VILNIUS UNIVERSITY

ALEKSANDRAS VILIONSKIS

PREDICTING OUTCOME OF INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE

Summary of the Doctoral Dissertation
Biomedical Sciences, Medicine (06 B)

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Dissertation was prepared at Vilnius University Neurology and Neurosurgery Clinic in 2010-2014.

Scientific supervisor:

Prof. Dr. Valmantas Budrys, MD, PhD (Vilnius University, biomedical sciences, medicine - 06 B)

Scientific consultant:

Prof. Dr. Dalius Jatužis, MD, PhD (Vilnius University, biomedical sciences, medicine - 06 B)

Dissertation will be defended at the Scientific Council of Medicine Sciences of Vilnius University:

Chairman:
Prof. Habil. dr. Aleksandras Laucevicius, MD, PhD (Vilnius University, biomedical sciences, medicine – 06 B)

Members:
Prof. Dr. Diana Obelieniene, MD, PhD (Kaunas University of Health Sciences, biomedical sciences, medicine – 06 B)
Assoc. prof. Dr. Ingrida Uloziene, MD, PhD (Kaunas University of Health Sciences, biomedical sciences, medicine – 06 B)
Assoc. prof. Dr. Katrin Gross-Paju, MD, PhD (Tallinn University of Technology, biomedical sciences, medicine – 06 B)
Dr. Ruta Mameniskiene, MD, PhD (Vilnius University, biomedical sciences, medicine – 06 B)

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VILNIAUS UNIVERSITETAS

ALEKSANDRAS VILIONSKIS

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Mokslinis vadovas:

prof. dr. Valmantas Budrys (Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B)

Konsultantas:

prof. dr. Dalius Jatužis (Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B)

Disertacija ginama Vilniaus universiteto Medicinos mokslų krypties taryboje:

Pirmininkas – prof. habil. dr. Aleksandras Laucevičius (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B)

Nariai:

Prof. dr. Diana Obelienienė (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06 B)
Doc. dr. Ingrida Ulozienė (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06 B)
Doc. dr. Katrin Gross-Paju (Talino technologijos universitetas, biomedicinos mokslai, medicina – 06 B)
Dr. Rūta Mameniškienė (Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B)

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CONTENT

ABBREVIATIONS

AF – Atrial Fibrillation

CI – Confidence Interval

CT – Computerized Tomography

ICH – Intracerebral Haemorrhage

IQR – Interquartile Range

IVT – Intravenous Thrombolysis

MCA – Middle Cerebral Artery

MRI – Magnetic Resonance Imaging

mRS – Modified Rankin Scale

NIHSS – National Institutes of Health Stroke Scale

OR – Odds Ratio

rt-PA – Recombinant Tissue Plasminogen Activator

RVUH –Republican Vilnius University Hospital

SENI –Significant Early Neurologic Improvement

TCD – Transcranial Doppler

VUHSK – Vilnius University Hospital Santariskių Klinikos

Introduction

Acute ischemic stroke is a serious medical emergency that affects around 1000000 people in Europe every year. Mortality rate from the first stroke is estimated to be 25.6%. In case of recurrent subsequent strokes it may reach as high as 49.2%. Approximately 80% of all ischemic strokes occur within the anterior cerebral circulation system. The remaining 20% - within the posterior circulation system. According to the Kaunas stroke register, in 1994, incidence of the first stroke was 184 per 100000 among men, aged 25 to 64, and 98 per 100000 among women. To date, no single treatment has been proven to be effective in treating patients with an acute ischemic stroke except intravenous thrombolysis (IVT). The aim of IVT is to break down the thrombus or embolus within a cerebral artery, restore blood flow and reduce brain tissue damage in the area of the ischemia. To this purpose, a clot dissolving agent (a recombinant tissue plasminogen activator, which catalyzes the conversion of plasminogen into the plasmin that is responsible for clot breakdown) is injected into the vein. However, IVT may only be applied to a very limited number of patients. First of all, the treatment is only safe and effective if applied within 4.5 hours of the stroke's onset. Secondly, there are some contraindications restricting IVT's application even among patients who have sought out treatment in time.

Worldwide, thrombolysis began to be applied in 1995. However in Europe it was only approved as the first choice treatment for acute ischemic stroke in 2002. Even after its approval, IVT's application in day to day practice continues to differ wildly not just from country to country, but often even within different regions of the same country. This depends on a number of factors, first and foremost on the ability to diagnose an acute cerebrovascular disorder in time, to deliver the patient to a specialized medical institution and to carry out, within a minimal period of time, all the tests necessary for the safe application of IVT. Therefore it is very important to optimize all tasks involved in treating such patients, starting with their arrival to the hospital. It is no less important that emergency medical services (EMS) personnel would also exercise the utmost vigilance in dealing with such patients.

Intravenous thrombolysis has its own specific complications that further limit its wider application. Among the most dangerous of them are haemorrhagic complications – bleeding in various areas of the body including the brain. Knowledge of symptomatic intracerebral haemorrhage risk factors is very important in selecting patients for this treatment, and also in explaining to the patient and their relatives the real danger of complications in a specific case.

When IVT first began to be applied in daily practice, its therapeutic time window was 3 hours after initial symptoms emerged. Studies conducted in 2008 demonstrated that IVT remains safe and effective when applied within 4.5 hours of the initial emergence of symptoms. However, it was not until 2012 that manufacturers first approved official recommendations allowing IVT to be applied within the 4.5 hour window. This expanded time window allowed a greater number of patients to be treated. Also, in recent years, endovascular methods of treatment have begun to feature more and more regularly in clinical practice: intra-arterial thrombolysis (dissolving the clot with medicaments injected into the clotted artery via catheter) and mechanical thrombectomy (physically removing the clot from the clogged artery with a catheter). This allows treatment of patients in cases where IVT is either not efficient enough, or impossible due to contraindications. All this together allows us to maximize the efficiency of the treatment supplied to patients, thus improving the treatment's results and reducing acute stroke-induced disability.

Even though IVT has been approved as the first choice of treatment for an acute ischemic stroke since 2002, a number of questions still remain unanswered. One of them is the case of older (over 80 years old) patients. According to official manufacturer recommendations, these patients are not eligible for IVT. However, in actual clinical practice its application is not uncommon.

Another relevant question is the combination of IVT and endovascular treatment. Since endovascular therapy is often used as a complementary treatment, there are no clear and uniform recommendations as to when it should be applied. It is believed to be especially beneficial for patients with otherwise poor prognosis. Therefore determining such prognosis prior to starting treatment could help to improve patient selection.

Relevance and Importance of the Study

In Lithuania, IVT has been applied since 2002 and in recent years around 200 IVTs are performed annually. However, to date, there have been no attempts at a complex analysis of questions such as the efficiency and safety of IVT in Lithuania, nor has the prognosis of patients been evaluated. Also, efficacy and safety of IVT in specific patient groups has never been assessed. It is likely that our patients suffer from more severe strokes and more complex comorbidities, which could impact upon the efficiency of IVT treatments. Prognostic factors for stroke outcomes in Lithuania might differ slightly from those of the Western European population. Therefore, outcome prognosis remains a very important problem in daily practice. At the moment, several prognostic models for outcome and complications have been offered, however they are only validated for Western European and Asian populations. There have not yet been any studies that would assess the validity and accuracy of these models for the populations of Eastern Europe, including Lithuania.

Application of new endovascular methods of treatment allows for the improvement of outcomes, however these methods cannot be applied to all the patients. Therefore careful and deliberate selection of patients eligible for such treatment is of the utmost importance. As of yet, there have been no attempts to examine this process in Lithuania. As a result, there are no clear recommendations as to what types of patients could or should be chosen for this treatment. The introduction of set guidelines would help to facilitate patient selection for endovascular or combined treatment. That could improve the results of these treatments. A prognostic model designed for the target population would also help to predict the efficiency of IVT treatments with more accuracy and provide more reliable information to patients and their relatives, as well as improve patient selection for IVT.

Aim of the Study

Identify prognostic factors for the outcome of an acute ischemic stroke treated with intravenous thrombolysis and assess prognostic models' suitability for the target population.

Objectives of the Study

1. To evaluate the short-term and long-term outcomes of ischemic stroke treatment with intravenous thrombolysis; assess the safety of intravenous thrombolysis.
2. To evaluate and compare the efficacy and safety of intravenous thrombolysis across different age groups.
3. To identify the prognostic factors for the outcome after 3 months in case of ischemic stroke treated with intravenous thrombolysis.
4. To identify the prognostic factors for early significant neurologic improvement.
5. To assess the accuracy of prognostic models for the outcome of an acute ischemic stroke treated with intravenous thrombosis in the target population.

The Scientific Novelty of the Study

The scientific novelty and originality of this work lies in the complex analysis of patients who have suffered from an acute ischemic stroke and were treated with IVT. Analysis included identifying the effects that various risk factors, the severity of the stroke and comorbidities may have on the efficiency and safety of IVT as well as evaluating the reliability of the prognostic factors and their combinations for the outcome of an ischemic stroke treated with thrombolysis. Over the course of this study, positive and negative prognostic factors for both short-term and long-term outcomes have been identified, and the safety and efficiency of IVT for older patients has been assessed.

This is the first time that issues of IVT's efficacy and safety, of the prognostic factors for stroke's outcome, and of the suitability of existing prognostic models for our population have been analysed in Lithuania. This is also the first time when original prognostic model for determining the long-term outcome of a stroke treated with IVT was composed. The model was created with reference to the prognostic factors identified during the study and is targeted specifically at our population.

Defended propositions

1. Intravenous thrombolysis remains to be an effective method of treatment for patients of advanced age.
2. The prognostic models for stroke outcome must be adjusted with regards to the particularities of the target population
3. Our created original prognostic model can be used in predicting stroke outcomes.

The Practical Value of the Study

The results of this study are relevant to doctors of various specialties dealing with patients who have suffered from an acute ischemic stroke.

The risk factors and comorbidities that are related to acute stroke treatment results and can help to identify patients in need of more intensive treatment and/or additional testing were analysed in this study. The proposed prognostic model for treatment outcomes enables to provide patients and their relatives with more accurate information.

The results of treatments administered outside the boundaries of protocol have also been investigated, and shown to be justifiable. This both allows IVT to be applied to a greater number of patients and improves the results of such treatments.

Subjects and Methods

This study was carried out in the Republican Vilnius University Hospital (RVUH) department of neurology and intensive care unit, and in the Vilnius University Hospital Santariskių Klinikos (VUHSK) department of neurology and intensive care unit. The study lasted from October 2010 to November 2013. These are the only two hospitals within the city and region of Vilnius eligible to treat ischemic strokes with intravenous thrombolysis.

The study was approved by the Vilnius regional biomedical research ethics committee (permits No. 158200-06-346-87, No. L-14-03/1, No. L-14-03/4).

Patients from RVUL and VULSK who had suffered from an acute ischemic stroke and had been treated with IVT were included in the study. Patients had to meet the following criteria to be included in the study:

1. Clinically diagnosed acute ischemic stroke;
2. Ischemic stroke treated with IVT, following the recommendations of the Lithuania Stroke Association (LIA) and the European Stroke Organization;
3. Patients had been informed about the protocol of the study, had agreed to take part in the study and had signed an informed consent form.

A control group was not formed due to ethical concerns. IVT is the standard method of treatment. Therefore failure to provide it to patients who have suffered from an acute ischemic stroke and have been declared to be eligible for IVT is inexcusable.

The relevant details regarding medical history of patients who had agreed to take part in the study and had been approved for it were collected by means of a study-specific form. The timing of the first onset of symptoms; the timing of the patient's arrival to the hospital; the time period between initial symptoms and arrival to the hospital; and the time period between arrival to the hospital and the application of IVT were assessed. Neurological symptoms were assessed using NIHSS scale before starting IVT. Assessment was repeated three more times: after two and 24 hours after starting IVT, and also seven days after IVT. Functional status was assessed using the modified Rankin Scale (mRS). Functional status was

assessed retrospectively up to the first onset of the stroke, and prospectively seven days and then three months after the stroke.

Upon a patient's arrival, their age, gender, vascular disease risk factors, usage of medications, blood pressure, neurological status according to NIHSS and functional status before the onset of the stroke were all recorded. If a patient's functional status according to the mRS was >0, the reason for this was also recorded. Two hours after IVT, the patient's condition would be re-evaluated and medication prescribed for stroke treatment would be recorded. After 24 hours, the patient's blood pressure and neurological status would be assessed once again, and medication prescribed for stroke treatment would be recorded. At the 24 hour mark, all patients were scheduled for repeated brain CT scans. Additionally, overall clinical outcome would also be assessed at this stage. After seven days blood pressure, neurological status, medication used and general clinical outcome would all be re-evaluated.

In order to analyse the long-term outcome, a patient's functional status would be assessed using the modified Rankin Scale and registered three months after the treatment; patients would also be asked about any vascular events that may have occurred over this period. In the event of a death, the patient's relatives would be consulted regarding the time and cause of death, and any new vascular events that may have occurred. A new vascular event was defined as a new stroke (cerebral infarction, intracerebral haemorrhage) or a myocardial infarction.

In order to assess IVT's efficacy in the early stages, the concept of significant early neurological improvement (SENI) was used. SENI was defined as either a neurological improvement of four or more points according to NIHSS, or a full reversal of neurological deficit (score of 0-1 according to NIHSS), recorded two hours after starting IVT.

Two categories were defined for evaluation of outcomes: good outcome (0 – 1 points according to mRS) and bad outcome (2-6 points according to mRS).

Several factors were considered in assessing the safety of IVT:

1. 3 months mortality;
2. 3 months mortality due to first ischemic stroke;
3. Mortality due to IVT complications;

4. Incidence of severe extracranial bleeding;
5. Incidence of symptomatic intracerebral haemorrhage.

IVT complications are defined as any new and unwelcome events that had emerged after IVT. Severe extracranial bleeding is defined as any extracranial bleeding that had appeared after IVT and was either the cause of death, or of at least one of the following actions:

1. Prolongation of inpatient treatment,
2. Transfusion of blood or blood components.

Symptomatic intracerebral haemorrhage is defined as a type II parenchymal intracerebral haemorrhage accompanied by a neurological deterioration of 4 or more points according to NIHSS. A type II parenchymal haemorrhage is described as a haemorrhage that exceeds 30% of the ischemic zone and has a pronounced mass effect. This definition is in accordance with the definition used in the SITS-MOST study. It was chosen due to its frequent usage in other studies.

On arrival, all patients were scheduled for a non-contrast head computed tomography (CT). The images were then used to evaluate the zone of acute ischemia, the hyperdense middle cerebral artery signal and symptoms of cerebral oedema. Head CT would then be repeated 24±6 hours after the initiation of IVT. In cases of deteriorating neurological condition, cranial CT would be repeated immediately. The images from the repeat CT scans were used to evaluate not only all the same elements that were assessed in the first head CT, but also the presence of haemorrhagic transformation. The same classification for haemorrhagic transformations as used by ECASS2 and other studies was applied in this study.

Since some patients' neurological condition was deteriorating due to progression of cerebral oedema caused by cerebral infarction, cerebral oedema and its size were evaluated separately. The COED classification was used to evaluate the extent of cerebral oedema in CT imaging.

Any of the following signs were considered to be neurovisual markers of an acute cerebral ischemia: 1) loss of grey-white matter differentiation; 2) local decrease in brain tissue density; 3) gyral effacement. In cases of deteriorating neurological condition, head CT was

performed immediately in order to confirm or rule out intracranial haemorrhage and cerebral oedema. The evaluation of CT images was then carried out in accordance with previously described methodology.

Statistical analysis

Data was analysed using the statistical software package SPSS 17.0 (version for Windows). Descriptive statistics for normally distributed quantitative variables are provided by using means (m) and standard deviations (SD); in other cases, the median (M) and the interquartile range (IQR) are provided instead. Descriptive statistics for qualitative (discrete) variables are provided by using an absolute number (N) and percentage in relation to the analysed sample (%). The averages of two independent samples of quantitative variables that fit rules of normal distribution were compared using Student's t-test; dependent samples were compared using Student's paired criteria. Other features of Quantitative variables were compared using the nonparametric Mann-Whitney test. Qualitative variables were compared with one another using the Chi square test ($\chi 2$). In cases of small sample sizes it was supplemented with Fisher's exact test. The significance level selected at $\alpha = 0.05$.

In order to examine the influence of independent variables and predict IVT's long-term consequences, logistic regression models (Forwald LR) were created. The stepwise selection of independent variables was used. Variables were included in the model if p was less than 0.05 and removed from it if p was more than 0.1. In cases where independent variables correlated strongly with one another, only one variable was selected for use. The Youden index was used to determine cut-off points. The reliability of prognostic models was evaluated using the ROC curves test. The test was considered to be positive when $p < 0.05$

Results

The results of this study are analysed in the following order:

1. The characteristics of the study population.
2. The treatment outcomes within the study population.

3. The comparison of features such as demographic, clinical, radiological examination and clinical status dynamics in patients with different treatment outcomes.
4. The comparison of demographic and clinical features, radiological examination results and treatment outcomes across different age groups.
5. The identification of factors that influenced clinical outcomes.
6. The analysis of various prognostic models‘ accuracy with regards to the study population.

206 patients treated for acute ischemic stroke by IVT in the RVUH and in the VUHSK were included in the study from 2010 to 2013.

51% of the patients included were male (n = 105) and 49% were female (n = 101). The average age of patients was 67.5 ± 11.7 years. Patients aged 80 and over comprised 13.1% of all study population (n = 27). Two patients (1%) had greater than mild degree of disability before the onset of the stroke; however, the pathology was temporary and had no relation to the stroke. Nine patients' functional condition prior to the onset of the stroke could not be determined.

31.7% of all patients had two risk factors, 10.9% – three risk factors, and 4.0% of all patients – four risk factors. In other words, 46.6% of all patients had two or more risk factors. The median neurological deficit according to NIHSS was 14 (IQR 11 – 18).

41 patients (19.9%) had been using antiplatelet before the onset of the stroke, 88 patients (42.7%) had been using antihypertensives, and 10 patients (4.9%) had been using blood glucose lowering medication.

Upon arrival, average blood glucose levels were 6.4 ± 1.8 mmol/l. Blood glucose levels of over 8.0 mmol/l were documented in 14.8% of all patients on arrival; in 6.2% of all patients, blood glucose levels were higher than 10 mmol/l.

Average time from the initial onset of symptoms to arrival to the hospital was 77.1 ± 43.9 minutes; average time from arrival to the initiation of treatment – 65.3 ± 28.1 minutes.

Average time from initial onset of symptoms to the initiation of treatment was 143.8 ± 43.1 minutes. Comprehensive analysis of logistical features is presented in Table 1.

Table 1. Logistic parameters of IVT treatment

Parameter			Result
Time from the initial onset of symptoms to the arrival at the hospital, min.		Mean ± SD	77.1 ± 43.9
Time from the arrival at the hospital to the initiation of treatment, min.		Mean ± SD	65.3 ± 28.1
		Median (IQR)	62 (47 – 80)
Time from the initial onset of symptoms to the initiation of treatment, min.		Mean ± SD	143.8 ± 43.1
		Median (IQR)	142 (115 – 170)
Percentage of patients who had IVT initiated in:	0 – 30 min. from the arrival at the hospital	%	8.1
	31 – 60 min. from the arrival at the hospital	%	42.1
	61 – 90 min. from the arrival at the hospital	%	39.1
	91 – 120 min. from the arrival at the hospital	%	10.7
Percentage of patients who had IVT initiated in:	0 – 90 min. from the initial onset of symptoms	%	9.7
	0 – 180 min. from the initial onset of symptoms	%	8.5
	181 – 270 min. from the initial onset of symptoms	%	15.5

IVT – intravenous thrombolysis, SD – standard deviation, IQR – interquartile range

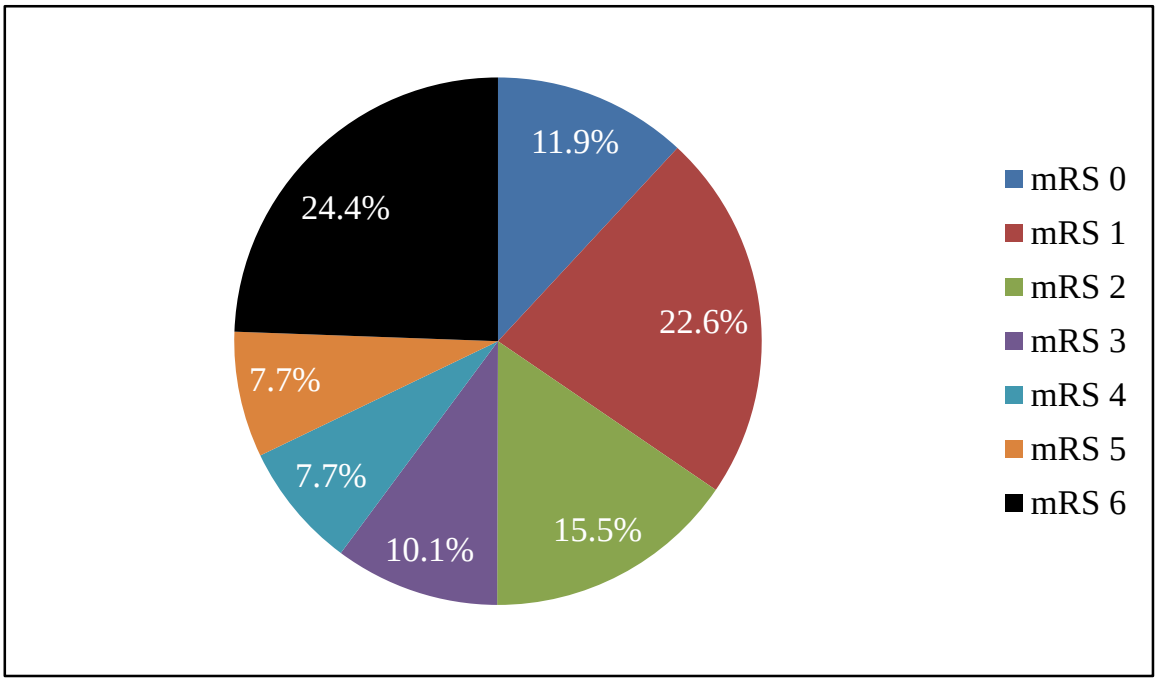
15% of all patients had IVT applied outside of the therapeutic time window as officially approved at the beginning of the study (the 4.5 hour therapeutic window was only approved in August 2012).It is worthy to note that only 8% of all patients received treatment within 30 minutes or less from the arrival to the hospital, and only half of all patients had been started on IVT within an hour of their arrival to the hospital. Only one tenth of all patients had IVT initiated within 90 minutes of the initial onset of symptoms. This indicates the need for further analysis in order to determine the reasons behind the delays in application of IVT.

A non-contrast head CT was performed on all patients prior to treatment. In the initial CT scans, 21 patients (10.2%) had signs of an acute ischemia, however these did not exceed one third of the vascularised territory. Symptomatic hyperdense MCA signal was diagnosed in 60 patients (29.1%).

After three months, functional status was assessed for 168 patients (81.6%) using mRS. A more detailed analysis of patient distribution according to their functional status is shown in Fig. 1. At that point, 58 patients (34.5%) were considered to have a good outcome. 41 patients (24.4%) had died during the period of three months. The main causes of death were ischemic stroke (16 patients), symptomatic ICH (4 patients) and pulmonary embolism (3 patients). In nine cases, the cause of death could not be determined; all nine patients had died after the discharge from hospital.

After two hours SENI was observed in 73 patients (39.0%). In 19 cases patient‘s condition was not evaluated. Average systolic blood pressure was 146.9 ± 21.3 mmHg, diastolic – 82.6 ± 13.5 mmHg. Two hours after initiation of IVT, average neurological deficit according to NIHSS was 11.7 ± 6.8 points; this constituted a significant decrease from the baseline (14.7 and 11.7, $p < 0.001$, Wilcoxon test). After 24 hours, the condition was assessed for 193 patients. Head CTs were performed for 190 patients. Changes characteristic of acute ischemic stroke were observed in 151 patients (78.2%), symptomatic hyperdense MCA signal - in 27 patients (14%). Intracranial haemorrhages were diagnosed in 39 patients (20.2%).

Fig 1. Functional status after 3 months.



mRS – modified Rankin scale

Symptomatic ICH was diagnosed in 4 patients (2.1%). Distribution of intracranial haemorrhages by type is listed in Table 2. Average neurological deficit according to NIHSS was 10.8 ± 8.0 points; compared to the baseline and to the results two hours after IVT, this constituted a significant decrease (14.7 and 10.8, $p < 0.001$; 11.7 and 10.8, $p < 0.001$, Wilcoxon test).

Patients with a good outcomes were younger (respectively 64.5 and 68.8 years of age, $p = 0.028$) and had lower blood glucose levels (respectively 5.9 and 6.7 mmol/l, $p = 0.011$). In the good outcome group, AF was observed in 17.2% of patients, while in the bad outcome group it was observed in 34.3% of patients ($p = 0.029$). Patients with good outcomes had better neurological status at the time of arrival ($p < 0.001$). No other demographic and clinical features or test results differed significantly between the two groups.

IVT had been started within 180 minutes of the initial onset of symptoms to 82.8% of patients assigned to the good outcome group and to 89.0% of patients assigned to the bad

outcome group ($p > 0.05$). Two hours after IVT, average neurological deficit had decreased by 6.1 points among patients assigned to the good outcome group and by 1.5 points among patients assigned to the bad outcome group ($p < 0.001$).

Table 2. Distribution of Intracerebral Haemorrhages after IVT by type.

Type of ICH	Number of patients (N)	Incidence (%)
HI1	12	6.2
HI2	11	5.7
PH1	5	2.6
PH2	7	3.6
PHr1	2	1.0
PHr2	2	1.0

IVT – intravenous thrombolysis, HI1 – haemorrhagic infarction type 1, HI2 — haemorrhagic infarction type 2, PH1 – parenchymal hematoma type 1, PH2 – parenchymal hematoma type 2, PHr1 – remote parenchymal hematoma type 1, PHr2 – remote parenchymal hematoma type 2.

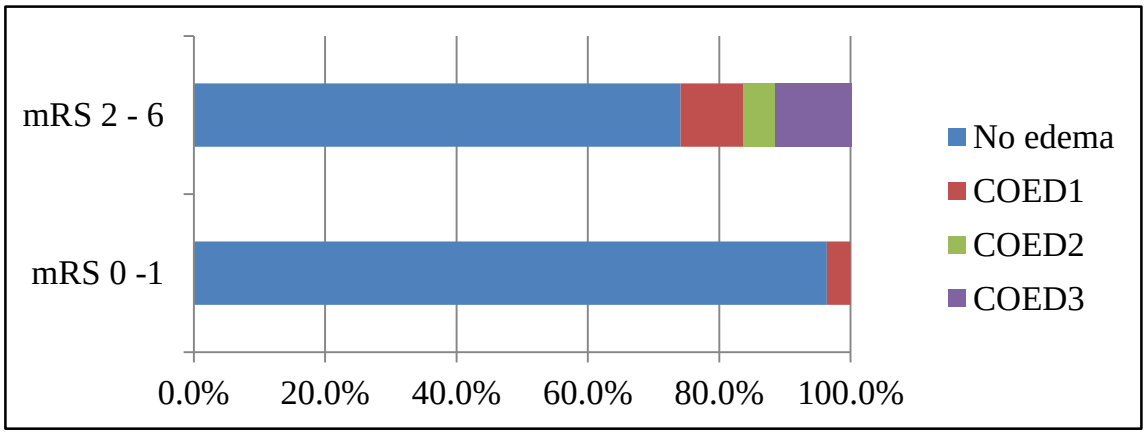
After 24 hours from IVT, the neurological deficit of patients assigned to the good outcome group had dropped by 8.6 points as compared to initial deficit, and averaged at 3.4 points according to NIHSS; meanwhile, among patients assigned to the bad outcome group, neurological deficit had dropped by 0.9 points and averaged at 15.1 points ($p < 0.001$).

In the control head CTs (performed after 24 hours), changes characteristic of acute ischemia were observed in 83.7% of patients assigned to the bad outcome group, compared to 60.7% of patients assigned to the good outcome group ($p = 0.004$). No symptomatic ICH was observed among patients assigned to the good outcome group, however it was diagnosed

in two patients assigned to the bad outcome group. The functional status of two further patients diagnosed with symptomatic ICH remained unknown.

Cerebral oedema was diagnosed in 3.6% of patients assigned to the good outcome group, compared to 26% of patients assigned to the bad outcome group ($p < 0.001$). All cases of cerebral oedema observed in patients assigned to the good outcome group were of the COED1 type. In the bad outcome group, COED1 type cerebral oedema was observed in 9.6% of patients, COED2 – in 4.8%, and COED3 – in 11.5% of patients (Fig. 2).

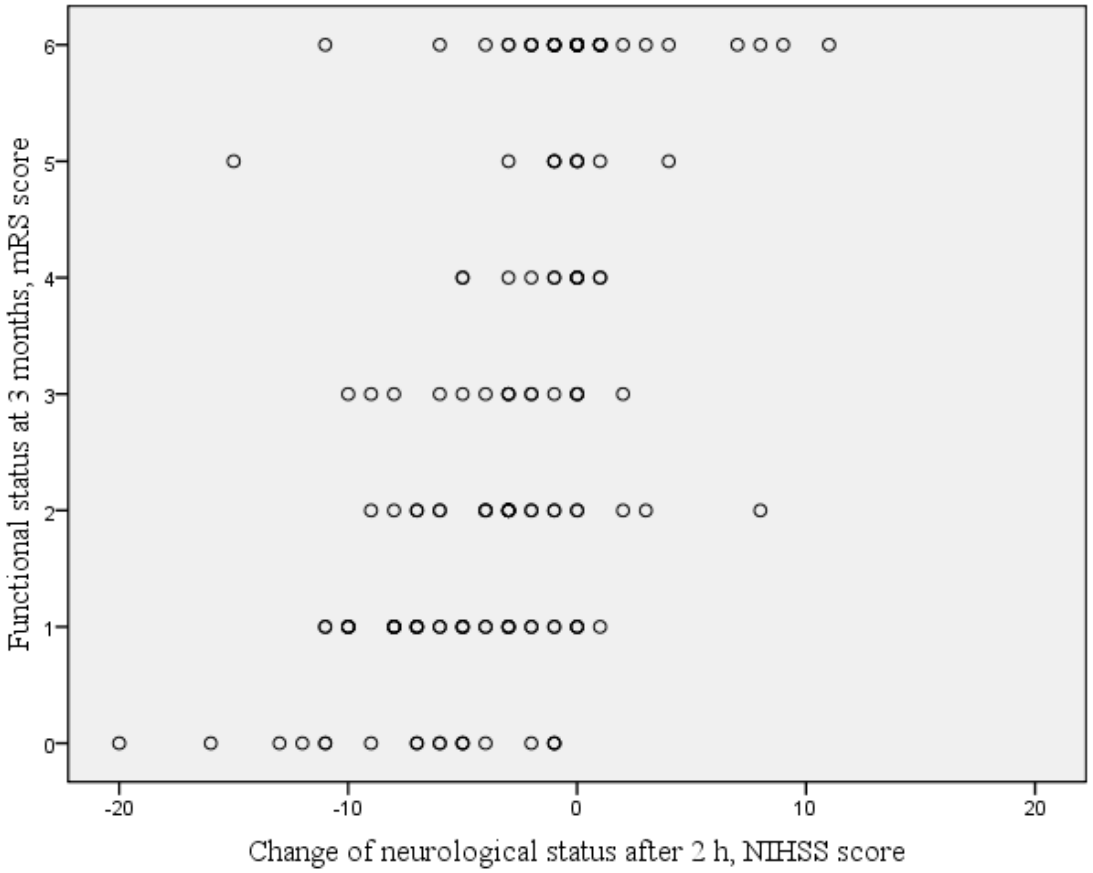
Fig. 2. Incidence of cerebral oedema in different outcome groups.



COED1 – cerebral oedema type 1, COED2 – cerebral oedema type 2, COED3 - cerebral oedema type 3

70.4% of patients (n = 38) assigned to the good outcome group after three months exhibited SENI, compared to 21.4% of patients (n = 21) assigned to the bad outcome group. The average period of time between the initial onset of symptoms and the initiation of treatment was 133 minutes for patients who later exhibited SENI, and 150 minutes for patients who did not ($p = 0.012$). Glycaemia on arrival was respectively 5.9 and 6.8 mmol/l ($p = 0.001$). The two groups of patients did not differ significantly in any other regards. Change in neurological condition over the course of two hours after initiation of IVT (as measured by NIHSS score) correlates inversely to functional status after three months ($r = -0.51$, $p < 0.001$) (Fig. 3).

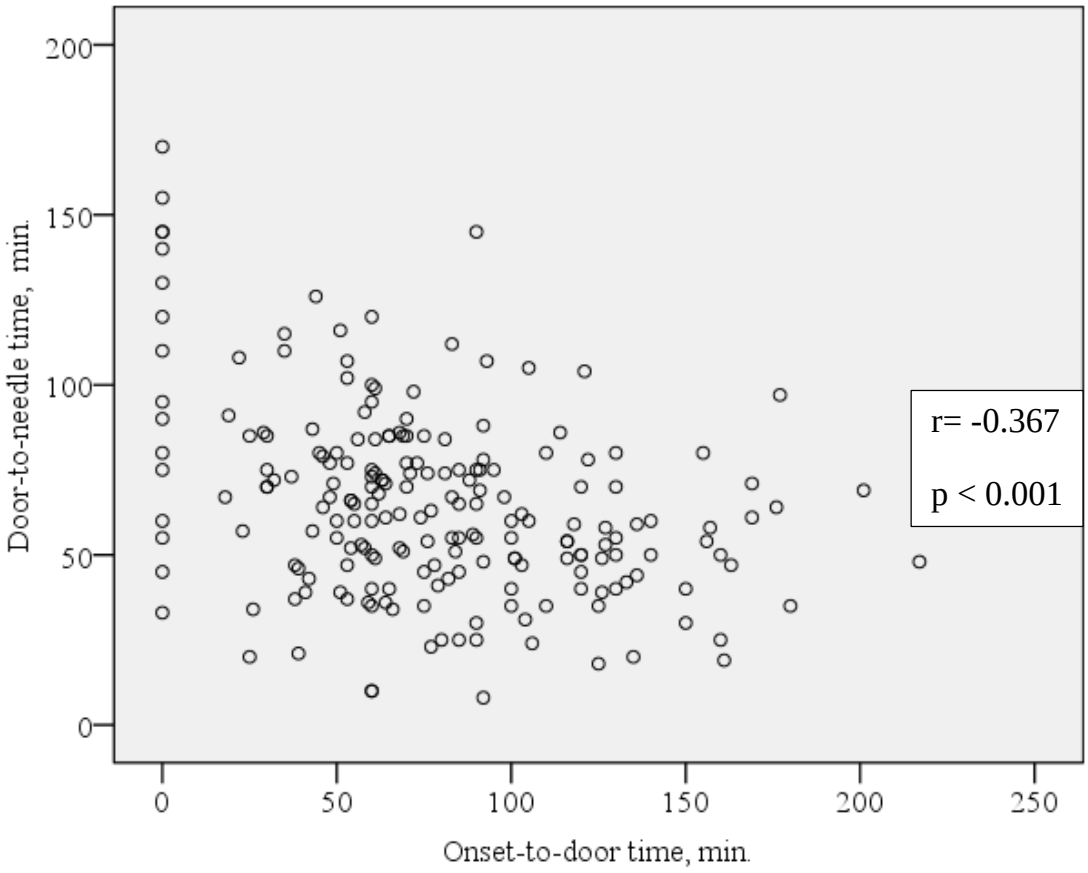
Fig 3. Correlation between change in neurological condition over the course of two hours after initiation of IVT (as measured by NIHSS score) and functional status after three months.



mRS – modified Rankin scale, IVT – intravenous thrombolysis, NIHSS – National institute of health stroke scale.

In the vast majority of cases (84.9%), patients had undergone IVT within 180 minutes of the initial onset of symptoms. This could be explained by the fact that the official therapeutic time window for IVT was only extended to 270 minutes in the latter half of 2012. It has been noted, however, that 50% of patients had IVT initiated more than 60 minutes after their arrival to the hospital. Therefore the reasons behind these delays were considered. Analysis revealed that the period of time between the patient's arrival and the beginning of treatment had a weak inverse correlation to the period of time between the initial onset of symptoms and the patient's arrival to the hospital ($r = -0.367$, $p < 0.001$) (Fig. 4).

Fig 4. Correlation between period between initial onset of symptoms and the arrival to the hospital and period between arrival to the hospital and the initiation of treatment



Regression analysis revealed that the only independent factors for the time period between patient arrival and the initiation of treatment were the period of time between initial onset of symptoms and the patient's arrival to the hospital, and glycaemia on arrival. Higher glycaemia increases the period of time between arrival to the hospital and the initiation of treatment, while a longer period of time between the initial onset of symptoms and arrival to the hospital decreases the period of time between arrival to the hospital and the initiation of treatment. Initial neurological status and age of a patient had no influence on the period of time between arrival to the hospital and the initiation of treatment and this finding requires a separate discussion. Older age was associated with the shorter period of time between initial onset of symptoms and the patient's arrival to the hospital.

As has already been mentioned, patients aged 80 and over comprised 13.1% (27 patients) of all patients that had undergone IVT. There are several explanations for this. First of all, while official manufacturer recommendations list an age of 80 years and over as a contraindication for treatment, no upper age limit is defined in current stroke treatment guidelines. Another possible explanation is that patients in this age group have more comorbidities and their neurological condition is more serious upon arrival.

The average age in the group of older patients was 83 ± 2.7 years, while in the younger patients group it was 65.2 ± 10.7 years ($p < 0.001$). The average period of time between initial onset of symptoms and the initiation of treatment was respectively 138 ± 39 and 145 ± 44 minutes ($p > 0.05$). Atrial fibrillations were more commonly observed among older patients, and they were more likely to have been using antiplatelet. Although there was no statistical difference in the time periods between arrival to the hospital and the initiation of treatment, they tended to be longer among older patients. This could be explained by the fact that examination of an older patient tends to take longer and also perhaps by the fact that the treatment of such patients is outside standard protocol, meaning the decision to begin treatment warrants lengthier deliberation than usual.

Analysis revealed that comorbidities were similar in both groups. This can be explained by the fact that only patients that had undergone IVT were considered – meaning patients with more severe comorbidities were not included in the study. It was also noted that groups did not differ in severity of initial neurological condition.

Considering that average life expectancy in Lithuania is shorter than in Western European countries, and that some of the risk factors for cardiovascular disease are more likely to be poorly controlled, we decided to compare the profile of risk factors across different age groups. Patients were divided into three age groups: 1) less than 65 years of age; 2) between 65 and 79 years of age; 3) 80+ years of age. All three groups of patients differed significantly in their average age (respectively 55.1, 72.2 and 83.0 years of age).

Several statistically significant differences were observed when analysing patients in the second and third age groups: the older group included more women (70.3% compared to 45.1% among patients aged between 65 and 79, $p = 0.03$), older patients were also more likely to have been using antiplatelet (40.7% in the third age group compared to 18.1% in the second, $p = 0.019$). Other parameters were similar in both groups. These results are easily understandable – women's average life expectancy is longer than men's. The difference in antiplatelet use can be explained by the fact that, while both groups included similar number of patients who had suffered from a previous stroke, prophylactic prescription of antiplatelet is acceptable for older patients even with no previous history of stroke. It is also worth noting that the prevalence of AF was similar across both groups. When comparing patients aged 65 or younger, and patients aged between 65 and 79, younger patients were less likely to have AF (respectively 19.2% and 33.7%, $p = 0.041$), heart failure (respectively 6.8% and 18.4%, $p = 0.043$) or hypertension (respectively 48.6% and 76.0%, $p < 0.001$). Younger patients had lower systolic blood pressure (respectively 144 and 155 mmHg, $p = 0.001$) and the period of time between their arrival to the hospital and the initiation of IVT was shorter (respectively 61 minutes and 68 minutes, $p = 0.027$). Younger patients' head CTs were also more likely to show a hyperdense MCA signal (respectively 37.0% and 22.9%, $p = 0.045$). Data analysis allows us to conclude that patients aged between 65 and 79 have a vascular risk factor profile that is worse than younger patients', and is similar to that of patients aged 80 and older.

After three months, the functional status of 21 patients assigned to the older age group, and of 148 patients assigned to the younger age group, were assessed. While we could not assess the functional status of the remaining patients at this time, they were alive, meaning mortality rates are accurate. Patients' functional status was assessed using mRS. Patients' distribution according to their functional status is shown in Figure 5.

Mortality rates were higher in the older age group (37.0% compared to 17.3%, $p = 0.013$). On the other hand, overall stroke mortality rates are known to be higher among older patients, meaning we cannot conclude that the older age group's mortality rates were higher due to treatment with IVT. There was no statistical difference in the incidence of good outcomes after three months between older and younger age groups (23.8% and 36.1% of

patients, p = 0.262) (Fig. 6). It can therefore be concluded that IVT remains an effective treatment method for older patients.

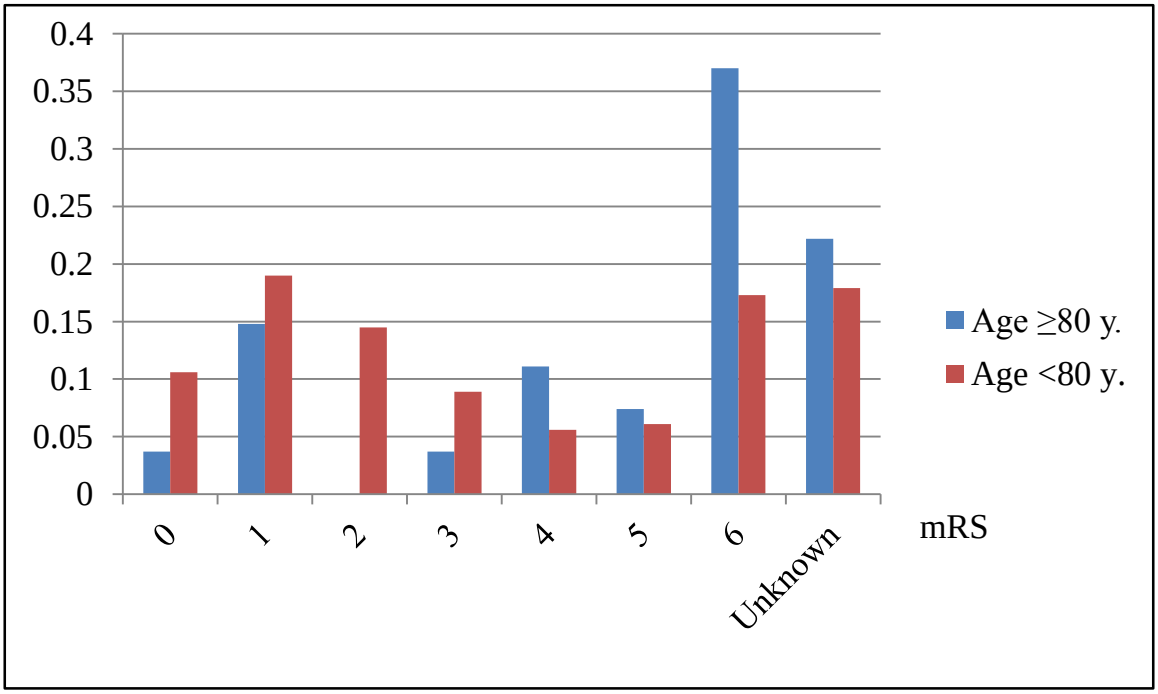
The efficacy and safety of IVT across different age groups was analysed separately. The results of our analysis are shown in Figure 7. With advancing age, IVT efficacy decreases, while mortality rates within three months increase. Even though the efficacy of IVT does not differ between separate age groups, a clear tendency might be observed between patients younger than 65 years of age and those aged between 65 and 79 in regard to both the efficacy and safety of IVT. This tendency is less pronounced among patients falling into other age groups.

An investigation into the possible correlation between significant early neurological improvement and a good outcome after three months among older patients yielded no reliable data (r = -0.440, p = 0.088); however, a trend does exist (Fig. 8). However, it is worth keeping in mind that our sample group for this study was quite small – and that a larger sample might therefore yield more reliable results. SENI was observed in 23.8% of all patients aged 80 and over, and in 41.0% of all patients younger than that (p = 0.158). As it seems likely that early improvement is more related to the effects of IVT, this also shows that IVT remains an effective method of treating older patients.

Analysis of the data presented in the tables reveals that patients exhibiting SENI were very similar regardless of whether they fell into younger or older age groups - except that the time period between the initial onset of symptoms and the beginning of treatment was shorter among younger patients exhibiting SENI, and that, among patients who smoke, SENI was more frequently observed in younger patients.

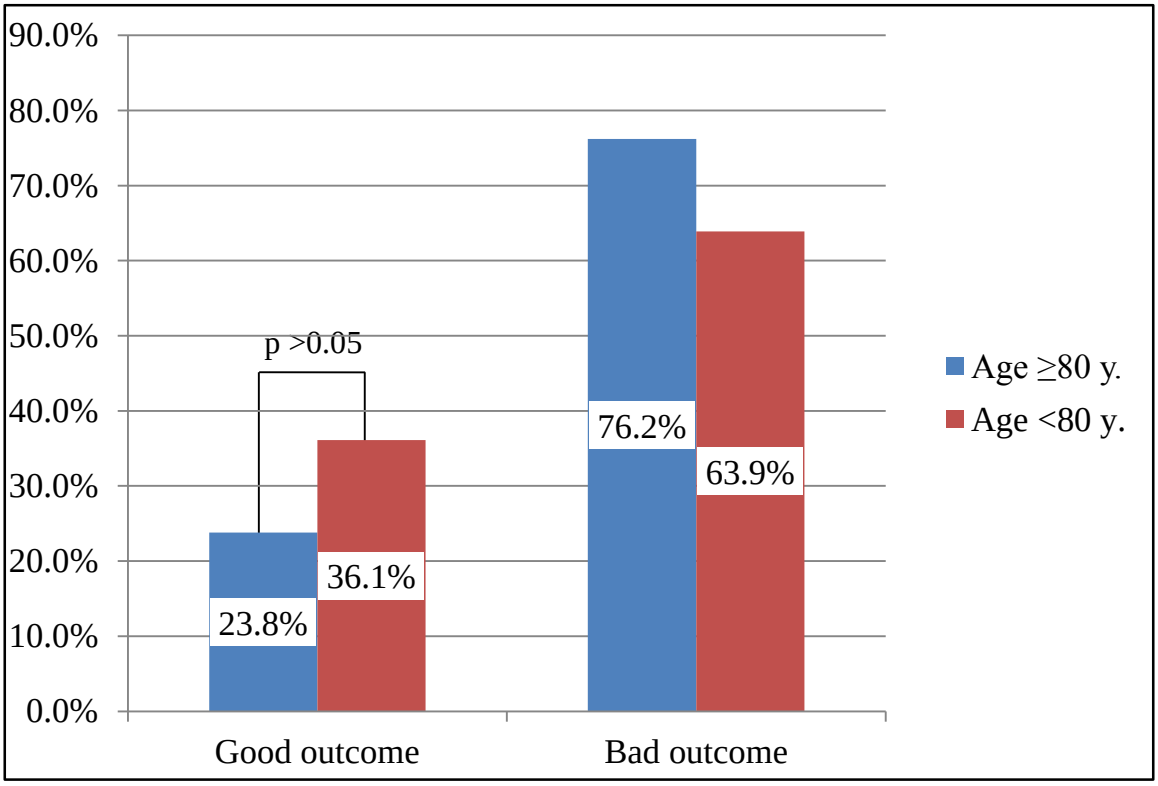
One of the goals of this study was to identify the prognostic factors behind good and bad outcomes three months after treatment. This is especially important when selecting patients for treatment, and when planning the course of further treatment. Prognostic factors were identified using stepwise logistic regression analysis (Forward Wald). Variables that reflected the patient's condition before treatment were included in the regression analysis.

Fig 5. Functional status in older age patients group after 3 months.



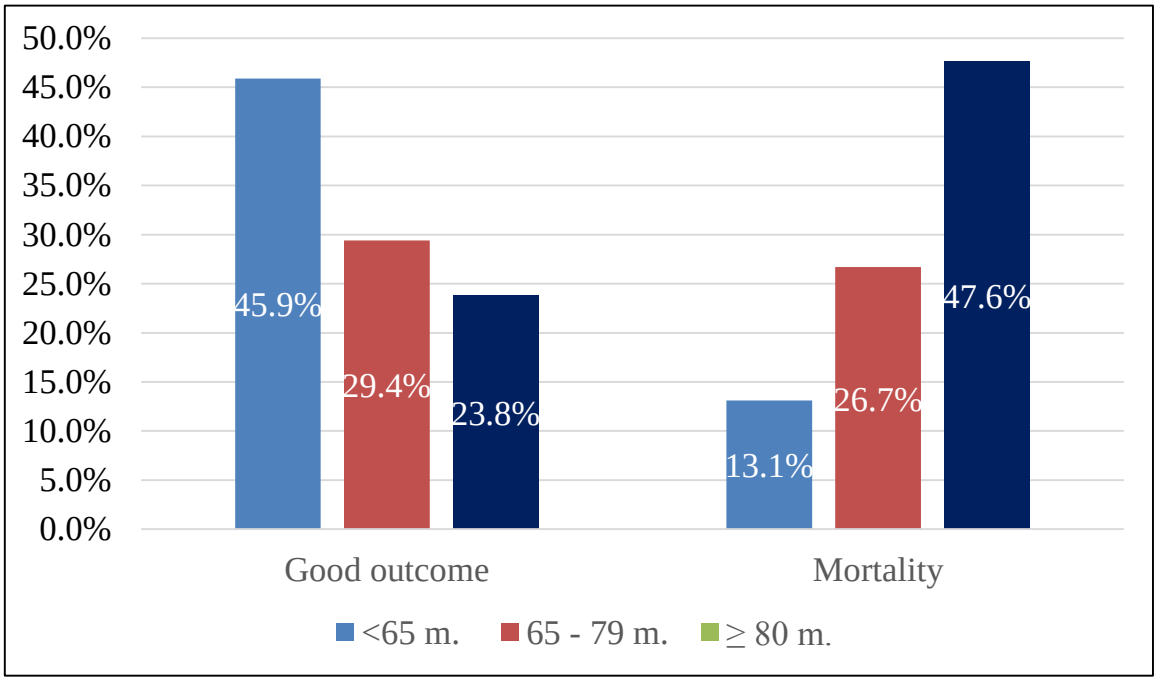
mRS – modified Rankin scale

Fig 6. Good outcomes after 3 months in older patients group.



mRS – modified Rankin scale

Fig 7. Good outcome after 3 months and mortality across different age groups.

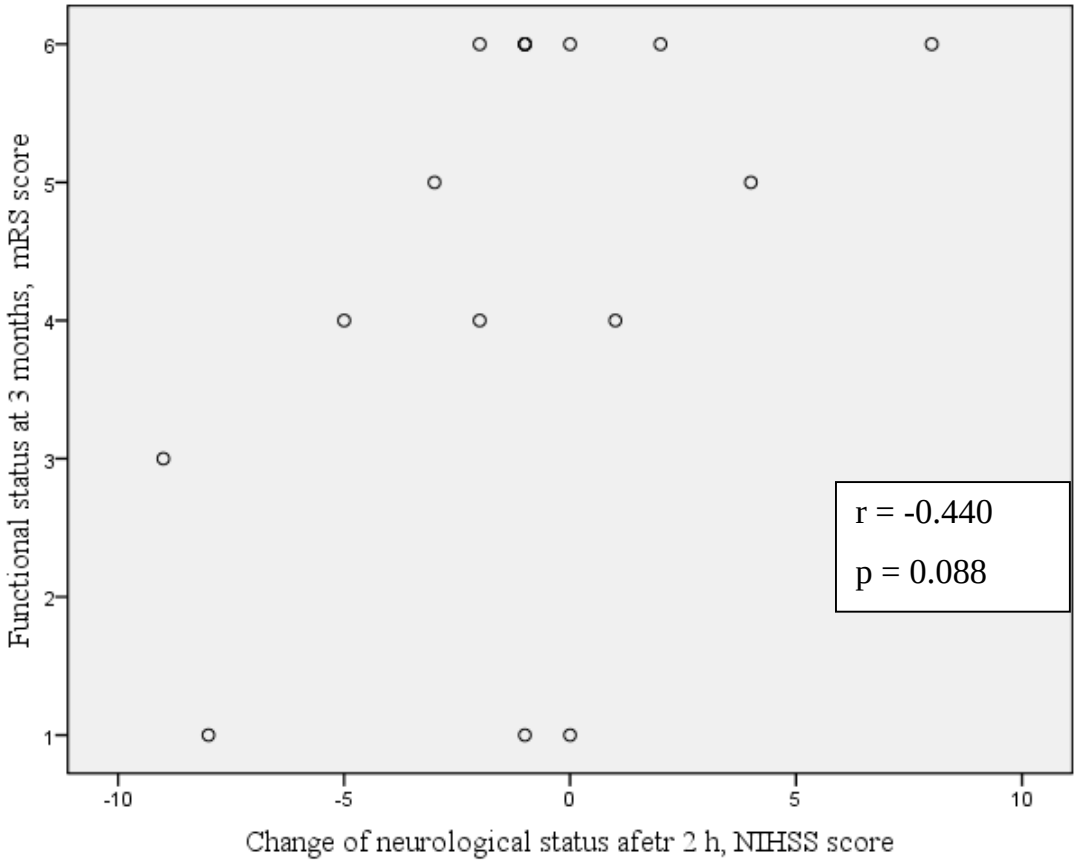


mRS – modified Rankin scale

The results of the regression analysis are presented in Table 3. Since prognostic factors behind early neurological improvement shall be considered later in this study, a separate table is included showing the prognostic factors behind good outcomes three months after the treatment (Table 4).

Analysis of the results shows that higher glycaemia, more severe initial neurological status and advanced age are all positive prognostic factors for a bad outcome after three months. While analysing the data collected, it was noted that the period of time between the initial onset of symptoms and the beginning of treatment had no prognostic value in determining the outcome.

Fig. 8. Change in the neurological status in 2 hours and functional status after 3 months.



mRS - modified Rankin scale, NIHSS - National Institute of Health Stroke Scale

One possible explanation for this is that this variable is partially subjective and might not always be completely accurate. It is possible that, with a larger sample, this variable could prove to be a significant prognostic factor. An attempt to assign the time periods between the initial onset of symptoms and the beginning of treatment into several different categories (0 to 90 minutes, 91 to 180 minutes, 181 to 270 minutes) did not change the results of the regression analysis. In this case, this could potentially be explained by the fact that the majority of our patients underwent IVT within 91 to 180 minutes after the initial onset of symptoms; a larger sample group might be required for more accurate results.

Table 3. Prognostic factors for the bad outcome after three months.

Model Chi square (χ^2) goodness of fit (p)	*Nagelkerke* R^2 coefficient of determination	Percentage of correct classification	Variable	P	Exp (B)	95% CI	
						Lower limit	Upper limit
<0,001	0,320	71,7	Age	0,009	1,046	1,011	1,082
			Initial glycaemia	0,012	1,367	1,070	1,747
			Initial neurological status	<0,001	1,229	1,127	1,339
			Constant	<0,001	0,001		

CI – Confidence interval

As several prognostic models for predicting patients' outcomes currently exist, in this study we assessed their suitability for our test group. Two models were chosen: DRAGON and iScore. For this purpose we used the ROC curves test, evaluating the area under the curve. The accuracy of these prognostic models is shown in Figures 9 and 10.

Having compared the prognostic factors we had ascertained to those used in the DRAGON model, we observed that factors like early changes in head CTs, disability before the onset of the stroke, and the period of time between the initial onset of symptoms and the beginning of treatment had no prognostic value in our sample group. In an attempt to determine the remaining variables' prognostic value for our sample group, additional analysis using the ROC curves test was carried out for each of the individual variables: glycaemia upon arrival, initial neurological status according to NIHSS, and age (Fig. 11, Fig. 12 and Fig. 13). Since the glycaemia threshold specified in the DRAGON prognostic model is 8 mmol/l, Youden's index – which shows a variable's critical value – was calculated. It was

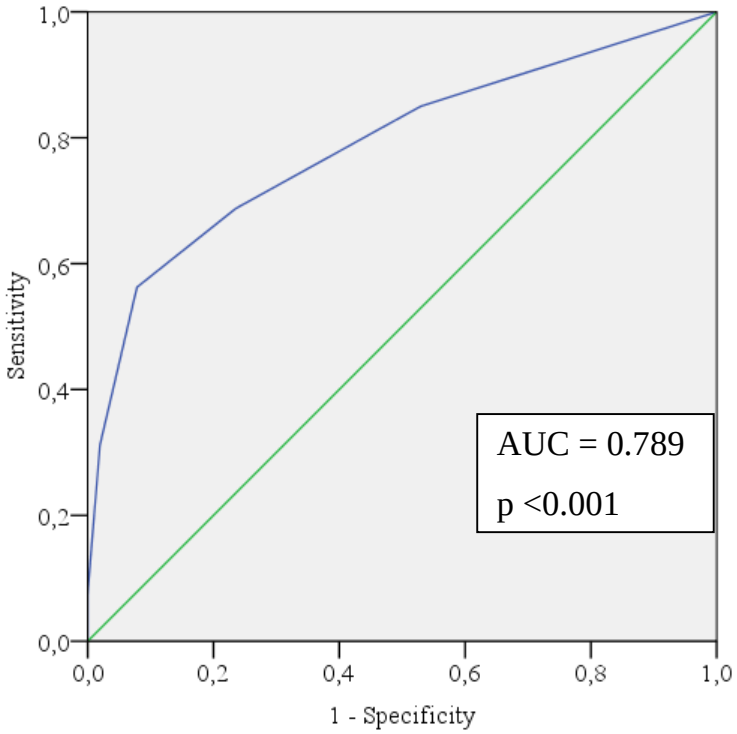
highest with glycaemia value 6,4 mmol/l. Therefore, the DRAGON model was adjusted and glycaemia threshold was set on 6.4 mmol/l. After recalculation of the area under the curve it changed to 0.801, $p < 0.001$ (Fig. 14). This shows that the adjusted DRAGON prognostic model is more suitable for our study group.

Table 4. Prognostic factors for the good outcome after three months

Model Chi square (χ^2) goodness of fit (p)	*Nagelkerke* R^2 coefficient of determination	Percentage of correct classification	Variable	P	Exp (B)	95% CI	
						Lower limit	Upper limit
<0,001	0,320	71,7	Age	0,009	0,956	0,924	0,989
			Initial glycaemia	0,012	0,731	0,572	0,935
			Initial neurological status	<0,001	0,814	0,747	0,887
			Constant	<0,001	0,001		

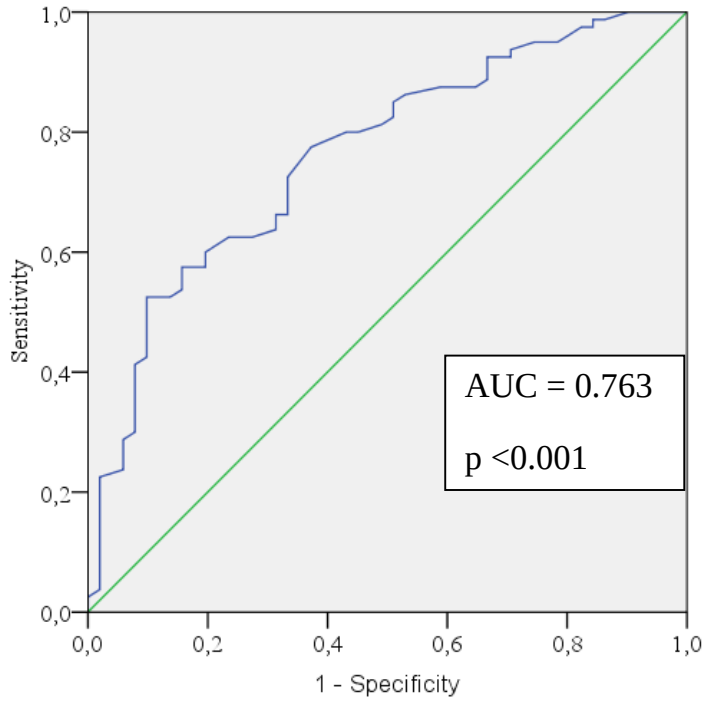
CI – confidence interval

Fig. 9. Accuracy of DRAGON prognostic model.



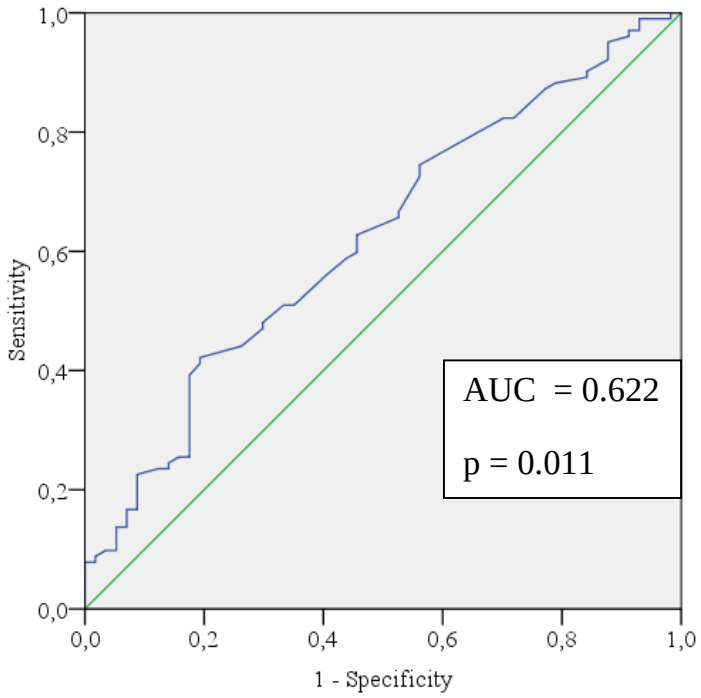
AUC – area under curve

Fig. 10. Accuracy of iScore prognostic model.



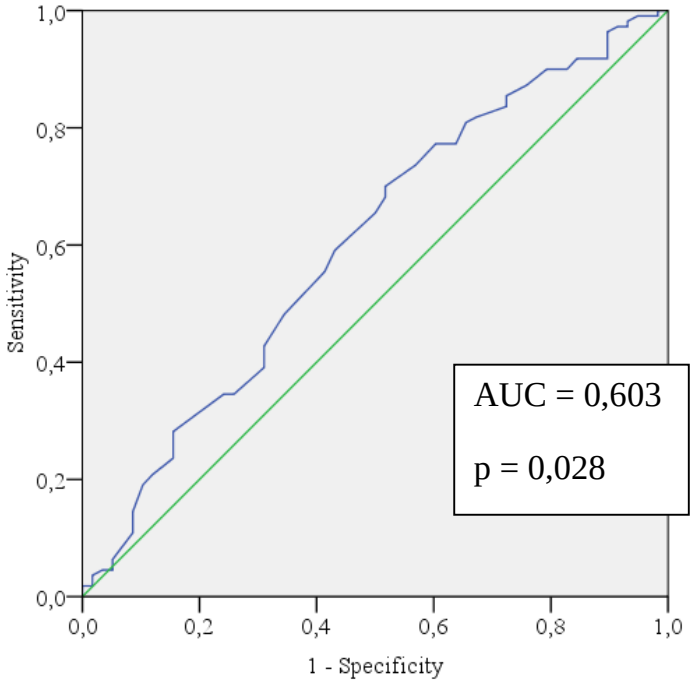
AUC – area under curve

Fig. 11. Prognostic accuracy of initial glycaemia.



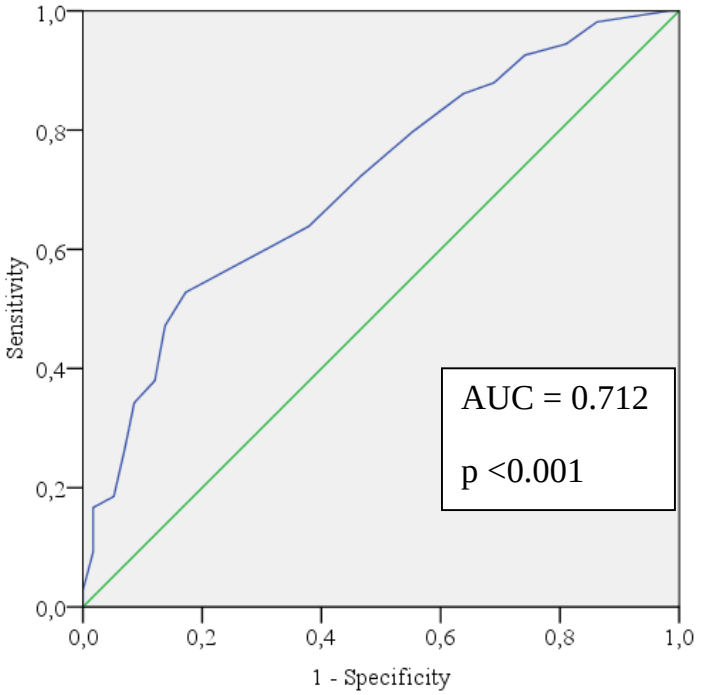
AUC – area under curve

Fig. 12. Prognostic accuracy of age.



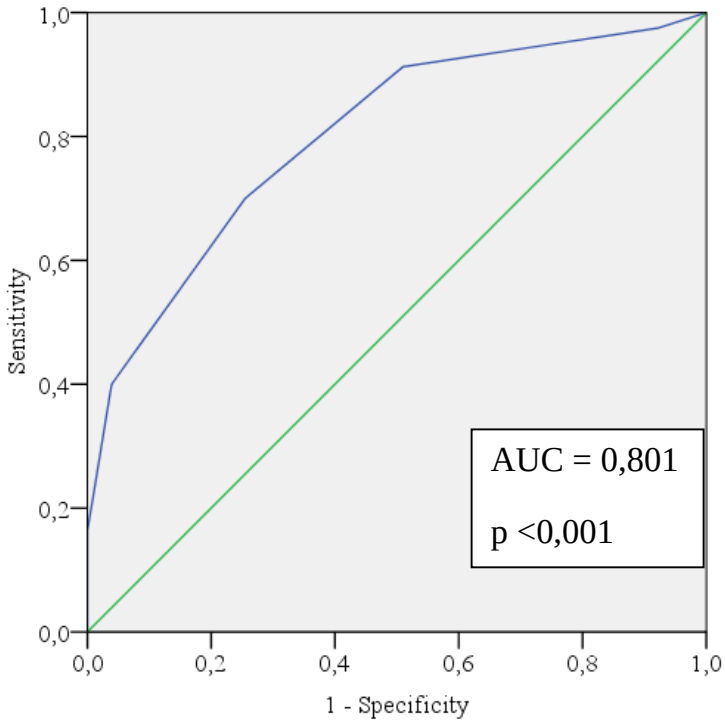
AUC – area under curve

Fig. 13. Prognostic accuracy of initial neurological status.



AUC – area under curve

Fig. 14. Accuracy of revised DRAGON prognostic model.



AUC – area under curve

The analysis of our results shows that only the severity of the initial neurological status, age and blood glucose levels on arrival have prognostic value in determining patients' outcomes in our study group.

Therefore an attempt was made to create a new prognostic model that included only variables relevant to our study group. Quantitative variables (age, glucose levels and severity of neurological status according to NIHSS) that were used to calculate patients' outcomes were replaced with nominal variables based on the following principles:

1. Ages up to 65 were coded as zero, ages 65 and over as one;
2. Blood glucose levels up to 6.5 mmol/l were coded as zero, 6.5 mmol/l and over as one;
3. Initial neurological status of up to 16 points according to NIHSS was coded as zero, 16 and over as one.

These limits were calculated using Youden's index – it was largest at the aforementioned values.

After these changes had been made, a repeat logistic regression analysis was carried out to determine the significance of these values in prognosis of three months outcomes. The results of this analysis are presented in Table 5. Our data shows that all variables are relevant in making a three-month outcome prognosis. The odds ratio values also make it clear that all variables have different prognostic significance. When creating our prognostic model, the prognostic significance of each variable was expressed in points. Initial neurological deficit up to 16 points was coded as zero, 16 and over – as four points; blood glucose levels up to 6.5 mmol/l were coded as zero, 6.5 and over – as three points; ages up to 65 were coded as zero, 65 and over – as three points.

Hence the minimal number of points possible is zero and the maximal is ten. The possible combinations are shown in Table 6, while the possibility of a good outcome (mRS 0 – 1), a bad outcome (mRS 2 – 5) or death (mRS 6) depending on the total score is shown in Figure 15.

Table 5. Prognostic value of age, glycaemia and initial neurological status for bad outcome after 3 months.

Model Chi square (χ^2) goodness of fit (p)	*Nagelkerke* R^2 coefficient of determination	Percentage of correct classification	Variable	B	P	Exp (B)	95% CI	
							Lower limit	Upper limit
<0,001	0,324	73,2	Age ≥65 years	1,096	0,008	2,993	1,339	6,691
			Initial glycaemia ≥6,5 mmol/l	1,393	0,001	4,027	1,723	9,409
			Initial neurological status according to NIHSS ≥16 points	2,168	<0,001	8,739	3,557	21,467
			Constant	-1,256	0,002	0,285		

NIHSS – National Institute of Health Stroke Scale

Table 6. Possible combinations of prognostic factors for three months outcome.

Variable	Points	Variable	Points	Variable	Points	Total
Age <65 years.	0	Glycaemia <6,5 mmol/l	0	Neurological status <16 points according to NIHSS	0	0
Age <65 years.	0	Glycaemia <6,5 mmol/l	0	Neurological status ≥16 points according to NIHSS	4	4
Age <65 years.	0	Glcaemia ≥6,5 mmol/l	3	Neurological status <16 points according to NIHSS	0	3
Age <65 years.	0	Glcaemia ≥6,5 mmol/l	3	Neurological status ≥16 points according to NIHSS	4	7
Age ≥65 years.	3	Glycaemia <6,5 mmol/l	0	Neurological status <16 points according to NIHSS	0	3
Age ≥65 years.	3	Glcaemia ≥6,5 mmol/l	3	Neurological status <16 points according to NIHSS	0	6
Age ≥65 years.	3	Glycaemia <6,5 mmol/l	0	Neurological status ≥16 points according to NIHSS	4	7
Age ≥65 years.	3	Glcaemia ≥6,5 mmol/l	3	Neurological status ≥16 points according to NIHSS	4	10
Age ≥65 years.	3	Glcaemia ≥6,5 mmol/l	3	Neurological status <16 points according to NIHSS	0	6
Age <64 years.	0	Glycaemia <6,5 mmol/l	0	Neurological status ≥16 points according to NIHSS	4	4

NIHSS – National Institute of Health Stroke Scale

The ROC curves test was used, and the area under curve and its reliability was calculated in order to determine the reliability of the model created (Fig. 16). The results show that the area under curve (AUC) is 0.780 ($p < 0.001$). This allows us to conclude that the model created is sufficiently accurate and does not differ from other methods in its reliability. The model's advantage is that it uses prognostic factors identified in our sample group ant the method itself is short and easy to apply in everyday clinical practice.

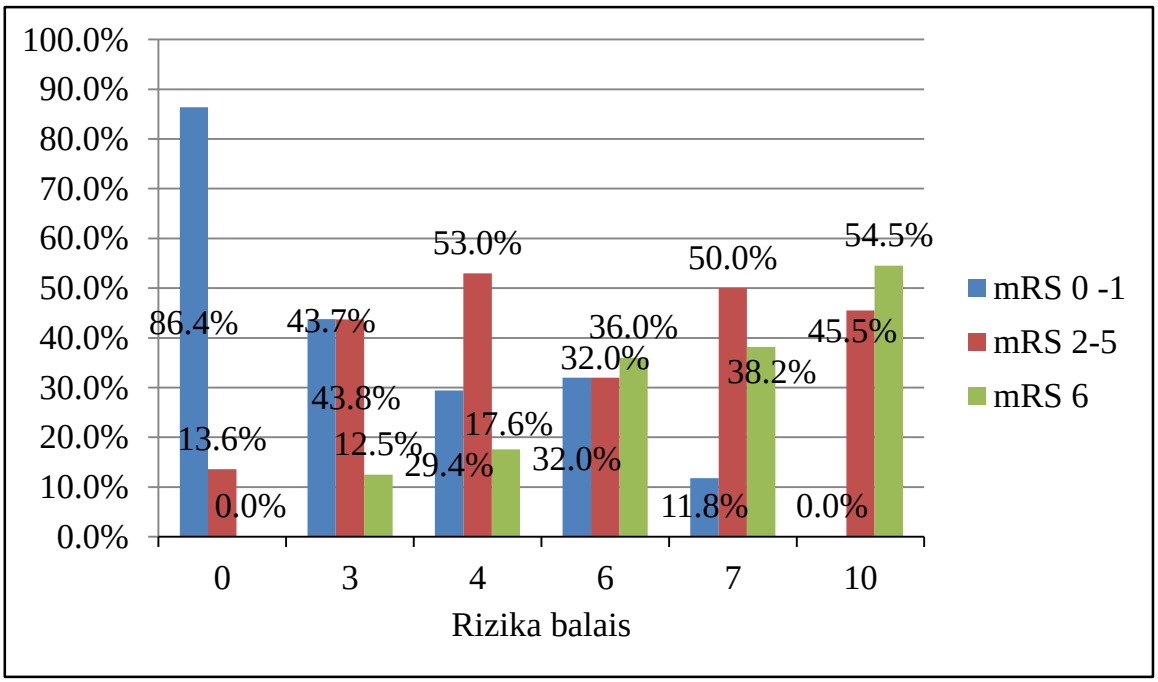
As has been shown previously, SENI has a moderate inverse correlation with the functional outcome after three months. As active treatment for stroke (especially

endovascular treatment) is only available within the first few hours after its initial onset, it is extremely important to identify the prognostic factors for SENI.

If patients with lower chances of improvement could be identified at an early stage, we could plan for more aggressive methods earlier in the treatment process.

A stepwise logistic regression analysis (Forward Wald) was used to determine these prognostic factors.

Fig. 15. 3-months outcomes depending on combination of prognostic factors.



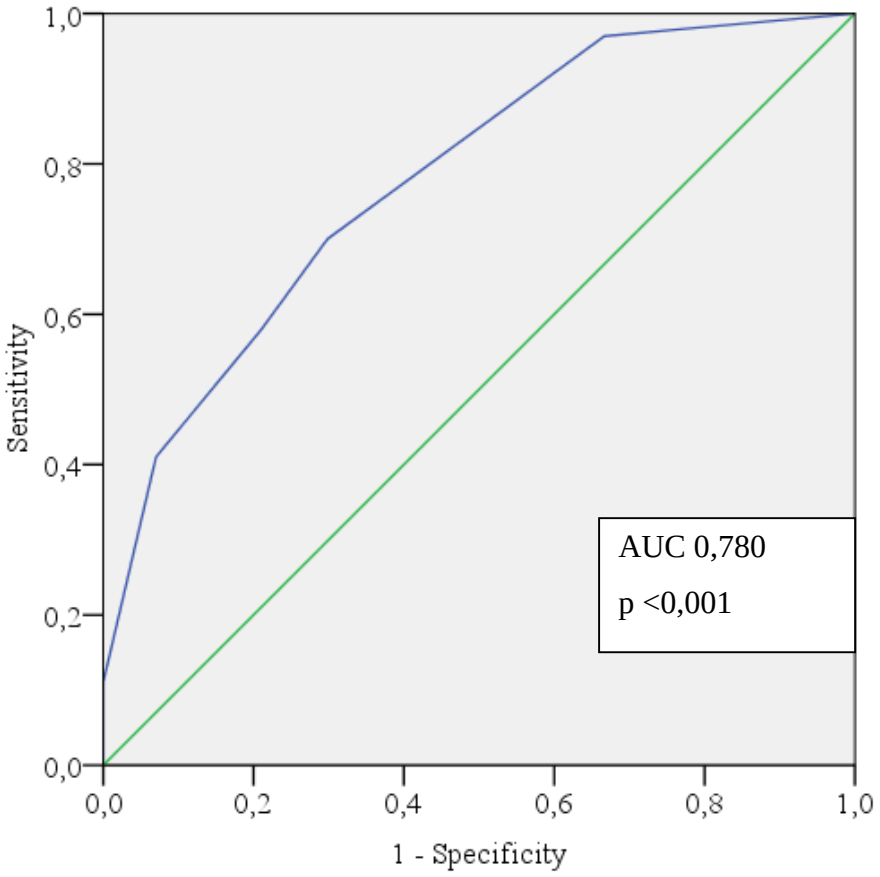
mRS – modified Rankin scale

Variables reflecting the patient's condition before treatment were included in the regression analysis. The results are presented in Table 7.

The analysis of the variables' effects on SENI revealed that the period of time between the initial onset of symptoms and the initiation of treatment is not a significant prognostic factor in this case. Arterial hypertension and higher glycaemia reduce the chance of SENI (odds ratio 0.43, 95% CI 0.210 – 0.881). Atrial fibrillation increases the chances of significant early neurological improvement (odds ratio 2.117, 95% CI 1.018 – 4.655). These results are

especially interesting considering that atrial fibrillation is typically considered to reduce the chances of a good outcome; this will be discussed later.

Fig. 16. Accuracy of our created prognostic model for 3-months outcome.



AUC – area under curve

A comparison between the prognostic factors of SENI and of a good outcome after three months (Table 8) revealed that the factors are all different, with the exception of glycaemia.

One possible explanation is that the prognosis of a long-term recovery is influenced by factors besides early improvement – including other existing medical conditions associated with acute stroke (infectious, thromboembolic complications, etc.) or related to potential later complications (recurrent stroke, other acute vascular diseases, etc.). The results of our study have shown that causes of death among our study group included not only acute stroke or

symptomatic ICH, but also myocardial infarction, pneumonia or pulmonary embolism. Several patients died after having been discharged from the hospital due to recurrent strokes. No data is available on the number of patients who suffered from pneumonia or other infectious complications that did not result in a fatal outcome after IVT. Another important aspect is the availability of rehabilitation after an acute stroke. It is likely that older patients due to their worse condition cannot access rehabilitation of the same level as that which is available to younger patients with less severe neurological deficits.

Table 7. Prognostic factors for significant early neurological improvement.

Model Chi square (χ^2) goodness of fit (p)	*Nagelkerke* R^2 coefficient of determination	Percentage of correct classification	Variable	p	Exp (B)	95% CI	
						Lower limit	Upper limit
<0,001	0,157	70,4	Hypertension	0,021	0,430	0,210	0,881
			Initial glycaemia	0,008	0,737	0,587	0,924
			Atrial fibrillation	0,045	2,177	1,018	4,655
			Constant	<0,017	6,151		

CI – Confidence interval

Table 8. Comparison of prognostic factors for three-month outcome and for significant early neurological improvement.

Prognostic factor	Bad outcome			Significant early neurological improvement		
	P	Exp (B)	95% CI	P	Exp (B)	95% CI
Age	0,013	0,948	0,909 – 0,989	0,108	-	-
Initial glycaemia	0,003	0,629	0,460 – 0,858	0,008	0,737	0,587 – 0,924
Hypertension	0,241	-	-	0,021	0,430	0,210 – 0,881
Atrial fibrillation	0,243	-	-	0,045	2,177	1,018 – 4,655
INS	<0,001	0,835	0,763 – 0,914	0,770	-	-

CI – Confidence Interval, INS – initial neurological status

Discussion

In our study we examined patients who suffered from an acute ischemic stroke and had been treated with IVT. Their neurological condition, demographic characteristics, risk factors at the time of the stroke, and outcome three months after the treatment were assessed. Factors that influence changes in neurological condition have been analysed, and prognostic factors for good outcome and significant early neurological improvement have been identified. Based on the results, an original prognostic scale for determining good outcomes after three months has been put forward; it is suitable for use in everyday clinical practice.

The study sample consisted of 206 patients who had suffered from an acute ischemic stroke and been treated with IVT. 13.1% of all patients were aged 80 or over. Older patients accounted for a relatively small part of the patients included. There are several reasons for that. Firstly, according to current manufacturer recommendations, patient ages of 80 years and over are considered a contraindication for IVT, therefore some patients do not undergo

IVT precisely because of their age. This is partially reflected in another study carried out in Lithuania, according to which 21% of patients who had not been treated with IVT had not been selected for the treatment just because of their advanced age. Another explanation might be attributable to society's view on older people; such patients simply cannot reach specialized treatment facilities equipped to administer IVT in time. Older patients are also more likely to have severe comorbidities, which means their functional condition may have been poor even before the stroke and that might constitute a contraindication for IVT. On the other hand, compared to recent studies carried out in other countries - where older patients comprise between 5.4 and 8.6% of all patients suffering from stroke and treated with IVT, - within our test group, older patients had been treated with IVT often enough.

Of the patients involved in our study, 30% had AF, 11.7% had diabetes and 66.3% had hypertension. 14.6% of all patients were smokers, 13.2% had suffered from a previous ischemic stroke, and 14.3% had chronic heart failure. In almost half of all cases (46.6%) two or more risk factors were identified. Compared with patients involved in other studies, ours were more likely to present with AF, chronic heart failure or hypertension, and less likely to present with diabetes. It should be noted that among our patients, neurological deficit upon arrival averaged at 14.7 points according to NIHSS and 25% of all patients presented with severe neurological deficit upon arrival (19 points or more according to NIHSS). Though the earliest international studies involving patients who had undergone thrombolysis reported similar average neurological deficit upon arrival (14 points according to NIHSS), later studies showed a marked decrease in average severity of neurological deficit (8 points according to NIHSS). It is very important to keep this in mind when comparing our results to other studies. It can also be noted that this was the first time that Lithuanian patients participated in a study that evaluated IVT's efficacy for patients presenting with an acute ischemic stroke.

The average period of time between the initial onset of symptoms and the initiation of treatment was 144 minutes, between patients' arrival to the hospital and the initiation of treatment – 65 minutes. Other studies report similar results. A detailed analysis of logistical features revealed that only 15.5% of all patients were treated with IVT when the period of time between the initial onset of symptoms and the initiation of treatment was between three

and 4.5 hours. This is explained by the fact that the official recommendations for treating acute ischemic strokes with IVT were only updated in 2012 when therapeutic time window was expanded up to 4.5 hours after the initial onset of symptoms; by that point, most of the patients taking part in our study had already been selected. Up until 2012, treating patients who fell into the 3 – 4.5 hour window after the initial onset of symptoms constituted a breach of IVT protocol, and depended on the individual doctor's decision. It must also be pointed out that only 10% of all patients received IVT within 90 minutes or less of the initial onset of symptoms, even though other studies report numbers up to 29% in this category.

34.5% of all patients were assigned to the good outcome group (mRS 0 – 1) after three months. Other studies report similar data. On the other hand, mortality rate after three months was 24% in our study. This is significantly higher than the numbers reported in other studies, where mortality rates after three months usually fall in the 12 – 19% range. According to our data, the main cause of death among our patients was acute ischemic stroke, which makes up 40% of all reported causes of death. Mortality rate from intracranial haemorrhage was 2.3% and this constituted 10% of all reported deaths. Other studies report similar data. Several assumptions can be made about the causes of this high rate of mortality in our study group. First of all, it should be noted that 2.3% of our patients presented with symptomatic ICH, compared to the usual average of 1.7% in other studies. This could be one of the reasons, however the low absolute number (four patients) makes detailed analysis impossible at this time. With a larger sample group, further analysis could be undertaken to ascertain the causes of symptomatic ICH and the impact it has on patients' outcomes. Another possible cause of high mortality rates – further treatment after patients' discharge from the hospital. Our study did not attempt to analyse patients' further treatment, however practice shows that patients who have suffered from an acute stroke often do not receive adequate rehabilitation and/or prophylactic treatment. The length of the patient observation period means that these factors could as well be relevant when considering the causes of high mortality rates. This is partially confirmed by the fact that the rates of good outcomes three months after undergoing IVT are very similar to those reported by other studies.

In summary, it can be concluded that our patients had a different risk factor profile from that of patients taking part in other studies. Their initial neurological condition was also more severe. Though the rates of good outcomes observed in our study are similar to those reported by other studies, further research is necessary to identify the causes behind higher mortality rates.

In this study, a good outcome was defined as a functional status of 0 – 1 points according to the mRS scale after three months. Patients assigned the good outcome group in our study tended to be younger, they were less likely to present with AF, and both their initial neurological deficit and blood glucose levels were lower. Other authors report similar results. The significance of diabetes in determining the outcomes of patients who have suffered from a stroke remains a subject for further debate. While some studies show that patients with a bad outcome are more likely to present with diabetes, recent works have emphasized that the key lies not in diabetes itself, but in patients' blood glucose levels. Our study yielded similar results – while the numbers of patients suffering from diabetes were similar in both groups, patients with a good outcome were more likely to have lower blood glucose levels.

The results of our study showed that patients within the good outcome group had less pronounced neurological deficit 24 hours after IVT, and that the improvement in their neurological status as compared to the baseline was significantly bigger. This is also confirmed by the correlation that was found between the decrease in neurological deficit and the patient's outcome. The observation that patients with a bad outcome were significantly more likely to present with an area of acute ischemia in their head CTs done 24 hours after treatment is easily understandable. Similar findings have been reported by other authors.

The results of our study have shown that patients with a good outcome were more likely to have undergone IVT within 180 minutes of the initial onset of symptoms. This is consistent with data presented in other resources, and confirms once again that time is a very important factor in predicting a good outcome. The influence of time on the efficacy of IVT and the outcome of the stroke is analysed separately elsewhere in our study.

As previously mentioned, the majority of our patients were treated with IVT within 90 to 180 minutes of the initial onset of symptoms. According to our data, the average period of

time between the initial onset of symptoms and the initiation of treatment is 144 minutes; other authors report similar findings (135 to 145 minutes). As such, it can be said that patients in our study group tended to arrive to the hospital within an adequate period of time when compared to reports from other centres. As the period of time between the initial onset of symptoms and the patient's arrival to the hospital depends on a number of different factors and is difficult to influence, this study focused largely on the period of time between arrival to the hospital and the initiation of treatment. This period of time is important in a number of ways. First of all, it is directly dependent on the organization of work in a given medical institution, and is one of the indictors of the institution's quality. Secondly, it reflects the stance that the medical institution's neurologists and other staff take on acute strokes, and whether or not they perceive it as an urgent condition. Thirdly, it is easy to monitor and relatively easy to influence by way of special interventions. According to our data, the average period of time between a patient's arrival to the hospital and the initiation of treatment was 65 minutes. The majority of patients had IVT initiated within 31 to 60 minutes (42.1%) or 61 to 90 minutes (39.1%) of their arrival to the hospital. 8.1% of all patients had IVT initiated within 30 minutes of their arrival to the hospital. These figures show that the ability to administer IVT within an adequate period of time from the patient's arrival to the hospital exists – however, for whatever reasons, the beginning of treatment is often delayed. Other studies report average time periods between patients' arrival to the hospital and the beginning of treatment that fall in the 45 to 68 minute range. The results show that the period of time between the initial onset of symptoms and arrival to the hospital is inversely correlated to the period of time between arrival and the initiation of treatment, and is an independent factor. This is in concordance with other authors' findings and shows that doctors, including neurologists, underestimate stroke as an urgent condition. Therefore it must be constantly emphasized in daily practice that the longer period of time remaining until the closure of the therapeutic time window must not be equated with IVT initiation time. Another independent factor revealed by our study and related to a longer period of time between arrival to the hospital and the initiation of treatment is glycaemia upon arrival. Other studies have not

shown glycaemia to have any influence on the period of time between arrival to the hospital and the beginning of treatment, therefore this finding requires further analysis.

Unlike other authors' findings, our data has not shown the severity of initial neurological condition and the patient's age to have any influence on the period of time between arrival to the hospital and the initiation of treatment. As most of the patients treated with IVT in our hospitals present with severe neurological deficit upon arrival, it can be assumed that this factor has little importance when making a decision on administering thrombolysis in daily practice. Also, it is important to keep in mind the fact that the sample group for this study was not very large, which might have affected the statistical reliability of our findings.

When assessing the influence of age on the period of time between arrival and the beginning of treatment, it is crucial to note that patient ages over 80 years officially constitute a contraindication for IVT, and that the administering of IVT to such patients depends largely on local laws and regulations. Another reason for the increased period of time between arrival and the initiation of treatment is the problem of the safety and efficacy of IVT when administered to older patients. Recent studies show that IVT remains a safe and effective method of treatment for older patients. Of the two medical centres taking part in this study, neither considers advanced age to constitute an absolute contraindication for IVT. This could partially explain why our study did not find patients' age to have any influence on the period of time between arrival and the initiation of treatment.

When analysing these results one has to take into account the fact that the two medical centres taking part in this study differ in infrastructure (eg. distance between emergency room and CT office) and work organization (prioritization of patients, emergency room work load, etc.). Due to the relatively small sample group, this study did not attempt to compare the differences between these two medical centres; however, any continuation of this work could include additional factors (distance between emergency room and CT office, location of IVT, number of patients who underwent IVT within a year, etc.) into their analysis in an attempt to identify additional factors that influence the period of time between a patient's arrival and the initiation of treatment.

In summary, it must be noted that the results of this study have important connotations for practical work - they show that not only must hospital infrastructure and work organization be improved, but also that neurologists themselves might need to undergo additional training in order for ischemic strokes to be understood as an extremely urgent pathology that requires immediate attention.

This study has shown that efficacy of IVT is similar among patients younger and older than 80 years of age. On the other hand, mortality rates are significantly higher among patients aged over 80. Other authors have reported similar results. It must also be pointed out that IVT-related complications were no more common among older patients than they were in younger age groups. The total absolute number of complications in our sample was very low; therefore, this received no further analysis. Further studies with larger sample groups could undertake more detailed analysis of complications.

Our study is also noteworthy because it analysed not just patients aged younger and older than 80 years of age, but instead divided them into smaller age groups. The results show that efficacy of IVT is similar across all three of our age groups; however, there is a clear tendency for patients aged younger than 65 to have a good outcome more frequently than for older patients. The same can be said about mortality rates, however the tendency there can be observed across all patient groups. These results could possibly be explained by the fact that patients younger than 65 years of age have a different vascular risk factor profile than older patients, while the profiles for patients aged 65 to 79, and for patients aged 80 and older, are very similar.

In conclusion, the results of this study show that IVT remains a safe and effective method of treatment for all age groups. A larger study group could allow us to confirm or deny differences between age groups, as well as to identify other aspects of IVT safety. A multicentre study is currently being planned, which would include all patients in Lithuania who have suffered from an acute ischemic stroke and were treated with IVT. The results of this larger study will most likely allow us to answer some of the aforementioned questions.

Outcome prognosis is a crucial part of everyday clinical practice. As medical technology improves and new methods of treatment emerge (e.g., mechanical

thrombectomy), outcome prognosis allows the early identification of patients who could require further testing and/or treatment. Currently, the treatment of acute ischemic stroke more and more commonly comes to involve a team of different specialists, meaning that setting an early treatment plan would allow us to improve time management and ensure more timely treatment. It is also important to remember the ethical aspect; outcome prognosis allows us to provide the patient and their relatives with more accurate information concerning the patient's long-term prognosis and possible outcome. It is also very important in the selection of possible treatment methods. This study was the first analysis of the prognostic factors in patients who had suffered from an acute ischemic stroke that was carried out in Lithuania.

The study has shown that independent prognostic factors for a good outcome were younger age, milder neurological deficit and lower blood glucose level upon arrival. Other authors' studies have also emphasized the importance of these factors. However, unlike other studies, ours did not show the period of time between the initial onset of symptoms and the initiation of treatment to have any effect on the efficacy of IVT. We do not have any single explanation for this result. First of all, it is worth noting that some of the information about our patients was collected from medical records rather than upon the patient's arrival. In particular, the time of the initial onset of symptoms was taken from medical history, where it had been entered by the attending physician or the doctor on call. This information was often not verified later (in many cases due to objective reasons). It can therefore be assumed that in some cases, the time of the initial onset of symptoms had not been accurately noted. Another possible explanation is the fact that some patients and their relatives are aware of the fact that treatment in these cases can only be administered within the first few hours. Therefore they might have knowingly specified a time for the initial onset of symptoms that was not entirely correct. The time of patients' arrival to the hospital and the point of initiation of IVT were both recorded in patients' medical histories and there is no reason to believe that these records were not accurate. It must also be noted that most patients underwent IVT within 90 to 180 minutes of the initial onset of symptoms; only a small fraction of them received treatment earlier than 90 or later than 180 minutes after the initial onset of symptoms. Considering the

small size of our study group, it is likely that this is one of the reasons why statistical reliability could not be achieved. In order to achieve more accurate results, we would have to refine the collection of anamnestic data and expand the test group. Thus, a study of this nature could be repeated when the number of patients who have suffered from an ischemic stroke and have been treated with IVT increases.

In our study, we evaluated the accuracy of the DRAGON prognostic scale with regards to our patients. The resulting area under the ROC curve (0.789) shows that the aforementioned scale allows for fairly accurate prognosis of outcomes; however, this is a lower number than that reported by other studies (0.82 – 0.89). Changing the values for blood glucose levels resulted in the AUC equal to 0.801, i.e. much closer to the numbers reported by other studies. Based on these results, the modified DRAGON scale can be recommended for use in predicting stroke patients' outcomes.

In view of our findings, we formulated a prognostic model for patients' outcomes that includes the independent prognostic factors identified in our study, adjusted by their respective importance. Statistical analysis showed that the area under the ROC curve for our model is 0.780, which indicates that this prognostic model is sufficiently accurate for use in predicting the outcomes of patients suffering from an acute ischemic stroke and treated with IVT. However, it must be noted that this prognostic model was not externally validated; therefore, it should be done before this model can see wider use in daily practice. This would be the logical continuation of this study.

To sum up, it can be said that younger age, lower blood glucose levels and milder initial neurological deficit are all significant and independent prognostic factors for good outcome. An additional study with a larger study sample is required in order to prove the influence that time has on outcome of acute ischemic stroke. When it comes to everyday practice, the DRAGON scale (or its modified version) and our original prognostic model can all be recommended for use in complex prognoses of stroke patients' outcomes. An external validation of the original prognostic scale suggested by this study is recommended in order to ascertain its accuracy for the wider population.

SENI has been shown to be directly related to good outcomes after three months. This can be also seen in other authors' studies. This study has shown that AF is an independent prognostic factor for SENI. This fact requires a separate discussion. The matter of AF's significance in stroke patients' outcomes remains controversial. While the majority of authors agree that ischemic stroke patients suffering from AF are usually in worse condition, and that their outcome prognoses are therefore also worse, several recent studies have challenged this data. One possible explanation for this is the fact that the cardiogenic thrombus is softer in structure and easier to dissolve using thrombolytic agents. On the other hand, cardiogenic thrombi are larger and therefore IVT can prove to be less effective. Studies have shown that thrombi longer than 8 mm constitute an independent prognostic factor for ineffective IVT, which makes it possible to assume that SENI depends more on the length of the thrombus rather than its source. This study did not endeavour to analyse thrombus length as a prognostic factor, as only a small fraction of all patients had a cerebral CT-angiography done before treatment. Currently, as mechanical thrombectomy become more and more popular, cerebral CT-angiographies are also performed more commonly, which allows for the assessment of thrombus length even before treatment. This could be one of the possible directions for further studies. The histological examination of thrombi could also provide some answers to these as-yet unanswered questions.

An analysis of the prognostic factors for SENI and a good outcome after three months reveals that only initial blood glucose level is an independent positive predictive factor for both cases. This suggests that a number of other factors can influence long-term prognosis, meaning that any further studies must take these factors into account and analyse them.

Our study has shown that the use of antiplatelet before the stroke does not influence either SENI or the outcome after three months. This is consistent with results reported by other authors, but ultimately remains a subject for further debate.

In conclusion, determining SENI is very important for everyday clinical practice. For patients unlikely to exhibit SENI, endovascular treatment options can be planned right after initiation of IVT. This would save time and potentially improve outcomes.

Conclusions

1. Intravenous thrombolysis is an effective and safe method of treating acute ischemic strokes. Good outcomes were observed in more than a third (38%) of all patients. The incidence of symptomatic intracranial haemorrhage is low.
2. Intravenous thrombolysis remains effective for patients of all age groups, however patients aged 65 and older face a higher mortality risk.
3. Advanced age, severe initial neurological deficit and high initial blood glucose level are all independent prognostic factors for a bad outcome.
4. Atrial fibrillation is a positive prognostic factor for significant early neurological improvement; arterial hypertension and higher blood glucose level on arrival decrease the chances of significant early neurological improvement.
5. Currently available prognostic models for predicting outcome in acute ischemic stroke can be applied to the target population. The original prognostic model proposed in this study allows for reliable outcome prognosis.

Practical recommendations

This study has shown that IVT is an effective and safe method of treating patients suffering from an acute ischemic stroke – even those aged 80 and older, despite the fact that they should not be treated with IVT according to current official manufacturer recommendations. Therefore, based on the results of our study and an assessment of available literature, IVT can be recommended for such patients in everyday clinical practice.

The prognostic factors for significant early neurological improvement identified in our study allow for the identification of patients who might require additional methods of treatment. This allows such patients to be selected early in the process of treatment. Therefore, we recommend assessing the possibility for significant early neurological improvement in all

patients scheduled to undergo IVT and identifying patients who might require additional methods of treatment.

The original prognostic model that was offered in this study and the modified DRAGON scale are both reliable tools that can be used in predicting the outcomes of patients suffering from an acute ischemic stroke. Both of these are recommended for use in everyday clinical practice when attempting to ascertain the outcomes of acute ischemic stroke patients.

While our study has not shown the period of time between the initial onset of symptoms and the initiation of treatment to be a significant prognostic factor for a good outcome, an evaluation of the limitations of this study lead us to recommend initiation of treatment as soon as possible. We recommend minimizing the period of time between the patient's arrival to the hospital and the initiation of treatment by performing tests as quickly as possible, limiting the number of tests performed to include only the most necessary of them, and encouraging doctors to consider an acute stroke to be an extremely urgent condition.

Dissertation abstract in Lithuanian

Iki šiol Lietuvoje nebuvo kompleksiškai nagrinėjami klausimai, susiję su intraveninės trombolizės (IVT) efektyvumu, saugumu, nebuvo įvertinama ligonių prognozė. Baigties prognozavimas yra labai svarbi problema kasdienėje praktikoje. Iki šiol nėra atliktų tyrimų, vertinančių šių prognozinių modelių tinkamumą bei tikslumą Rytų Europos, kartu ir Lietuvos, gyventojams.

Prognozinis modelis, pritaikytas tiriamajai populiacijai, leistų tiksliau numatyti IVT efektyvumą ir pateikti išsamesnę informaciją ligoniams ir jo artimiesiems, taip pat pagerinti ligonių atranką IVT ir endovaskuliniam gydymui.

Darbo tikslas

Nustatyti ūminio išeminio insulto gydymo intravenine trombolize baigties prognozinius veiksnius ir įvertinti prognozinių modelių tinkamumą tiriamajai populiacijai.

Darbo uždaviniai

6. Nustatyti išeminio insulto gydymo intravenine trombolize ankstyvuosius ir vėlyvuosius rezultatus, įvertinti intraveninės trombolizės saugumą.
7. Nustatyti ir palyginti intraveninės trombolizės efektyvumą ir saugumą skirtingų amžiaus grupių žmonėms.
8. Nustatyti trombolize gydyto išeminio insulto baigties po trijų mėnesių prognozinius veiksnius.
9. Nustatyti ženklaus ankstyvo neurologinio pagerėjimo prognozinius veiksnius.
10. Įvertinti ūminio išeminio insulto gydymo intraveninės trombolizės būdu prognozinių modelių tikslumą tiriamajai populiacijai.

Tiriamieji ir tyrimo metodika

Tyrimas atliktas Respublikinės Vilniaus universitetinės ligoninės (RVUL) Reanimacijos ir intensyviosios terapijos ir Neurologijos skyriuose bei Vilniaus universiteto ligoninės Santariškių klinikų (VULSK) Reanimacijos ir intensyviosios terapijos ir Neurologijos skyriuose. Tyrimo trukmė – nuo 2010 m. spalio mėn. iki 2013 m. liepos mėn. Tyrimui atlikti gauti Vilniaus regioninio biomedicininių tyrimų etikos komiteto leidimai (Nr. 158200-06-346-87, Nr. L-14-03/1, Nr. L-14-03/4). Insulto vėlyvosioms baigtims vertinti po 3 mėn. buvo registruojama ligonio funkcinė būklė pagal modifikuotą Rankino skalę. mRS 0 -1 balas buvo vertinta kaip gera baigtis, 2 – 6 balai – kaip bloga. Ženklus ankstyvas neurologinis pagerėjimas (ŽANP) apibūdinamas kaip neurologinės būklės pagal Nacionalinio sveikatos instituto insulto skalę (NIHSS) pagerėjimas ≥4 balais arba 0 – 1 balas praėjus dviem valandoms nuo IVT pradžios. IVT saugumo profiliui įvertinti buvo vertinamas trijų mėnesių mirštamumas ir simptominės intrasmegeninės kraujosruvos (ISK) dažnis. Simptominė intrasmegeninė kraujosruva apibūdinama kaip II tipo parenchiminė intrasmegeninė kraujosruva, lydima neurologinės būklės pablogėjimo 4 ir daugiau balų pagal NIHSS.

Rezultatai

Tyrimo dalyvių charakteristikos

Į tyrimą buvo įtraukti 206 ligoniai, 2010–2013 m. RVUL (buv. Vilniaus greitosios pagalbos universitetinėje ligoninėje) ir VULSK gydyti nuo ūminio išeminio insulto IVT metodu.

Iš įtrauktų ligonių 51 % sudarė vyrai (n=105) ir 49 % moterys (n=101). Vidutinis tiriamųjų amžius – 67,5±11,7 metų. Pradinio neurologinio deficito pagal NIHSS mediana buvo 14 (IQR 11–18), Vidutinis laikas nuo simptomų atsiradimo pradžios iki atvykimo į ligoninę – 77,1±43,9 min., nuo atvykimo iki gydymo pradžios – 65,3±28,1 min. Vidutinis laikas nuo simptomų atsiradimo pradžios iki gydymo pradžios buvo 143,8±43,1 min.

Po 3 mėnesių funkcinė būklė pagal mRS buvo įvertinta 168 ligoniams (81,6 %). Gera baigtis po 3 mėn. buvo nustatyta 58 ligoniams (34,5 %). Per 3 mėn. mirė 41 ligonis (24,4 %).

Pagrindinės mirties priežastys buvo išeminis insultas (16 ligonių), simptominė ISK – 4 ligoniai, plaučių arterijos trombembolija – 3 ligoniai.

Po dviejų valandų ŽANP stebėtas 73 ligoniams (39,0 %). Praėjus 2 val. nuo IVT pradžios vidutinis neurologinis deficitas pagal NIHSS buvo 11,7 ± 6,8 balų; lyginant su pradiniu sumažėjimas buvo reikšmingas (14,7 ir 11,7, p<0,001, Vilkoksono kriterijus).

Simptominės ISK buvo nustatytos 4 ligoniams (2,1 %). Intrakranijinių kraujosruvų po IVT pasiskirstymas pagal tipus

Geros ir blogos insulto baigties ligonių duomenų lyginamoji analizė

Ligoniai, turintys gerą baigtį, buvo jaunesni (atitinkamai 64,5 ir 68,8 m., p = 0,028), turėjo mažesnę glikemiją (atitinkamai 5,9 ir 6,7 mmol/l, p = 0,011). Geros baigties grupėje PV buvo nustatytas 17,2 % ligonių, o blogos baigties – 34,3 % ligonių (p = 0,029). Neurologinė būklė atvykus taip pat buvo lengvesnė geros baigties ligonių (p < 0,001).

Galvos smegenų edema buvo nustatyta 3,6 % ligonių, kurių ligos baigtis gera, ir 26% ligonių, kurių baigtis bloga (p <0,001).

ŽANP buvo nustatytas 70,4 % ligonių (n = 38) su gera 3 mėn. baigtimi, ir 21,4 % ligonių (n = 21) su bloga baigtimi (p <0,001). Vidutinis laikas nuo simptomų atsiradimo pradžios iki gydymo pradžios tarp ligonių su ŽANP ir be ŽANP buvo atitinkamai 133 min. ir 150 min., p = 0,012. Glikemija atvykus buvo atitinkamai 5,9 ir 6,8 mmol/l, p = 0,001. Neurologinės būklės pokytis (NIHSS balais) per 2 val. nuo IVT pradžios atvirkščiai koreliuoja su 3 mėn. funkcine būkle (r = -0,51, p <0,001).

Laiko nuo simptomų atsiradimo iki gydymo pradžios analizė

Didžiausiai ligonių daliai (84,9 %) IVT atlikta per 180 min. nuo simptomų atsiradimo pradžios. Koreliacinė analizė parodė, kad laikas nuo atvykimo iki gydymo pradžios turi silpną atvirkštinę priklausomybę nuo laiko nuo simptomų atsiradimo iki atvykimo į ligoninę (r = -0,367, p <0,001).

Laikas nuo simptomų atsiradimo pradžios iki atvykimo į ligoninę ir glikemija atvykus yra laiko nuo atvykimo iki gydymo pradžios nepriklausomi veiksniai. Didesnė glikemija

didina laiką nuo atvykimo iki gydymo pradžios, o ilgesnis laikas nuo susirgimo iki atvykimo mažina laiką nuo atvykimo iki gydymo pradžios.

Skirtingo amžiaus ligonių analizė

80 metų ir vyresnio amžiaus ligoniai sudarė 13,1 % (27 ligoniai) visų ligonių, kuriems buvo taikyta IVT. Mirštamumas vyresnio amžiaus žmonių grupėje buvo 37,0 %, o jaunesnių žmonių grupėje – 17,3 % (p = 0,013). Gera baigtis vyresnio amžiaus tiriamųjų grupėje buvo nustatyta 23,8 % ligonių, o jaunesnio amžiaus grupėje – 36,1 % ligonių (p = 0,262).

Papildomai ligoniai pagal amžių buvo suskirstyti į tris grupes: 1) iki 65 m.; 2) 65–79 m.; 3) 80 m. ir vyresni. Visų grupių ligoniai statistiškai patikimai skyrėsi pagal vidutinį amžių (atitinkamai 55,1, 72,2 ir 83,0 m.). Analizuojant ≥80 m. ir 65–79 m. amžiaus grupių skirtumus nustatyta, kad vyresnio amžiaus grupėje statistiškai patikimai buvo daugiau moterų (atitinkamai 70,3 % ir 45,1 %, p=0,03) ir vyresni ligoniai dažniau vartojo antiagregantus (atitinkamai 40,7 % ir 18,1 %, p=0,019). Palyginus iki 65 m. ir 65–79 m. amžiaus ligonių grupes, jaunesni ligoniai rečiau turėjo PV (atitinkamai 19,2 % ir 33,7 %, p = 0,041), širdies nepakankamumą (6,8 % ir 18,4 %, p = 0,043) ir rečiau sirgo PAH (48,6 % ir 76,0 %, p < 0,001). Jaunesnio amžiaus ligonių sistolinis AKS buvo žemesnis (atitinkamai 144 ir 155 mmHg, p = 0,001) ir jiems greičiau nuo atvykimo į ligoninę buvo pradedama IVT (vidutinis laikas atitinkamai 61 min. ir 68 min., p = 0,027). Jaunesnio amžiaus ligoniams natyvinėje galvos smegenų KT dažniau buvo matomas hiperdensinis VSA signalas (37,0 % ir 22,9 %, p = 0,045).

Nors IVT efektyvumas tarp atskirų amžiaus grupių nesiskiria, tačiau matoma aiški tendencija tarp iki 65 metų ir 65–79 metų amžiaus tiek pagal IVT efektyvumą, tiek saugumą, tačiau tokia tendencija silpnesnė tarp kitų amžiaus grupių ligonių.

ŽANP buvo nustatytas 23,8 % ligonių 80 metų ir vyresnių amžiaus grupėje ir 41,0 % ligonių iki 80 metų amžiaus (p = 0,158).

Skirtingą klinikinę baigtį lemiantys prognoziniai veiksniai

Didesnė glikemija, sunkesnė pradinė neurologinė būklė ir vyresnis amžius turi teigiamą prognozinę reikšmę blogai baigčiai po 3 mėn.

Taikomo DRAGON prognozinio modelio plotas po kreive (AUC) yra 0,780 (p <0,001), modifikuoto DRAGON prognozinio modelio plotas po kreive (AUC) yra 0,801 (p <0,001). Originalaus pasiūlyto prognozinio modelio, į kurį įtrauktas amžius, glikemija atvykus ir pradinė neurologinė būklė pagal NIHSS, plotas po kreive (UAC) yra 0,780 (p <0,001).

Ženklaus ankstyvo neurologinio pagerėjimo prognoziniai veiksniai

ŽANP turi vidutinio silpnumo atvirkštinę koreliaciją su funkcine baigtimi po 3 mėn. Arterinė hipertenzija ir didesnė glikemija atvykus yra neigiamas nepriklausomas ŽANP prognozinis veiksnys (atitinkamai ŠS 0,43, 95 % PI 0,210–0,881 ir ŠS 0,737, 95 % PI 0,587–0,024), o prieširdžių virpėjimas yra teigiamas prognozinis veiksnys (ŠS 2,177, 95 % PI 1,018-4,655)

Išvados

1. Intraveninė trombolizė yra efektyvus ir saugus išeminio insulto gydymo metodas. Gera baigtis po 3 mėn. nustatyta daugiau nei trečdaliui (38 %) ligonių. Simptominių intrasmegeninių kraujosruvų dažnis yra mažas.
2. Intraveninė trombolizė išlieka efektyvi visų amžiaus grupių ligoniams, tačiau vyresnių kaip 65 metų amžiaus ligonių mirštamumo rizika yra didesnė.
3. Vyresnis ligonio amžius, sunkesnė pradinė neurologinė būklė ir didesnė gliukozės koncentracija kraujyje atvykus yra nepriklausomi blogos baigties prognoziniai veiksniai.
4. Prieširdžių virpėjimas yra teigiamas ženklaus ankstyvo neurologinio pagerėjimo prognozinis veiksnys; arterinė hipertenzija ir didesnė gliukozės koncentracija kraujyje atvykus mažina ženklaus ankstyvo neurologinio pagerėjimo tikimybę.
5. Šiuo metu pasiūlyti baigties prognoziniai modeliai gali būti taikomi tiriamajai populiacijai. Pasiūlytas originalus prognozinis modelis leidžia patikimai prognozuoti insulto baigtį.

Praktinės rekomendacijos

Tyrimas parodė, kad ligoniams, patyrusiems ūminį išeminį insultą, IVT yra efektyvus ir saugus gydymo metodas, net ir vyresniems kaip 80 metų ligoniams, nors pagal oficialiai šiuo metu galiojančias vaisto gamintojo rekomendacijas IVT jiems neturėtų būti atliekama. Todėl, remdamiesi mūsų atlikto tyrimo duomenimis ir įvertinę literatūros duomenis, rekomenduojame tokiems ligoniams atlikti IVT kasdienėje klinikinėje praktikoje.

Mūsų darbe nustatyti ženklaus ankstyvo neurologinio pagerėjimo prognoziniai veiksniai leidžia patikimai numatyti ligonius, kuriems gali būti reikalingi papildomi gydymo metodai, ir jau pradiniu etapu atrinkti tokius ligonius. Todėl visiems ligoniams, kuriems numatomas gydymas IVT, rekomenduojama įvertinti ženklaus ankstyvo neurologinio pagerėjimo tikimybę bei atrinkti ligonius, kuriems gali prireikti papildomų gydymo metodų.

Mūsų sukurtas insulto baigties originalus prognozinis modelis ir modifikuotas DRAGON modelis yra patikimi įrankiai siekiant numatyti ūminio išeminio insulto baigtį, todėl jie abu rekomenduojami kasdienėje klinikinėje praktikoje.

Nors mūsų tyrimas neparodė, kad laikas nuo simptomų atsiradimo pradžios iki gydymo pradžios yra svarbus geros baigties prognozinis veiksnys, tačiau įvertinę tyrimo trūkumus vis dėlto rekomenduojame stengtis kuo anksčiau pradėti gydymą – maksimaliai mažinti laiką nuo ligonio atvykimo į ligoninę iki gydymo pradžios, atliekant visus tyrimus kiek įmanoma greičiau ir tik reikalingus tyrimus, skatinti gydytojų požiūrį į ūminį insultą kaip į labai skubaus gydymo reikalaujančią patologiją.

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3. **A. Vilionskis**, R. Balčytytė, D. Jatužis, O. Knoknerienė, V. Lukošaitis, M. Filipavičius, N. Tutlienė. Intravenous thrombolysis for acute stroke patients in Vilnius area: the barriers for broader implementation in daily practice. 16th Nordic Congress on Cerebrovascular Diseases, September 28 - October 1, 2011, Tallinn, Estonia.
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BRIEF INFORMATION ABOUT AUTHOR

First name:	Aleksandras
Surname name:	Vilionskis
Data and place of birth:	March 18, 1972, Vilnius, Lithuania
Business address	Republican Vilnius University Hospital, Siltnamiu 29, Vilnius, 04130, Lithiuania
E-mail:	aleksandras.vilionskis@gmail.com

Education

1990 – 1996	Kaunas University of Medicine, Faculty of Medicine, degree of Medicine Doctor
1996 – 1997	Postgraduate study of General Medicine
1997 – 1999	Postgraduate study of Internal Medicine
1999 – 2001	Postgraduate study of Neurology, license of Neurologist

Professional activity

1999 – 2001	Vilnius University Emergency hospital, Department of Neurology, Assistant physician
August 1, 2001 - present	Republican Vilnius University Hospital, Dprt. of Neurology, Neurologist

International fellowships

2003, 2006	EFNS Academy for Young Neurologists, Czech Republic
2004	Stroke Summer School, Austria.
2007	EFNS Department to Department Cooperation Programme, Denmark
2014	Winter stroke school, Switzerland

Activity in Scientific Societies:	Fellow member of European Stroke Organization Member of Lithuanian Stroke Association (since 2014 - member of board) Member of World Stroke Organization Member of World Neurological Federation Member of Lithuanian Association of Neurologist

Scientific works:

The main research area is acute stroke treatment and critical care in neurology. He has published papers in national and international scientific journals, including Stroke and International Journal of Stroke. He prepared and presented oral presentations “Conservative prevention of stroke after TIA”, “Atrial fibrillation and stroke – present and future”, “Prevention of cardioembolic stroke: the role of a novel anticoagulants" and other at local scientific conference. With co-authors prepared oral and poster presentations at international scientific conferences. He is co-author of Lithuanian guidelines for diagnosis, treatment, prevention and rehabilitation of stroke.

He given lectures about acute stroke service and acute stroke treatment for ambulance and emergency department staff.

He is the Lithuanian national coordinator in SITS-EAST project.

TRUMPA INFORMACIJA APIE AUTORIŲ

Vardas:	Aleksandras
Pavardė:	Vilionskis
Gimimo data ir vieta:	1972 03 18, Vilnius, Lietuva
Darbo adresas	Respublikinė Vilniaus universitetinė ligoninė, Šiltnamių 29, Vilnius, 04130, Lietuva
El. paštas:	aleksandras.vilionskis@gmail.com

Išsilavinimas

1990 – 1996	Kauno medicinos universitetas, Medicinos fakultetas, Medicinos gydytojo diplomas
1996 – 1997	Pirminė rezidentūra
1997 – 1999	Vidaus ligų rezidentūra
1999 – 2001	Neurologijos rezidentūra, Neurologo licencija

Profesinė patirtis

1999 – 2001	Vilniaus greitosios pagalbos universitetinė ligoninė, Neurologijos skyrius, gydytojas asistentas
2001 08 01 – iki šiol	Respublikinė Vilniaus universitetinė ligoninė, Neurologijos skyrius, gydytojas neurologas

Tarptautinės stažuotės

2003, 2006	Europos neurologų draugijų federacijos jaunųjų neurologų akademija, Čekijos Respublika
2004	Vasaros insulto mokykla, Austrija
2007	Europos neurologų draugijų federacijos „skyrius - skyrius“ programa, Danija
2014	Žiemos insulto mokykla, Šveicarija

Narystė profesinėse draugijose:	Europos insulto organizacijos tikrasis narys Lietuvos insulto asociacijos narys (nuo 2014 m. - valdybos narys) Pasaulio insulto organizacijos narys Pasaulio neurologų federacijos narys Lietuvos neurologų asociacijos narys

Mokslinė veikla:

Pagrindinė mokslinių interesų sritis yra ūminio insulto gydymas ir intensyvi terapija neurologijoje. Jo moksliniai straipsniai atspausdinti nacionaliniuose ir tarptautiniuose moksliniuose žurnaluose, įskaitant „*Stroke"* ir *"International Journal of Stroke"*. Nacionalinėse konferencijose skaitė pranešimus „Insulto medikamentinė profilaktika po PSIP", „Prieširdžių virpėjimas ir insultas: realybė ir perspektyvos", „Kardioembolinių insultų profilaktika: naujųjų antikoaguliantų vieta" ir kt. Kartu su bendraautoriais paruošė stendinius ir žodinius pranešimus tarptautinėse mokslinėse konferencijose. Jis yra Lietuvos insulto diagnostikos, gydymo, profilaktikos ir reabilitacijos rekomendacijų bendraautorius.

Jis skaitė paskaitas, skirtas GMP ir skubios pagalbos skyriaus darbuotojams apie ūminio insulto gydymo darbo organizavimą.

Jis yra Lietuvos nacionalinis koordinatorius *SITS-EAST* projekte.