

# **Knowledge System of Differential Diagnosis**

The State of the Art and the Concept of Ph.D. Thesis

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## Abstract

This report documents the preliminary work towards implementing a decision support system in stroke care. To understand the system context, current approaches in ischemic stroke treatment and the state of the art in evaluation of the treatment efficacy and safety is researched. Common statistical methods used in the relevant publications are described as well. In the latter section, availability and quality of the datasets pertaining to the problem is analyzed. Several risks are identified and their mitigation strategy is provided. Proposition of knowledge system structure is presented while taking the findings into account.

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## Acronyms

**CI** confidence interval. 12

**CT** computerized tomography. 2, 3, 7, 11, 19

**ETL** extract, transform, load. 19, 21

**EU** European Union. 2, 6

**IVT** intravenous thrombolysis. 3, 4, 9, 10

**MRI** magnetic resonance imaging. 2, 3, 7

**mRS** modified Rankin Scale. 3–5, 7, 9–11, 21, 22

**NIHSS** National Institutes of Health Stroke Scale. 3–5, 7–10, 17, 21

**OR** odds ratio. 9, 12, 13

**RES-Q** Registry of Stroke Care Quality. 6

**RRSE** root relative squared error. 17, 18

**SICH** symptomatic intracerebral hemorrhage. 7–11

**SITS** Safe Implementation of Treatments in Stroke. 6–8, 10, 11, 17–19

**TIA** transient ischemic attack. 2

# 1 Introduction

Healthcare is considered to be a knowledge-driven discipline, because of the continual improvement in diagnosis and treatment options. The pace in which various studies publish their new findings is rapid. Medical workers need to efficiently share knowledge to stay updated about the trends if they want to be able to provide best care possible for their patients. One of the tools that might assist them is a knowledge system crafted for a specific domain. For example a decision support system, that would assist in selecting optimal treatment. A variety of different data need to be combined to make the decision – lab test results, diagnosis, patient history, physical examination, previous treatment. The system would be the consulting voice making sure the clinician did not overlook something important.

This work focus on creating such a system for the context of ischemic stroke treatment. To achieve that, this report provide an overview of the disease and options for treatment. After that, two contemporary worldwide registries are presented including some of the publications using their data. Five statistical method that are commonly used in medical researched publications are described in more detail. Analysis of available datasets and possible risks follows. Proposition of the knowledge system is in the last section.

## 2 Background

### 2.1 Stroke overview

Stroke, or cerebrovascular accident as a medical term, is defined by World Health Organization as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin [1].” It is the second most frequent cause of death worldwide with more than 5 million deaths per year, which accounts for about 10 % of all deaths. Locally in Czech Republic, the incidence of stroke was estimated to be 320 per 100 000 persons in year 2010, which is about two times higher than the average incidence in European Union (EU). The stroke recurrence rate is indicated to be 40 %, which is once again higher than the EU average. Half of the stroke cases end up with severe and lasting disability of the patient. Up to 70 % of the patients experience other long-lasting problems such as depressions, dementia or epilepsy. [2]

Stroke is categorized into three distinct types based on its etiology – ischemic stroke (80 – 85 % of all strokes), intracerebral hemorrhage (10 – 15 %) and subarachnoid hemorrhage (5 %). Ischemic stroke is a situation in which neuron necrosis happens due to the insufficiency of oxygen-rich blood supply to the brain tissue. That could be caused by an acute arterial occlusion or a hemodynamic issue. There is a special case of an ischemic issue called transient ischemic attack (TIA), which causes temporary neurological deficit usually lasting less than an hour. [3]

There are disputes whether TIA should be classified as stroke. By its nature, TIA is in contradiction with the time clause of the stroke definition. Some authors include TIA cases in their calculations, while others filter them out. This may affect resulting incidence numbers, ratios of hemorrhaging stroke cases and other statistics. Comparison of epidemiological data from various centers and providers may be difficult and misleading due to this. [2] Another statistical issue lays in the process of stroke incidence estimation in Czech Republic. It is calculated either based on the mortality data, or based on the hospitalizations data of stroke patients. Neither of the approaches is considered to be reliable. [4]

### 2.2 Treatment of ischemic stroke

According to the Bulletin of the Ministry of Health of the Czech Republic [5], any patient with suspected stroke must be transported to the nearest complex cerebrovascular center or stroke center unless 24 hours have certainly passed since the symptoms onset.

After arrival, each patient undergoes either computerized tomography (CT) scan or magnetic resonance imaging (MRI) to differentiate hemor-

rhaging and ischemic type of stroke and to rule out other etiologies such as abscess or tumor. In case of ischemic stroke, angiography is used as a supplementary procedure to native CT scan to confirm the location and length of the vascular occlusion and to determine the condition of patient's collateral bed. Brain perfusion scan may be utilized to quantitatively describe the blood flow, volume or mean time of blood passage through the brain tissue. The appropriate therapy approach is chosen after evaluation of the imaging examinations. [2]

### **2.2.1 Intravenous thrombolysis**

Intravenous thrombolysis (IVT) is a contemporary standard technique for the specific treatment of ischemic stroke. It involves a systematic administration of recombinant tissue plasminogen activator, which facilitates dissolution of blood clots. Treatment is considered effective if it is applied within 4.5 hours of the first symptoms of the disease [2]. Treatment is associated with an increased risk of intracranial or systemic hemorrhage because the dissolving agent is not targeted onto the area of occlusion, but it acts in the entire bloodstream [2]. The increased risk of hemorrhage due to this treatment is weighed against increased odds of achieving good clinical outcome and functional independence of the patient.

Any CT or MRI finding of intracranial hemorrhage, suspected subarachnoid hemorrhage, presence of acute internal hemorrhage, or recent history of such hemorrhage is an absolute contraindication to this procedure. In addition, uncontrollable high blood pressure or low blood glucose level is also an absolute contraindication. There are several relative contraindications, i.e. those that can be ignored in justified cases based on the risk vs. benefit assessment. Those contraindications are presence of too severe neurological deficit (NIHSS score  $> 25$ ), presence of only mild neurological deficit (NIHSS score  $< 4$ ), previous ischemic stroke resulting in persistent severe neurological deficit (mRS score  $> 3$ ), presence of epileptic seizure at the onset of stroke, myocardial infarction in the previous 3 months, surgery or injury in the last 2 weeks, pregnancy. [6]

### **2.2.2 Thrombectomy**

Thrombectomy is a relatively new method that aims to mechanically remove the occluding thrombus using device inserted into the femoral artery. The device is then guided through the blood vessels to the affected area. Depending on the type of device, the thrombus will be aspirated, extracted or fragmented at the target area. Devices also differ by the position relative to the thrombus from which they act. [2]

This method can be used to remove thrombus with its length exceeding 8 mm, which is considered to be an upper limit for effective IVT treatment.

There was a set of randomized clinical studies for thrombectomy performed with stent retrievers with results published in 2015 – MR CLEAN, ESCAPE, SWIFT-PRIME, EXTEND-IA and REVASCAT. The studies showed that patients with acute ischemic stroke in experimental group had significantly better clinical outcomes. Significantly lower mortality rate for experimental group was observed in two of the studies, while no difference in mortality was observed in the rest of them. [7]

Another advantage of the method is its larger therapeutic time window relative to IVT. The European Stroke Organization states in its recommendations [8] that thrombectomy can be used up to 7 hours and 18 minutes after the onset of stroke symptoms, in special cases even after a longer period of time.

There are some known complications of the procedure mentioned in the literature [2]. Those include malignant cerebral edema (the most common), intracerebral vasospasm, intracranial hemorrhage, distal embolization, breakage or damage of the device.

### **2.3 Assessment scales used in stroke**

Various metrics describing the efficacy and safety of treatment are being used in clinical studies and research of ischemic stroke treatment. In an effort to objectively assess the severity and description of the stroke, several scales have been developed and published. Due to the wide-spread use of standardized scales, it is possible to compare patient treated in different medical facilities by different specialists. Some of the scales can be used to track the development of the clinical condition and long-term effects over time. The most commonly used and validated stroke scales are Modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS). [9]

The Modified Rankin Scale is a seven-point scale shown in table 1, which is commonly used for indicating the degree of disability or functional independence of the patient suffering from a stroke. It was introduced in 1988 [10] as a modification of the previously used Rankin Scale from 1957 [11].

The scale is simple, relatively easy and quick to evaluate using a structured interview with the patient. A single point change in mRS assessment indicates a significant deterioration or improvement in quality of patient's life. This scale is widely used as an outcome measure in clinical stroke trials. The mRS score is usually assessed at the time of discharge from the hospital and during the check-up scheduled 3 months after the stroke onset. It is problematic to determine baseline mRS score referring to the situation before the stroke onset, because it would be assessed in retrospect and the distinction in scores 0-2 is not well defined in the questionnaire for this case [12]. The scale does not account for comorbidity, previous operations and other factors that may have a direct impact on the mRS. Clinicians need to take these limitations into account to correctly apply and analyze



the scale score. [9, 13]

<b>mRS</b>	<b>Description of score</b>
0	No symptoms.
1	No significant disability. Able to carry out all usual activities.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead.

Table 1: Modified Rankin Scale score definitions [9]

The NIHSS scale is used to quantify the current neurological deficit of a patient. It is more detailed than mRS as it is composed of 11 items and the score total ranges from 0 to 42, with lower value indicating lesser impairment. It was introduced and validated in 1989 [14]. Each item focuses on a specific ability and has a set of potential results defined with a corresponding score value assigned. The item scores are summed in order to establish final NIHSS score. The score is assessed at multiple timepoints – during the initial checkup, 2 hours after treatment, 24 hours after stroke onset, 7 days after the event and 3 months after the event.

The NIHSS score correlates with the severity of stroke. The score value assessed soon after onset of stroke symptoms is a statistically significant predictor of the patient’s condition at 7 days and 3 months after stroke event [15]. The average time required to determine the NIHSS score was measured to be 6.6 minutes [14], which can be considered too lengthy if the score is used in the decision making process before commencing treatment [16].

## 3 Existing data sources and study outputs

### 3.1 SITS registry

One of the most important sources of medical data on stroke patients are the Safe Implementation of Treatments in Stroke (SITS) registries. SITS is presented as a non-profit, research, independent and international collaboration of treatment centers in order to assure excellence in acute treatment of strokes, prevention of recurrence of strokes and facilitate the conduct of clinical trials [17]. This initiative originated in 1996 in a form of randomized stroke thrombolysis study by a European-Australian collaborative effort. In 2002, the European Medicines Agency (an agency of the European Union) endorsed SITS as the registry for follow-up on thrombolysis treatment in acute ischemic stroke. All patients treated with thrombolysis in the European Union member states had to be kept in the relevant SITS registries, which led to a significant expansion. The SITS network kept expanding in other regions as well. More than 1 700 treatment centers from 86 countries were involved in SITS in 2019. The scope of the registries has been extended to also include patients who have been treated with thrombectomy, or who have been treated with a bridge therapy combining thrombolysis and thrombectomy. [17]

In addition to the registries themselves, SITS also manages several studies, two of which are relevant to the topic of this work. SITS-MOST II is a prospective observational study that monitors the safety and efficacy of routine treatment practices in the treatment of stroke (thrombolysis, thrombectomy, preventive treatment). The second one is a prospective SITS-OPEN study that evaluates thrombectomy treatment compared to conventional ischemic stroke treatment.

### 3.2 RES-Q registry

Another notable initiative is Registry of Stroke Care Quality (RES-Q) which is managed by St. Anne's University Hospital in Brno. The primary goal of RES-Q is declared to be the improvement in quality of stroke care in Central and Eastern Europe by providing data that can be translated into healthcare policies and guidelines on both national and European level [18]. Even though its original scope was Central and Eastern European countries, the registry is open to all interested parties regardless of region.

The registry is running for a shorter period of time compared to SITS. The first publication citing the registry is from 2019. As of 1st September 2021, there were 380 thousand patients registered originating from 1 580 medical centers and 73 countries [19], which is slightly smaller in size compared to SITS.

### 3.3 Evaluated outcome measures

SITS studies put safety and efficacy of treatment interventions in acute stroke as the primary topic of research. Efficacy refers to the formal evaluation of several outcomes that are typically compared in studies to standard treatment. The efficiency measures are:

- Difference in mRS score at 3 months after event.
- Proportion of patients with functional independence after 3 months, which is defined as mRS score 0-2.
- Proportion of patients with excellent recovery after 3 months, which is defined as mRS score 0-1.
- Recanalization of the occluded artery, defined as TICI<sup>1</sup> grade 2b or 3 in the operated area.
- Time from stroke onset to artery recanalization in the sense of TICI grade 2b or 3.
- Achieved neurological improvement at 12 hours, 1 day, and 7 days compared to the baseline and determined by the difference between the NIHSS scores.
- Length of in-hospital stay.
- Proportion of patients with recurrent stroke or other vascular events within 3 months.

Safety outcome measures include complications such as intracerebral hemorrhage, the main risk of thrombolytic therapy, and mortality. The SITS-OPEN study declares the following outputs:

- Symptomatic intracerebral hemorrhage (SICH) according to the definitions of SITS-MOST, SITS-MOST with extended criterion for bleeding location, ECASS III with extended criterion for bleeding location.
- All-cause mortality within 3 months.
- Death within 7 days post treatment.
- Distal embolism/reocclusion demonstrated by follow-up CT/MRI in 22-36 hours after treatment.

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<sup>1</sup>TICI is a radiology scale by Higashida et al. from 2003 [20]. Grade 3 represents complete perfusion after thrombolytic treatment. Grade 2b is complete perfusion, but slower than normal.

- Systemic embolism.
- Other complications associated with thrombectomy procedure.

As shown in the list, there are multiple existing definitions for SICH used in different studies. The SITS-MOST definition of SICH states: a local or remote Type 2 parenchymal hemorrhage on imaging 22 to 36 hours after treatment or earlier if the imaging scan was performed due to clinical deterioration combined with a neurological deterioration of  $\geq 4$  NIHSS points from baseline or from the lowest NIHSS score between baseline and 24 hours or leading to death within 24 hours. A grading of Type 2 parenchymal hemorrhage for intracranial hemorrhage indicates a coagulum exceeding 30 % of the infarct with substantial space occupation. [21]

SICH defined per ECASS III: hemorrhage demonstrated on imaging associated with aggravation of neurological deficit (increase in NIHSS score by at least 1 point) in 24 hours after the thrombolytic treatment. [21]

### **3.4 Overview of approaches and results using SITS registry data**

As of 10 January 2020, 76 articles were published in affiliation with SITS using data from the registries. The complexity of analytics and utilized statistical methods vary in the publications. There are some publications containing only descriptive statistics of a subset of the patient dataset without any further modeling or processing of the data. A common approach found in the publications is to do a univariate analysis of the dataset to determine which variables have some effect on the outcome variables named in chapter 3.3. The most significant variables are then used to construct a multivariate logistical regression model.

There is no publication focused on comparing different possible treatment plans and assessing their risk-benefit relation for a particular patient. The publications either filter patients with a specific treatment, or do not differentiate the treatment method at all. Thrombectomy treatment has not been studied on its own yet. As of 10 January 2020, there was only a single publication with SITS affiliation containing the keyword thrombectomy in its title.

I will provide a brief overview of 10 arbitrarily selected recent publications. Each of the publication has its cohort mentioned in table 2 together with its size. Most of the publications used simple descriptive statistics to compare their cohorts. Those tests and methods are explained in chapter 4.

In the first sampled publication, models using only subsets of NIHSS attributes were researched as a possible triage tool to identify occlusion in large artery [16]. Many logistic regression models having between 1 to 4 NIHSS items as predictors were trained. Model with all NIHSS items

was used as baseline reference. The performance of a logistic model with 2 items of arm-motor functions was statistically significantly worse than the reference, but authors claimed that from clinical perspective the difference is not big. However, the 2-item model is much faster to evaluate than the complete one and thus might be viable in triage.

Effect of dual antiplatelets pretreatment was evaluated in [22]. The authors used Propensity score matching as a subsampling technique to balance the cohort sizes. In addition to commonly used univariate cohort comparison, the authors utilized Cochran–Mantel–Haenszel test to compare mRS distribution in the cohorts. No significant difference was found in the cohorts and it was concluded, that history of antiplatelets should not be a contraindication for IVT.

Publication [23] evaluated safety and efficacy of IVT in Greece. The authors provided descriptive statistics for the attributes. Outcome attributes were placed in a summary table with quoted values from other countries. The method of comparison is unknown. Authors conclude that safety and efficacy in Greece is similar to Italy, Austria, Belgium and Poland.

Authors of [24] researched the effect of Transcranial Doppler ultrasound application before IVT administration. Multivariate logistic regression was used to adjust for confounding effects in the analysis. Ultrasound application did not increase the chance of SICH, it delayed the start of IVT treatment by 14 minutes, but it increased the OR of excellent outcome and reduced the OR of death within 3 months.

Publication [25] examines the outcomes of IVT in patients with cardioembolic stroke. Univariate and multivariate logistic regression models are built to explain output variables: mRS 0-1, mortality, SICH, NIHSS after 24 hours. The authors conclude that cardioembolic stroke is not connected with higher mortality, but it has better odds of excellent recovery and lower odds of SICH.

Retrospective analysis [26] examined 11 IVT off-label criteria and their relation with SICH. Numbers of patients and numbers of off-label IVT in individual centers were evaluated using zero-inflated Poisson regression. Multivariate logistic regression for SICH prediction were built from selected input attributes. Missing values were dealt with using Multiple imputation by chained equation technique. Authors observed that centers with higher number of administered IVT has higher off-label ratio. SICH was statistically significantly more common in off-label IVT. High blood pressure, high glucose level, serious stroke, diabetes and high age were positive independent predictors of SICH. Most of the off-label criteria had no effect on SICH odds.

Predictors for cerebral edema were examined in [27]. The edema cohort was further divided to three edema subtypes. Univariate logistic regression has been used to analyze no edema cohort against all subtypes. Three multivariate logistic models were created to find predictors of cerebral edema, one

for each subtype. NIHSS, hyperdense artery sign, blood glucose level, impaired consciousness and signs of acute infarct were found to be independent predictors of all types of edema.

Authors of [28] were interested in effects of applying IVT in so called Golden hour, i.e. less than an hour after the onset of symptoms. There were too few patients with such a quick treatment, so Propensity score matching was used to make cohorts more balanced. Univariate and multivariate logistic regression were created to model treatment outcomes. Authors conclude, that administering IVT in Golden hour increases the odds of functional independence and neurological deficit improvement. Mortality and SICH odds are not affected.

Opposite issue than Golden time was explored in [29]. All the patients with unknown onset time were assigned to the cohort. Logistic regression models were constructed to predict mortality, SICH, functional independence and mRS  $> 2$ . It was noted, that patient with unknown onset time has significantly higher age, NIHSS score, door-to-needle time. SICH and functional independence odds were indifferent.

Publication [30] demonstrates nomogram tool for SICH prediction. Attributes for the nomogram were chosen based on the univariate analysis. To calculate the coefficients, authors used multivariate logistic regression. Ten independent predictors of SICH were found. The nomogram was validated and has better performance than previously used scales.

Pub.	SITS study	Cohorts and their size
[16]	SITS-ISTR	LAO (2 042), no LAO (2 881)
[22]	SITS-ISTR	DAPP (1 043), no DAPP (1 043 <sup>†</sup> )
[23]	SITS-ISTR	(523)
[24]	SITS-ISTR	TCD before IVT (1 701), no TCD (9 564)
[25]	SITS-EAST	CS (4 131), AS (6 197), LS (1 792), other (1 653)
[26]	SITS	SICH (1 037), no SICH (55 221)
[27]	SITS	CED (9 579), no CED (32 608)
[28]	SITS-EAST	<1 hour after onset (71), other (6 882)
[29]	SITS-ISTR	unknown onset time (502), OTT < 4.5 h (44 875)
[30]	SITS-ISTR	training (12 030), test (3 919)

Table 2: Overview of sampled publication using SITS registry.

LAO = large artery occlusion; DAPP = dual antiplatelet pretreatment; TCD = transcranial doppler ultrasound; IVT = intravenous thrombolysis; CS = cardioembolic stroke; AS = atherothrombotic stroke; LC = lacunar stroke; SICH = symptomatic intracerebral hemorrhage; CED = cerebral edema; OTT = onset to treatment time

<sup>†</sup> matching technique was used

### 3.5 Approaches and results using other datasets

There are other works not affiliated with SITS that are using data from other studies and sources and that are relevant to this thesis topic. Ganash et al. [31] dealt with long-term monitoring of stroke patients in order to establish whether the standard 3 months, after which the final mRS output score is routinely evaluated, is sufficient time to describe the efficacy and safety of the treatment. They used Kaplan-Meier techniques to estimate the survival function. The conclusion of the work is that mRS score at 3 months after the event is a good predictor for the level of disability and mortality at 5 years after the event. They also observed that there tend to be some improvement in mRS score between 3 and 12 months after the event in about 25 % of the patients. However, an improvement in mRS score or further recovery is unlikely after 1 year has passed since the stroke event.

Kupershtein et al. [32] have developed a hybrid medical support system for stroke diagnosis. The system is formed by two models. The initial diagnosis is estimated by a neural network. The network has 17 input nodes representing relevant symptoms chosen by an expert group. There are 4 output nodes representing three different stroke types and a general other diagnosis. In the next stage of the system workflow, CT images are evaluated by the radiologists and their findings are input into the rule system module together with the previously estimated diagnosis. The output of the rule system is presented as a final diagnosis to the clinician. After deploying this system in practice, the average time required to complete the diagnosis has been decreased.

Sung Lee et al. [33] have built a decision support system for individualized treatment for stroke patients. They use 2 multivariable logistic regression models with 15 and 18 predictors chosen by an expert panel. The regression models predict mRS at 3 months and the risk of SICH when using thrombolytic treatment. The models were formed using a small patient sample and then validated on new dataset.

The RESOLVE decision support tool from the University of Missouri is focused in a slightly different direction. Its authors use a validated model with 6 input attributes to predict thrombolytic treatment output [34]. The results of the model are presented in a web interface that can be used by a clinician and its patient to discuss the prognosis and potential risks [35]. Due to this, the clinician can communicate more efficiently with the patient and the patient can in turn make better informed decision regarding undertaking the thrombolytic treatment.

## 4 Commonly used statistical methods

This chapter contains selected statistical methods and tests that are often used in existing solutions mentioned in section 3.4 and which were used in the analysis on usability of available data sources further mentioned in section 5.1.

### 4.1 Odds ratio

An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Odds ratios are most commonly used in case-control studies. [36]

The calculation can be shown on a  $2 \times 2$  contingency table with aggregated values of frequencies. The scheme of such table is shown as Table 3. The formula for OR calculation (2) uses concept of odds defined in (1). The odds ratio value ranges from zero to positive infinity.

	Target group (+)	Control group (-)
Exposure (+)	a	b
Absence of e. (-)	c	d

Table 3: contingency table for Odds Ratio calculation

$$Odds_{target} = \frac{a}{c}; Odds_{control} = \frac{b}{d}; \quad (1)$$

$$OR = \frac{Odds_{target}}{Odds_{control}} = \frac{\frac{a}{c}}{\frac{b}{d}} = \frac{ad}{bc} \quad (2)$$

By analyzing the OR value, it is possible to determine whether an exposure is a risk factor for a particular outcome, and to compare the magnitude of various risk factors for the outcome [36]. OR value of 1 indicates that the exposure does not affect the odds of the outcome. Higher OR values suggest that the exposure is a risk factor. On the other hand, lower OR values suggest that the exposure is a protective factor.

The value of OR is by its nature a point estimate and it is commonly reported with its confidence interval (CI) to give reader a better idea on precision of the finding. Wide CI indicates a low level of precision of the OR, whereas tight CI indicates higher precision of the OR [36]. A standard error can be calculated for the log odds ratio and hence a confidence interval. The log odds ratio can take any value and has an approximately Normal distribution. The standard error of the log odds ratio is estimated simply



by the square root of the sum of the reciprocals of the four frequencies in contingency table. A 95 % confidence interval for the log odds ratio is obtained as 1.96 standard errors on either side of the estimate. These limits can be transformed by antilog to give a 95 % confidence interval for the odds ratio itself (3). [37]

$$95\% \text{ CI limit} = \exp \left( \ln(OR) \pm 1.96 \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}} \right) \quad (3)$$

The 95 % confidence interval does not report a measure's statistical significance. It indicates a level of precision. In practice, the 95 % CI is often used as a proxy for the presence of statistical significance if it does not overlap the null (OR = 1) value. [36]

## 4.2 Logistic regression

Logistic regression is used to obtain odds ratio in the presence of more than one explanatory variable. The target attribute has to be binomial, i.e. it can only have one of two possible values. The result is a set of coefficients describing the impact of each explanatory variable on the observed target attribute. The coefficients can be converted to Odds ratios. The main advantage is to avoid confounding effects by analyzing the association of all variables together. [38]

$$\ln \left( \frac{\pi}{1 - \pi} \right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_n x_n \quad (4)$$

Logistic regression model has a form of (4), where  $\pi$  indicates the probability of an event,  $\beta_i$  are the regression coefficients associated with the reference group and  $x_i$  are explanatory variables. Reference group is meant as a group of individual records having all  $x_i$  equaled to zero. The regression coefficients can be transformed by exponential function ( $e^{\beta_i}$ ) to provide odds ratio which can be interpreted as a multiplicative change in chance of the target event in individuals with  $x_i$  present. To calculate the OR for combination of multiple variables, the calculation  $e^{\beta_i + \beta_j}$  is used. [38]

Choosing suitable set of explanatory variables for a logistic model is a major issue to consider. A common approach found in medical research papers is to test all the candidate variables using univariate models (i.e. containing a single explanatory variable) or statistical tests. The attributes having the most significant effect on the target attribute are then selected to be included in the multivariate regression model.

## 4.3 Pearson's $\chi^2$ test of independence

Pearson's  $\chi^2$  (chi-squared) test is commonly used to assess whether observations of two nominal attributes  $X$  and  $Y$  are independent. The observations

are structured into a contingency table. The test uses the following null and alternative hypothesis:

$H_0$ : the attributes  $X$  and  $Y$  are statistically independent;

$H_A$ : there is an association between the attributes  $X$  and  $Y$ .

A contingency table is a matrix of dimensions  $R \times C$ , with  $R$  being the number of distinct values of the nominal attribute  $X$  and  $C$  is the number of distinct values of the nominal attribute  $Y$ . The values  $n_{ij}$  in the matrix represents frequencies of particular combination of attributes in sampled population. To calculate  $\chi^2$  test criterion  $K$  (6), it is necessary to express the expected frequencies  $E_{ij}$  as marginal relative frequencies (5). [39]

$$E_{ij} = \left( \frac{n_{i.}}{n} \cdot \frac{n_{.j}}{n} \right) \cdot n = \frac{n_{i.} \cdot n_{.j}}{n} \quad (5)$$

$$K = \sum_{i=1}^R \sum_{j=1}^C \frac{(n_{ij} - E_{ij})^2}{E_{ij}} \quad (6)$$

The criterion  $K$  has approximately  $\chi^2$  distribution with  $(R - 1) \cdot (C - 1)$  degrees of freedom in case the null hypothesis is valid while assuming the fulfillment of two conditions for good approximation. The first condition states there should be no expected frequency  $E_{ij}$  lesser than 2. The second requirement is that at least 80 % of all expected frequencies  $E_{ij}$  are greater than 5. If the above mentioned is met, a p-value is calculated as  $p = 1 - F_0(K)$ , with  $F_0(x)$  being the  $\chi^2$  distribution function. [39]

In some cases, the conditions for good approximations cannot be met due to low expected frequencies. It is possible to use the Yates correction technique (7) to handle such cases. This correction reduces the overall value of the test criterion and thus makes it less likely to reject the null hypothesis. [39]

$$K_{Yates} = \sum_{i=1}^R \sum_{j=1}^C \frac{(|n_{ij} - E_{ij}| - 0.5)^2}{E_{ij}} \quad (7)$$

#### 4.4 Fisher's exact test

Fisher's test is an alternative to Person's  $\chi^2$  test that can be used in situation with smaller sample sizes, where the latter is not suitable. It is defined for contingency tables with  $2 \times 2$  dimensions and it has the same null and alternative hypothesis as the  $\chi^2$  test, i.e.:

$H_0$ : the attributes  $X$  and  $Y$  are statistically independent;

$H_A$ : there is an association between the attributes  $X$  and  $Y$ .

The idea behind the test is to calculate the probability that one observes such an extreme or even more extremely distributed sample population assuming the null hypothesis and given marginal totals. The probability  $P$  of the observed instance is calculated as (8) with the notation corresponding to table 3 and  $n$  being the sum total of all contingency table values.

$$P = \frac{\binom{a+c}{a} \cdot \binom{b+d}{d}}{\binom{n}{a+b}} = \frac{(a+b)!(a+c)!(c+d)!(b+d)!}{a!b!c!d!n!} \quad (8)$$

The test statistic is calculated as the sum of probabilities  $P^*$  of all the contingency tables which can be formed with the same marginal totals and which has  $P^*$  less or equal to  $P$  of the observed distribution. The test statistic is exactly the p-value of the test. [40]

## 4.5 Mann–Whitney U test

Mann–Whitney U test is a nonparametric test of median equality applied on two independent samples  $X_1 \dots X_n$  a  $Y_1 \dots Y_m$  ( $X$  is chosen to be the sample with more measurements). The samples are assumed to originate from continuous distributions with the same shape and dispersion. The null hypothesis states:

$H_0$ : the medians of  $X$  and  $Y$  are the same.

The alternative hypothesis can be stated in multiple forms and the proper choice is based on the relation of the sample medians. [39]

$H_A$ : the median of  $X$  is less than the median of  $Y$ ,

$H_A$ : the median of  $X$  is greater than the median of  $Y$ ,

$H_A$ : the median of  $X$  differs from the median of  $Y$ ,

The test statistics calculation is done by following steps: [39]

- Sort all observations (from both samples) by their value in ascending order and assign numeric ranks to them, i.e. the observation with the smallest value would be assigned number 1 and the observation with the highest value would be assigned number  $m + n$ . In case of tied values, the midpoint rank of the group is assigned to them.
- Calculate  $T_1$  as the sum of ranks of observation in  $X$  and calculate  $T_2$  as the sum of ranks of observations in  $Y$ .
- Calculate  $U_1$  and  $U_2$  statistics (9).
- Calculate the test criterion  $T$  (10).

$$U_1 = nm + \frac{n(n+1)}{2} - T_1; U_2 = nm + \frac{m(m+1)}{2} - T_2 \quad (9)$$

$$T(X, Y) = \min(U_1, U_2) \quad (10)$$

Referencing the tables with critical values of  $T$  for particular significance level, one can reject the null hypothesis if the criterion value is smaller than or equal the critical one.

## 5 Preliminary results

As the first step, a search for available data sources and datasets has been conducted. Their suitability and usability for the thesis goals has been evaluated. The SITS registries mentioned in chapter 3.1 appeared to be an interesting data source for this work in theory. Their worldwide scope and well-structured data would be good starting point in building the knowledge base of the decision-support system. However, full access to the datasets could not be acquired.

Only data of stroke patients originating from the Department of Neurology in University Hospital in Pilsen were available due to the long-term cooperation between this department and the Department of Computer Science and Engineering in University of West Bohemia. The Department of Neurology serves as complex cerebrovascular center for Pilsen Region based on the methodological instruction of the Ministry of Health [5], which means that all the patients in the region with acute stroke should be transported and treated here unless more than 24 hours have passed since the stroke onset.

The description of the dataset and potential risks are covered in more detail in following sections.

### 5.1 UH Pilsen dataset analysis

There were 2 207 patient records in the dataset as of 15th January 2020. According to the treatment attribute, 1 003 of them underwent thrombolysis, 51 underwent thrombectomy and 232 were treated with combination of thrombolysis and thrombectomy. Relative frequencies were calculated for nominal attributes in the dataset, while median and interquartile range were given for numerical attributes. The statistics were calculated for each treatment group (thrombolysis, thrombectomy, combined) and for the entire dataset as a reference point. Each statistic was compared to the reference group and p-values were calculated using Pearson's  $\chi^2$  test (section 4.3) and Mann-Whitney U test (section 4.5) where applicable. The populations of the treatment groups were statistically significantly different from the common population in some of the observed characteristics and it might be possible to gain some insight by studying the associations.

To further look into the dataset usability, I have created several trivial regression models predicting one of the treatment outcome (specifically the NIHSS value after 24 hours) for the three treatment groups and for the reference. The models were validated using common 10-fold cross-validation to prevent overfitting. Performance of tried regression models for thrombectomy and combined treatment subsets were highly unsatisfactory. The root relative squared error (RRSE) metric of the model were higher than 1, meaning the model were not able to explain the outcome using the input data.

This result could be caused by several issues. The dataset might not contain the attributes that has actual effect on the treatment outcome. More complex model might be needed to properly predict the outcome. There might be insufficient records in the data subsets or even in the dataset as a whole to create a proper model.

The trivial regression models for thrombolytical treatment subgroup and for the entire dataset performed somewhat better (RRSE were around 0.7) than the previously mentioned ones. Since many publications dealing with efficacy and safety of the stroke treatments (section 3.4) successfully employs regression models with low number of input attributes, it seems likely that the main issue with the unsatisfactory models was the low amount of records.

Looking back at the complete dataset, there are many records with missing values. To illustrate the issue, laboratory measurement of glucose level is missing in 4 % of the records, activated partial thromboplastin time value is not reported in 6 % of the records, cholesterol and creatine values are missing in 10 % of the records. The values are missing in asymmetric fashion – i.e. the record is usually missing only some of the laboratory values, not all of them. In this case, 17.5 % of the records are missing at least one of the four aforementioned laboratory measurements. The scale of this problem will not allow to filter out the incomplete records and work with the perfect records only. It will therefore be necessary to examine this in more detail and devise a non-trivial solution if the dataset is to be used for the knowledge base building.

The fact that the patients originate from a single medical center, and thus a single region, might also be an issue for the knowledge system construction. It might be the case that the patients with similar characteristics are treated in the same way due to the internal policies and procedures. This might make it impossible to retrospectively compare the courses and results of alternative treatment plans. Having such comparisons would be crucial to build a decision support system that is supposed to evaluate potential treatment options and describe the expected outcomes.

## 5.2 Risk mitigation strategies for the dataset issues

In case the low number of records for thrombectomy and combined treatment would make building proper models unfeasible, established models of other authors could be incorporated into the system either in a form of an ensemble model or as a standalone. While using the models as standalone, the user would get the predicted outcome together with the information about the model used and its annotation.

The issue with the potential bias in the treatment choice due to the existing internal policies could be alleviated by using statistical pairing technique (e.g. propensity score matching, which was used in two of the sampled publications affiliated with SITS [22, 28]) in order to choose the records in a way

to make cohorts with similar overall characteristics. Using this approach might also help in balancing the population between the treatment groups, as currently there are about 4 times more records in the thrombolytical group compared to the thrombectomy one. In addition, thrombectomy is a relatively new approach and it is therefore safe to assume, there are some cases in the dataset of thrombolytical treatment on patients that would be treated differently nowadays. Due to that, there should be at least some comparable records of patients treated in alternative ways.

The missing values needs to be dealt with in multiple ways. Some of the values might be obtained from another source during the ETL (extract, transform, load) process. Laboratory values might be extracted from the structured medical report for example. Similar text-processing technique has been employed in the ETL process for the IBDS<sup>2</sup> prospective database to fill several of the attribute fields [41]. In case of missing values on input while using the model to make a prediction, the missing values could be treated as parameters. The user would be shown a possible range of model output value depending on the parameter.

The available dataset has a broader scope than the SITS registries. In particular, it also contains images from routinely performed imaging examinations and dynamic CT angiography. The images could be processed to extract additional features. Using those features might allow for building more accurate and complex models and it would mitigate the risk that the treatment outcome could not be modeled with sufficient accuracy by merely using the clinical data attributes. Appropriate quantification of the characteristics of the patient's collateral bed might lead to a better understanding of the course of the stroke and would contribute to better assessment of the risks and outcomes of the treatment for the patient. It is assumed that the condition of collateral bed plays a crucial role in stroke treatment [7, 42].

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<sup>2</sup>IBDS is prospective database for patients with inflammatory bowel disease (mainly Crohn's disease) developed by Medical Information Systems Research Group in the University of West Bohemia in collaboration with University Hospital in Pilsen

## 6 Proposed knowledge system

The structure of proposed knowledge system is illustrated in figure 1. Main purpose of the system would be to assist clinicians in making decisions concerning alternative treatment options for stroke patients. It will consist of a knowledge base module and a presentation module as is usual in knowledge systems. The knowledge base itself would be formed by medical dataset and formalized knowledge models. Models are expected to be both custom made and imported validated models of other authors. The presentation module would provide web interface for the user to evaluate the current patient and to browse data of previously treated patients. The module would also provide the means to configure knowledge model imports.

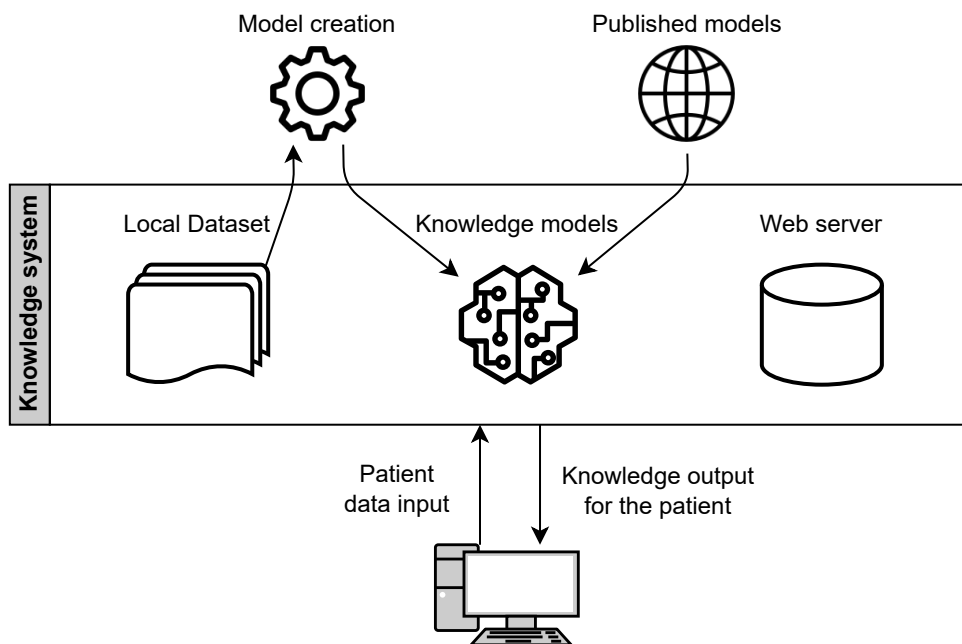


Figure 1: Knowledge system schematic overview.

### 6.1 Data storage

Due to the long term cooperation with University Hospital in Pilsen, there is an existing solution for transferring, preprocessing and storing of the data originating from the hospital. Data channel is built for the transmission of structured medical data in DASTA<sup>3</sup> format and image data in DICOM<sup>4</sup> format. Data in both formats are preprocessed before transmission to not

<sup>3</sup>DASTA is Czech national data standard for data interchange between hospital information systems. It is published by Ministry of Health of the Czech republic.

<sup>4</sup>DICOM is data standard for the communication and management of medical imaging information and related data.



include any personal data. In textual DASTA format, the problematic attributes are pseudonymized, i.e. replaced by special placeholder identifier which can be later used to pair data associated with the same person. However, the identity of the person is concealed this way. DICOM files contains both textual metadata and raw image data. Text attributes in DICOM are dealt with in the same way as in DASTA. The image data might have personal data burnt-in by radiological software. This issue was solved by deploying a custom solution which identifies and blacks out the pixels with burnt-in texts [43].

As we use RDF<sup>5</sup> repositories to store both the raw data and various metadata related to the process, the incoming data are transformed to set of RDF triples in the ETL process. Additionally, indexing metadata about the incoming DASTA and DICOM files are extracted and stored as well. The RDF terms used during the transformation are backed by well-known ontologies and RDF vocabularies when applicable. Since the context of the data is rather atypical, several custom ontologies has been created and published to define needed terms [44].

The proposed knowledge system does not impose special requirements on the primary data storage or knowledge model serialization. It is thus suitable to build upon the existing storage structure, which already stores received medical records. This solution is also flexible and allows seamless arbitrary extension of stored data structures (compared to rigid relational database table definitions). It would be therefore possible to update the ETL process transformations or add metadata extraction modules in the future without any concern for the storage scheme.

In addition to primary data storage, the knowledge models will be serialized in a standalone RDF graph. There are already ontologies [45] facilitating model serializations, which might be suitable for this case. The definitions of links between the model attributes and patient data needs to be solved by custom solution.

## 6.2 Knowledge models

The knowledge system will contain its own models for predicting outcomes of different treatment types. The models will be trained using the dataset from University Hospital in Pilsen, which was described in chapter 5.1. Three primary outcome measures has been chosen for modeling with regards to the characteristics of the dataset – NIHSS score at 24 hours after the onset, mRS score at 3 months after the event and survival of the patient at 1 year after the event. The NIHSS score will be evaluated as a difference to initial NIHSS gathered at the checkup, thus providing an information whether a short-term

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<sup>5</sup>RDF is a standard model for data interchange on the Web. It enables effective data integration from multiple sources.

improvement or deepening of the neurological deficit is probable after the chosen treatment. The mRS metric indicating the patient's functional self-sufficiency tends to be used in the studies mentioned in chapter 3.4 in terms of achieving a certain score range. A range of 0-1 or 0-2 mRS is generally considered to be a good result. I will choose the same approach which will make the model comparable to the models of other authors.

Apart from the regression based outcome prediction models, there will be knowledge models based on similarity of instances. Those will be of two types, clustering models and a simple nearest-neighbor model. The clustering models have potential to uncover a set of archetypical patients who might for example have high risk of developing post-treatment complications. If the modeled problem dimension is low enough, such a model could be effectively visualized and it might give the clinician better insight about the current patient in relation to the patients treated before. The nearest-neighbor model would be used by the web application to find patients with similar characteristics to the current patient and to provide information about their treatment and outcomes.

The dataset used for model training may contain invalid or untrue data points in addition to the issue of missing data mentioned in chapter 5.1. To improve the quality of data, validation check will be run before the training to scan the dataset. There are two validation approaches to be used. The more straightforward approach is to check the validity against the ontological range definitions of the attributes, e.g. the mRS score is supposed to be an integer between 0 and 6 inclusive. The other method employed is to check for outlier values and see if they persist in multiple checkup reports of the patient or if it might have been a one-time input mistake.

In addition to the custom models based on the local dataset, the knowledge system would contain other imported models from the publications affiliated with SITS. This will suppress the issue of low records for some forms of treatment, as discussed in section 5.1.

### 6.3 User interface

A web application built in Java using the Spring framework will be used to facilitate the user interaction with the knowledge models and the dataset. The application will have three main functionalities:

- Providing a web-based input form for entering patient data to be evaluated in the model.
- Providing the results of applied models in a comprehensive way to support clinician's decision regarding the treatment options.
- Provide the view on historical medical records and allow searching for patients with similar characteristics or searching by specified criteria.

The web forms for providing user input data for model evaluations will only contain the fields relevant for the stored knowledge models. The inputs will be validated both on server and client side for user comfort and faster feedback. The nominal fields would provide lists of possible options for the user. The numerical fields would have a range of allowed values defined in referential ontology. The method for web form generation based on the ontological definitions has been published [46] and is used in practice in IBDS project [41].

After filling in the data, the application will run the knowledge models and will display an overview of predicted outcomes for the considered treatments. Every predicted value will be annotated in order for the user to understand, which model has been used. For model types that would support such an operation, a detail view or a drill down would be available on demand to explain the major constituents of the model influencing the predicted value. To illustrate the concept, a logistic regression model could provide an explanation, that the biggest factors for the low predicted probability of full recovery for the specified patient is his positive history of stroke and his high age.

The other use-case for the web form is to easily conduct a what-if analysis by simply changing some of the values and observing the change in model outputs. Users can get a better understanding of the underlying models by tweaking with the model inputs this way. It also serves as a mean to mitigate the issues with uncertain data. It might happen that the clinician does not have accurate information on the time elapsed since the stroke onset which tends to be important information in decision making process. The clinician could try to input several hypothetical situation and see how the model outputs would differ.

The web interface will allow users to query the medical records from the University Hospital in Pilsen dataset, which will be used for building the custom models. It will be thus possible to find patients with similar characteristics to the current patient and see their treatment plans and the outcomes. Since the dataset is stored in an RDF store and the clinicians cannot be expected to know how to build SPARQL queries necessary to use the data, a visual interactive query builder [47, 48] tool has been developed and published to accommodate the needs of the application users. Users will be provided a visualization of the RDF relations in the data and by clicking on the attributes of interests and filling the particular values, the tool will create ad-hoc queries corresponding to the user selections. Apart from that, a collection of SPARQL query examples will be available in case the user wants to build the queries by modifying the example ones.

## 6.4 Knowledge model management interface

In addition to the user interface described in the previous section that is intended for the role of clinicians dealing with an acute stroke case, there will be an interface for managing the knowledge models. The interface will have these primary functionalities:

- Import external prediction model into the knowledge system.
- Update the mapping of prediction models input attributes onto local dataset attributes.
- Enable, disable or delete existing models.
- Assess model calibration on local dataset.

Option to import external validated models is crucial for trustworthiness of the knowledge system, because the custom models use limited learning dataset and serve experimental purpose. Only logistic regression models will be supported for import. Support for other prediction model types could be added in the future, but it is not deemed necessary at the moment, because majority of the published models on this topic are in a form of logistic regression as reported in chapter 3.4. The model is imported in a form of tuples of attribute name and its coefficient. The attribute name is empty for regression intercept value.

The imported models need to have their input attributes mapped on the attributes in the local dataset for proper integration with other system functionalities. If the mapping is not provided, the web form would have to be generated separately for each model and it would not be possible to reuse the filled in attributes as common inputs in other models. To set the mappings, user is provided with an interactive graph scheme to select the appropriate attributes. The interactive scheme uses the same technology as the interactive SPARQL query builder [47] mentioned in the previous chapter. Completed mappings will be stored in a separate graph of the RDF store.

Having multiple imported models might make the input web form cluttered if the models does not have many input attributes in common. To solve the issue, it is possible to temporarily disable some of the knowledge models or even remove them completely. This is done by changing a meta-data flag for the particular model in RDF store, or deleting the RDF triples containing the model's serialization.

The last action available in the management interface is the ability to assess model calibration on local dataset. According to the paper [49], the prediction models can be updated to better reflect the local circumstances and to eliminate systematic overestimation or underestimation of the predicted outcomes. The recommended updating action is to adjust the intercept of

the model. Apart from updating the intercept, it is possible to evaluate the accuracy of the models on local data and to report the results to the user.

## 7 Conclusion

I have introduced current approaches to stroke treatment and ongoing stroke registry initiatives as a background to my thesis domain. I have provided an overview of common techniques found in publications affiliated with the registries and results of selected publications. I have also noted four results of other authors relevant to my domain.

The research question of choosing the best available treatment plan for a specific patient is open. There seems to be no publication focused on comparing different possible treatment plans and assessing their risk-benefit relation for a particular patient.

I have analyzed available stroke dataset from the Department of Neurology in University Hospital in Pilsen and identified several risks in using it to build the knowledge base for the decision support system. I have provided mitigation strategies for the identified risks. Access to global registry dataset could not be acquired at the time.

I have proposed structure of the knowledge-based system intended to assist clinicians when deciding about potential treatment options for stroke patient.

### 7.1 Aims of the doctoral thesis

- Implementation of knowledge-based decision support system for evaluation of stroke treatment options.
- Development of methods for harmonization and management of different knowledge models.
- Development of methods for interactive exploration of knowledge model outputs and underlying datasets.

## References

- [1] R. L. Sacco, S. E. Kasner, J. P. Broderick, L. R. Caplan, J. Connors, A. Culebras, M. S. Elkind, M. G. George, A. D. Hamdan, R. T. Higashida, *et al.*, “An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association,” *Stroke*, vol. 44, no. 7, pp. 2064–2089, 2013.
- [2] D. Školoudík and D. Šaňák, *Rekanalizační terapie akutní ischemické cévní mozkové příhody*. Maxdorf, 2013.
- [3] O. Škoda, “Diagnostika, léčba a prevence cévních mozkových příhod,” in *Bulletin Sdružení praktických lékařů ČR*, pp. 46–55, 2012.
- [4] T. Bryndziar, P. Šedová, and R. Mikulík, “Incidence cévní mozkové příhody v Evropě—systematická review,” *Cesk Slov Neurol*, vol. 2, p. 180–189, 2017.
- [5] M. zdravotnictví ČR, “Metodický pokyn – péče o pacienty s akutní cévní mozkovou příhodou,” *Věstník MZ ČR*, vol. 10, p. 2–22, 2012.
- [6] J. Neumann, A. Tomek, D. Školoudík, O. Škoda, R. Mikulík, and R. Herzig, “Doporučený postup pro intravenózní trombolýzu v léčbě akutního mozkového infarktu—verze 2014,” *Cesk Slov Neurol*, vol. 77, p. 381–385, 2014.
- [7] J. Vaníček, *Mechanická rekanalizace v léčbě ischemické cévní mozkové příhody*. Habilitation thesis, Klinika zobrazovacích metod LF MU Brno, 2019.
- [8] G. Turc, P. Bhogal, U. Fischer, P. Khatri, K. Lobotesis, M. Mazighi, P. Schellinger, D. Toni, J. de Vries, and P. White, “European stroke organisation (ESO)—European society for minimally invasive neurological therapy (ESMINT) guidelines on mechanical thrombectomy in acute ischaemic stroke endorsed by stroke alliance for Europe (SAFE),” *European stroke journal*, vol. 4, no. 1, p. 6–12, 2019.
- [9] M. Reif, “Hodnotící škály používané u pacientů,” *Neurologie pro praxi*, vol. 12, p. 12–15, 2011.
- [10] J. Van Swieten, P. Koudstaal, M. Visser, H. Schouten, and J. Van Gijn, “Interobserver agreement for the assessment of handicap in stroke patients,” *Stroke*, vol. 19, no. 5, pp. 604–607, 1988.
- [11] J. Rankin, “Cerebral vascular accidents in patients over the age of 60: II. Prognosis,” *Scottish medical journal*, vol. 2, no. 5, pp. 200–215, 1957.

- [12] A. Bruno, J. A. Switzer, V. L. Durkalski, and F. T. Nichols, “Is a prestroke modified Rankin Scale sensible?,” 2011.
- [13] J. L. Banks and C. A. Marotta, “Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis,” *Stroke*, vol. 38, no. 3, pp. 1091–1096, 2007.
- [14] T. Brott, H. P. Adams Jr, C. P. Olinger, J. R. Marler, W. G. Barsan, J. Biller, J. Spilker, R. Holleran, R. Eberle, and V. Hertzberg, “Measurements of acute cerebral infarction: a clinical examination scale,” *Stroke*, vol. 20, no. 7, pp. 864–870, 1989.
- [15] H. P. Adams, P. Davis, E. Leira, K.-C. Chang, B. Bendixen, W. Clarke, R. Woolson, and M. D. Hansen, “Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST),” *Neurology*, vol. 53, no. 1, pp. 126–126, 1999.
- [16] C. Cooray, M. V. Mazya, M. Bottai, J. F. Scheitz, A. H. Abdul-Rahim, T. P. Moreira, R. Mikulik, A. Krajina, M. Nevsimalova, D. Toni, *et al.*, “Are you suffering from a large arterial occlusion? Please raise your arm!,” *Stroke and vascular neurology*, vol. 3, no. 4, 2018.
- [17] SITS, “SITS international report 2019.” [https://sitsinternational.org/wp-content/uploads/2020/11/SITS-Report-2019\\_final-for-print.pdf](https://sitsinternational.org/wp-content/uploads/2020/11/SITS-Report-2019_final-for-print.pdf), 2019. Online; accessed 29 January 2021.
- [18] RES-Q, “About - RES-Q - the ESO Quality Registry.” <https://qualityregistry.eu/the-project/about-uk#intro>, 2021. Online; accessed 1 September 2021.
- [19] RES-Q, “RES-Q Live Metrics · Metabase.” <https://qualityregistry.eu/live-metrics>, 2021. Online; accessed 1 September 2021.
- [20] R. T. Higashida and A. J. Furlan, “Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke,” *stroke*, vol. 34, no. 8, pp. e109–e137, 2003.
- [21] D. Václavík, R. Mikulík, P. Kadlecová, M. Bar, K. Blejchařová, R. Herzig, S. Peška, and P. Ševčík, “Prediktory symptomatického intracerebrálního krvácení po systémové trombolýze mozkového infarktu,” *Cesk Slov Neurol*, p. 75, 2012.
- [22] G. Tsivgoulis, A. H. Katsanos, D. Mavridis, Z. Gdovinova, M. Karliński, M. J. Macleod, D. Strbian, and N. Ahmed, “Intravenous thrombolysis for ischemic stroke patients on dual antiplatelets,” *Annals of neurology*, vol. 84, no. 1, pp. 89–97, 2018.



- [23] G. Tsivgoulis, O. Kargiotis, J. Rudolf, A. Komnos, A. Tavernarakis, T. Karapanayiotides, J. Ellul, A. H. Katsanos, S. Giannopoulos, M. Gryllia, *et al.*, “Intravenous thrombolysis for acute ischemic stroke in Greece: the safe implementation of thrombolysis in stroke registry 15-year experience,” *Therapeutic advances in neurological disorders*, vol. 11, p. 1756286418783578, 2018.
- [24] M. V. Mazya, N. Ahmed, E. Azevedo, A. Davalos, L. Dorado, M. Karlinski, S. Lorenzano, J. Neumann, D. Toni, T. P. Moreira, *et al.*, “Impact of transcranial Doppler ultrasound on logistics and outcomes in stroke thrombolysis: results from the SITS-ISTR,” *Stroke*, vol. 49, no. 7, pp. 1695–1700, 2018.
- [25] D. Vaclavik, A. Vilionskis, D. Jatuzis, M. Karlinski, Z. Gdovinova, J. Kõrv, G. Tsivgoulis, and R. Mikulik, “Clinical outcome of cardioembolic stroke treated by intravenous thrombolysis,” *Acta Neurologica Scandinavica*, vol. 137, no. 3, pp. 347–355, 2018.
- [26] S. Mundiyanapurath, K. Hees, N. Ahmed, N. Wahlgren, L. Uhlmann, M. Kieser, P. Ringleb, W. Hacke, and S. Nagel, “Predictors of symptomatic intracranial haemorrhage in off-label thrombolysis: an analysis of the Safe Implementation of Treatments in Stroke registry,” *European journal of neurology*, vol. 25, no. 2, pp. 340–e11, 2018.
- [27] M. Thorén, E. Azevedo, J. Dawson, J. A. Egido, A. Falcou, G. A. Ford, S. Holmin, R. Mikulik, J. Ollikainen, N. Wahlgren, *et al.*, “Predictors for cerebral edema in acute ischemic stroke treated with intravenous thrombolysis,” *Stroke*, vol. 48, no. 9, pp. 2464–2471, 2017.
- [28] G. Tsivgoulis, A. H. Katsanos, P. Kadlecová, A. Czlonkowska, A. Kobayashi, M. Brozman, V. Svirgelj, L. Csiba, K. Fekete, J. Kõrv, *et al.*, “Intravenous thrombolysis for ischemic stroke in the golden hour: propensity-matched analysis from the SITS-EAST registry,” *Journal of neurology*, vol. 264, no. 5, p. 912, 2017.
- [29] L. Dorado, N. Ahmed, G. Thomalla, M. Lozano, B. Malojcic, M. Wani, M. Millán, A. Tomek, and A. Dávalos, “Intravenous thrombolysis in unknown-onset stroke: results from the safe implementation of treatment in stroke-international stroke thrombolysis registry,” *Stroke*, vol. 48, no. 3, pp. 720–725, 2017.
- [30] M. Cappellari, G. Turcato, S. Forlivesi, C. Zivelonghi, P. Bovi, B. Bonetti, and D. Toni, “Starting-SICH nomogram to predict symptomatic intracerebral hemorrhage after intravenous thrombolysis for stroke,” *Stroke*, vol. 49, no. 2, pp. 397–404, 2018.

- [31] A. Ganesh, R. Luengo-Fernandez, R. M. Wharton, S. A. Gutnikov, L. E. Silver, Z. Mehta, P. M. Rothwell, and O. V. Study, “Time course of evolution of disability and cause-specific mortality after ischemic stroke: Implications for trial design,” *Journal of the American Heart Association*, vol. 6, no. 6, p. e005788, 2017.
- [32] L. M. Kupershtein, T. B. Martyniuk, M. D. Krencin, A. V. Kozhemiako, Y. Bezsmertnyi, H. Bezsmertna, M. Kolimoldayev, A. Smolarz, R. Weryńska-Bieniasz, and S. Uvaysova, “Neural expert decision support system for stroke diagnosis,” in *Photonics Applications in Astronomy, Communications, Industry, and High Energy Physics Experiments 2017*, vol. 10445, p. 104453I, International Society for Optics and Photonics, 2017.
- [33] J. S. Lee, C. K. Kim, J. Kang, J.-M. Park, T. H. Park, K. B. Lee, S. J. Lee, Y.-J. Cho, J. Ko, J. Seo, *et al.*, “A novel computerized clinical decision support system for treating thrombolysis in patients with acute ischemic stroke,” *Journal of stroke*, vol. 17, no. 2, p. 199, 2015.
- [34] D. M. Kent, R. Ruthazer, C. Decker, P. G. Jones, J. L. Saver, E. Bluhmki, and J. A. Spertus, “Development and validation of a simplified stroke–thrombolytic predictive instrument,” *Neurology*, vol. 85, no. 11, pp. 942–949, 2015.
- [35] C. Decker, E. Chhatrwalla, E. Gialde, B. Garavalia, D. Summers, M. E. Quinlan, E. Cheng, M. Rymer, J. L. Saver, E. Chen, *et al.*, “Patient-centered decision support in acute ischemic stroke: qualitative study of patients’ and providers’ perspectives,” *Circulation: Cardiovascular Quality and Outcomes*, vol. 8, no. 6\_suppl\_3, pp. S109–S116, 2015.
- [36] M. Szumilas, “Explaining odds ratios,” *Journal of the Canadian academy of child and adolescent psychiatry*, vol. 19, no. 3, p. 227, 2010.
- [37] J. M. Bland and D. G. Altman, “The odds ratio,” *Bmj*, vol. 320, no. 7247, p. 1468, 2000.
- [38] S. Sperandei, “Understanding logistic regression analysis,” *Biochimica medica*, vol. 24, no. 1, pp. 12–18, 2014.
- [39] M. Litschmannová, *Úvod do statistiky*. VŠB–TU Ostrava, Fakulta elektrotechniky a informatiky, 2011.
- [40] J. Holčík and M. Komenda, *Matematická biologie: e-learningová učebnice [online]*. Masarykova univerzita, Brno, 2015.
- [41] J. Klečková, M. Kryl, and P. Včelák, “IBDS – extension of the prospective database and operations automation,” comprehensive research report, 2019.

- [42] D. S. Liebeskind, “Collateral circulation,” *Stroke*, vol. 34, no. 9, p. 2279–2284, 2003.
- [43] P. Včelák, M. Kryl, M. Kratochvíl, and J. Klečková, “Identification and classification of DICOM files with burned-in text content,” *International Journal of Medical Informatics*, vol. 126, p. 128–137, 2019.
- [44] Medical Information Systems Research Group, “MRE Ontology.” <https://mre.zcu.cz/ontology/ontologies.html>, 2021. Online; accessed 1 September 2021.
- [45] P. Haug, J. Holmen, X. Wu, K. Mynam, M. Ebert, and J. Ferraro, “Ontology-based tools to expedite predictive model construction,” *AMIA Summits on Translational Science Proceedings*, vol. 2014, p. 32, 2014.
- [46] P. Vcelak, M. Kryl, M. Kratochvil, and J. Kleckova, “Ontology-based web forms—Acquisition and modification of structured data,” in *2017 10th International Congress on Image and Signal Processing, BioMedical Engineering and Informatics (CISP-BMEI)*, pp. 1–5, IEEE, 2017.
- [47] M. Kryl, P. Vcelak, and J. Kleckova, “Interactive exploration and querying of RDF data,” in *HEALTHINFO 2018 - The Third International Conference on Informatics and Assistive Technologies for Health-Care, Medical Support and Wellbeing*, pp. 65–68, 2018.
- [48] P. Vcelak, M. Kryl, and J. Kleckova, “SPARQL query-builder for medical temporal data,” in *2018 11th International Congress on Image and Signal Processing, BioMedical Engineering and Informatics (CISP-BMEI)*, pp. 1–9, IEEE, 2018.
- [49] K. J. Janssen, Y. Vergouwe, C. J. Kalkman, D. E. Grobbee, and K. G. Moons, “A simple method to adjust clinical prediction models to local circumstances,” *Canadian Journal of Anesthesia/Journal canadien d’anesthésie*, vol. 56, no. 3, pp. 194–201, 2009.