SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Investigation of predictors influencing the outcome of acute ischemic and hemorrhagic stroke

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1. Introduction

Cerebrovascular diseases are the second most common cause of death and the predominant cause of disability worldwide. 80-85% of cases are ischemic strokes which are defined as acute focal neurological dysfunction caused by focal infarction at single or multiple sites of brain, spinal cord or retina. Rest of the cases are hemorrhagic strokes caused by the rupture of blood vessels. Hemorrhagic stroke may be further subdivided into spontaneous intracerebral hemorrhage (ICH) which is a focal hematome within the brain parenchyma, and subarachnoid hemorrhage (SAH) which is bleeding into the subarachnoid space usually caused by the rupture of an aneurysm. According to the WHO statistics, 15 million people suffer a stroke in the world annually. 1/3 of stroke patients die, other 1/3 of them are left permanently disabled, placing heavy burden on the family and community. This problem particularly affects the Central-Eastern European countries where the stroke is more frequent, the mortality rate is higher, and the risk factors such as obesity, hypertension and alcohol abuse are more prevalent than is western Europe.

Age is the most remarkable non-modifiable risk factor for stroke and a major predictor of clinical outcome. More than 1/3 of acute strokes occur over 80 years old, and as the life expectancy increases, the incidence of stroke in this age group will continue to rise. Currently, recombinant tissue plasminogen activator (rt-PA) is the only approved and validated treatment for pharmacological revascularisation in AIS. However, despite the high prevalence of stroke in the elderly, data on the safety and efficacy of thrombolysis in the >80 years population were limited for long. This age restriction came from the potential higher risk of cerebral bleeding and caused uncertainty about the risk-benefit profile in these patients. However, more and more data support that patients from this age group still seem to benefit from this treatment. The conclusion of all these studies is that age alone should not be the reason to exclude patients from treatment with iv. rt-PA. On the other hand, in order to select the elderly patients who benefit the most from thrombolysis, we must know the risk factors associated with a worse outcome, thus improving the chances of these patients to survive and have a better functional status.

Hemorrhagic complications are the most feared and least treatable consequences of thrombolytic therapy, which may limit the use of rt-PA in AIS patients. Hemorrhagic complications cover a wide spectrum, which can be defined from a clinical (symptomatic vs. asymptomatic) or radiological (hemorrhagic infarction vs. parenchymal hematoma) point of view. Among them, symptomatic intracranial hemorrhage (sICH) has the greatest importance, occuring in 2-8%of thrombolysed patients. Several studies have demonstrated that hemorrhagic transformation after AIS is associated with poor functional outcome and higher mortality rates, thus it is the main aspect regarding the safety of treament in studied related to thrombolysis. A number of risk factors for sICH

after thrombolysis have been identified. They include older age, greater stroke severity assessed NIHSS, higher blood pressure on admission, history of diabetes mellitus, atrial fibrillation and baseline antithrombotic use, and the presence of acute ischemic changes in the CT scan, all of which are proven poor prognostic factors. Knowledge of these predictors is important and may help clinicians to select the most suitable patients for treatment and improve the safety of thrombolysis.

Spontaneous intracerebral hemorrhage is less frequent compared to the ischemic stroke, but its mortality is higher and the therapeutic are still limited. The emphasis of treatment remains on the conservative management, such as vigorous blood pressure reduction, immobilization and decreasing the elevated intracranial pressure. Neurosurgical interventions are indicated only in selected patients. A number of clinical and radiological prognostic factors have been identified, knowledge of these factors is crucial for choosing the optimal treatment.

In recent decades, new methods have been implicated in the treatment of acute stroke. Although, the result in our center are excepctionally good, examination of individual subgroups may result further improvement. On one hand, our investigations may help to identify more vulnerable, high-risk stroke patients, furthermore they may contribute to the development of even more targeted treatment options for individual patients.

2. Objectives

We investigate the predictors influencing the outcome of acute ischemic and hemorrhagic stroke. We performed three single-center studies:

I. First, we aimed to investigate the risk factors, outcomes and complication rates in *patients older vs. younger than 80 years* treated with intravenous alteplase. The main purpose of the study was to clarify how effective the treatment is, how common they are and what influences the complications of intravenous thrombolysis in the older age group.

II. In our second study, we evaluated the predictors and outcome of intracranial *hemorrhage complications in patients received thrombolytic therapy for AIS*. Beside the well-known risk factors we analyzed the impact of large vessel occlusion and the route of rt-PA. We also evaluated the clinical characteristics and prognosis by hemorrhage type based on Heidelberg Bleeding Classification

III. Third, in a prospective single-centre study we investigate the clinical and radiological predictors influencing the *outcome of spontaneous ICH.*

3. Patients and methods

For the investigation of the effectiveness and safety of thrombolysis in older age and the predictors of postthrombolysis ICH we analyzed 1,253 patients treated with rt-PA at the Stroke Unit (Department of Neurology, University of Debrecen). The data have been collected prospectively for the period between January 1, 2004, and August 31, 2016. Patients are admitted from a 90 km radius of the center, with a catchment area of 600,000 inhabitants and 600–700 acute stroke hospitalizations per year. All the patients were treated and the parameters recommended in the ESO guideline were monitored in the Neurological Intensive Care Unit. For all patients treated over 80 years, permission was obtained from the National Institute of Pharmacy and Nutrition. The studied were also approved by the Regional Istitutional Research Ethics Committee of University of Debrecen (license number: 5473-2020).

For the investigation the predictors influencing the outcome of non-traumatic ICH we enrolled prospectively 116 consecutive patients with ICH between June 1 2017 and June 15 2021 in our observational study, conducted at the Stroke Centre within the framework of GINOP "IRONHEART Study." The study design was developed in accordance with the guiding principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the University of Debrecen and the Ethics Committee of the National Medical Research Council (license number: 16343-5/2017/EÜIG). All patients or their relatives provided written informed consent. Personal data of patients were handled anonymously.

3.1. Investigation the outcome of iv. rt-PA treatment in patients older 80 years

3.1.1. Patients, database

An analysis of 1,253 patients treated with IV-rtPA was conducted. All the patients were treated and the parameters recommended in the ESO guideline were monitored in the Neurological Intensive Care Unit. Some cases, where treatment indications did not follow the guidelines, were excluded, and 1,125 patients' data were analyzed. The patients were divided into two subgroups: patients aged under 80 years and patients aged 80 years or over.

The following parameters were recorded: age, gender, logistic data (stroke onset-to treatment, door-to-imaging, door-to-treatment). Risk factors for stroke, past history, hypertension, diabetes mellitus, atrial fibrillation, prestroke anticoagulation, congestive heart failure and smoking habits were also evaluated. Furthermore, all the patients were tested for blood glucose, cholesterol and triglyceride levels, as well as systolic and diastolic blood pressure on admission. Stroke severity was assessed in accordance with the NIHSS by the neurologist currently on duty in the stroke unit on admission and 24 h later. All the patients underwent brain imaging with computed tomography on

admission, at 24 h after thrombolytic therapy and in case of later neurological deteroriation. Blood pressure, laboratory parameters and onset to treatment time were expressed as mean ± standard deviation. NIHSS scores were presented as medians (1,;3. quartile). The severity of symptoms based on NIHSS was classified as follows: mild (1-7), moderately severe (8-14), severe (15-22), very severe (> 22).

3.1.2. Imaging

Patients with acute stroke were admitted directly to the CT laboratory, where neurological examination, blood sampling and imaging were performed. Non-contrast computed tomography was performed on admission. Arterial occlusion (trunk or at least one branch of any large artery) was identified by CT-angiography. To evaluate hemorrhagic changes, CT was repeated 1 day after treatment and in case of clinical deterioration. We used three definitions for symptomatic sICH as follows: the SITS, the ECASS and the RCT NINDS criteria. The Alberta Stroke Programme Early CT Score (ASPECTS) was determined unblinded to patient characteristics and was stratified to <7 (group I severe) and ≥7 (group II mild), within the mild group patients scoring 10 and less, were examined separately.

3.1.3. Treatment

Intravenous thrombolysis (IVT) was administered according to valid guidelines. Intravenous rtPA (0.9 mg/kg body weight, maximum 90 mg), with 10% of the dose was given as a bolus followed by a 60-min infusion. Elevated blood pressure was decreased below 185/110 mmHg according to guideline recommendations. Neurological status, side effects (allergic reactions, minor bleedings), pulse, blood pressure, temperature and oxygen saturation were monitored continuously.

3.1.4. Outcome

The change in 24-hours NIHSS score was used to characterize the short-term outcome. The modified Rankin Scale (mRS) was used to assess 3 months' outcome. The outcome was dichotomized to favorable (mRS 0-2) and unfavorable (mRS>2) points. At 1 year, the outcome was dichotomized to “dead” and “alive” status. The follow-up took place through a personal visit or phone call (with the patient, relatives, social instituite or family doctor). Patients with missing outcome information were excluded from long-term analysis. Furthermore we assessed the presence of HT, especially sICH, as a separate outcome factor. Beside these patients data, we compared the long-term outcome in patients over 80 years who underwent thrombolysis with the non-thrombolysed patients of the same age using the data from an Eastern European stroke epidemiological study, the MUD (Marosvásárhely-Ungvár-Debrecen) database. This database was chosen as a medical historical

control. Only outcomes could be compared, since imaging workup in 1999–2000 differed from the present, and CT scans were not stored digitally.

3.1.5. Statistical analysis

Statistical analysis was carried out using the SPSS for Windows 19.0 program suite (SPSS Inc. Chicago, USA). Descriptive statistics was performed. Two-group analysis was assessed with Pearson $\chi 2$ test for categorical variables. For continuous variables, Mann –Whitney U test was used. The level of significance was set at $p < 0,05$. Logistic regression models were used to identify the independent predictors of 3-month disability and 1-year case fatality. The analysis was performed with the multivariate general linear model (GLM). In the models, disability at 3 months (mRS >2), and case fatality at 1 year were the dependent variables, and the factors found to be associated with outcome by univariate analyses were entered as confounding variables. The variables were excluded from the analysis one by one, and the variable with $p > 0,05$ and closest to 1.0 was removed, until all features left in the model had $p < 0,05$.

3.2. Investigation the predictors and long-term outcome of intracranial hemorrhage after rt-PA treatment

3.2.1. Patients, database

We performed a single-center prospective study. We analysed 1252 consecutive AIS patients treated with rt-PA, of whom 1124 had IVT, 61 patients underwent IAT while, 67 were given bridging therapy. Data were collected between January 1, 2004, and August 31, 2016. All of the patients were treated at the Neurological Intensive Care Unit, and we monitored the parameters recommended in ESO guideline. The patients were categorized into two subgroups: patients with ICH, and patients without ICH. In the latter group, 37 patients (2.95%) had symptomatic ICH, while 101 patients 116 (8.06%) had asymptomatic ICH.

The collected data included baseline characteristics, common stroke risk factors, prestroke anticoagulation, occurence and location of large vessel occlusion, type of ICH, treatment modality, stroke severity, clinical outcome at 3 months, and mortality at one year. Upon admission, we also checked every patient's blood glucose, cholesterol and triglyceride levels, and systolic and diastolic blood pressure. Blood pressure and laboratory parameters were expressed as mean ± standard deviation. Stroke severity was assessed by the neurologist in the stroke unit, based on NIHSS on admission and 24 hours later. NIHSS scores were presented as medians (1;3. quartile). Three-month outcome was evaluated using mRS scale. Good clinical outcome was defined as score of 0-2. The assessment of mRS was performed during follow-up clinical visits by certified neurologists. At one year, we dichotomized patients into groups 'dead' and 'alive'. The follow-up took place through a

personal visit or phone call (with the patient, relatives, social instituite or family doctor). Patients with missing outcome information were excluded from long-term analysis.

3.2.2. Imaging

All patients underwent non-contrast CT on admission. Arterial occlusion (trunk or at least one 143 branch of any large artery) was identified by CT-angiography. Where available (93.7%), the ASPECTS)was used to assess early ischemic signs on admission. The CT was repeated 24 hours after treatment and in the case of clinical relapse in order to evaluate hemorrhagic changes. Any hemorrhage detected intracranially with imaging within 24 hours after treatment was defined as post-thrombolysis ICH. We rated all follow-up CT scans based on the anatomical description of ICH according to the Heidelberg Bleeding Classification, where hemorrhagic infarction (HI) and parenchymatous hematoma (PH) was used as basic: ***HI-1*** refers to hemorrhagic transformation of infarcted tissue as scattered small petechiae without mass effect (**class 1a**); ***HI-2*** is more confluent petechiae within the infarcted area, but without space-occupying lesion (**class 1b**); ***PH-1*** is defined as a hematoma not exceeding 30% of the infarcted area but with some mild space-occupying lesion (**class 1c**); ***PH-2*** represents hematoma occupying 30% or more of the infarcted tissue, with obvious mass lesion (**class 2**). Other bleeding types are classified as ICH outside the infarcted tissue (**class 3a**), intraventricular (**class 3b**), subarachnoid (**class 3c**) or subdural (**class 3d**). The following parameters were compared in the categories of the Heidelberg Bleeding Classification score: age, ASPECTS on admission and at 24 hours, NIHSS score on admission and at 24 hours, serum glucose level, mRS at 3 months, sICH. Patients with ICH were categorized into sICH and asymptomatic ICH groups. We used three definitions for sICH: SITS, ECASS and RCT NINDS criteria, while asymptomatic ICH was defined as the presence of any hemorrhage without neurological worsening.

3.2.3. Treatment

IVT was performed in accordance with the ESO guidelines. Continuous monitoring of neurological status, pulse, blood pressure, body temperature and oxygen saturation was performed according to guideline recommendations. Patients diagnosed with large vessel occlusion were started on intravenous treatment which was followed by intraarterial administration (“bridging” therapy). IAT was used alone in patients who were not candidates for IV rt-PA. A microcatheter (Progreat TERUMO) was used for endovascular intervention. We navigated it at the site of the occlusions until the occlusion and repeated doses of 5 mg rt-PA were given by electric syringe (1 mg/min) until the artery opened up or the maximum weight adjusted dose was reached. After every 5 mg of rtPA contrast material was given and, if the vessel did not open, we continued the procedure. The study and the intra-arterial use of rt-PA were approved by the Local Research Ethics Committee of the

University of Debrecen. In 11 cases – among which only one patient had ICH – another therapeutic approach, mechanical thrombectomy, which was used, when it was already avaliable. This was negligible compared to other interventions.

3.2.4. Statistical analysis

Statistical analysis was carried out using the SPSS for Windows 19.0 program suite (SPSS Inc. Chicago, USA). Descriptive statistics was performed. Correlations between categorical variables were identified using the Pearson's chi-squared test, and correlations between continuous variables were determined using Mann-Whitney U-test. In order to compare each hemorrhagic transformation group we used the Kruskal-Wallis test for non parametric variables, and one-way ANOVA test for metric variables. Binary logistic regression analysis was used to assess outcomes at 3 months and at one year. Logistic regression models were used to identify the independent predictors of 3-month disability and 1-year case fatality. The analysis was performed with the multivariate general linear model (GLM). In the models, disability at 3 months (mRS >2), and case fatality at one year were the dependent variables, and those factors that were found to be associated with outcome by univariate analyses were entered as confounding variables. The variables were excluded from the analysis one by one, and the variable with $p > 0,05$ and closest to 1.0 dropped out, until all features left in the model had $p < 0.05$. All tests were performed at a level of significance $p<0,05$.

3.3. Investigation of predictors influencing spontaneous ICH

3.3.1. Patients, database

116 consecutive patients with ICH were enrolled prospectively in our observational study, conducted at the Stroke Centre. Inclusion criteria were as follows: patients older than 18 years with acute non-Traumatic ICH, verified with non-Contrast CT (NCCT) scan, not meeting exclusion criteria, and written informed consent. Exclusion criteria included the presence of cerebral aneurysm, arteriovenous malformation, traumatic intracerebral bleeding (epidural or subdural hemorrhage, brain contusion), malignancy, hemorrhagic brain metastasis, severe hepatic and renal insufficiency, hemorrhagic diathesis, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on hospital admission or during follow-up.

The time at symptom onset, baseline characteristics (age, sex, cerebrovascular risk factors, history of cerebrovascular and cardiovascular diseases, previous medications, systolic and diastoloc blood pressure, on admission blood glucose and international normalized ratio (INR) value were recorded on admission. Stroke severity was given according to the NIHSS on admission, 14 ± 2 days and 3 months $\pm$ 7 days after the onset of hemorrhagic stroke. GCS was used to assess the level of consciousness. Categories were formed as follows: ≤ 8 points (severe disturbance, usually means

coma), 9 to 12 points (moderate disturbance), and 13 to 15 points (minor disturbance); in case of 15 points, the patient is fully alert. The following primary outcomes were defined: (1) case fatality at discharge, (2) 3-month mortality, (3) long-term outcome at 3 months ± 7 days after the onset of stroke. mRS 0–2 is defined as favorable long-term outcome. mRS was estimated by two neurologists of the study (including physical examination) on admission, at 14 ± 2 days, at discharge, and 3 months after the onset of stroke. If the patients did not come back for their 3 month follow-up examinations, we arranged for a telephone consultation in order to gather information of mRS.

3.3.2. Imaging

On admission, an NCCT scan was done and when necessary, contrast-enhanced CT or CT angiography was performed to exclude secondary causes of ICH. Follow-up NCCT scans were performed at 14 ± 2 days and at 3 months ± 7 days after the onset of stroke. CT images were analyzed simultaneously by three senior independent radiologists trained in neuroradiology, and a detailed list of radiological data, such as location and volume of bleeding, extent of perihematomal edema, bilateral ventricular/bilateral cortical diameter, degree of midline shift, involvement of pyramidal tract, and presence of intraventricular or subarachnoid component, were recorded. Manual CT volumetry was performed by tracing the focal hyperdense (blood) and perifocal hypodense area surrounding the hemorrhage (edema) on each slice. Total lesion volume was calculated by multiplying the traced area (ROI, cm2) with slice thickness and adding up the results. All tracings were performed by one radiologist.

3.3.3. Statistical analysis

For this study, descriptive statistical analysis was carried out using the SPSS for Windows 19.0 program suite (SPSS Inc. Chicago, IL, USA). Two-group analysis was assessed with Pearson $\chi 2$ test for categorical variables. For continuous variables, Mann-Whitney U test was used. The level of significance was set at $p < 0,05$. Logistic regression models were used to identify the independent predictors of 3 month disability. The analysis was performed with the multivariate general linear model. In the models, disability at 3 months (mRS > 2 was the dependent variable, and the factors found to be associated with outcome by univariate analyses were entered as confounding variables. The variables were excluded from the analysis one by one, and the variable with $p > 0,05$ and closest to 1.0 was removed, until all features left in the model had $p > 0,05$.

4. Results

4.1. Investigation the outcome of iv. rt-PA treatment in patients older 80 years

4.1.1. Baseline characteristics

The patients' age ranged between 17 and 99 years. The mean age of the total population was 68,2 ± 12,4 years, i.e., 64,7 ± 10,8 years and 84,3 ± 3,4 years in the younger and the older groups, respectively, ($p < 0.001$). The majority of the patients in the general population were males (56,3%). There was a significant difference in gender ratio ($p < 0.00001$): in the older group the percentage of female patients (63,3%) was higher than that in the younger group (39,5%).

The risk factors for stroke differed between older and younger patients. Hypertension was the most remarkable risk factor in both groups and was more prevalent among older patients, but the difference was not statistically significant. The history of current or past smoking was the second most common risk factor (42,2%) and was significantly more likely among younger patients.

Atrial fibrillation was significantly more prevalent among patients over 80 years than among younger study participants ($p < 0,00001$). However, only 39,1% of the older patients received anticoagulant treatment before the stroke, while among those who are under 80 this rate was 59,6% ($p<0,0001$). Most of the younger subjects (60.9%) did not receive anticoagulation therapy before stroke, but the patients over 80 had previously been treated with oral anticoagulants much more often than in the younger ones ($p = 0,02$). Among the elderly, congestive heart failure was more common, near the significance level ($p < 0,07$) statistically.

Regarding other risk factors, such as diabetes mellitus, hyperlipidemia and previous stroke, there were no significant differences between the two groups.

Baseline stroke severity was significantly higher ($p < 0,0001$) among patients over 80 years than the younger ones. The median (1;3 quartile) NIHSS scores on admission being 14 (8, 18) and 10 (5, 15), respectively. Time from symptom onset to treatment did not differ significantly in the two groups.

4.1.2. CT characteristics

Significant correlation can only be declared between ASPECT score and outcome at 24 h because of the small numbers of patients in different categories, despite the trends seen in the table. Groups were created according to ASPECT Score on admission CT scan and CT scan done at 24 h. Most strokes were located in the anterior circulation in both age groups. Probability of developing a large artery occlusion was higher among the elderly (63 vs. 53,4%), but the difference is not significant ($p = 0,09$). Most of the patients had ASPECT score ≥7 on admission in both age groups. However, median (1;3 quartile) NIHSS score on admission was higher (14 [9:18] vs. 9 [5:14]) and

ratio of mild strokes (NIHSS score 1–7) was less frequent (20,8 vs. 40,8%) in the older group. At 24 h, 59,6% of patients over 80 years had ASPECT score<7 (p = 0,007) accompanied with higher median (1;3 quartile) NIHSS score. Suprisingly, the ratio of mild strokes after 24 hours was higher in older patients in all ASPECTS groups.

Nevertheless at 24 h there was an improvement, which was significant, and according to the Mann–Whitney U test the improvement was more pronounced in patients ≥80 than in the younger ones (p<0,0001). So altogether the elderly patients had scored more on the NIHSS Scale, but the improvement was better by them.

4.1.3. Outcome

At 24 h, the patients over 80 had higher NIHSS scores than the ones under 80, the median (1;3 quartile) NIHSS scores seen at 11 [4.5;18] and 7 (3, 14), with the difference also being statistically significant (p<0,0001). More than two points of worsening in NIHSS score were seen in 17% of patients over 80 years which is significantly worse (p = 0,034) deterioration compared to the younger ones (14,7%). In addition, significantly less patients (p = 0,00016) achieved at least two points improvement in NIHSS score over the age of 80 compared to the younger group (39,7 and 47,4%, respectively). The mean rank of on admission NIHSS Score by patients under 80 was 599,7 and at 24 h 601,5, while by patients ≥80 years on admission 755,2, at 24 h 731,75 (p<0,0001).

At 3 months, 59,8% of the patients in the older group had unfavorable outcomes (mRS: 3-6), which was significantly worse (p<0,0001) compared to the younger age group (43,2%). However, 34,7% of the patients over 80 had independent outcomes (mRS: 0-2), and more than two thirds of them were able to continue their pre-stroke activities (mRS: 0-1). There was an unfavorable trend regarding the 90-day outcomes for the over-80 patients treated for atrial fibrillation compared to patients of the same age group without atrial fibrillation. While in the former group 27,7% of patients had favorable outcomes, the particular proportion was 41,5%, among the patients without atrial fibrillation. The one-year survival in the older group was 41,7%, while the proportion in the younger group was 63,9% (p<0,0001).

In a logistic regression model of the patients under 80 years, atrial fibrillation and heart failure were significant independent risk factors for worse outcomes at 3 months, whereas among the elderly subjects diabetes mellitus was also a risk factor for a worse outcome. At 1 year, smoking and diabetes mellitus were significant risk factors in the younger group, while no independent risk factor was found among the elderly at 1 year follow-up.

We compared the mortality rates for the patients over 80 years of age having undergone thrombolysis, to the MUD database's non-thrombolyzed patients of the same age at 3 months and 1

year. The results are as follows: at 3 months, in the over-80-group, the mortality rate was 30.1%, and in the under-80 it was 33.3% while, at 1 year, the relevant figures were 46.7 and 56.8%, respectively), but the difference was not significant.

4.1.4. Safety

Regarding the hemorrhagic complications of thrombolytic therapy, intracranial hemorrhage occurred in 125 patients (9%), 69 of them (6,1%) had hemorrhagic infarction, 41 (3,7%) had parenchymal hematoma, while 17 (1,5%) had SAH. sICH was detected in 36 patients (3.2%). Intracranial hemorrhage and SICH did not differ significantly between the elder and younger patients.

4.2. Investigation the predictors and long-term outcome of intracranial hemorrhage after rt-PA treatment

4.2.1. Baseline characteristics

A total of 1252 patients, 702 males (56%) and 550 (44%) females, with AIS received rt-PA treatment (aged 17-99 years; mean age, 67,7±12,9). ICH was detected in 138 patients (11%); sICH occured in 37 patients (2.95%), while asymptomatic ICH affected 101 patients (8,06%). Out of these 138 patients 94 had ischemia-related HT, 6 patients had intracerebral hemorrhage outside the infarcted tissue, 26 had subarachnoid hemorrhage, 11 had intraventricular hemorrhage and only one patient had subdural hematoma. The patients with ICH were significantly older than those without ICH (70±10,3 vs. 67,5±13,2, p=0,041).

None of the analyzed stroke risk factors showed significant differences between the two groups. Compared with the non-ICH group, ICH patients presented with lower serum cholesterol level on admission (4.9±1.04 vs. 4.7±0.49 mmol/l), but the difference was not significant (p=0.053). Baseline stroke severity was significantly higher (p<0,0001) in patients with ICH compared to non-ICH patients (median NIHSS scores on admission were 14 [10;18] and 10 [5;15], respectively).

4.2.2. Imaging and treatment modality

For the entire patient population, LVO was detected in 688 patients (54,9%). The incidence of LVO was significantly higher in the ICH group compared to the non-ICH group (70,7% vs. 52,8%, p=0,0095). ICH was more/most likely to develop as a result of an occlusion in the middle cerebral artery (40,7% vs. 25,6%, p=0,0062), basilar artery (7,1% vs. 4%, p=0,097) and posterior cerebral artery (7,1% vs 2,8%, p=0,15), or in the case of multiple arterial occlusions (9% vs. 4,9%, p=0,27).

Regarding the route of rt-PA administration, IVT occured in 1124 patients, 61 patients received IAT, while „bridging" therapy was done in 67 patients. In the ICH group, the distribution of treatment modalities was as follows: IVT and IAT were given to 100 patients (72,5%) and 24 patients

(17,4%), respectively, while 14 patients (10,1%) received combined therapy. The relevant percentages in the non-ICH group were 89,7%, 4,9% and 5,4%, respectively. The risk of ICH was 9,1% in intravenous thrombolysis, significantly lower than in intra-arterial (39,3%) or combined thrombolysis (20,9%) including mechanical thrombectomy. These data show that the intra-arterial use of rt-PA is associated with a significantly higher rate of ICH (p<0,0001).

4.2.3. Outcome

At 24 hours, the patients in the ICH group had higher NIHSS scores than non-ICH patients (median NIHSS scores 15 [9; 20] and 7 [3;14], p<0,0001). At 3 months, only 26 % of the ICH patients had favorable outcomes (mRS: 0-2), which was significantly worse (p<0,0001) compared to non-ICH group (53,6%). More than one-third of the ICH patients (36,9%) had moderate or severe residual symptoms (mRS: 3-5) and, unfortunately, 35,5% of patients were dead at 3 months. In the non-ICH group, however, those rates were 29.8% and 14.5%, respectively (p<0,0001). At one year, 52.2% of the ICH patients had passed away, while the figure was 23,6% in patients without ICH (p<0.0001).

With logistic regression model (Table 4) at 3 months, significant difference was detected in patients with diabetes mellitus, previous atrial fibrillation, previous cardiac failure and intracerebral bleeding after thrombolysis. From them intracerebral bleeding after thrombolysis was the variable that had a major negative impact on outcome at 3 months and at one year not only ICH, but smoking also.

4.2.4. Characteristics and outcome by the extent of thrombolysis-related HT

HI-2 was more frequent than HI-1, PH-1 and PH-2. Patients who experienced HT were in advanced age, especially in the PH-2 and class 3a groups (p=0,04). Elevated serum glucose levels were more likely in patients with HT, especially in the HI-1 group and in patients with intraventricular hemorrhage (p=0,019). The means of ASPECTS on admission did not differ significantly in the groups, but with follow-up CT scans at 24 hours, significantly lower ASPECT scores were identified in all HT groups. PH-1 and PH-2 were more frequently associated with higher baseline NIHSS scores when compared with no HT (p=0,0004). At 24 hours, the median NIHSS was significantly higher in all HT groups. Mortality and poor outcome were more prevalent in all hemorrhage types with a tendency for massive bleeding associated with unfavorable prognosis. The rates of sICH did not differ significantly in the HT groups.

4.3. Investigation the predictors of spontaneous ICH

4.3.1 Baseline characteristics

Among the 116 patients, significant male predominance ($p < 0.05$) was observed. The patients' mean age was 70 ± 11 years, the oldest and the youngest patients being 93 and 43 years old, respectively. The mean age of women was 73,4 years, whereas the relevant figure for men was 68,6 years (p=0,017). Majority of them (89%) had hypertension in their history, but more than half of the cases had been untreated. From the patients 25% suffered from diabetes mellitus, and 20,6% had cardiac failure or atrial fibrillation.

Systolic blood pressure was generally high, and in 19.85% of the patients, it measured extremely high (>200 mmHg). Similarly, 21.5% of the patients had hyperglycemia. More than one-third (39.6%) of the patients received antithrombotic therapy. On admission, 68,2% of patients had moderately severe or severe stroke (median NIHSS 14,25 [IQR 8;19,25]), but if the subsequent disability was regarded in terms of mRS, the outcome was much poorer, because most of the patients' (69,8%) scores were mRS 5. Based on the GCS score, 34,5% of patients had moderately severe disturbance of consciousness (GCS 9-12), while 13% had coma (GCS≤8).

4.3.2. Imaging

Bleeding was more frequent in the left hemisphere (56%). Bleeding mostly affected the basal ganglia and/or thalamus (75%), lobes (15%), brainstem, and cerebellum (10%). On admission, hematoma volume was between 0,15 cm^3 and 133 cm^3, the mean volume was 26±30.6 cm3 which showed a decreasing tendency during the control examinations. 28% of patients had >30 cm3 hematoma volume which has proven poor a poor prognostic factor (p<0,0001). The mean volume of the perihematomal edema was 12.9±15 cm^3 on admission, and reached the maximal value at 14 days (24.6±29 cm^3). Almost half of the CT scans revealed hydrocephalus, which improved over 3 months. The severity of our cases could be established by, e.g., the presence of blood in the prepontine cistern (7.7%), or by the intraventricular or subarachnoid propagation of the ICH in almost half of the patients (47,4%). Midline shift was apparent on admission in 50% of the cases, and improvement could only be detected in 3 months. Based on the CT scans, a lesion of the pyramidal tract could be confirmed on admission in the majority of the patients (74,1%). At 14 days, involvement of the pyramidal fibers still could be detected more than half of the patients (57,1%), due to the perihematomal edema. At 3 months, lesion of the pyramidal tract could only be detected in less than one-quarter of patients (24,4%) due to the resorption of hematoma.

4.3.3. Logistic regression analysis of outcome predictors

Age was only predictor of functional outcome at discharge [mean discharge time was 19.8 days (1;79)] and previous ischemic stroke at 3 months. Severe disturbance of consciousness (GCS<8) was a strong predictor of poor outcome (p<0,001). Localization was an important predictor, if both

the basal ganglia and thalamus or pons and the midbrain had been affected, a patient's prognosis was poor. >30 cm3 hematoma volume has proven a poor prognostic factor. Blood in the subarachnoid space; ventricles were predictors of mRS on admission and outcome at 14 days and 3 months. Bleeding, edema, and their combined volume all altered the disability significantly. If the CT scan revealed the pyramidal tract was affected, it had an impact on the admission and discharge mRS.

5. Discussion

5.1. Investigation the outcome of iv. rt-PA treatment in patients older 80 years

As life expectancy increases, the proportion of the elderly population is constantly growing. In absolute terms, the number of older persons has doubled over the last 20 years and will more than triple again over the next 30 years. The aging society puts a heavy burden on healthcare, not sparing the stroke care either, especially in very old age. Though, more and more studies come to light on the safety of IV-rtPA treatment in acute ischemic stroke among patients over 80 years, the uncertainty still exists in clinical practice. In this single center study, we analyzed the data of 1,125 patients who underwent intravenous thrombolysis, comparing the baseline characteristics and clinical outcomes between patients over and under 80 years.

5.1.1. Risk factors and outcome

Consistent with previous studies, our findings showed that hypertension was the most important risk factor in both subgroups, and it was more prevalent in older patients. Therefore our study points out that optimizing antihypertensive treatment and maintaining blood pressure below the target level may lower the risk for stroke.

As described in previous studies, older patients were significantly more likely to develop atrial fibrillation than the younger ones. Atrial fibrillation is associated with a five-fold increase in the risk for ischemic stroke, but anticoagulant therapy may reduce the risk of recurrent stroke by ~by 60%. Despite the finding that more than one-third of the patients over 80 years had atrial fibrillation, only 39% were previously medicated with oral anticoagulants. Atrial fibrillation was a significant prognostic factor for more severe functional status in univariate model. More detailed in a logistic regression model, there was a difference between the risk factors among patients under and over 80 years. Atrial fibrillation and heart failure were significant independent risk factors for worse outcomes at 3 months among the younger subjects, whereas diabetes mellitus was also a risk for worse outcome among the elderly. At 1 year, smoking and diabetes mellitus were significant risk factors in the younger group, while no independent risk factor was found among the elderly at 1 year follow-up. These findings suggest that by proactively searching for atrial fibrillation and providing effective anticoagulant therapy, the risk of stroke can be reduced and better functional outcome can be achieved. Regarding other vascular risk factors, the prevalence of diabetes and hyperlipidemia did not show significant differences between the two groups, but the history of current or past smoking was more common in younger age. These findings suggest that changing unhealthy lifestyles is of great importance in the prevention of ischemic stroke in both age groups.

5.1.2. Stroke severity on admission and at 24 hours

Multiple studies have proven that both admission and 24-h stroke severity are poor prognostic factors for long-term outcome. An important result of our study shows that older patients tend to experience stroke of higher severity than younger patients previously reported (median NIHSS score of 14 vs. 10). Furthermore, patients over 80 years of age also had significantly higher NIHSS scores at 24 h than younger patients did. Nevertheless according to the Mann–Whitney U test, by the elderly patients the improvement was better. These results suggest that thrombolytic therapy has a positive effect in patients above 80 years.

5.1.3. CT parameters and outcome

Regarding the correlation of CT parameters and outcome, we found that on admission ASPECT score was similar in the groups of patients above and under 80 years ($p = 0.319$), but despite this the on admission NIHSS score was higher in the elderly and less patients had milder strokes on admission. Large artery occlusion was more frequent in the elderly ($p = 0.09$), and although there was no sign of hyperacute ischemia, it had an effect on ASPECT at 24 h. ASPECT score at 24 h was less favorable in elderly patients ($p = 0.007$). Not surprisingly with the help of 24 h ASPECT score prognosis could be estimated closer than with the on-admission ASPECT score. Interestingly, the ratio of mild strokes at 24 h was less with all ASPECT score by younger patients. This might emphasize the importance of functional collaterals in older ones. Analyzing the 3 months mortality, a higher rate can be detected among elderly patients especially, if the ASPECT score is <7 points, younger patients have a better chance to survive at 3 months even with more severe CT abnormalities.

5.1.4. Long-term outcome

As for the long-term outcome, the functional status at 3 months turned out to be significantly worse in the older age group. This result is consistent with most of the recent studies which have shown lower rates of favorable and independent outcomes at day 90 among patients over 80 years of age. Despite the above, older patients still benefited from IV-rtPA because more than one-third of them were able to live independently. It should also be noted that the modified Rankin Scale not only estimates function loss due to stroke, but the prevalence of disability increases with age, regardless of stroke. Similarly, the one-year mortality rate does not only reflect deaths due to stroke, as its prevalence increases with age regardless of stroke.

5.1.5. Safety

The occurrence of the ICH, SICH was similar in patients below and above 80 years. This is especially important, if we consider that the ratio of the large artery occlusion was more frequent in

patients above 80 years. This confirms the safety of thrombolysis in elderly patients. Concerning the risk of therapy, in our study SICH occurred in 3.2% which is somewhat less than reported in major rtPA trials (NINDS 6.4%, ECASS II 8.9%). A hypothesized higher risk for intracerebral hemorrhage is often cited as the reason for excluding very old patients from thrombolytic treatment. Amyloid angiopathy, decreased renal rtPA clearance, and frail vasculature in the elderly are asserted as explanations for a possibly increased risk of suffering an intracerebral hemorrhage. However, many other studies had previously reported that the occurrence of SICH did not differ significantly between younger and older groups of patients. Our results are in line with these studies as we have found that the prevalence of SICH tended to be lower in older than younger patients (2.1 and 3.5% respectively, not significant). Further investigation is needed to determine the underlying cause.

The comparison of our results with the MUD database also supports the safety of thrombolysis because the mortality rates do not differ among over 80-year-old patients after thrombolysis compared with the non-thrombolyzed patients of the same age.

5.2. Investigation the predictors and long-term outcome of intracranial hemorrhage after rt-PA treatment

Currently rt-PA is the only approved and validated treatment for pharmacological revascularisation in AIS. The treatment option for rtPA has been selected is according to the current gudielines for IV treatment, at the time of our study IAT could be given according to the ESO 2008 guideline. But today IA is given after mechanical thrombectomy in the frame of studies or alone in mild acute ischemic strokes. The majority of patients undergoing thrombolysis have a good prognosis compared with patients not receiving thrombolysis. However, the use of thrombolytic therapy is associated with an increased risk of ICH, which can reduce the chances of favorable outcomes. In this prospective single-center study, we analyzed the data of a total of 1252 AIS patients having undergone thrombolysis. We estimated the incidence, predictors and outcome of ICH after treatment. The rate of sICH in our study was 2.95%, while asymptomatic ICH occured in 8.06%, which, in line with previous international studies, shows that it is one of the most common and serious complications of thrombolysis.

5.2.1. Baseline characteristics and risk factors

Age is the most remarkable non-modifiable risk factor for stroke and a major predictor of clinical outcome. The literature on the risk of sICH after thrombolysis in the elderly is divisive. Several studies have previously shown that advanced age is an independent risk factor for sICH, and was considered as a relative contraindication for 3-4.5 hour IVT by many guidelines. However, many other articles have reported that the incidence of sICH does not differ significantly between younger

and older patients, and this age group still seems to benefit from treatment, as it was mentioned in our previous publication. In the present study, the patients with ICH were significantly older than those without ICH. At the same time, in our previous study, when thrombolyzed patients were dichotomized into those aged ≥ 80 years and those 80 years, statistically speaking, the risk of sICH was not significantly greater in the older group. These data suggest that patients over 80 and suffering from acute stroke should not be excluded from treatment with rt-PA based on their risk for sICH.

Although a history of hypertension, being the most significant pre-existing risk factor, was present in 76.3% of the patients in the overall population, we could not find any significant correlation in either the presence of hypertension or the mean blood pressure values on admission between the ICH and non-ICH groups. Other comorbidites, including diabetes mellitus, previous stroke, smoking, atrial fibrillation, pre-stroke anticoagulation, congestive heart failure and alcohol consumption were not correlated with ICH in present study. However, we found that elevated baseline blood glucose was more likely in the HI and PH subgroups, which was consistent with previous findings where it had been shown that serum glucose was a predictor of ICH in patients treated with rtPA treated. Some reports suggest that lower serum total cholesterol and triglyceride levels are associated with an increased risk for ICH. We also found a similar trend, although no statistical significance was reached (p=0,053). A possible explanation for this relationship is that cholesterol plays an important role in the integrity of small cerebral vessels and the neurovascular unit.

5.2.2. Stroke severity

It is an important finding of our study that the NIHSS scores at presentation and at 24 hours are significantly higher in patients with ICH. NIHSS measures stroke severity, which is primarily associated with the size of a cerebral infarction. The higher the NIHSS score values are, the more severe the strokes and the larger the infarcts may become. Most of the previous studies including NINDS and ECASS trials have also shown that the severity of a baseline stroke is one of the most important predictors of ICH after thrombolysis. In our study, subgroup analyses across the HT groups showed that PH-1 and PH-2 were associated with higher baseline NIHSS scoresthan the HI groups were. It has been suggested that the underlying mechanism of HI and PH differ from each other. Previous studies revealed that HI frequently occured without the use of rt-PA as a natural phenomenon in the course of ischemic stroke, while severe PH was mainly associated with treatment using alteplase. It can be an explanation to our finding that severe ischemic stroke with higher baseline NIHSS is suggestive of larger areas of infarcted tissue, including injured blood vessels, which are more likely to bleed after thrombolytic treatment. However, in our study the median NIHSS scores at 24 hours were significantly higher in all HT groups compared to no HT. These data suggest that

post thrombolysis hemorrhage is associated with early deteroriation of neurological symptoms regardless of the extent of bleeding.

5.2.3. The impact of large vessel occlusion and treatment modality

In the present study, the incidence of LVO was found to be 54.9%, slightly higher than the rate (24-46%) reported in the literature. Our results showed that LVOs, especially occlusions in the middle cerebral artery (MCA) were significantly more prevalent in ICH patients, as also found in previous studies. The MCA is the largest intracranial artery and by far the most commonly affected vessel in AIS. The occlusion of this artery may lead to massive cerebral infarction which is one of the most dangerous factors of HT. Development of an extensive brain edema and enchanced permeability of vascular walls caused by prolonged ischemia and hypoxia may be the possible explanation for the higher probability of HT. Therefore, the presence of a LVO obviously shows positive correlation with the incidence of ICH after thrombolysis.

Regarding the route of administering rt-PA we found that the hemorrhage rate in patients treated with IVT was comparable to the rates reported in large thrombolysis trials. Another conclusion of our study is that intra-arterial use of rt-PA is associated with a significantly higher rate of ICH, which is also consistent with previous findings. Large multicenter studies (PROACT II, MELT, IMS II) have proven the efficacy of performing intraarterial thrombolysis in LVO, although the indications and dosage of IAT remained less well standardized. The rate of ICH in the aforementioned studies has ranged from 10% to 15%, which is comparable in agreement with our results (11%). In the CHOICE trial IAT was given after mechanical thrombectomy - this is different from our scenario, because our IAT patients did not undergo mechanical thrombectomy - in 61 patients (vs. 52 placebo) sICH was 0% compared with placebo, but overall cerebral haemorrhage was 19%. Based on our results, it seems that intra-arterial use of rt-PA is a risk factor for ICH after thrombolysis. However, it should be noted that in those patients where IAT was performed, there was always LVO, which was associated with more severe stroke, so this alone predisposes to hemorrhagic transformation. Therefore, the IAT alone is presumably not responsible for the worse outcome. Nowadays the first choice of LVO treatment is thrombectomy, but rt-PA treatment should be started, if needed before it, emphasizing the impact of our study in every-day use.

5.2.4. Long-term outcome

Finally, as far as the long-term outcome is considered, the functional status at 3 months has turned out to be significantly worse in the ICH group. This result is consistent with most previous studies which showed lower rates of favorable and independent outcomes in patients with ICH at day 90. Similarly, the one-year mortality rate is also significantly higher in the ICH patients. Based on

these studies, the fatality rates are between 50 and 80%, which is consistent with our result (50,7%). However, two factors need to be mentioned regarding the effect of ICH on outcome. First, it is still unclear how the extent of HT influences the long-term functional outcome. An ECASS-II study reported that none of the radiological subtypes of hemorrhage have the same effect on outcome. There is no doubt that massive HT is likely to be associated with clinical worsening, while HI might be a clinically irrelevant phenomenon of ischemic damage and reperfusion. Our results showed that both HI and PH have a negative impact on patient outcome, which is consistent with some previous studies suggesting that HI grades of HT may not be benign. Second, there is an overlap between risk factors for thrombolysis-associated ICH and risk factors for poor outcome following thrombolytic therapy in the absence of ICH. Thus the observed poor outcomes are more probably related to the combination of the ICH and the underlying ischemic event itself.

The logistic regression model shows the importance of regular screening of the population suffering from diabetes mellitus, atrial fibrillation, cardiac failure, stroke, and the quitting smoking. Intracerebral bleeding was a strong predictor of worse outcome even in these models at 3 months and at one year as well.

5.3. Investigation the predictors of spontaneous ICH

5.3.1. Baseline characteristics and admission parameteres

There were significantly ($p < 0,05$) more male patients in our database. It is also important to note that—compared to females—male patients were younger on average (mean difference was 4.8 years). Our previous studies among ischemic stroke patients have also shown male predominance, and they have had more severe stroke, at a younger age. This shows that their health condition is generally worse. This might mean that being a male patient means a higher risk for stroke.

Hypertension is a known risk factor for ICH, which can also be demonstrated by the history of our patients; 89% of them had hypertension, and what is even more important, half of them were not treated for it. Especially their systolic blood pressure was high; the diastolic values were mostly normal or only mildly elevated. Untreated hypertension and high systolic blood pressure on admission are more commonly found in this study than in certain previous databases. These facts emphasize the importance of primary screening and education among laypeople. By means of screening and education, some of the tragic ICH cases could have been prevented. Although blood sugar levels were not fasting values, in one in five patients (21.5%), the serum glucose concentration exceeded 10 mmol/L. The prevalence of ischemic stroke was similar to previous data, but previous hemorrhagic stroke was rare, and 12.9% of the patients received chronic anticoagulation treatment, whereas 19.8%

was given antiplatelet drug. Among the patients, 12.9% had atrial fibrillation, but heart failure was rare. These data are similar to our findings with ischemic stroke patients.

5.3.2. Neurological findings and imaging

One of the important clinical signs influencing the outcome and mortality in ICH patients is the disturbance of consciousness. On admission, more than half of our patients had only mild impairment or none, but with univariate analysis, it was a significant prognostic factor of outcome. On admission, the enrolled patients had moderate and severe symptoms based on the NIHSS score and mRS, respectively, which alone might indicate a poor prognosis. High hospital (39.1%) and 3 month mortality figures (46.5%) have been similar to those in recently published studies.

ICH was more frequent in the left hemisphere (56%). The size and site of the bleeding influenced the prognosis. Worse prognosis was noted, when the bleeding destroyed both the basal ganglia and thalamus or pons, or the midbrain.

As expected, on-admission bleeding volume gradually decreased over 14 days and 3 months. Contrarily, the edema volume increased over 14 days, and then in 3 months, it reached the value as in the first CT scan. We found that the bleeding volume together with the volume of the perihematomal edema was high not only on admission, but also at 14 days, and might even have caused a midline shift. This combined volume seemed to be a better predictor according to our neurophysiological examinations, where the on-admission normal findings or mild abnormalities worsened for 14 days but improved at 3 months. With univariate analysis, the blood and edema volume and their combined sum all had a significant effect on the outcome. Gebel et al. investigated the absolute and relative edema (edema volume divided by hematoma volume). They found that only relative edema was strongly predictive of functional outcome.

Almost 50% of the patients had intraventricular and subarachnoid appearance, which decreased relatively quickly and was predictive of a poor outcome. Similarly, intraventricular bleeding was a risk for worse prognosis in the literature. IVH extension after spontaneous supratentorial ICH is a risk of worse outcome and neurological deterioration, resulting in death in 32 to 43%. The volume of the IVH alone is not always informative; sometimes even a smaller amount of blood in the intraventicular space can cause severe symptoms, and higher amount less significant (e.g., occlusion of the foramens or the third and fourth ventricles contains the majority of the bleeding and disturbs the cerebrospinal fluid's circulation, leading to extended ventricles).

In the literature, some useful quantitative and semiquantitative methods can be found measuring IVH extension and modified Graeb Scale, but measuring IVH volume is possible too.

6. Summary

Background: Cerebrovascular diseases are the leading causes of morbidity and mortality worldwide. However, limited data is available regarding the outcome in some of it's subgroup. In our study, we analysed the factors affecting the short- and long-term outcome of acute ischemic stroke (AIS) and spontaneous intracerebral hemorrhage (ICH).

Methods: First, data of 1,253 thrombolysed patients were analyzed retrospectively using the Debrecen Thrombolysis Database. Vascular risk factors, stroke severity based on the National Instituite of Health Stroke Scale (NIHSS) score, functional outcome using modified Rankin Scale (mRS), mortality and symptomatic intracerebral hemorrhage (sICH) were compared between patients <80 and ≥80 years. In our second study, vascular risk factors, stroke severity, functional outcome and mortality at one year were compared between patients with and without ICH following rt-PA treatment. Third, 116 patients with ICH were enrolled prospectively in our observational study. Clinical examinations and non-contrast computed tomography (NCCT) scan were performed on admission, 14±2 days and 3 months±7 days after stroke onset.

Results: NIHSS scores on admission and at 24 h were higher in elderly patients ($p < 0.0001$). At 3 months, 59.8% of the patients from the older group had an unfavorable outcome ($p < 0.0001$), however 34.7% had independent outcome. The incidence of sICH not differed significantly between the two groups. Higher on admission and 24 hour NIHSS score, large vessel occlusion and intraarterial thrombolysis were significant predictors of postthrombolysis ICH. Both at 3 months and at one year the outcome was worse in ICH patients compared to the non-ICH group ($p<0.0001$). Mortality and poor outcome were more prevalent in all hemorrhage types with a tendency for massive bleeding associated with unfavorable prognosis. In almost 20% of the spontaneous ICH patients excessive hypertension was measured on admission, accompanied with >10 mmol/L blood glucose level, whereas 47,5% had Glasgow Coma Scale ≤12. >30 cm^3 blood and perihematomal volumes, and presence of blood in the ventricles or subarachnoid space meant poor prognosis.

Conclusion: Although, the outcomes were less favorable in patients over 80 years of age, our results support the feasibility of using intravenous thrombolysis among patients over 80 years of age. Older age, higher NIHSS, large vessel occlusion and intra-arterial thrombolysis may correlate with ICH. Unfavorable outcome is more common in ICH patients. Precise scoring of post-thrombolysis bleeding might be a useful tool in the evaluation of the patients' prognosis. Together with the clinical symptoms, the volume of bleeding, perihematomal edema (or their combined volume) and presence of intraventricular or subarachnoideal hemorrhage play an important role in the neurological outcome of patients with ICH.

7. Main findings and conclusions

I. Regarding the investigation the outcome of iv. rt-PA treatment in patients older 80 years, according to our results, patients with acute ischemic stroke and over 80 years seem to have an increased risk for unfavorable outcome and a higher mortality rate compared to their younger counterparts. However, intravenous thrombolysis is an effective and safe treatment in this age group, as more than one-third of the patients were capable of living independently and the rate of SICH was lower compared to younger patients. Although, the outcomes were less favorable in patients over 80 years of age, our results support the feasibility of using intravenous thrombolysis among patients over 80 years of age. Consequently, these data support that age by itself should not be a reason to exclude patients over 80 years old from IV-rtPA treatment.

II. Regarding the investigation the predictors and long-term outcome of intracranial hemorrhage after rt-PA treatment we found that patients of older age, having higher NIHSS, suffering from an occlusion affecting a large intracranial artery and treated with intra-arterial rt-PA were at an increased risk for ICH after thrombolysis. Those patients seemed to have worse long-term functional outcome and higher mortality rates than patients without ICH, so ICH after thrombolysis was a strong predictor of worse outcome in univariate and multivariate analysis as well. We found that precise scoring of post-thrombolysis bleeding might be a useful tool in the evaluation of the patients' prognosis. To our knowledge this was the first study with real life scenario in our region on this patient population.

III. We created a prospective database to investigate the outcome of spontaneous ICH patients. With logistic regression analysis we found that lower (<12) GCS score on admission, elevated blood pressure and glucose values and higher age were significant predictors of poor outcome. Localization of the bleeding was an important predictor, similarly to the presence of blood in the subarachnoid space and cerebral ventricles. If the CT scan revealed the pyramidal tract was affected, it had an impact on the admission and discharge mRS. Bleeding, edema, and their combined volume all altered the disability significantly.

8. Publications

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Registry number: DEENK/21/2023.PL
Subject: PhD Publication List

Candidate: Máté Héja
Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. Fekete, K., **Héja, M.**, Marton, S., Tóth, J., Horváth, L., Harman, A., Fekete, I.: Predictors and long-term outcome of intracranial hemorrhage after thrombolytic therapy for acute ischemic stroke: A prospective single center study.
Front. Neurol. [Epub ahead of print], 2023.
DOI: http://dx.doi.org/10.3389/fneur.2023.1080046
IF: 4.086 (2021)

2. **Héja, M.**, Fekete, I., Horváth, L., Márton, S., Fekete, K.: Experiences With Intravenous Thrombolysis in Acute Ischemic Stroke by Elderly Patients?: a "Real World Scenario".
Front. Neurol. 12, 1-10, 2021.
DOI: http://dx.doi.org/10.3389/fneur.2021.721337
IF: 4.086

3. Fekete, K., Tóth, J., Horváth, L., Márton, S., **Héja, M.**, Csiba, L., Árokszállási, T., Bagoly, Z., Sulina, D., Fekete, I.: Neurophysiological examinations as adjunctive tool to imaging techniques in spontaneous intracerebral haemorrhage: IRONHEART study.
Front. Neurol. 12, 1-15, 2021.
DOI: http://dx.doi.org/10.3389/fneur.2021.757078
IF: 4.086

List of other publications

4. Lóczi, L., Orbán-Kálmándi, R. A., Árokszállási, T., Fekete, I., Fekete, K., **Héja, M.**, Tóth, J., Csiba, L., Bagoly, Z.: Thrombin generation as a predictor of outcomes in patients with non-traumatic intracerebral hemorrhage.
Front. Neurol. 13, 1-12, 2022.
DOI: http://dx.doi.org/10.3389/fneur.2022.912664
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5. Orbán-Kálmándi, R. A., Árokszállási, T., Fekete, I., Fekete, K., **Héja, M.**, Tóth, J., Sarkady, F., Csiba, L., Bagoly, Z.: A Modified in vitro Clot Lysis Assay Predicts Outcomes in Non-traumatic Intracerebral Hemorrhage Stroke Patients: the IRONHEART Study.
Front. Neurol. 12, 1-11, 2021.
DOI: http://dx.doi.org/10.3389/fneur.2021.613441
IF: 4.086

6. Árokszállási, T., **Héja, M.**, Bagoly, Z., Kovács, K. B., Orbán-Kálmándi, R. A., Sarkady, F., Tóth, J., Fekete, K., Fekete, I., Csiba, L.: Prognostic value of various hemostasis parameters and neurophysiological examinations in spontaneous intracerebral hemorrhage: the IRONHEART study protocol.
Front. Neurol. 12, 1-6, 2021.
DOI: http://dx.doi.org/10.3389/fneur.2021.615177
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