs such as labetalol, esmolol, or nicardipine, should be aggressive if systolic blood pressure (SBP) is >200 mmHg or mean arterial blood pressure (MAP) is >150 mmHg and modest if SBP is >180 mmHg or MAP is >130 mmHg and there is no evidence or suspicion of increased ICP, in which case the goal is 160/90 mmHg and MAP 110 mmHg. While using intravenous medication to control BP, patient should be re-examined every 15 minutes. The optimal timing of conversion from IV to oral antihypertensive therapy is unclear, but it is usually recommended between 24 to 72 hours with stable patients.

2.8.9 PREVENTION AND MANAGEMENT OF SEIZURES

Post-stroke seizure and post-stroke epilepsy may occur as the presenting symptom or complication of hemorrhagic or ischemic stroke. Early seizures are more common in patients with ICH in comparison to other stroke subtypes, and it also associates with lobar lesion location. Clinical seizures occur in 2.7 to 25% of patients with ICH, with most of them occurring near ICH onset. Seizure occurring more than 2 weeks after ICH onset is higher risk for recurrent seizure than one occurring within 2 weeks, and long-term prophylactic anticonvulsant treatment may be needed. Chronic epilepsy develops in 13% of 30-day to 2-year survivors and in 7% of the 2- to 5-year survivors. Electrographic seizures have been reported to occur in 28 to 31%, despite most having received prophylactic anticonvulsants. The clinical impact of those subclinical seizures detected only in EEG is uncertain. Seizures occurring within one week after ictus are defined as early seizures, and a rate of 14% of early seizures has been reported after ICH. One RCT investigated the adverse effects of diazepam. These investigators reported diazepam being associated with increased pneumonia and
death. Investigators from another RCT found that patients receiving valproic acid were less likely to suffer from early seizures, but overall seizure rates by one-year follow-up did not differ.552 While early seizures are not associated with worsened neurological outcome or mortality at short- or long-term follow-up, phenytoin use and prophylactic antiepileptic drug (AED) use have been reported to associate with worse outcome after ICH.536,547,550,553-556 In one large single-center study prophylactic AED use significantly reduced clinical seizures in patients with lobar ICH.557 AHA guidelines state that only patients with clinical seizures or electrographic seizures accompanied by change in mental status should be treated with AED. Patients with depressed mental status out of proportion to the degree of brain injury should be monitored by continuous EEG. Both AHA and ESO guidelines state, that due to the lack of RCTs, utility and optimal use of AED remains unresolved.154-155 Intravenous lorazepam is usually the first-line drug for acute management of seizure, and AED treatment should follow the local hospital guidelines.

2.8.10 GLYCEMIC CONTROL

Hyperglycemia is common after ICH and associates with increased ICU and hospital length of stay and worsened outcome.17,558 Hyperglycemia is considered deleterious to damaged brain, but the exact underlying mechanisms are yet to be resolved.312,313,559,560 Often present among patients with ischemic stroke, it is associated with poor outcome, and recommended by AHA and ESO guidelines to be treated with intravenous insulin.561-563 Hyperglycemia has been reported to worsen the outcome after ICH also with or without diabetes.312,313,564,565 High blood glucose level has been associated with more profound brain edema and perihematomal cell death in experimental ICH, but the slight retrospective evidence did not support this, nor was it associated with hematoma expansion.313,566 Excessive use of insulin among patients with ischemic stroke or ICH may result in hypoglycemia with reduced cerebral extracellular glucose concentration, which also causes increased mortality.567-575 Rapid decrease in serum glucose level also decreases serum osmolality and may theoretically worsen cerebral edema. Some guidelines recommend lowering glucose levels if exceeding 10.0 mmol/L (180 mg/dl) with avoiding hypoglycemia and large swings in blood glucose concentration.5,200 Glucose-containing fluids should be avoided in ICH patients unless they are hypoglycemic. Other systemic medical complications, such as infections and fever, may also cause hyperglycemia, and should be treated accordingly. No uniform guidelines yet exist for the treatment of ICH-associated hyperglycemia and the optimal criteria, target levels, and method of treatment of hyperglycemia are not solidly defined.
2.8.11 FLUID MANAGEMENT AND ELECTROLYTE IMBALANCE

Electrolyte disturbances may arise after brain injury due to the major role of the central nervous system on controlling sodium, potassium, chloride, calcium, magnesium, and water homeostasis (CSWS, Cerebral Salt Wasting Syndrome), dehydration, as well as cardiac failure. Hypo- and hypervolemia both have harmful effects on cerebral perfusion and functioning of other organs. Establishing and maintaining normovolemia is, therefore, the main goal of fluid management in acute ICH.

A 15.6% prevalence of hyponatremia among ICH patients has been reported and it has been identified as a predictor of in-hospital mortality in two recent studies. Hypnatremia resulted in 57% one-month mortality among ischemic and hemorrhagic stroke. Interestingly, the latter investigators reported hyponatremia and hypernatremia being associated with cortical lesion instead of basal ganglia or infratentorial lesion with ischemic stroke, but hypernatremia being associated with brain stem lesion with ICH. Data on other electrolyte disturbances and their effect on ICH prognosis are still very limited, but sodium and potassium imbalance have been reported to associate with worse outcomes after ischemic stroke.

Rapid increase of natrium concentration may cause fatal pontine myelinolysis, while potassium disturbances may cause cardiac arrhythmias.

Isotonic infusion of intravenous fluids without glucose should be used in general to maintain adequate intravascular volume to optimize cerebral perfusion. Hypotonic solutions are contraindicated, because of the risk of increase of brain edema as a consequence of reduced plasma osmolality, and high glucose concentration has detrimental effects on injured brain. Electrolyte disturbances should be investigated and corrected according to the severity, suspected duration, and cause. Severe hyperpotassemia may require temporary intravenous glucose and insulin treatment.

2.8.12 CONTROLLING BODY TEMPERATURE

Central fever and infections may complicate ICH, and fever is an independent predictor of poor outcome in these patients. Body temperature should be, therefore, maintained at normal to near-normal levels. Acetaminophen or cooling blankets can be used to treat hyperthermia >38.5°C. Catheter-based cooling techniques have been tested in two RCTs, but the number of ICH patients has been too small to evaluate their effect on clinical outcome. These may be used with persistent fever refractory to acetaminophen and without infectious cause. Some patients might even benefit from hypothermia, which acts as anti-inflammatory cytokine, reduces oxidative stress, and has been reported to improve the outcome. Our knowledge on hypothermia for ICH, however, is still
minimal, and guidelines recommend targeting normothermia. Due to the lack of RCTs, no strong recommendations are currently available for optimal treatment of fever in patients with ICH. Early treatment with antipyretics may be considered in clinical practice, but preventive treatment is not recommended. Appropriate cultures and smears (tracheal, blood, urine, CSF) should be obtained, and patient physically examined to determine the source of infection in febrile patients and in those at risk for infection, as well as appropriate antibiotics initiated.

2.8.13 VENOUS THROMBOEMBOLISM PROPHYLAXIS AND TREATMENT

In the acute phase of ICH, patients are most often immobilized due to neurological deficit or impaired consciousness, putting them at risk for deep vein thrombosis (DVT), and subsequently for pulmonary embolism (PE). Without any preventative measures DVT develops in up to 50% of ICH patients. Women and those of African American ethnicity are in higher risk for DVT. Measuring D-dimer after 2 weeks from ICH may be useful to detect DVT. As many as 30% of patients with pulmonary embolism show no evidence of lower extremity DVT. Thigh-high or below-knee elastic stockings, intermittent pneumatic compression (IPC), and anticoagulation by subcutaneous low-molecular-weight heparin (LMWH) and unfractionated heparin have been investigated in multiple RCTs for DVT prevention after ICH. Elastic stockings alone are ineffective, while IPC has been proved superior in comparison to other methods and is currently recommended by AHA and ESO both to improve outcome and reduce the risk of DVT in immobile patients with ICH. LMWH seems to be safe initiated on the second day after ICH onset in neurologically stable patients, but may not be more effective than elastic stockings. IPC and elastic stockings are rational choices particularly in patients with ongoing bleeding demonstrated by hematoma expansion. Inferior vena cava filters or 5 to 10-day course of full-dose LMWH followed by 3-months of low-dose LMWH is preferable than vitamin K antagonist for DVT treatment.

2.8.14 INFECTION COMPLICATIONS

Stroke induces systemic immunosuppression by cellular pathways. Infections are frequently complicating the early course and recovery from stroke, and seem to be more often present in patients with ICH than those with ischemic stroke. A meta-analysis of 87 studies involving 137817 patients investigated infections and other complications among stroke patients. The key message of these studies is that infections are common, most often include pneumonia and urinary tract infection (UTI), and associate with higher mortality, worse functional outcome,
and increased hospital length of stay. Same findings were reported in a recent study focusing on infections among ICH patients.\textsuperscript{549} Stroke severity is the most substantial factor that increases risk for all complications, including infections.\textsuperscript{633,637,640-643}

In addition to cellular and biochemical mechanisms of immunosuppression induced by ICH, dysphagia, mechanical ventilation, tracheostomy, and tube feeding have also been reported to increase risk for pneumonia.\textsuperscript{650-652} Impaired consciousness is the single most important risk factor for pneumonia. Dysphagia is a frequent symptom of ischemic and hemorrhagic stroke both, being present in up to 50\% of stroke patients, and may cause bronchoaspiration with subsequent pneumonia.\textsuperscript{653} Pneumonia develops in 14\% to 20\% of all ICH patients, and associates with increased morbidity, mortality, and length of stay.\textsuperscript{338,610,650-652,654,655} Pneumonia plays an important role, since it increases risk for other complications among ICH patients, such as gastrointestinal bleeding, decubitus ulcer, DVT, atrial fibrillation, and recurrent stroke.\textsuperscript{652}

UTI complicates the course of ICH in up to 21\% of patients.\textsuperscript{654} Stroke-induced immunosuppression, bladder dysfunction, use of Foley urinary catheter, and female gender predispose for UTI.\textsuperscript{641,656} Even without a catheter, stroke patients have more than double the odds of developing UTI in comparison to general medical and surgical populations.\textsuperscript{657} UTI alone predicts poor outcome, but may also progress into sepsis with fever, and cause delirium, even stronger predictors of increased mortality.\textsuperscript{586,654,658-660} Several strategies have been proposed to reduce UTI after stroke. Prophylactic use of antibiotics has been studied in few RCTs, but due to contradictory findings, and questions regarding the risk of selecting resistant organisms, feasibility of prophylaxis has remained unanswered.\textsuperscript{656,661-663} Unnecessary use of Foley catheters should be avoided. New strategies such as condom catheters and antiseptic/antibiotic-covered catheters are under development.

2.8.15 CARDIAC COMPLICATIONS

Cardiorespiratory instability usually occurs within 24 hours following ICH onset.\textsuperscript{47,398} Knowledge regarding occurrence, impact, and underlying mechanisms of cardiac complications after ICH, as well as strategies to prevent them is still limited. Severe in-hospital cardiac events include myocardial infarction (MI), heart failure, ventricular arrhythmias, and sudden death due to cardiac arrest.\textsuperscript{659} They likely result from brain injury causing disturbance in central autonomic control. Post-stroke cardiac complications result in higher mortality, need for intensive monitoring, and increased length of stay with higher costs.\textsuperscript{664-668} Between 2\% to 6\% of patients die from a cardiac cause within three months after ischemic stroke, and up to 19\% suffer a serious cardiac adverse event.\textsuperscript{365,646,668-672} MI has been reported occurring in 2\% within 3 months after ICH.\textsuperscript{606} In-hospital occurrence of MI after ischemic stroke
or ICH has been reported being between 1% and 5%. Potentially lethal arrhythmias in telemetric monitoring was seen among 1% in patients with ischemic stroke in one study, but another study reported up 25% of patients with acute cerebrovascular event having significant cardiac arrhythmias. Arrhythmias may precede or be caused by heart failure, which may further lead to neurogenic pulmonary edema. Cardiovascular comorbidities, higher age and stroke severity have been identified to increase the risk of cardiac morbidity and mortality after stroke. Troponin elevation, atrial fibrillation, and ischemic ECG changes may be associated with higher in-hospital mortality. Both troponin T elevation and ECG changes, however, are frequent after stroke, and most often are unrelated to acute myocardial ischemia. Elevated troponin I independently associates with higher in-hospital mortality and cardiac causes of death after ICH, but is present only in 1% of ICH patients. Takotsubo cardiomyopathy is a phenomenon caused by stress, in which sudden reversible weakening of left ventricle occurs. ICH may provoke Takotsubo cardiomyopathy, but the rates have not been investigated. It has been reported to occur in 1% of patients with ischemic stroke, with most occurring during 10 hours after onset, but some even after 12 days, and female gender and insular damage being risk factors. It may cause heart failure, ventricular arrhythmias, and ventricular rupture, all potentially lethal, particularly in vulnerable ICH patients. Most sudden deaths and serious non-fatal cardiac events after stroke are probably due to interactions between cardiovascular and neurological causes that are not yet fully understood. Telemetric monitoring and readiness for cardiorespiratory support are, therefore, vital after stroke.

2.8.16 RENAL FAILURE

More evidence exists on renal failure being associated with poor outcome after ischemic stroke, but only few studies have investigated renal failure among ICH patients. Chronic kidney disease has been reported in as many as one third of ICH patients, and acute renal failure in 7%, more often among women, elderly, and those with other comorbidities, such as diabetes. Chronic kidney disease and renal failure seem to increase mortality by kidney function: the lower the glomerular filtration rate (GFR) is, the higher the mortality rates are. The proportions of renal failure preceding and appearing during acute ICH, the pathophysiological mechanisms by which ICH affects kidney function, and the strategies of prevention and treatment to address this issue and improve outcome remain unresolved.
2.8.17 NEUROPROTECTION

Neuroprotective strategies to reduce secondary brain injury after ICH, caused by oxidative stress, inflammation, and blood degradation, has been investigated in animal studies, including iron chelation by deferoxamine, heme oxygenase inhibition, blocking inflammatory pathways, inhibition of toxic neurotransmitters, antioxidants, matrix metalloproteinase inhibition, and antiapoptotic strategies. The impact of microglia and macrophages in hematoma resolution is being investigated. Autophagy may be a cellular process that could be targeted to prevent apoptosis. So far, only rosuvastatin has shown beneficial effects, but further studies are ongoing.

2.8.18 OTHER MEDICAL MANAGEMENT

ICH patients are at risk of stress-induced gastric ulcers, which has been reported to develop in approximately 20% of these patients. Prophylactic treatment with H₂ receptor antagonists or proton pump inhibitors is, therefore, indicated. No uniform guidelines based on RCTs addressing prevention of gastric hemorrhages on ICH patients yet exist. ICH may also cause delirium, stupor, disorientation, and agitation, which may further result in hyperactivity – distressing to other patients, caregivers, and family, and may lead to self-injury. Psychological support is paramount, but prudent use of minor and major tranquilizers, such as short-acting benzodiazepines or propofol may be necessary for some patients. Analgesics and neuroleptics may be added, if needed. Titration of doses and regimen according to clinical needs is of primary importance. Body posture in bedridden patients must be altered and skin checked for pressure sores regularly.

2.8.19 NUTRITION

Mobilization out of bed is recommended soon after ICH according to patients’ tolerance to reduce risk of bronchoaspiration and effectively initiate rehabilitation. Tracheostomized patients are not protected from bronchoaspiration. Dysphagia has been reported to be present in as much as 50% of stroke patients, and causatively to associate with aspiration pneumonia. It is imperative that early nutrition is managed by nasogastric tube, and oral nutrition is cautiously and gradually resumed after evaluation and with the help of a speech therapist when the patient can swallow increasing volumes of water without coughing or changing of the voice. Until then, bedside water swallow test should be repeated daily. A proposition has been made that tube feeding should be halted for 4 hours during the night when the risk of gastric reflux is higher. If the need for nasogastric tube is prolonged due to
impaired consciousness parenteral nutrition admixture should be complemented. In case oral nutrition cannot be resumed within 2-4 weeks, percutaneous placement of an endogastric tube (PEG) may be beneficial. Weight loss of 5-10% in the first weeks after stroke is frequent.

2.9 LONG-TERM OUTCOME OF INTRACEREBRAL HEMORRHAGE

2.9.1 MORTALITY

As mentioned earlier, ICH is the most catastrophic subtype of strokes, with one-month mortality of 40%, and great proportion of the survivors left with functional impairment. Among the one-month survivors of ICH, risk for long-term mortality is highest in the first year following: 4.5-fold fold the risk in people from the general population. An average annual risk of death of 9.1% has been reported for long-term mortality among one-month survivors of stroke. In the subgroup analysis of this study, mortality was similar between those who had suffered ischemic stroke and those with ICH. According to another study, annual rate of vascular death in acute phase survivors of ICH is 3.2%. Among the one-month survivors of ICH, annual rate of vascular death in acute phase survivors of ICH is 3.2%. Five-year and 10-year mortality reached up to 71% and 82%, respectively. Long-term mortality among stroke patients is mainly due to cardiovascular diseases, but also cancer, other diseases, accidents, and suicide are other significant causes of death in ICH patients. Higher age, male gender, diabetes, and heart failure have been reported to increase the risk of long-term mortality after ICH.

Studies on ischemic stroke in young adults have revealed that young people with ischemic stroke have lower mortality, 7.9% at five years among one-month survivors, lower than their elder counterparts, but higher than general population. The very recent FUTURE study was the first to investigate long-term mortality after ICH at young age: among 91 one-month survivors 5-year, 10-year, and 20-year cumulative mortality were 6.1%, 10.3%, and 13.7%, respectively, with annual risk ranging between 0.6% to 2.9%. Half of the deaths of young victims of ischemic stroke are attributable to a vascular origin, but no similar data exist for young ICH patients.
2.9.2 STROKE RECURRENCE AND SECONDARY PREVENTION

Annual rate of ICH recurrence has been reported ranging from 1.3% to 7.4% by several studies. Investigators of one, relatively large, population-based study reported cumulative 5- and 10-year rates of recurrence of 9.6% and 14.2%, respectively. Age ≥65 years, lobar hematoma location, and previous ischemic stroke have been found to associate with increased risk for recurrence in multiple reports. Lobar location seems to be the most significant single risk factor with a 3.8-fold increased risk of recurrence. Hypertension has been reported associating with recurrence in some studies. IVH, OAC use, diuretic monotherapy, α- or β-blocker monotherapy, poor functional outcome after initial ICH, basal ganglion location of hematoma, and absence of hyperlipidemia, however, have been reported associating with recurrence in single studies. Diabetes is a risk factor known to increase risk for recurrent ischemic stroke, and a tendency with recurrent ICH was reported by one study. The only investigators to address ICH recurrence in the young very recently reported 10-year cumulative recurrence rate of 12.2%, all with the index ICH attributable to structural vascular malformations. Approximately one third of the recurrent ICH occur within the first year following the initial ICH, but it may occur even up to 10 years. Mean and median interval between initial and recurrent ICH has been reported 30 (range from 2 to 158) and 33 (range from 1 to 120) months. Among those with hypertensive ICH, initial and recurrent hemorrhages most often have different site of bleeding. Patients with ICH have even higher risk for ischemic stroke than ICH recurrence. Annual occurrence of vascular events in total, including all stroke subtypes and MI, is almost three-fold to ICH-recurrence, with higher age and male gender identified as predictors.

Studies on stroke, particularly those of ischemic stroke in the young, have emphasized the need for aggressive stroke secondary prevention, likely as a lifelong endeavor. Hypertension is the single most important target for prevention of ICH recurrence. Specific data on the optimal BP are not available, but AHA recommends targeting <140/90, and <130/80 in the presence of diabetes or chronic kidney disease. Risk of recurrent ICH probably outweighs the risk of thromboembolism in patients with atrial fibrillation, and OAC use, therefore, should be avoided. Antiplatelet agents have substantially smaller effect on ICH recurrence and severity suggesting their use being safer than OAC. As with primary prevention of ICH, appropriately frequent physical activity and avoiding smoking most likely are beneficial for secondary prevention also, though no published data exist.
2.9.3 REHABILITATION AND RECOVERY

Neuronal damage caused by ICH results in symptoms and subsequent disabilities depending on the location and magnitude of the brain injury. These disabilities may often present as one-sided motor paresis of upper, lower, or both extremities, paresthesia, dysarthria, dysphasia, and visual impairment. Other symptoms include neglect, vertigo, headache, central poststroke pain (CPSP), impaired memory, and other neuropsychological or cognitive handicaps. A recent study reported better survival and functional outcomes in patients for whom early rehabilitation was initiated within 48 hours following ICH. Initial evaluation by physical therapist, occupational therapist, speech therapist, and neuropsychologist is of grave importance, and intensive and well-organized multidisciplinary rehabilitation should begin in ICSU, since it has been shown to improve survival, recovery, and returning home. Early mobilization has been proposed to decrease complications, but avoiding falls, another complication of stroke, is also important. Once the patient is stable, no evidence of neurological deterioration is observed for several days, and patient’s condition improves, rehabilitation may be continued either as outpatient or in a rehabilitation center. Early supported discharge and home-based rehabilitation have shown to be cost-effective and to produce comparable results to conventional outpatient rehabilitation. Recovery is more rapid in the first weeks, but may continue for many months after ICH. Speed and grade of recovery are individual, and no hard rule exists on when recovery is over. Cognition, mood, motivation, and social support all are important for recovery. Since the nature of poststroke disability is complex and includes physical and mental impediments, rehabilitation programs should be individually tailored and to enable lifestyle changes. Recovery after ICH can be improved through progress in the field of neurorehabilitation. Depending on stroke severity, a number of important long-term consequences such as sick leave, prohibition for driving, and early retirement must be considered in working-age patients. Available consultation of social worker concerning the patients’ financial affairs is also in the best interest of the patient.

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Glasgow Outcome Scale, mRS, and Barthel Index have commonly been used to measure the functional outcome. The independence rates have varied between 12% and 39%, but different end-points have been used in the studies. Approximately half of the survivors remain dependent on others on the daily living. Recovery differs between ischemic stroke and ICH, and ICH has been found to independently predict poor neurological outcome. Results, however, are partly contradictory, since two studies have reported ICH patients...
making greater gains, while another study reported ICH patients to improve until 10 weeks post-stroke, and ischemic stroke patients until 26 weeks. Another study, however, reported mRS score increasing in 34% of acute phase survivors of ICH between hospital discharge and 12 months, decreasing in 22%, and a proportion of patients improving even after 6 months. Same investigators found that besides early mortality, ICH score accurately predicts functional outcome at 12 months. This is in line with other reports. In addition, pre-ICH cognitive impairment also predicts poor functional outcome. As many of the strongly disabled patients die after the acute phase, the relative proportion of functionally independent patients increases over time. Spasticity may develop in those with motor hemiparesis – its prevalence in unselected ICH patients at 12 months is 36%.

Young adults are usually living the most active and demanding phase of their lives, and often have many responsibilities. Many quality-weighted-years are, therefore, lost and the economic consequences for society are dire, when young adult becomes a victim of stroke. Treatment for stroke survivors, therefore, is of grave importance. This may include treatment for central post-stroke pain (CPSP), hemiplegic shoulder pain (HSP), painful spasticity, tension-type headache, fatigue, incontinence, sexual dysfunction, and sleep-disordered breathing. The quality of life varies markedly among young victims of stroke. A deficit persists in 61%. Only one study has been composed to investigate young-onset ICH in particular. Among the 30-day survivors, poor functional outcome (mRS >2) was present in half of the survivors at 30 days. The proportion remained approximately the same in the long-term follow-up. Only 18% of the survivors, however, were dependent on daily life, when measured with Instrumental Activities of Daily Living (<8). In a Dutch cohort, after eight years from ICH, the young survivors still had 2- to 3-fold risk for unemployment than the general population.

2.9.4 POST-STROKE DEPRESSION

Post-stroke depression (PSD), often measured by Beck Depression Index II (BDI-II), is a rather common neuropsychiatric complication of ischemic and hemorrhagic stroke. Mood depression is considered the strongest predictor of quality of life in stroke survivors. PSD occurring in approximately 30% of general stroke survivors has been reported by several studies and one meta-analysis. Among ICH patient cohorts, depressed mood (Hamilton Depression Rating Scale score >10) has been present in 20% of 596 patients in one study, and PSD detected by Zung Self-Rating Depression Scale in five out of twelve patients (42%). It has been reported occurring more often in the young stroke patients, females, and those with more severe symptoms, and hypertension. PSD also associates with increased cognitive impairment, disability, falls, and short- and long-term
mortality, as well as worse rehabilitation outcome. Conversely, absence of PSD predicts ability to return to work in the young, and recovery from PSD associates with functional improvement.

PSD most likely is caused by combination of the brain injury and psychological reaction to the illness. Etiology of PSD has been proposed as a “complex mixture of prestroke personal and social factors, and stroke-induced social, emotional, and intellectual handicap”. One study reported symptoms of PSD being stable and chronic, while other studies have reported the prevalence of PSD being rather dynamic with some patients recovering and others becoming chronically affected. A meta-analysis studied whether the lesion location associates with PSD, but no association was found. Multidisciplinary approach has been promoted to treat PSD.

A major proportion of patients with PSD, unfortunately, go untreated. Antidepressants have been reported to improve the outcome in patients even without clinical depression suggesting their possible beneficial effects on neural recovery. Even prophylactic use of antidepressants has been reported to improve the outcome, but the optimal timing and duration of the medication, and the best benefiting patients for the use of antidepressants is yet to be resolved. In addition, multidisciplinary approach has been promoted to treat PSD. Reports on cognitive therapy have shown promising results. In addition to treating PSD, fluoxetine has also been reported to enhance motor recovery after ischemic stroke by modulating neural recovery, which may prove useful in the future.

Anxiety, pain, and cognitive dysfunction also play a role in young ICH patients’ outcome. A recent retrospective study showed that 19% of young ischemic stroke patients had anxiety after 12 years follow up. Post-stroke fatigue occurs in 41% to 45% of stroke survivors, is predicted by anxiety and depression symptoms, and associates with poor functional outcome. Cognitive impairment is present among 50% of the survivors of ischemic stroke at young age, and subjective memory failures among as many as 86%.
3 AIMS OF THE STUDY

I To define risk factors, etiology, clinical presentation, and neuroimaging characteristics in young patients with first-ever ICH and compare these features with older patients.

II To determine baseline clinical, treatment, and neuroimaging characteristics associated with increased early mortality in young patients with ICH.

III To describe acute medical complications and their impact on early mortality in young ICH patients.

IV To investigate long-term depression after young-onset ICH.

V To assess long-term mortality rates, functional outcome, and predictors of poor outcome for ICH in younger patients.
4 PATIENTS AND METHODS

At first, a retrospective single-center hospital-based cohort study of consecutive patients aged between 16 and 49 years with a first-ever non-traumatic ICH treated in the Helsinki University Hospital (HUH), Departments of Neurology, Neurosurgery, or both, between January 1, 2000 and March 31, 2010 was performed, the Helsinki ICH in the Young Study. Consent for registration was not required by the Finnish legislation as this was a registry-based study with no patient contact. Thereafter, we executed a prospective follow-up study of that cohort of patients. Written informed consent for participation was obtained from the surviving patients taking part in the follow-up study. Both studies have been approved by the Ethics Committee and institutional authorities of HUH.

Our hospital serves a population of 1.5 million inhabitants and has the only 24/7 neurological and neurosurgical emergency units in the catchment area. All neurological emergency cases, particularly the young patients, are brought to emergency rooms at either of these units within our hospital’s catchment area – either directly or via other hospitals. As >95% of acute stroke cases in Finland are hospitalized, therefore, our series closely resembles a population-based study.44

4.1 PATIENT SELECTION

A total of 1325 patients aged 16 to 49, who at any time during their hospitalization or outpatient visit had an International Classification of Diseases, 10th Revision (ICD-10) diagnosis code of Q28.1, Q28.3, I60.8, I61, I67.3, I67.4, I67.5, I67.6, I67.7, I67.8, I67.9, I68 or I78, were screened by evaluation of patient records and imaging databases (Table 5). This set of ICD-10 codes was designed to cover all potential conditions where an ICH could emerge as e.g. AVM with ICH. Patients with imaging-verified first-ever episode of non-traumatic ICH were considered eligible. We excluded patients with ICH accompanied by SAH or subdural hemorrhage. Those with an aneurysm as the underlying cause of ICH were excluded, even if no clear SAH was present, since a small SAH always occurs in the rupture of cerebral aneurysm. Those treated initially outside of HUH and those with missing medical records were excluded. Patients with hemorrhagic transformation of a cerebral infarction with or without thrombolytic therapy were not screened and thus not included, since their primary disease was brain infarction. Those with a tumor or CVT as the cause of ICH were included. Those with a structural lesion without a bleeding episode were ineligible. Excluded patients appear in Table 6. Included patients in the Helsinki ICH in the Young Study amounted 336. For comparisons,
a cohort of ICH patients aged >50 years was used. This cohort includes patients treated due to non-traumatic first-ever ICH in HUH between January 2005, and March 2010, and data regarding this cohort was gathered similarly by retrospective analysis of medical chart notes, imaging, and laboratory databases.\textsuperscript{814}

After an initial determination of mortality from our national cause-of-death registry, surviving patients received an invitation to participate in the follow-up study, with those providing their written informed consent being included (Figure 11).

Table 5. ICD-10 codes used to identify patients from the hospital discharge registry.

<table>
<thead>
<tr>
<th>ICD-10 code</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q28.1</td>
<td>Precerebral aneurysm or arteriovenous malformation</td>
</tr>
<tr>
<td>Q28.3</td>
<td>Cerebral aneurysm or arteriovenous malformation</td>
</tr>
<tr>
<td>I60.8</td>
<td>Rupture of cerebral arteriovenous malformation</td>
</tr>
<tr>
<td>I61</td>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>I67.3</td>
<td>Progressive vascular leukoencephalopathy</td>
</tr>
<tr>
<td>I67.4</td>
<td>Hypertensive encephalopathy</td>
</tr>
<tr>
<td>I67.5</td>
<td>Moyamoya disease</td>
</tr>
<tr>
<td>I67.6</td>
<td>Nonpyogenic thrombosis of intracranial venous system</td>
</tr>
<tr>
<td>I67.7</td>
<td>Cerebral arteritis, not elsewhere classified</td>
</tr>
<tr>
<td>I67.8</td>
<td>Other specified cerebrovascular diseases</td>
</tr>
<tr>
<td>I67.9</td>
<td>Cerebrovascular disease, unspecified</td>
</tr>
<tr>
<td>I68</td>
<td>Cerebrovascular disorders in diseases classified elsewhere</td>
</tr>
<tr>
<td>I78</td>
<td>Diseases of capillaries</td>
</tr>
</tbody>
</table>

Table 6. Excluded patients

<table>
<thead>
<tr>
<th>Reason for exclusion</th>
<th>Number of patients n=1325 (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ICH</td>
<td>765 (57.7)</td>
</tr>
<tr>
<td>Primary subarachnoid hemorrhage</td>
<td>67 (5.1)</td>
</tr>
<tr>
<td>Trauma</td>
<td>57 (4.3)</td>
</tr>
<tr>
<td>Recurrent ICH episode</td>
<td>38 (2.9)</td>
</tr>
<tr>
<td>Missing patient records</td>
<td>20 (1.5)</td>
</tr>
<tr>
<td>Initially treated in another hospital</td>
<td>18 (1.4)</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>11 (0.8)</td>
</tr>
<tr>
<td>Incorrect primary diagnosis of ICH</td>
<td>8 (0.6)</td>
</tr>
<tr>
<td>Subdural hemorrhage</td>
<td>5 (0.4)</td>
</tr>
</tbody>
</table>
Figure 11. Inclusion scheme for the follow up study of ICH in the Young Study.

Helsinki ICH in the Young Study
336 (100.0%)

Died within 30 days after ICH onset
55 (16.4%)

30-day survivors
281 (83.6%)

Lost to follow-up
13 (3.9%)

Long-term mortality after ICH study population
268 (79.8%)

Died after 30 days from ICH onset
32 (9.5%)

Invitation to participate sent
236 (70.2%)

Declined participating in study on long-term functional outcome after ICH
101 (30.1%)

Initially consenting to participate
135 (40.2%)

Withdraw consent
4 (1.2%)

Functional outcome after ICH study population
131 (39.0%)

Patients examined and interviewed
77 (22.9%)

Patients only interviewed
54 (16.1%)
4.2 CLINICAL DATA

4.2.1 RISK FACTORS AND STROKE SEVERITY

A chart review including patient medical records, imaging, and laboratory databases was performed. All patients had been seen by a neurologist or a neurosurgeon. The risk factors and symptoms at arrival and recorded GCS and NIHSS values were registered. If these were not reported in the medical records, they were reconstructed from diligent chart notes. Province-wide hospital notes of all specialties provided information on comorbidities and previous medications. Hypertension was considered a risk factor if (1) there was a mention of previously elevated blood pressure by patient, relatives, or medical records together with a left ventricular hypertension as a biomarker of hypertension; or (2) any pre-ICH use of blood pressure medication. Current smoking, heavy use of alcohol, type 1 and type 2 diabetes mellitus, any liver disease, and a previous non-ICH-stroke as a risk factor were recorded if they were noted in the medical records. Cancer, atrial fibrillation, coronary artery disease, and heart failure diagnosed prior to ICH were considered as comorbidities.

4.2.2 ETIOLOGIC CLASSIFICATION

The etiologic classification was based on discharge notes, imaging data, pathological analysis from surgical preparates, and laboratory findings. Hypertension was considered the cause in case it was present in the absence of any other causes, and hematoma was located in basal ganglia, thalamus, deep periventricular white matter, brain stem, or cerebellum. Structural causes were identified by brain and vascular imaging, and most often verified by pathological analysis. CVT and vasculitis were diagnoses on the basis of MR imaging. Illicit drug use was established by a urine sample, and considered the cause if no other cause was evident. Liver disease, other coagulation deficits, hematologic disorder, and diabetic microangiopathy were considered the etiology in case no other cause was found, as well as anticoagulation or other medication. Eclampsia and syndrome of hemolysis, elevated liver enzymes and low platelet count (HELLP) were diagnosed per standard practice. If no cause was found, it was considered unknown. Underlying etiologies of ICH were classified according to “Structural-Medication-Amyloid angiopathy-Systemic or other disease-Hypertension-Undetermined” classification scheme (SMASH-U) that was proposed fairly recently, with the exception, of including those with tumor in the category of structural causes, and those with CVT in the category of other causes. In this Thesis, we used a simplified modification of SMASH-U classification, and divided our patients in four categories: (1) hypertensive microangiopathy, (2) structural
causes, (3) other cause, and (4) unknown cause. In some substudies, we also used a two-class division in structural and non-structural (all the rest) causes.

4.2.3 TREATMENT DETAILS

Our patients were treated according to the institutional guidelines in the ICSU, regular stroke unit (ward), general or neurosurgical ICU, or at the neurosurgical ward. All the ICUs can treat patients requiring ventilator support. We recorded neurosurgical operations performed. As this was a retrospective study, our criteria for operative treatment did not follow any predetermined scheme and was not systematically guided by any guideline. Operative treatment was thus performed using individual consideration in patients with a large ICH, declining GCS, symptomatic hydrocephalus, or imminent brain herniation who were still considered salvageable. The evacuation of the hemorrhage was always performed through a small open craniotomy using standard microsurgical techniques and a neurosurgical high magnification microscope. Mini-invasive or other experimental surgical techniques were not used. If needed, image-guided neuronavigation was used to localize the lesion. In patients with a ruptured AVM, the primary surgical goal was to occlude and remove the malformation. Obstructive hydrocephalus was treated with an EVD inserted through a standard frontal paramedian burr hole. In case IVH was present, intraventricular injection of tissue plasminogen activator was used. Finally, as a last resort, a decompressive hemicraniectomy was performed on patients with an uncontrollable high intracranial pressure.

Use of nasogastric tube, intubation, tracheostomy, central venous catheter, urinary tract catheter, antibiotic treatment, compression stockings, and low-molecular-weight-heparin was recorded. Vomiting as a risk factor for aspiration and potential cause of electrolyte disorders, or hypoglycemia was recorded. Our written institutional stroke treatment guidelines have recommended treatment of hyperglycemia with subcutaneous insulin every hour until level of plasma glucose <8.0 mmol/L is reached. Intravenous insulin is used in treatment-resistant cases. Intravenous fluids with calculated percentage of sodium and potassium are administered to patients routinely to correct sodium or potassium disturbances if present. Early rehabilitation included physiotherapy, speech therapy, occupational therapy, and neuropsychological rehabilitation when judged necessary by the clinician. Length of hospital stay was recorded.
4.2.4 MEDICAL COMPLICATIONS

Medical complications suffered by the patients any time during their acute hospital stay due to ICH were recorded, including infections, venous thrombotic events, cardiac complications, renal failure, hypoglycemia, hyperglycemia, sodium or potassium imbalances, bedsores, and gastric ulcers.

Pneumonias verified as infiltrate in chest radiograph together with fever, aural temperature >38 °C, and tracheal infections verified by bacterial growth in tracheal culture in intubated or tracheostomized patients, were both considered as respiratory infections. Septicemia was defined by bacterial growth in blood culture together with fever. Urinary tract infections (UTI) were registered by positive urine dipstick for nitrate or pyuria together with bacterial growth in urine sample culture. Meningitis was recorded by bacterial growth in cerebrospinal fluid sample accompanied by fever. Gastrointestinal infection was diagnosed by diarrhea or peritonitis verified in laparotomy.

DVT was recorded only when verified by ultrasound imaging of veins, and pulmonary embolism (PE) had to be verified by pulmonary CT angiography imaging. Cardiac complications comprised of first-ever atrial fibrillation, atrial flutter, and ventricular fibrillation diagnosed by ECG or myocardial infarction verified by ECG and elevated myocardial enzyme levels.

4.3 NEURORADIOLOGICAL DATA

Brain imaging was performed on admission to the hospital within 24 hours of the first observation of the symptoms. Initial head CT, MRI, and any angiography performed to define the underlying cause were investigated. All the scans were initially evaluated by neuroradiologists. Measurements and classification of ICH were performed on digital images. ICH originating at the cortex and subcortical junction were classified as lobar, whereas ICH exclusively involving the thalamus, basal ganglia, internal capsule, and deep periventricular white matter were classified as deep ICH. Infratentorial ICH of cerebellum or brainstem, and solitary IVH were initially classified separately. Solitary IVH was, however, analyzed as a deep ICH. Intracerebral hemorrhages involving more than one parenchymal site were classified as mixed, as reported previously. Location of ICH in uncertain cases was decided by mutual consensus. Volumes were calculated with the ABC/2 method. IVH was recorded, but not included in volume calculations. ICH was classified as multiple if more than one separate sites of bleeding without connecting hematoma-bridge between the clots. Hydrocephalus was defined as increased radius or decreased ventricular angle in frontal horns, rounding and enlargement of atrium with sulcal effacement, increased width of third ventricle, or ballooning of fourth ventricle. Cingulate herniation was defined as at least 8 mm of horizontal displacement of
pineal body from the midline. Any displacement of brain parenchyma behind tentorium or through the foramen magnum was also classified as herniation.

4.4 LABORATORY DATA

Hyperglycemia was defined as plasma glucose >8.0 mmol/L (>144mg/dL) at any time during acute hospital ward. Hypoglycemia was defined as plasma glucose <4.0 mmol/L (72mg/dL). Renal failure was defined as plasma creatine level >100 μmol/L measured by enzymatic method. Highest and lowest plasma sodium and potassium levels during hospital stay were recorded, and were defined as normal by the range of values used by the laboratory of Helsinki University Hospital: 136-145 mmol/L (313-333 mg/dL) for sodium and 3.3-5.0 mmol/L (12.9-19.6 mg/dL) for potassium. Use of bacterial culture sample from cerebrospinal fluid, urinary tract catheter, and tracheostomy or intubation tube was recorded.

4.5 MORTALITY AND INCIDENCE DATA

The primary outcome measure was 3-month all-cause case-fatality. Secondary outcome measures were mRS score at discharge, reconstructed according to discharge notes, and in-hospital mortality. Discharge to rehabilitation center or home was also recorded. Mortality and demographic data, to calculate incidence of ICH, were obtained from Statistics Finland initially on June 25, 2013. For the long-term follow-up studies, we performed a second data collection on June 16, 2014.

4.6 POST-STROKE DEPRESSION

PSD at follow-up was assessed with structured questionnaires. Due to the severe aphasia and substantially impaired cognition, one patient taking part in the follow up study was excluded from the analyses of PSD. Beck Depression Inventory II (BDI-II) was used to identify patients with depression, Hospital Anxiety and Depression Scale (HADS) was used to identify patients with anxiety, Pain Anxiety Symptoms Scale (PASS-20) to verify pain-related anxiety, and Brief Pain Inventory (BPI) to identify patients with pain. Several different questionnaires have been used to detect PSD, BDI-II being one of them. BDI-II and HADS have been accepted as relevant tools to measure prevalence of PSD. Montreal Cognitive Assessment (MoCA) was performed on all those patients invited to a clinical follow-up, except one who was unable to comprehend the tasks. In stroke patients, MoCA has been validated as a screening measure of cognitive impairment. Fatigue was assessed by three fatigue-related questions in BDI-II.
4.7 FUNCTIONAL OUTCOME

After mortality check on June 25, 2013 surviving patients living within a 50 km radius of HUH were invited to a clinical follow-up, amounting 77. Those participating underwent detailed neurological examination by a single investigator. Those living more distant than 50 km were interviewed with a structured questionnaire by mail and telephone, and they numbered 54. Employment status, Barthel Index score (BI), residual symptoms, presence of post-ICH epilepsy, and recurrent strokes reported by the patients were verified by medical records. Degree of disability was measured by the mRS score, judged as well by a single investigator on the basis of clinical follow-up or interview. The definition of unfavorable functional outcome at follow-up was mRS 2 to 5. Employment and marital status were recorded, as well as dwelling. Patient’s quality of health was measured by EuroQualityOfHealth-5D-3L – questionnaire (EQ-5D). Since no health value sets have been recorded for the Finnish population, Danish value sets were used instead. Those patients with no information of mortality, and no real-time contact information in hospital database were lost to follow-up. Those patients, numbering 13, were from foreign countries and visiting Finland at the time of their ICH.

4.8 STATISTICAL METHODS

Continuous variables were tested for normal distribution and reported as medians with interquartile range (IQR). Categorical variables were compared with Chi-square and Fisher’s exact test. Mann-Whitney-U test, and Kruskal-Wallis test were used to compare continuous variables with skewed distribution of 2 or >2, respectively. A two-sided P value <0.05 was considered significant. All analyses used SPSS 22 for Windows (IBM Inc., Armonk, NY, USA).

4.8.1 BASELINE DATA

Incidence of ICH was calculated according to demographic data on residents in the area of Helsinki and Uusimaa Hospital District between January, 2000 and March 2010. Age was categorized into 3 groups for analysis of trends: 16 to 29 years, 30 to 39, and 40 to 49 years. Additionally, all these 336 patients aged between 16 and 49 were compared to patients aged between 50 and 99 registered in the Helsinki ICH Study, numbering 921. Comparisons concerning age, gender, risk factors, etiology, NIHSS score, imaging, treatment and hematoma volume were performed.
4.8.2 PREDICTORS OF EARLY MORTALITY

Predictors of 3-month mortality were analyzed on patients aged between 16 and 49 years as well as those over 49. Multivariate analysis with binary logistic regression using backwards likelihood ratio method was performed separately in patients aged 16 to 49 years (n=319), 50 to 59 years (n=182), 60 to 69 years (n=261), 70 to 79 years (n=267), and 80 to 99 years (n=195) to identify factors independently associated with 3-month case-fatality in the age-specific subgroups. Six patients with tumor as the etiology of ICH, and eleven patients with missing imaging data were excluded in this multivariate analysis. Covariates for logistic regression were selected based on previous studies on ICH mortality and variables with P-value <0.5 in univariate analysis. NIHSS score instead of GCS was used in our analyses, since NIHSS involves more information on the patient’s condition, including the level of consciousness (items 1a, 1b, and 1c).

A separate univariate analysis and multivariate analysis with binary logistic regression using backwards likelihood ratio method, and confounding factors included, was performed to define whether initial hydrocephalus, multiple hemorrhages, herniation, or any neurosurgical procedure, including hematoma evacuation, decompressive craniectomy, and insertion of EVD, associate with increased 3-month mortality. In this analysis baseline ICH volume was categorized as 0-29 ml, 30-60 ml, and >60 ml. NIHSS scores were analyzed in three categories: 0-6, 7-14, and >14, reflecting mild, moderate, and severe symptoms. To further assess the impact of early surgery on mortality, a propensity score for the probability of hematoma evacuation was calculated based on variables influencing treatment decisions (age, sex, NIHSS score, hematoma location and volume, structural cause, presence of IVH, hydrocephalus, herniation, and multiple hemorrhages), and patients undergoing surgery were matched to those not undergoing surgery using the nearest-neighbor-matching method. Patients operated were then compared with those not operated.

To study the impact of medical complications on mortality, we constructed a binary logistic regression model using complications associated with 3-month mortality in univariate analysis with adjustment for confounding factors as covariates. These covariates included age, gender, hematoma volume, infratentorial hematoma location, presence of intraventricular hemorrhage, NIHSS score, and hematoma evacuation. Urinary tract infection was excluded from this analysis due to possible observational bias. Because preexisting diabetes and hyperglycemia are intercorrelated, we forced diabetes in the model. To illustrate the additive impact of multiple different complications, we also performed a multivariable analysis with number of complications (score) as a covariate instead of individual complications.
4.8.3 POST-STROKE DEPRESSION

Presence of PSD was classified as having more than 13 points measured by BDI-II. HADS was used to find the proportion of patients with symptoms of depression (more than 11 points measured by HADS-total), and with symptoms of anxiety (more than 6 points measured by HADS-total). Pain-related anxiety was defined as having more than 30 points by PASS-20. Pain was defined non-existent, mild, moderate, or severe by BPI scores 0, 1-48, 49-72, and 73-120, respectively. Mild cognitive impairment was defined by the MoCA score between 18 and 26; moderate cognitive impairment between 10 and 17; and severe cognitive impairment less than 10. Results were analyzed between males and females and between 3 patient age groups (from 16 to 29, from 30 to 39, and from 40 to 49 years at ICH onset). The effect of ICH treatment was analyzed by comparing those who had hematoma surgically evacuated with those who had no hematoma evacuation.

Correlations between the degree of disability were measured by the mRS. Univariate analysis was performed to identify factors associated with PSD including gender, age, hypertension, diabetes, cardiac diseases, hematoma volume IVH, infratentorial hematoma location, arrival NIHSS score, presence of herniation, hydrocephalus, or multiple hemorrhages, hematoma evacuation, follow-up mRS, MoCA, BPI, and PASS-20 score, as well as current employment and living alone. Logistic regression analysis with backwards likelihood ratio method was performed with factors with tendency to associate with PSD (P<0.1) in our univariate analysis.

4.8.4 LONG-TERM OUTCOME

To define patients’ residual symptoms and current mRS, 77 (22.9%) patients underwent clinical examination and interview, whereas 54 (16.1%) were interviewed only by telephone and structured questionnaire. Baseline data was compared between those patients included in the follow-up study and those excluded due to being lost, refusing to participate, and withdrawing their consent. Life table function served to calculate cumulative survival rates, cumulative ICH recurrence rates, and cumulative rates for late seizures after ICH. Univariate Cox regression analysis served to create hazard ratios and their 95% CIs. Known factors associated with mortality in the studies of ICH were included in the univariate analysis, including gender, age, hypertension, diabetes, cardiac diseases, arrival NIHSS score, hematoma volume, infratentorial hematoma location, presence of IVH, hydrocephalus, herniation, or multiple hematomas, and structural etiology, as well as surgical hematoma evacuation. In addition to age and sex, factors tending to associate with mortality (P<0.1) were entered in a multivariable Cox regression model to identify independent factors associated with mortality. Kaplan-Meier survival analysis using the log-rank test was also performed to compare long-term mortality between surgically and
non-surgically treated patients. For analysis of unfavorable outcome (mRS 2-5) at follow-up, we first tested the same baseline factors as in the survival analysis in a univariate analysis. Subsequently, we constructed a binary multivariate logistic regression model with a backward likelihood-ratio method to identify factors independently associated with unfavorable outcome. This analysis included age, gender, and parameters tending to associate with unfavorable outcome (P<0.1). Data from EQ-5D were analyzed with linear regression using backward method with demographic factors and those with association in univariate analysis.
5 RESULTS

5.1 CLINICAL AND RADIOLOGICAL FEATURES OF THE STUDY POPULATION

A total of 336 patients (200 [59.5%] males, between the age of 16 and 49 years (median age 42 [IQR 34-47]; males 42 [34-46], females 44 [33-47]; P=0.471) were eligible (Figure 12).

![Graph showing age and gender distribution of patients included](image)

**Figure 12.** Age- and gender distribution of patients included

5.1.1 INCIDENCE

The annual incidence of ICH was 4.9 (95% CI 4.5-5.3) cases per 100 000 population, being 6.2 (5.0-7.3) in males and 4.0 (3.4-4.7) in females. The incidence increased with age, being 2.6 (2.1-3.1) for age group 18 to 29 years, 3.0 (1.1-4.9) for 30 to 39 years, and 9.2 (7.5-10.9) for those aged 40 to 49 years. The annual incidence ranged from 3.0 to 6.0 per 100 000 with no clear trend over time (P=0.206).
5.1.2 RISK FACTORS AND ETIOLOGY OF ICH

The most common risk factor was hypertension (29.8%), particularly in males (34.5%), while almost absent in those between age 16 and 29 (3.2%). Heavy drinking was more prevalent in males (20.0%). Those with no risk factors amounted 126 (37.5%). Comparing the young patients to 921 patients over 49 years of age with ICH (median age 70 years [61-79]), the young had significantly less often hypertension (P<0.001), type 2 diabetes mellitus (P<0.001), and cardiac disease (coronary heart disease, heart failure, or atrial fibrillation, P<0.001). The most prevailing etiology was hypertensive microangiopathy (25.0%). Structural lesions, mostly AVMs or cavernous hemangiomas, altogether caused approximately one-fourth of all ICH (26.5%). Systemic diseases and other conditions accounted for 16.4% of ICH. In one-third of our patients the etiology was undetermined (Table 7). The four-dimensional distribution of etiologies appears in Figure 13. Hypertensive microangiopathy (P=0.002), CAA (P<0.001), and medication (P<0.001) were considerably more frequent causes of ICH among the elderly while a structural (P<0.001), systemic, and other (P<0.001) or unknown cause (P<0.001) was substantially more prevalent among the young.

5.1.3 SYMPTOMATOLOGY

Symptoms upon arrival included motor hemiparesis (57.1%), headache (48.8%), nausea (35.7%), sensory hemiparesis (27.7%), vomiting (26.8%), dysphasia/aphasia (31.3%), dysarthria (24.4%), seizure (11.6%), disorientation (11.3%), vertigo (9.2%),

![Figure 13. Distribution of underlying etiologies of ICH](image-url)
visual field deficit (6.8%), ataxia (6.0%), and diplopia (5.4%). One out of five patients had severely decreased level of consciousness (GCS < 9, 21.4%). Males had 45% larger median baseline hematoma volumes than females (P=0.024). ICHs caused by hypertensive microangiopathy were 119% larger than hemorrhages caused by a structural cause, but 29% smaller than ICH caused by other diseases, and 54% smaller than ICH caused by unknown etiology (P<0.001) (Figure 14). The NIHSS scores at arrival were lower among the young (8 [2-19] vs. 12 [5-20], P<0.001), but no difference was detected in the hematoma volumes (11 [3-36] vs. 11 [4-30] mL, P=0.823). IVH was more often present (52.4% vs. 19.0%, P=0.001), and hematomas were larger (20 [9.2-34] ml vs. 5.9 [0.7-23] ml, P=0.014) among those with hydrocephalus in comparison to those without.

Table 7. Baseline characteristics of young ICH patients treated in the Helsinki University Hospital between January, 2000 and March, 2010.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>336</td>
</tr>
<tr>
<td>Males</td>
<td>200 (59.5)</td>
</tr>
<tr>
<td>Age</td>
<td>42 [34-47]</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>100 (29.8)</td>
</tr>
<tr>
<td>Smoking</td>
<td>75 (22.3)</td>
</tr>
<tr>
<td>Excessive alcohol use</td>
<td>49 (14.6)</td>
</tr>
<tr>
<td>Diabetes, type 1</td>
<td>17 (5.1)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>14 (4.2)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td>Diabetes, type 2</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td>Cardiac disease *</td>
<td>11 (3.3)</td>
</tr>
<tr>
<td>Cancer</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Hematoma characteristics</td>
<td></td>
</tr>
<tr>
<td>Hematoma volume (mL)</td>
<td>11 [3-36]</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>117 (34.8)</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>52 (15.5)</td>
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<tr>
<td>NIH Stroke Scale score</td>
<td>8 [2-19]</td>
</tr>
<tr>
<td>GCS score</td>
<td>15 [10-15]</td>
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<tr>
<td>Etiology structural</td>
<td></td>
</tr>
<tr>
<td>AVM</td>
<td>45 (13.4)</td>
</tr>
<tr>
<td>Cavernoma</td>
<td>36 (10.7)</td>
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<tr>
<td>Brain tumor</td>
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<td>Epitheloid hemangioendothelioma</td>
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<td>Capillary teleangiectasy</td>
<td>1 (0.3)</td>
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<tr>
<td>Etiology non-structural</td>
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</tr>
<tr>
<td>Hypertensive microangiopathy</td>
<td>84 (25.0)</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>55 (16.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>108 (32.1)</td>
</tr>
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Data are n (%) or median [interquartile range].
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<thead>
<tr>
<th>Factor</th>
<th>All (n=325)</th>
<th>Evacuation of hematoma (n=102)</th>
<th>P-value</th>
<th>Decompressive craniectomy (n=6)</th>
<th>P-value</th>
<th>Ventriculostomy (n=31)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Males</td>
<td>193 (59.4)</td>
<td>61 (59.8)</td>
<td>0.917</td>
<td>3 (50.0)</td>
<td>19 (61.3)</td>
<td></td>
<td>0.820</td>
</tr>
<tr>
<td>Females</td>
<td>132 (40.6)</td>
<td>41 (40.2)</td>
<td></td>
<td>3 (50.0)</td>
<td>12 (38.7)</td>
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<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td>0.137</td>
<td></td>
<td>0.059</td>
<td></td>
<td>0.031</td>
</tr>
<tr>
<td>16-29</td>
<td>57 (17.5)</td>
<td>23 (22.5)</td>
<td></td>
<td>2 (33.3)</td>
<td>7 (22.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>65 (20.0)</td>
<td>23 (22.5)</td>
<td>0.059</td>
<td>3 (50.0)</td>
<td>11 (35.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>203 (62.5)</td>
<td>56 (54.9)</td>
<td>0.031</td>
<td>1 (16.7)</td>
<td>13 (41.9)</td>
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<td></td>
</tr>
<tr>
<td><strong>NIHSS Score</strong></td>
<td></td>
<td></td>
<td>0.047</td>
<td></td>
<td>0.044</td>
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<td>&lt;0.001</td>
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<tr>
<td>0-6</td>
<td>146 (44.9)</td>
<td>39 (38.2)</td>
<td></td>
<td>1 (16.7)</td>
<td>7 (22.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-14</td>
<td>64 (19.7)</td>
<td>17 (16.7)</td>
<td>0.031</td>
<td>0</td>
<td>1 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;14</td>
<td>115 (35.4)</td>
<td>46 (45.1)</td>
<td>&lt;0.001</td>
<td>5 (83.3)</td>
<td>23 (74.2)</td>
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<tr>
<td><strong>Location of ICH</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>0.583</td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>Lobar hemisphere</td>
<td>68 (20.9)</td>
<td>19 (18.6)</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep hemisphere</td>
<td>142 (43.7)</td>
<td>29 (28.4)</td>
<td>&lt;0.001</td>
<td>3 (50.0)</td>
<td>16 (51.6)</td>
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</tr>
<tr>
<td>Infratentorial</td>
<td>52 (16.0)</td>
<td>18 (17.6)</td>
<td>0.019</td>
<td>1 (16.7)</td>
<td>8 (25.8)</td>
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<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>63 (19.4)</td>
<td>36 (35.3)</td>
<td>&lt;0.001</td>
<td>2 (33.3)</td>
<td>7 (22.6)</td>
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<td></td>
</tr>
<tr>
<td><strong>Volume of ICH</strong></td>
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<td>&lt;0.001</td>
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<td>0.438</td>
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<td>0.492</td>
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<tr>
<td>0-29ml</td>
<td>231 (71.1)</td>
<td>48 (47.1)</td>
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<td>3 (50.0)</td>
<td>21 (67.7)</td>
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<tr>
<td>30-60ml</td>
<td>51 (15.7)</td>
<td>23 (22.5)</td>
<td></td>
<td>2 (33.3)</td>
<td>7 (22.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60ml</td>
<td>43 (13.2)</td>
<td>31 (30.4)</td>
<td>&lt;0.001</td>
<td>1 (16.7)</td>
<td>3 (9.7)</td>
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<td></td>
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<tr>
<td><strong>IVH present</strong></td>
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<td></td>
<td>0.189</td>
<td></td>
<td>0.471</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>86 (26.5)</td>
<td>33 (32.4)</td>
<td>0.103</td>
<td>5 (83.3)</td>
<td>0.001</td>
<td>22 (71.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple hemorrhages</td>
<td></td>
<td></td>
<td>0.030</td>
<td></td>
<td>0.475</td>
<td></td>
<td>1.326</td>
</tr>
<tr>
<td>Herniation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology structural</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>0.021</td>
<td></td>
<td>0.197</td>
</tr>
</tbody>
</table>

Table 8. Patient characteristics and operative treatment
5.1.4 IMAGING

A brain CT scan was performed in 328 (97.6%), brain MRI in 142 (42.3%), brain CT angiography in 147 (43.8%), brain MR angiography in 51 (15.2%), and DSA in 55 (16.4%) of the patients. Any angiography was performed in 204 (60.7%) of all the patients. Structural etiologies were defined as the etiology of ICH more frequently in those who underwent either MRI (P<0.001), or any angiography (P=0.035), or both (P=0.002). The cause was considered hypertensive microangiopathy less frequently if MRI (P=0.007), or angiography (P<0.001) was performed, and the cause remained less often unknown in those who underwent MRI (P=0.006). Other causes combined, excluding medication, were more frequently seen in those on whom both MRI and angiography (P=0.023) were performed. Young patients received more often comprehensive imaging and intensive treatment including intubation and neurosurgical procedure in comparison to the elderly.
5.1.5 TREATMENT

During their hospital stay, 32.1% of patients received treatment in ICSU, 53.6% received treatment in a neurosurgical unit, and 33.9% had a neurosurgical procedure, including hematoma evacuation among 31.3% (49% within a day of ICH), placement of EVD among 9.8% (47% within a day and 73% within 3 days of ICH), and decompressive craniectomy among 1.8% (median 3 [2-5] days) (Table 8). Those patients who received treatment in a general or neurosurgical ICU amounted to 53.0%.

Hematoma volumes were significantly larger in surgically versus non-surgically treated patients (36.1 mL [13.7-65.4] vs. 7.6 mL [1.7-21.9], p<0.001). Notably, operated patients with herniation had significantly larger hematomas than those not operated (80.2 [44.2-114.6] ml vs. 40.2 [17.3-50.1] ml, P=0.033), while the distribution of hematoma location did not markedly differ. Subfalcine herniation was recorded in 40 (12.3%) patients, transtentorial herniation in 16 (4.9%) patients, and downward cerebellar herniation in 4 (1.2%) patients. Median highest and lowest levels of plasma glucose, sodium, potassium, and creatinine are presented in Table 9.

5.2 MEDICAL COMPLICATIONS

Hyperglycemia was the most frequent complication (50.8%), followed by hyponatremia (44.9%), hypopotassemia (32.0%), and hypernatremia (28.0%). Respiratory infection was the most common of infections. Electrolyte disturbances, respiratory infection, meningitis, renal failure and arrhythmias were associated with initial stroke severity (Table 10).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Highest</th>
<th>Lowest</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>8.1 (6.5-10.1)</td>
<td>5.5 (4.9-6.2)</td>
<td>2.7-30.5</td>
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<tr>
<td>Sodium (mmol/L)</td>
<td>143 (141-147)</td>
<td>137 (134-139)</td>
<td>115-166</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.3 (4.0-4.6)</td>
<td>3.5 (3.2-3.7)</td>
<td>2.0-7.8</td>
</tr>
<tr>
<td>Creatinine (Qmol/L)</td>
<td>75 (62-92)</td>
<td>59 (47-74)</td>
<td>18-831</td>
</tr>
</tbody>
</table>

Data are median (IQR) highest and lowest recorded values and range during acute phase.
Table 10. Association of in-hospital complications and stroke severity in young adults with intracerebral hemorrhage.

<table>
<thead>
<tr>
<th>Complication</th>
<th>NIHSS score at arrival</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=325)</td>
<td>8 (2-19)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Infections (n=110)</td>
<td>18 (10-28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sepsis (n=7)</td>
<td>13 (5-20)</td>
<td>0.602</td>
</tr>
<tr>
<td>Respiratory infection (n=82)</td>
<td>18 (10-28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Meningitis (n=2)</td>
<td>33 (31-34)</td>
<td>0.040</td>
</tr>
<tr>
<td>Gastric infection (n=4)</td>
<td>10 (7-12)</td>
<td>0.838</td>
</tr>
<tr>
<td>Urinary tract infection (n=40)</td>
<td>14 (7-19)</td>
<td>0.054</td>
</tr>
<tr>
<td>Deep venous thrombosis (n=11)</td>
<td>10 (3-15)</td>
<td>0.755</td>
</tr>
<tr>
<td>Pulmonary embolism (n=4)</td>
<td>12 (8-15)</td>
<td>0.715</td>
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<tr>
<td>Arrhythmia (n=4)</td>
<td>27 (20-34)</td>
<td>0.016</td>
</tr>
<tr>
<td>Renal failure (n=59)</td>
<td>15 (4-21)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hyperglycemia (n=165)</td>
<td>12 (4-28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia (n=15)</td>
<td>18 (10-26)</td>
<td>0.020</td>
</tr>
<tr>
<td>Hyponatremia (n=146)</td>
<td>11 (2-21)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypernatremia (n=91)</td>
<td>18 (8-28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypopotassemia (n=104)</td>
<td>16 (7-26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperpotassemia (n=27)</td>
<td>21 (8-32)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

NIHSS, National Institutes of Health Stroke Scale
Data are median (IQR).

Respiratory infections (P<0.001), meningitis (P=0.049), hyperglycemia (P<0.001), hyponatremia (P<0.001), hypernatremia (P<0.001), and hypopotassemia (P=0.022) were more common among those who received surgical treatment. Furthermore, use of endotracheal intubation (P<0.001), tracheostomy (P<0.001), nasogastric tube (P<0.001), central vein catheter (P<0.001), and administration of antibiotics (P<0.001) were more frequent in patients undergoing surgical treatment.

Respiratory infection was not associated with vomiting as a symptom of ICH (27.4% vs. 24.5%, p=0.598). However, it was significantly more common among those intubated or tracheostomized than those who did not need ventilatory support (44.1% vs. 4.5%, p<0.001, and 84.9% vs. 17.4%, p<0.001, respectively). Vomiting was not associated with hypoglycemia or sodium or potassium disturbance. However, it was more often present in those who suffered from hyperglycemia (33.3% vs. 18.1%, p=0.002). DVT and PE were infrequent, yet medical prophylaxis with subcutaneous enoxaparin or dalteparin had been used in 9 of 11 (82%), and compression stockings in 5 of 11 (45%) of patients with DVT.

None of our young patients suffered from ischemic heart event, bed sores or gastric bleeding. Arrhythmias recorded included one brief ventricular fibrillation in a patient who was successfully resuscitated. One flutter and two new-onset atrial fibrillations were also diagnosed during the hospital stay. Out of 59 patients with
Table 11. Univariate analysis of in-hospital complications on short-term outcome and length of acute hospital stay in young patients with intracerebral hemorrhage.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Acute ward length of stay (days)</th>
<th>3-month mortality</th>
<th>P-Value</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complication present</td>
<td>Complication absent</td>
<td></td>
<td>Complication present</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P-Value</td>
<td></td>
</tr>
<tr>
<td>Sepsis (n=7)</td>
<td>41 (6-46)</td>
<td>9 (5-18)</td>
<td>0.177</td>
<td>2 (28.6)</td>
</tr>
<tr>
<td>Respiratory infection (n=82)</td>
<td>15 (7-26)</td>
<td>8 (4-15)</td>
<td>&lt;0.001</td>
<td>19 (23.2)</td>
</tr>
<tr>
<td>Meningitis (n=2)</td>
<td>31 (N.A.)</td>
<td>9 (5-18)</td>
<td>0.034</td>
<td>0</td>
</tr>
<tr>
<td>Gastric infection (n=4)</td>
<td>23 (8-36)</td>
<td>9 (5-18)</td>
<td>0.431</td>
<td>0</td>
</tr>
<tr>
<td>Urinary tract infection (n=40)</td>
<td>26 (18-35)</td>
<td>8 (4-15)</td>
<td>&lt;0.001</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Deep venous thrombosis (n=11)</td>
<td>17 (14-33)</td>
<td>9 (5-18)</td>
<td>0.019</td>
<td>1 (9.1)</td>
</tr>
<tr>
<td>Pulmonary embolism (n=4)</td>
<td>18 (14-21)</td>
<td>9 (5-18)</td>
<td>0.255</td>
<td>1 (25.0)</td>
</tr>
<tr>
<td>Arrhythmia (n=4)</td>
<td>6 (1-13)</td>
<td>9 (5-18)</td>
<td>0.332</td>
<td>3 (75.0)</td>
</tr>
<tr>
<td>Renal failure (n=59)</td>
<td>13 (6-19)</td>
<td>9 (5-17)</td>
<td>0.131</td>
<td>16 (27.1)</td>
</tr>
<tr>
<td>Hypoglycemia (n=15)</td>
<td>11 (4-31)</td>
<td>9 (5-18)</td>
<td>0.505</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Hyperglycemia (n=165)</td>
<td>10 (5-18)</td>
<td>9 (5-18)</td>
<td>0.678</td>
<td>43 (26.1)</td>
</tr>
<tr>
<td>Hyponatremia (n=146)</td>
<td>13 (6-19)</td>
<td>8 (5-15)</td>
<td>0.006</td>
<td>29 (19.9)</td>
</tr>
<tr>
<td>Hypernatremia (n=91)</td>
<td>14 (7-28)</td>
<td>8 (5-16)</td>
<td>0.001</td>
<td>25 (27.5)</td>
</tr>
<tr>
<td>Hypopotassemia (n=104)</td>
<td>14 (6-25)</td>
<td>9 (4-15)</td>
<td>&lt;0.001</td>
<td>23 (22.1)</td>
</tr>
<tr>
<td>Hyperpotassemia (n=27)</td>
<td>13 (5-44)</td>
<td>9 (5-18)</td>
<td>0.101</td>
<td>8 (29.6)</td>
</tr>
</tbody>
</table>

Data are n (%) or median (IQR).
*Patient discharged to home in contrast to dying or being discharged to rehabilitation center.
renal failure, pre-ICH creatinine level was available in 27 (45.8%) patients, 18 of which had already then renal failure, and post-ICH chronic phase creatinine level was available in 37 patients, 17 (45.9%) of which had persisting renal failure.

Respiratory infection (P<0.001), urinary tract infection (P=0.005), hypoglycemia (P=0.033), hyperglycemia (P<0.001), hyponatremia (P<0.001), hypernatremia (P<0.001), hypopotassemia (P<0.001) and hyperpotassemia (P=0.016) reduced the proportion of patients discharged to home, while respiratory infection, meningitis, urinary tract infection, DVT, hyponatremia, hypernatremia and hyperpotassemia increased the length of median hospital stay (Table 11).

5.3 PREDICTORS OF EARLY MORTALITY

In-hospital mortality was 14.9% (n=50) with median length of stay being 13 days (IQR 5-18). Mortality at 3 months was 17.0% (n=57), half of these occurring within 3 days and 95% within 19 days of ICH. A do-not-resuscitate decision was made in 46 patients (13.7%) and a total of 22 patients were declared brain dead and organ donor candidates. At discharge, one third (37.5%) of the patients were functionally independent (mRS from 0 to 2).

5.3.1 COMPARISON BETWEEN THE YOUNG AND OLDER PATIENTS

Three-month mortality was substantially lower among the young than the elderly (17.0% vs. 32.7%, P<0.001). More thorough imaging performed in opposite to CT only, and treatment in ICSU in comparison to ICU decreased mortality, while DNR order and intubation increased mortality in the young and the elderly.

In patients aged 16-49, 50-59, 60-69, 70-79, and 80-99 hematoma volume had no trend with age (P=0.324). In all age groups, hematoma volume, NIHSS score at arrival, and IVH correlated with mortality at 3 months in univariate analysis. In logistic regression analysis of 3-month mortality performed separately for age groups including gender, NIHSS score, hematoma volume, IVH presence, infratentorial hematoma location, hypertension, cardiac disease, diabetes, and ICH etiology, the only factor significant in each age group was arrival NIHSS score, while hematoma volume was associated with mortality in all older age groups but not in the young patients.
5.3.2 EFFECT OF SURGICAL HEMATOMA EVACUATION

In addition to severe symptoms (P<0.001), non-structural ICH etiology (P=0.006), infratentorial or mixed hematoma location (P<0.001), hematoma volume of >30 ml (P=0.031), multiple hematomas (<0.001), presence of IVH (P<0.001), hydrocephalus (P<0.001), and brain herniation (P<0.001) associated with higher 3-month mortality of young adults after suffering ICH in univariate analysis. On the contrary, hematoma evacuation was associated with a lower risk of death (P=0.003).

Of the 48 patients with imminent herniation, 28 (58.3%) underwent surgical hematoma evacuation, and mortality among those operated was significantly lower than among those not operated (17.9% vs. 85.0% p<0.001). No correlation emerged between mortality and EVD or decompressive craniectomy.

In multivariate analysis, independent factors associated with increased 3-month mortality were more severe symptoms, infratentorial hematoma location, hydrocephalus, multiple hemorrhages, and herniation. However, age 30-39, age 40-49, and hematoma evacuation were significant factors associated with lower mortality. Even if age was removed from the model, the effect of surgical evacuation remained the same (OR 0.07, 95% CI 0.02-0.22, P<0.001) (Table 12).

Table 12. Logistic regression on the factors associated with mortality at 3 months.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-29 years</td>
<td>1</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>30-39 years</td>
<td>0.06</td>
<td>0.01-0.35</td>
<td>0.002</td>
</tr>
<tr>
<td>40-49 years</td>
<td>0.19</td>
<td>0.05-0.75</td>
<td>0.017</td>
</tr>
<tr>
<td>NIHSS Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6</td>
<td>1</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>7-14</td>
<td>6.25</td>
<td>1.23-31.78</td>
<td>0.027</td>
</tr>
<tr>
<td>&gt;14</td>
<td>39.00</td>
<td>7.77-195.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar</td>
<td>1</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>Deep</td>
<td>1.74</td>
<td>0.35-8.65</td>
<td>0.501</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>13.89</td>
<td>2.33-82.84</td>
<td>0.004</td>
</tr>
<tr>
<td>Mixed</td>
<td>3.21</td>
<td>0.60-17.27</td>
<td>0.174</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>4.00</td>
<td>1.61-9.90</td>
<td>0.003</td>
</tr>
<tr>
<td>Multiple hemorrhages</td>
<td>6.82</td>
<td>1.65-28.20</td>
<td>0.008</td>
</tr>
<tr>
<td>Brain herniation</td>
<td>5.94</td>
<td>1.71-20.60</td>
<td>0.005</td>
</tr>
<tr>
<td>Evacuation of hematoma</td>
<td>0.06</td>
<td>0.02-0.21</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Female gender (P=0.803), non-structural etiology (P=0.762), hematoma volume 0-29 mL (P=0.315), >60 mL (P=0.152), and IVH (P=0.152) are included, but not shown due to not reaching significance.

National Institutes of Health Stroke Scale, NIHSS; odds ratio, OR; confidential interval, CI
In the propensity-score nearest-neighbor matched analysis with matching criterion of ±0.28 difference, 3-month mortality was over three times higher among those not operated (27.5% vs. 7.8%, P<0.001). In comparison between the matched group, large hematomas (>60 mL) and herniation were more often present in those operated. A sensitivity analysis with a more strict criterion for matching (±0.03 difference) and the groups entirely balanced resulted in a four-fold higher mortality in the non-surgical group (7.7% vs. 33.8% p<0.001) (Table 13). When the effect of hematoma evacuation on short-term mortality was analyzed separately in those with structural cause or non-structural cause underlying ICH, the differences did not reach statistically significant difference (2.4% vs. 11.9%, p=0.090, and 11.7% vs. 23.2%, P=0.054, respectively), likely due to the relatively small number of patients.

Table 13. Propensity-score-matched comparison between patients with and without ICH evacuation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Analysis I</th>
<th>Analysis II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICH evacuated (n=102)</td>
<td>ICH evacuated (n=65)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.774</td>
<td>0.596</td>
</tr>
<tr>
<td>Males</td>
<td>61 (59.8)</td>
<td>63 (61.8)</td>
</tr>
<tr>
<td>Females</td>
<td>41 (40.2)</td>
<td>39 (38.2)</td>
</tr>
<tr>
<td>Age</td>
<td>0.392</td>
<td>0.848</td>
</tr>
<tr>
<td>16-29 years</td>
<td>23 (22.5)</td>
<td>20 (19.6)</td>
</tr>
<tr>
<td>30-39 years</td>
<td>23 (22.5)</td>
<td>24 (23.5)</td>
</tr>
<tr>
<td>40-49 years</td>
<td>56 (54.9)</td>
<td>58 (56.9)</td>
</tr>
<tr>
<td>NIHSS Score</td>
<td>0.392</td>
<td>0.770</td>
</tr>
<tr>
<td>0-6</td>
<td>39 (38.2)</td>
<td>46 (45.1)</td>
</tr>
<tr>
<td>6-14</td>
<td>17 (16.7)</td>
<td>11 (10.8)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>46 (45.1)</td>
<td>45 (44.1)</td>
</tr>
<tr>
<td>Structural etiology</td>
<td>0.887</td>
<td>0.587</td>
</tr>
<tr>
<td>Lobar</td>
<td>19 (18.6)</td>
<td>24 (23.5)</td>
</tr>
<tr>
<td>Deep</td>
<td>29 (28.4)</td>
<td>37 (36.3)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>18 (17.6)</td>
<td>21 (20.6)</td>
</tr>
<tr>
<td>Mixed</td>
<td>36 (35.3)</td>
<td>20 (19.6)</td>
</tr>
<tr>
<td>Volume of hemorrhage</td>
<td>0.002</td>
<td>0.848</td>
</tr>
<tr>
<td>0-29 ml</td>
<td>48 (47.1)</td>
<td>65 (63.7)</td>
</tr>
<tr>
<td>30-60 ml</td>
<td>23 (22.5)</td>
<td>26 (25.5)</td>
</tr>
<tr>
<td>&gt; 60 ml</td>
<td>31 (30.4)</td>
<td>11 (10.8)</td>
</tr>
<tr>
<td>IVH</td>
<td>0.472</td>
<td>0.857</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>33 (32.4)</td>
<td>26 (25.5)</td>
</tr>
<tr>
<td>Multiple hemorrhages</td>
<td>3 (2.9)</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>Herniation</td>
<td>28 (27.5)</td>
<td>16 (15.7)</td>
</tr>
<tr>
<td>Mortality at 3 months</td>
<td>8 (7.8)</td>
<td>28 (27.5)</td>
</tr>
</tbody>
</table>

Nearest-neighbor-matched analysis was first conducted including all patients having hematoma evacuated (matching criterion of ±0.28 propensity score difference, analysis I), and subsequently, using more strict matching criterion of ±0.03 (analysis II).

Data are n (%)

National Institutes of Health Stroke Scale, NIHSS; intraventricular hemorrhage, IVH; intracerebral hemorrhage, ICH
Arrhythmia, renal failure, hyperglycemia, and hypernatremia associated with increased 3-month mortality in univariate analysis (Table 11). In the logistic regression model with gender, age, hematoma volume, infratentorial location of hematoma, presence of IVH, NIHSS score at arrival, neurosurgical evacuation of hematoma performed and diabetes adjusted for, the only independent complication associated with mortality at 3 months was hyperglycemia, which increased the odds of dying nearly six-fold (OR 5.90, 95% CI 2.25-15.48, P<0.001). In the regression model with the number of separate complications as the covariate of interest, 3 or more complications independently were associated with the risk of death by over seven-fold increase (Table 14).

**Table 14.** Univariable and multivariable analysis on 3-month mortality with number of different complications.

<table>
<thead>
<tr>
<th>Factor</th>
<th>3-month mortality all 55/325 (16.9%)</th>
<th>P-Value</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of complications</td>
<td>&lt;0.001</td>
<td>0 (n=66) 2 (3.0%)</td>
<td>1</td>
<td>N.A.</td>
</tr>
<tr>
<td></td>
<td>1 (n=65) 1 (1.5%)</td>
<td>0.649 (0.05-8.40)</td>
<td>0.649</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (n=66) 16 (24.2%)</td>
<td>5.36 (0.90-31.86)</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 or more (n=128) 36 (28.1%)</td>
<td>7.76 (1.42-42.48)</td>
<td><strong>0.018</strong></td>
<td></td>
</tr>
</tbody>
</table>

Multivariable analysis was adjusted for gender, hematoma volume, infratentorial location of hematoma, presence of intraventricular extension, arrival National Institutes of Health Stroke Scale score, and neurosurgical evacuation of hematoma.

OR, odds ratio; CI, confidence interval

### 5.4 POST-STROKE DEPRESSION

Of the 336 patients initially included in the Helsinki ICH in the Young Registry, 55 (16.4%) had died in the first 30 days after ICH; 32 (9.5%) had died after that, 13 (3.9%) lived abroad and were lost to follow-up; 101 (30.1%) declined to participate, 4 (1.2%) withdrew their consent, and one (0.3%) was excluded due to severe aphasia and impaired cognition, leaving 130 eligible patients participating in the follow-up study of PSD. The median follow-up time was 9.7 (7.0-12.0) years. The follow-up interview was done for 130 (38.7%) (median age 50.3 [44.6-55.3] years) and a structural clinical examination for 76 (22.6%) patients (Figure 11). In those included, proportion of females was higher (48.5% vs 36.1%, P=0.049), etiology of ICH was more often structural (36.9% vs 20.2%, P=0.004) and NIHSS scores at arrival to hospital were lower (median 4 [1-11] vs. 9 [2-18], P=0.002).

PSD was present among 23.1% of patients, 40.0% had symptoms of anxiety, and pain-related anxiety was present among 19.2%. Mild, moderate, or severe
pain was present among 50.8%, 7.7%, and 0.8%, respectively. Those with more severe disability had higher scores in BDI-II (P=0.001), HADS (P=0.004), PASS-20 (P=0.008), and BPI (P=0.003), while gender, follow-up time, and age at ICH onset were not associated with any of these. Those who had hematoma evacuation had lower BDI-II scores (P=0.031), BPI scores (P=0.008), and PASS-20 scores (P=0.001). Antidepressant medication was used by 9.2%. In addition to the one patient excluded from analyses of PSD, nobody suffered from severe cognitive impairment, while 3.9% suffered from moderate cognitive impairment, and 48.7% from mild cognitive impairment. Median MoCA score was 26, and interquartile range was between 22 and 28. MoCA scores decreased with higher age (P=0.004), and more severe disability (P<0.001), but no correlation was found with follow-up time (P=0.325), gender (40 [53%] males, P=0.714), hematoma evacuation in comparison to conservative treatment (22.4% operated, P=0.522), or presence of PSD (P=0.119). 62% of our patients were currently employed.

In our univariate analysis, baseline hydrocephalus (P=0.014) was the only baseline factor associated with PSD in addition to higher BPI (P<0.001), PASS-20 (P<0.001), and mRS scores (P=0.011), and being currently unemployed (P=0.027). In our multivariate model, adjusted for IVH for tending to associate with PSD (P=0.099), only hydrocephalus (OR 4.78, 95% CI 1.55-14.77, P=0.007), and PASS-20 score (OR 1.05, 95% CI 1.03-1.08, P<0.001, per point) were independently associated with increased prevalence of PSD.

5.5 LONG-TERM MORTALITY, FUNCTIONAL OUTCOME, AND RECURRENT STROKE

The mortality analysis included all but those dying in the first 30 days or lost to follow-up, numbering 268 (79.8%). Analysis of long-term functional outcome included ICH recurrence, post-ICH epilepsy, return to work, and residual symptoms of those 131 (39.0%) alive and willing to participate (Figure 11).

5.5.1 SURVIVAL

Among the 30-day survivors, 1-year survival was 98.1% (95% confidential interval [CI] 96.2-100%), 5-year survival 93.2% (95% CI 89.3-97.1%), and 10-year survival 88.8% (95% CI 84.9%-92.7%).

Factors associated with increased mortality in univariate analysis included male gender (HR 3.9, 95% CI 1.49-10.08, P=0.005), diabetes (HR 3.33, 95% CI 1.37-8.11, P=0.008), and IVH (OR 2.11, 95% CI 1.04-4.28, P=0.039). After Cox regression model adjusted for age and factors tending to associate with mortality in univariate...
analysis (NIHSS score [$P=0.094$] and structural etiology [$P=0.096$]), higher risk of death was independently associated with male gender (OR 3.36, 95% CI 1.28-8.80, $P=0.014$) and diabetes (OR 2.64, 95% CI 1.01-6.89, $P=0.047$). Those with IVH (OR 1.89, 95% CI 0.93-3.84, $P=0.081$) tended to die slightly earlier than those with no IVH after that adjustment. Mortality among diabetic males with IVH was higher than for females without diabetes and IVH (50.0% vs. 11.4%, $p=0.018$). Hematoma evacuation had no significant effect on long-term mortality when measured by Kaplan-Meyer survival analysis ((log rank $P=0.326$).

5.5.2 FUNCTIONAL OUTCOME

As Figure 15 shows, in mRS distribution of the 131 patients, 67 (51.1%) achieved favorable functional outcome (mRS 0 or 1). Median BI was 100 (IQR 100-100, range 15-100) with an association with age group ($P=0.004$), but no association with gender ($P=0.470$) or with hematoma evacuation ($P=0.751$).

In the univariate analysis, increasing age ($P<0.001$), hypertension ($P=0.004$), presence of IVH ($P=0.013$), brain herniation ($P=0.020$), onset NIHSS score ($P<0.001$), and non-structural underlying etiology of ICH ($P=0.048$) were associated with unfavorable outcome. In the multivariate logistic regression analysis including these same covariates and other parameters with a univariate trend, hematoma volume ($P=0.070$), presence of hydrocephalus ($P=0.067$), surgical hematoma evacuation ($P=0.061$), as well as gender ($P=0.669$), we found that independent factors associated with poor outcome at follow-up were higher age (OR 1.09, 95% CI 1.03-1.15, $P=0.002$ per year), higher initial NIHSS score (OR 1.17, 95% CI 1.08-1.27, $P<0.001$, per point), and IVH (OR 3.26, 95% CI 1.11-9.55, $P=0.031$).

5.5.3 STROKE RECURRENCE

Recurrent ICH occurred 12 times in 10 patients (7.6%), at a median of 3.9 (2.6-4.8) years after the index ICH. Etiology of initial and recurrent ICH was hypertension in 2, cavernoma in 2, AVM in 2, Moya-Moya disease in 1, vasculitis in 1, and unknown in 2 patients. Ischemic stroke struck 4 patients (3.1%) at a median of 2.7 (1.4-4.1) years after the index ICH. Cumulative rate of ICH recurrence was 1.9% (95% CI 0-3.8%) during the first year and 11.2% (95% CI 7.3-15.1%) at 10 years.
5.5.4 RETURN TO WORK

Of the 131 patients, 119 (90.8%) were employed before the ICH, and 63 (48.1%) were employed at follow-up. Rate of current employment was higher among younger patients: of 21 (75.0%) out of 28 patients aged 16-29;16 (61.5%) out of 26 patients aged 30-39; 25 (32.5%) out of 77 patients aged 40 to 49 years at ICH onset (P<0.001), but no association emerged between current employment and gender (P=0.324) or hematoma evacuation (P=0.879).

5.5.5 DWELLING

Of the 131 patients, 110 (84.0%) were living in their homes without requiring assistance from outside their family, 14 (10.7%) required assistance in their daily living, and 7 (5.3%) were living under continuing institutional care. Those with favorable outcome were more often living at home without assistance (Table 15).
Table 15. Residence and functional outcome after intracerebral hemorrhage at a young age

<table>
<thead>
<tr>
<th>Factor</th>
<th>At home without assistance (n=110)</th>
<th>At home with assistance (n=14)</th>
<th>Nursing home (n=7)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0</td>
<td>30 (27.3)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>mRS 1</td>
<td>37 (33.6)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>mRS 2</td>
<td>27 (24.5)</td>
<td>3 (21.4)</td>
<td>1 (14.3)</td>
<td></td>
</tr>
<tr>
<td>mRS 3</td>
<td>15 (13.6)</td>
<td>9 (64.3)</td>
<td>3 (42.9)</td>
<td></td>
</tr>
<tr>
<td>mRS 4</td>
<td>1 (0.9)</td>
<td>1 (7.1)</td>
<td>3 (42.9)</td>
<td></td>
</tr>
<tr>
<td>mRS 5</td>
<td>0</td>
<td>1 (7.1)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%)  
mRS, modified Rankin Scale

5.5.6 EPILEPSY

Pre-ICH epilepsy had been diagnosed among 4 (3.1%), and post-ICH epilepsy among 30 (22.9%) patients, 27 (20.6%) of whom currently received AED. No association appeared between post-ICH epilepsy and hematoma evacuation (P=0.470). Early seizures within 7 days of ICH had occurred in 8 (6.1%) patients and late seizures (>7 days after ICH) in 22 (16.8%). The initial late seizure occurred with a median of 1.3 years (0.7-1.6) after ICH; early seizure occurred in 8 of 30 patients with post-ICH epilepsy (26.7%). The cumulative rate for late seizures was 5.1% (95% CI 1.2-9.1%) during the first year following ICH, and 13.7% (95% CI 7.8-19.6%) during the following 10 years. Post-ICH epilepsy developed among 13 (36.1%) patients with lobar hematoma, 6 (11.8%) with deep hemispheric location, 1 (5.3%) with infratentorial, and 9 (45%) with mixed location (P=0.001).

5.5.7 RESIDUAL SYMPTOMS

Some level of one-sided motor dysfunction symptoms were reported by 55 (42.0%) patients, and some kind of one-sided sensory dysfunction by 52 (39.7%). Difficulties in producing or understanding speech were reported by 27 (20.6%), spasticity by 36 (27.5%), visual field impairment by 21 (16.0%), and diplopia by 14 (10.7%). Sixty-one (46.9%) patients reported to have currently less energy than before ICH, and 5 (3.8%) patients reported difficulties to carry out daily activities due to fatigue. Mild difficulties with sleeping were reported by 53 (40.8%), and moderate or severe difficulties by another 24 patients (18.5%).
5.5.8 QUALITY OF LIFE

Forty-six patients (35.4%) in total stated being in full health in terms of EQ-5D health state being 1-1-1-1-1, and the value for health 1. The median health value was 0.824 (0.708-1) with range from 0.077 to 1. The distribution across the variables of EQ-5D are shown in Figure 16. Higher initial NIHSS score at baseline, as well as developed PSD and unfavorable outcome independently predicted worse quality of life (Tables 16 and 17).

Figure 16. Quality of life of survivors of intracerebral hemorrhage at young age.
Table 16. Univariate analysis on factors associated with health-related quality of life measured by EQ-5D.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Health value (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.824 (0.708-1)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.818 (0.66-1)</td>
<td>0.372</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>16-29</td>
<td>0.919 (0.818-1)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>0.824 (0.715-1)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>0.785 (0.655-1)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.723 (0.618-0.826)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.723 (0.592-0.785)</td>
<td>0.086</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>0.733 (0.627-0.879)</td>
<td>0.608</td>
</tr>
<tr>
<td>NIHSS score at arrival</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-6</td>
<td>0.838 (0.793-1)</td>
<td></td>
</tr>
<tr>
<td>7-14</td>
<td>0.723 (0.654-0.818)</td>
<td></td>
</tr>
<tr>
<td>&gt;14</td>
<td>0.66 (0.592-0.760)</td>
<td></td>
</tr>
<tr>
<td>Hematoma volume</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-30 mL</td>
<td>0.824 (0.723-1)</td>
<td></td>
</tr>
<tr>
<td>30-60 mL</td>
<td>0.723 (0.634-1)</td>
<td></td>
</tr>
<tr>
<td>&gt;60 mL</td>
<td>0.66 (0.624-0.747)</td>
<td></td>
</tr>
<tr>
<td>Infratentorial hematoma location</td>
<td>0.824 (0.721-0.879)</td>
<td>0.870</td>
</tr>
<tr>
<td>IVH</td>
<td>0.723 (0.654-0.919)</td>
<td>0.093</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>0.794 (0.659-1)</td>
<td>0.425</td>
</tr>
<tr>
<td>Herniation</td>
<td>0.723 (0.658-0.797)</td>
<td>0.143</td>
</tr>
<tr>
<td>Multiple hemorrhages</td>
<td>0.886 (0.564-1)</td>
<td>0.858</td>
</tr>
<tr>
<td>PSD present</td>
<td>0.716 (0.626-0.803)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unfavorable outcome (mRS 2-5)</td>
<td>0.706 (0.618-0.785)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are median (IQR)

Table 17. Linear regression analysis on factors associated with quality of health measured by EQ-5D health value.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Unstandardized Coefficient for Health value (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.031 (-0.014-0.077)</td>
<td>0.173</td>
</tr>
<tr>
<td>Age at onset per year</td>
<td>-0.001 (-0.004-0.002)</td>
<td>0.375</td>
</tr>
<tr>
<td>NIHSS score at onset per point</td>
<td>-0.004 (-0.008-[-0.001])</td>
<td>0.016</td>
</tr>
<tr>
<td>Hematoma volume per 10 mL</td>
<td>0.003 (-0.007-0.014)</td>
<td>0.517</td>
</tr>
<tr>
<td>PSD present</td>
<td>-0.089 (-0.144-[-0.033])</td>
<td>0.002</td>
</tr>
<tr>
<td>Unfavorable outcome (mRS 2-5)</td>
<td>-0.180 (-0.231-0.129)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
6 DISCUSSION

6.1 GENERAL DISCUSSION

In this study, a hospital-based registry of young adults with first-ever ICH was created and survivors were reevaluated by inviting for a follow-up visit. The database was linked to the national cause-of-death register to obtain reliable data on vital status. Until now, most data on ICH in the young have based on relatively small patient samples. We collected data on over 300 consecutive young patients with ICH and compared their risk factors, underlying causes, imaging, treatment, and outcome to over 900 older ICH patients in an existing database. To the best of our knowledge, we are the first to execute such a comparison. Moreover, data on functional outcome of survivors of ICH at young age have been practically absent. Our results therefore substantially improve our understanding of young-onset ICH.

ICH in the young has been studied in a dozen hospital-based cohorts, two of which were published only very recently.110,244-254 These studies have been constructed in a similar pattern, by retrospectively defining the risk factors, causes, and mortality on the basis of chart notes and imaging archives. Distribution between sexes in our study (59.5% men and 40.5% women), and our results regarding the incidence of ICH are in line with previous studies, as well as on our finding that the incidence of ICH rises substantially after 40 years of age.16

6.2 RISK FACTORS AND CAUSES OF INTRACEREBRAL HEMORRHAGE IN THE YOUNG

The most common risk factor in our series was hypertension, followed by smoking, and excessive alcohol consumption, which was more common among our ICH patients than reported among Finnish population on average (9.8%).829 Our results regarding the prevalence of hypertension, smoking, and heavy drinking are consistent with previous studies of ICH in the young. Our results, however, also conclude that young victims of ICH have less cardiovascular risk factors, e.g. hypertension, diabetes, and cardiac diseases, than the elderly.

The most common etiology in our series, causing one-fourth of all ICH, was hypertensive microangiopathy, which has been reported from 11% to 79 %,109,252 Structural lesions also caused approximately one-fourth of the ICH, having ranged from 17% to 65% in previous studies.110,245 These differences probably result from
small sample sizes, local settings, and non-uniform diagnostic strategies. According to our and others’ findings, the etiology underlying ICH at young age is far more often attributed to structural and rare causes as compared to elderly patients.\textsuperscript{109,246,247} The cause underlying ICH, especially a structural or rare cause, was significantly more frequently defined, if both angiography and MRI was performed besides head CT. MRI and angiography should be, therefore, considered in routine basis on young adults with ICH.

6.3 SHORT-TERM MORTALITY AND PREDICTORS OF EARLY MORTALITY AFTER INTRACEREBRAL HEMORRHAGE

In perspective of other studies reporting high early mortality after ICH, the short-term outcomes of our patients were fairly good. Over one-third were functionally independent at hospital discharge and 3-month mortality was less than 20%, substantially lower than that in the elderly. These findings are mostly in accordance with prior young ICH studies, although many of them have reported higher than 20% early death rates. The prognosis thus appears to be much better in the young than in the elderly. ICH in the young appears less fatal compared to ICH in the elderly without a trend in hematoma volume by age. This may result from the facts that they have less comorbidities and more active treatment strategies carried out. Furthermore, our results indicate, that hematoma volume was independently associated with 3-month mortality only in the elderly. Reasons for this finding are unclear and further research is warranted.

The effect of neurosurgical intervention on mortality in patients with ICH has remained controversial so far. In our observational study, surgical hematoma evacuation was drastically associated with reduced 3-month mortality in young adults: their odds for dying were >90% lower as compared with non-surgically treated patients after adjusting for confounders. The relative risk reduction was 71% lower even after comparison with propensity-matched patients who did not undergo hematoma evacuation. The effect of evacuation was assessed both by adjusting for confounders in a traditional logistic regression model and by comparing similar propensity-matched patients with and without intervention. In the latter comparison including patients who underwent hematoma evacuation, the most surprising observation was that those patients undergoing hematoma evacuation had larger hematoma volumes and more often brain herniation, and, despite these disadvantageous features, they fared better. These parameters should rather indicate higher mortality, as pointed out by multiple reports.\textsuperscript{10,275,277,281-283} The effect of surgical hematoma evacuation on short-term mortality in nonselected patients has been analyzed specifically in one retrospective study focusing on ICH in the young, and the finding was similar, yet not as striking as our results (OR 0.21 vs.
OR 0.06 in multivariable analysis).\textsuperscript{110} In clinical trials on the general population with ICH, however, no substantial difference between the death rates of those treated conservatively or with surgery has been found.\textsuperscript{432,433,484} Young patients, virtually absent in these trials, according to our results have often lesser risk factors and comorbidities, and therefore recover better from surgery in comparison to their elder counterparts. In our cohort, most patients undergoing evacuation of hematoma had a non-structural cause underlying ICH. Etiology underlying ICH being structural or not was included in our regression model, and in the nearest matching neighbor analysis. Structural causes were sufficiently frequent in propensity score analysis. In this regard the evacuation of hematoma was associated with better prognosis whether the cause was structural or not. Therefore, when significant deterioration occurs in a young patient with ICH and surgical options are considered, physicians should not make pessimistic treatment decisions based on negative randomized controlled trials, instead, an active approach seems to be in the best interest of these patients. Our results indicate that the value of surgical interventions needs to be tested separately in young patients in a future randomized controlled trials as benefit may be much higher in this subgroup.

Other independent factors associated with increased 3-month mortality on our study included more severe symptoms on admission, infratentorial hematoma location, hydrocephalus, herniation, and multiple hemorrhages. These are in accordance with other studies on general and young patients with ICH.\textsuperscript{76,109,110,274,275,279,281,830} In patients with hydrocephalus, no difference was found in functional outcome if a ventriculostomy was placed in one study, a finding in accordance with ours.\textsuperscript{279}

The distribution of locations of ICH has varied in previous studies on ICH in the young with lobar accounting for 25 to 55\%, deep 22\% to 50\%, and infratentorial 16 to 20\%.\textsuperscript{109,110,251,830} Thus, our results are in accordance with prior findings. Furthermore, comparing with ICH in the general population, the distribution of ICH location seems similar at all ages. Multiple hemorrhages have been reported in 3\% of young and general ICH patients, which is less than in our cohort (8\%).\textsuperscript{109,110,831,832} In our study, intraventricular extension of hemorrhage was considerably more frequent than previously reported in the young (36\% versus 3-4\%).\textsuperscript{109,110} However, in the general population the results concerning the presence of IVH (41-57\%) are similar to our finding.\textsuperscript{275,279,432,433}

### 6.4 COMPLICATIONS OF INTRACEREBRAL HEMORRHAGE

Electrolyte and glucose disturbances, hyperglycemia and hyponatremia in particular, were common in the acute phase among young patients with ICH. After adjusting for confounders, only hyperglycemia was independently associated with increased 3-month mortality. Infections were as well rather frequent, but young patients seem
to survive them. Importantly, increasing number of separate complications was associated with increasing odds for death. Our observations suggest that randomized trials aiming to investigate not only treatment of hyperglycemia in ICH but a holistic approach to treatment of medical complications to improve patient outcomes is warranted. Further, this finding underlines one of the mechanisms how stroke unit care reduces mortality rates as prevention and quick treatment of complications in stroke patients is a hallmark of well-organized stroke units.

Hyperglycemia has been reported to worsen the outcome after ICH, but the underlying mechanisms remain unresolved.\(^{312-313}\) One possibility is that hyperglycemia and diabetes may cause pathologic reaction on vasculature.\(^{165-167}\) Our and others’ results indicate that better understanding on the role and mechanisms of hazard of hyperglycemia is needed. Hypoglycemia in our cases most likely occurred due to excessive insulin treatment. The rates of hypoglycemia among stroke patients have not been previously reported. No association was observed with hypoglycemia and mortality, as was shown for ischemic stroke, which may have occurred due to our relatively small patient sample.\(^{567}\) The optimal criteria and method for treatment of hyperglycemia are not solidly defined, and should, be further investigated in a properly designed clinical trial.\(^{559,560}\)

Potassium disturbances and outcome after ICH has not yet been previously studied. Prevalence of hyponatremia among ICH patients has been reported 15.6\%, and it has been identified as a predictor of in-hospital mortality in a recent study.\(^{581}\) Our findings, in contrast, suggest that hyponatremia or other individual electrolyte disturbances do not increase mortality in young ICH patients. Our results are also in contrast to previous studies reporting respiratory infections being associated with poor outcome in general patients with ICH or ischemic stroke.\(^{338,610,650,652,654,655}\) Possible explanations include our patient sample being relatively small, young adults tolerating small electrolyte disturbances better than their elderly counterparts with more comorbidities, as well as more aggressive treatment strategies. Our results, however, are in line with previous studies regarding the incidence of respiratory infections, and they causing longer hospitalization.\(^{610,650}\)

According to a previous report, UTI is more severe than pneumonia among patients with ICH, which is in contrary to our findings.\(^{654}\) Reason for this is also unclear, but this could be explained with UTIs being discovered early by routine urine samples and being treated effectively with antibiotics. Antibiotic treatment was initiated in half of our patients, which is markedly more than number of patients in which the infection site could be detected, suggesting that only a suspicion of an infection based on fever or mildly elevated inflammatory parameters frequently leads to administration of antimicrobial treatments.

In regard of venous thrombotic events, more aggressive DVT surveillance is probably needed, since even in our series of young ICH patients, approximately 5\% suffered from DVT or pulmonary embolism. By our results, no myocardial ischemic
in-hospital events were encountered and arrhythmias were considerably rare, which is in accordance to our previous report in nonselected ICH patients. Although arrhythmias were more common in those dying within 3 months, no significant correlation with short-term mortality was observed after adjusting for confounders, which is probably due to the low number of cardiac events (n=4).

A recent study found chronic kidney failure in nearly one-third of general ICH patients and it was associated with higher mortality. Renal failure was associated with higher risk of death in our univariate analysis, but not after adjusting for other prognosticators. The relatively high number of renal failure observed in our study reflects the criteria we used and that many patients having renal failure even before ICH, but nevertheless, requires further studies in various ICH patient populations on the same topic.

### 6.5 LONG-TERM OUTCOME OF INTRACEREBRAL HEMORRHAGE AT YOUNG AGE

Among the 30-day survivors cumulative mortality 10 years after ICH was approximately 11%, with diabetes and male sex independently predicting shorter survival. Only half of the survivors achieved a favorable outcome, and less than half were by then employed. Higher age, more severe initial stroke, and IVH were prognostic factors for poor functional outcome, while hematoma volume and surgical evacuation of the hematoma were not independently associated with outcome.

Long-term survival of young ICH patients has been reported only once, very recently. Those investigators reported a cumulative 5-year mortality of 6.1%, 10-year mortality of 10.3%, and 20-year mortality of 13.7% among 91 patients surviving one month, findings in accordance with ours. In comparison to young adults with ischemic stroke, their reported 5-year mortality of 7.9% looks comparable to that of young ICH patients. Furthermore, long-term survival from ICH also appears to be markedly better among the young in comparison to general population, since a recent meta-analysis reported fewer than one-third surviving the first 5 years. One possible explanation for this is that the young have fewer risk factors and comorbidities affecting survival, as we have shown. We identified male gender and diabetes as independent factors predicting survival, which have also been identified as prognostic for poor outcome in ischemic stroke, and diabetes specifically associated with increased mortality among ICH patients. Diabetes may cause deleterious effects on the microvasculature, resulting in hematoma expansion and impaired neuroregeneration.

Regarding functional outcome among the young long-term survivors, our results are in agreement with those of the only study that has reported long-term functional outcome among young ICH patients: approximately half of the survivors achieved
an mRS score of 0 or 1. Poor functional outcome in 57% (mRS 3–5) and an independence rate of 47% among the acute-phase survivors has been reported for unselected ICH patients, implying that young patients recover better also with regard to functional outcome. Several studies have investigated the predictors of functional outcome in the general ICH population, but with no studies concerning this issue particularly for young patients. With few differences, they have reported consistent prognostic factors for poor outcome: larger hematoma volume, IVE, infratentorial hematoma, more severe symptoms at arrival, and higher age. In our analysis, increasing age, initial symptom severity, and IVE were associated with unfavorable outcome at long-term follow-up.

Our results concerning return to work are in line with the only study that has investigated this after young-onset ICH. They reported a 2- to 3-fold higher risk for unemployment than in the general population. Only 48.1% of our patients were employed at follow-up, despite the fact that more than half had no or only mild residual symptoms. This indicates that returning to modern-day vocational activity after young-onset ICH is a major challenge, and that need for and room for development in rehabilitation schemes may be unmet. Our findings on the quality of life of these patients support this.

A recent meta-analysis reported annual rates of recurrent ICH ranging from 1.3% to 7.4%. Age ≥65 years, lobar hematoma, and previous ischemic stroke have all been associated with increased risk for recurrence. These ICHs most likely resulted from hypertension or CAA. Our results indicate that the risk for recurrence is lower in a young than in a general ICH population. Reasons for this may include more frequent surgically-treatable structural causes underlying young-onset ICH, absence of CAA, and lower frequency of advanced small-vessel pathology. Due to the low number of recurrent events recorded in our series, independent prognosticators could not be analyzed.

Early seizures occurred approximately as often as in an unselected cohort of ICH patients. Late seizures, however, occurred more frequently among our young individuals (17%) than among our unselected ICH patients (9%). Reasons for this remain unresolved, but a possible explanation is those elderly with severe ICH more often dying in comparison to the young. Our results and others’ findings indicate that post-ICH epilepsy is associated with hematoma location.

PSD has been reported to occur in 30% of stroke survivors, with physical disability, stroke severity, hypertension, and cognitive impairment associated identified to predict PSD, which is in line with our findings. Hydrocephalus has not previously been reported to directly associate with PSD. This association seen in our patients may, therefore, be of chance. Hydrocephalus is, however, often associated with increased tissue damage, which could be the cause for PSD by both the pathophysiological and psychological mechanisms. More studies are needed.
to draw conclusions on this matter, and to identify the underlying mechanisms. Current employment in our study was associated with decreased prevalence of PSD. This is in contrary to a recent retrospective study of young stroke patients.\textsuperscript{809} Those able to do work most likely have lesser disabilities, which quite certainly affects their mental health. According to our findings, those having surgical hematoma evacuation seem to have lesser symptoms of depression and pain, but no clear association with increased or decreased prevalence of PSD was found. Severity of PSD correlated with increased disability, which is in line with prior studies.

A major proportion of patients with PSD go untreated.\textsuperscript{798} Our findings support this notion, since only 9% received antidepressant medication, while PSD was present among 23%. The best benefiting patients for the use of antidepressants, as well as the optimal timing for antidepressant initiation is yet to be resolved.\textsuperscript{802,803}

6.6 STRENGTHS AND LIMITATIONS OF THE PRESENT STUDY

Our study has limitations. This is a single-center study. Our patient registry was collected retrospectively based on hospital records. Our criteria for hypertension may have resulted in some bias in the frequency of ICH related to hypertensive microangiopathy. Systematic autopsies were not performed in the study cohort and no uniform brain vascular imaging or MRI protocol was applied. Both of these factors may have led to underestimation of structural causes underlying ICH. The inclusion of ICH caused by tumor may have resulted in some selection bias, since not all diagnoses of tumor were included. Information regarding smoking or drinking habits lacked in almost half of our patients, likely due to their severe strokes hampering reliable communication. No definite uniform guidelines were available upon decision to pursue surgical treatment. Selecting only salvageable hematomas to be evacuated may have caused bias favoring surgery. It is possible that infective and thromboembolic complications may have occurred after the acute hospital period. The ascertainment of PE and DVT depended on the physician pursuing the diagnostic work-up, and clinically silent DVTs have probably also gone undetected. Due to low number of deaths, some of our multivariable estimates concerning impact of complications may be instable and should be interpreted with caution.

The main limitation of our follow-up study is that one-third of the invited patients did not wish to participate in the in-person follow-up, which may be due to being free from physical or emotional symptoms, and so our results in such areas as functional outcome should be treated with caution. Furthermore, some of the residual symptoms may have gone unrecorded in patients not examined in-person. Those patients excluded from the follow-up study represented a group with more severe baseline deficits. Being too disabled was probably the major reason for declining. This may cause a shift towards those less disabled being included; we thus
probably overestimated the true proportion of young ICH patients with favorable outcome. This makes ICH in the young an even more dismal disease than we are able to show. Since our sample size also was relatively small, our results, especially the effect of surgical hematoma evacuation, and association between hydrocephalus and PSD, should be confirmed in a larger prospective study.

Our study’s main strength is the large number of patients making it one of the largest young ICH series to date. Since our hospital serves as the only emergency unit for young stroke patients within the catchment area of 1.5 million inhabitants, our study is rather close to a population-based setting. We also have very detailed medical records based on strict legislation along with electronic imaging and laboratory archives facilitating data retrieval and in part compensating for the disadvantages of the study design. Further, our study, to the best of our knowledge, is the largest to date to include long-term data on young ICH patients, and it provides the longest median follow-up time.

### 6.7 IMPLICATIONS FOR PRACTICE AND FUTURE RESEARCH

Aggressive preventive measures against hypertension, smoking, and excessive alcohol use may be key in reducing risk of first-ever ICH and recurrences. Our data regarding imaging studies performed and establishment of the underlying cause behind ICH, suggests that MRI and vascular imaging should be considered in every young ICH patient. As most young ICH patients, even those with large hematoma, seem to survive their disease, nihilistic approaches, and decisions to limit or withdraw treatment should be avoided. Surgical treatment might be considered more often in these young patients, whether the cause of ICH is structural or not. It remains unresolved, however, should small hematomas be evacuated as well, and the optimal timing for surgery. Further randomized studies are needed to clarify these issues. Optimal strategy is needed to treat and avoid glucose disturbance and other medical complications in the acute phase. In regard of the long-term outcome, more effort in rehabilitation is needed to improve the functional outcomes of the survivors. Our study identified a few baseline factors that may prove useful in modifying long-term outcomes. Large-scale studies are warranted to confirm these results in this understudied patient population. Failing to do so may produce disastrous consequences such as unnecessary mortality and morbidity. ICH patients under rehabilitation, particularly those with severe disability, should also be more attentively followed at the outpatient clinic or rehabilitation unit, and treatment of PSD should be initiated earlier. Reason for hydrocephalus associating with late PSD remains unresolved, and this finding should be verified by another, prospective study.
ICH at young age is rare, but catastrophic incident, with early death-rate being almost 20%, nevertheless less than among the elderly. Cardiovascular risk factors are relatively often present in young ICH patients, but the spectrum of causes differs to that of the elderly. Structural causes and hypertensive microangiopathy cause approximately half of ICH suffered, but rare causes must be kept in mind. ICH caused by medication or CAA are almost non-existent. After careful work-up, an assumed cause could be identified in most young ICH patients. Most predictors of short-term case-fatality are alike in young and elderly ICH patients, but the effect of hematoma volume is not as straightforward as it has been previously considered. In addition, initial hematoma evacuation was associated with substantially lower 3-month case-fatality in young ICH patients. Hyperglycemia is a frequent complication of ICH in young adults and is independently associated with increased early mortality. However, a load of multiple separate complications increased mortality even further. A holistic, multidimensional strategy in their treatment, therefore, is imperative. Of every ten survivors of acute phase ICH at a young age, only one died within 10 years after onset, male sex and diabetes being associated with increased mortality. On the contrary, as many as half the survivors failed to achieve a favorable functional outcome, fewer than half were employed, and a fourth of the patients suffered from PSD. Factors predicting unfavorable outcome included increasing age, initial stroke severity, and IVH. These findings underline the grave importance to improve our current methods of rehabilitation, as well as to develop new and more effective methods. Treatment of depression also appears as an unmet need in young ICH survivors. Post-stroke fatigue, anxiety, pain, and sleeping difficulties were very common in this cohort.
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