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The Computer Database of 1421 Belarusian Patients with Ischemic Stroke: Design, Methods, Baseline Characteristics, and Evolving Clinical Course

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Abstract

Introduction: The purpose of the study is to provide information about the database of 1421 adult patients with acute ischemic stroke (IS) developing ≤ 48 hours before admitting, research methods, study protocol, and clinical predictors of the evolving stroke course (EIS).

Methods and Materials: EIS outlined as an increase of NIHSS ≥ 2 points within seven days or in-hospital lethal outcome. Clinical, demographic, instrumental, laboratory data acquisition, as well as the IS course variant and the functional outcome assessment, were carried out prospectively. Statistical analyses were performed using R V.3.2.5 statistical package software and IBM SPSS Statistics 26.0.

Results: The incidence of EIS reached 30.0%. The average age of patients with EIS was 72.6 ± 10.2 years, compare the age of patients without EIS - 68.1 ± 11.3 years; p = 0.005. Female sex increased the odds of EIS (OR, 1.36; 95% CI 1.08 - 1.73). Total anterior carotid stroke (OR, 7.78; 95% CI 5.91 - 10.23), the initial NIHSS score > 14 points (OR, 3.74; 95% CI 2.83 - 4.94) and the right anterior circulation was also associated with EIS (OR, 1.30; 95% CI 1.02 - 1.66). The odds of EIS were significantly higher in the presence of diabetes mellitus (OR, 1.29; 95% CI 1.01 - 1.66), cerebral artery stenosis ≥ 70% (OR, 1.96; 95% CI 1.30 - 2.93), atrial fibrillation (OR, 1.89; 95% CI 1.51 - 2.39), congestive heart failure (OR, 1.90; 95% CI 1.51 - 2.39) and peripheral artery disease (OR, 1.69; 95% CI 1.27 - 2.25). Respiratory (OR, 2.82; 95% CI 2.22 - 3.59), gastrointestinal (OR, 1.34; 95% CI 1.05 - 1.70) and urologic diseases (OR, 2.10; 95% CI 1.65 - 2.66), stroke-associated infection (OR, 3.47; 95% CI 2.09 - 5.76) and gradual development of initial IS symptoms before admitting increased the odds of progression of the neurological deficit during treatment (OR, 2.37; 95% CI 1.78 - 3.15) were associated with the evolving clinical course of IS. The patients with the EIS compared with patients without EIS, showed higher serum levels of glucose (p < 0.001), urea (p = 0.001), creatinine (p < 0.001), sodium (p = 0.025), and direct bilirubin (p = 0.015). Potassium level in EIS group was lower than in the group without EIS (p < 0.001). In patients with EIS, a higher amount of RBC (p = 0.030) and WBC (p < 0.001) was found.

Conclusion: The in-hospital database contains information about EIS by the bases subtypes of IS, patient demography, cardiovascular risk factors, comorbid pathology, clinical and laboratory tests, instrumental methods of examination, medications, the severity of neurological deficit, and post-stroke outcome.

Keywords: *Clinical Characteristics; Clinical Course; Database; Deterioration; Evolving Ischemic Stroke; Stroke Progression*

Abbreviations

BMI: Body Mass Index; CI: Confidence Interval; CT: Computer Tomography; DBP: Diastolic Blood Pressure; ECG: Electrocardiogram; EIS: Evolving Ischemic Stroke; IQR: Interquartile Range; IS: Ischemic Stroke; IV: Intravenous; LACS: Lacunar Syndrome; LMWH: Low-Molecular-Weight Heparins; MRI: Magnetic Resonance Imaging; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; No EIS: Non-Evolving Ischemic Stroke; OCSP: Oxfordshire Community Stroke Project; OR: Odds Ratio; PACS: Partial Anterior Circulation Syndrome; POCS: Posterior Circulation Syndrome; Q1: Lower Quartile; Q3: Upper Quartile; RBC: Red Blood Cells; RSPCNN: The Republican Scientific and Practical Center for Neurology and Neurosurgery of the Ministry of Health of the Republic of Belarus; rtPA: Recombinant Tissue Plasminogen Activator; SBP: Systolic Blood Pressure; SD: Standard Deviation; SSS: Scandinavian Stroke Scale; TACS: Total Anterior Circulation Syndrome; TIA: Transient Ischemic Attack; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; UFN: Unfractionated Heparin; UI: Uncertainty Interval; WBC: White Blood Cells; WHO: World Health Organization

Introduction

According to epidemiological studies, as of 2009, the incidence of stroke in economically developed countries has decreased by 42%, while in low and middle-income countries the incidence of stroke has increased by more than 100% [1]. At the same time, there were significant differences in the incidence and mortality rates from stroke in residents of countries with different income levels [2].

As per comprehensive research program "The Global Burden of Disease Study" (GBD) that unites more than 2700 scientists from 132 countries [3], in 2017 in the Republic of Belarus, observed life expectancy was 78.8 years for women and 69.0 years for men [4]. Among the five leading causes of death in the first place in frequency resides coronary heart disease, followed by stroke, Alzheimer's disease, lung cancer, alcohol use disorders.

The leading risk factors identified as the main cause of death and disability of the Belarusian population are arranged in the following order: high blood pressure (BP), dietary risks, tobacco use, alcohol use, high body mass index (BMI), high low-density lipoprotein level, high fasting plasma glucose, air pollution, impaired kidney function, and low physical activity. The hierarchy of primary risk factors did not change significantly from 2007 to 2017, except for the transfer of dietary risks from first to second place [4].

The GBD 2016 Stroke Collaborators online resource presents data on the number of deaths and incidence of stroke in Belarus, taking into account the lower and upper bounds of the 95% uncertainty interval (95% UI) [5]. In 2016, deaths and incidence of ischemic stroke (IS) reached 10 349 (95% UI: 8 751 to 11 971) and 30 112 (95% UI: 26 751 to 33 673), respectively. Similar indicators of hemorrhagic stroke were significantly lower - 4 088 (95% UI: 3 425 to 4 782) and 7 827 (95% UI: 7 056 to 8 694), respectively. Thus, the incidence of brain infarct is almost four times higher than the incidence of hemorrhagic stroke.

Nowadays, it is difficult to find a vascular neurologist who is not familiar with such notorious complication of an acute ischemic cerebral catastrophe, like an evolving IS (EIS). According to published studies, EIS is recorded in approximately one in three patients [6-11]. The incidence of progressing stroke, its main pathophysiological mechanisms, demographic and clinical predictors were analyzed several decades ago in such fundamental prospective stroke registers as the Harvard Cooperative Stroke Registry [12-14], the Lausanne Stroke Registry [15], the Besançon Stroke Registry [16] and the European Cooperative Acute Stroke Study (ECASS) [17].

In consideration of the notorious relevance of the problem of stroke for Belarus, we found it important and well-timed to create a database of patients with IS, including demographic data, modifiable and non-modifiable risk factors, clinical manifestations of the disease, information about the clinical course of IS, functional outcome and survival, results of laboratory and instrumental investigations, ongoing therapy. Our research was conducted to create a comprehensive computer dataset of hospitalized patients, which allows us to systematize the information obtained for the analysis of the clinical course, outcome, and survival of patients with IS. The purpose of the study presented in this article is to provide information about the database of 1421 Belarusian patients with acute IS, the applied research methods, study protocol, and clinical predictors of EIS.

Materials and Methods

Study population and definition of stroke

Diagnose of acute IS was defined according to the World Health Organization (WHO) criteria [18] and verified on computed tomography (CT), or/and magnetic resonance imaging (MRI), or/and autopsy. We have entered in the computerized database information about 1421 in-patients with acute IS, selected randomly. These patients were the objects of prospective clinical cohort studies conducted at the clinical bases of the Republican Scientific and Practical Center for Neurology and Neurosurgery of the Ministry of Health of the Republic of Belarus (RSPCNN). From May 13, 2002, to August 18, 2005, recruitment of 148 (10.4%) patients for participation in research was carried out based on the stroke department of the 5th Minsk City Clinical Hospital. From August 19, 2005, to October 9, 2014, 1273 (89.6%) patients of the stroke department No. 1 of the Minsk Emergency Hospital became objects of our investigation. Criteria for inclusion in the study: 1. The presence of acute IS, developing ≤ 48 hours before admission to the emergency department of the clinic. 2. The patient is over 18 years old. The exclusion criteria were: non-ischemic stroke (intracranial hemorrhage, venous sinus thrombosis), TIA, traumatic brain injury, as well as oncological, autoimmune, or degenerative diseases of the central nervous system.

Demographic characteristics, clinical data, neuroimaging, ultrasound, electrocardiographic records (ECG), and blood samples of patients with IS were prospectively and uniformly gotten together. The data sources were records in the in-patient medical chart, extracts from the out-patient chart, results of consultations and examinations at the pre-stroke stage, and other documents. Anamnestic information regarding individual personal habits and present diseases was clarified, if necessary, from both the patients themselves and their family members. The survey was conducted in Russian or Belarusian. The collected information was further added by the author of this article (IG) to a specially created 18-page paper formalized IS patient history. Then the information from the paper carrier was entered into a computer database based on Microsoft Excel. Collecting chief complaints, anamnestic information, physiological parameters, neurological examination, chest X-rays, laboratory tests, and 12-lead ECG were routinely done in the emergency departments of the hospitals. CT and/or MRI were performed in 100% patients with IS.

Information about the period time from the appearance of the first warning IS symptom to the delivery of the patient to the hospital was recorded in 1417 cases. Time was expressed in hours, at the time of the study starting (2002 year), intravenous (IV) and intra-arterial thrombolytic therapy in the patients with the brain infarct was not introduced into the clinical practice of Belarusian clinics. Patients were stratified according to the following time intervals: up to 6 hours, from 6 to 24 hours, 24 - 48 hours. In 524 people hospitalized in 2011-2014, we conducted an additional assessment of the symptom onset-to-hospitalization time, expressed in hours. Distribution of patients (n = 1327) was carried out according to the IS onset by time of the 24-h day as follows: 06:00 am - 09:00 am; 09:00 am - 12:00 pm; 12:00 pm - 06:00 pm; 06:00 pm - 09:00 pm; 09:00 pm - 12:00 pm; 12:00 am - 06:00 am.

In refining the anamnestic information, neurologists took into account both the patient's story and the members of their inner circle who were witnesses to the stroke manifestations. So, the research team tried to recognize which of the listed circumstances could be provoking factors for IS: sleep, bathing, eating, bleeding, or excessive alcohol drinking, or physical exercises, stress, BP rise, or the absence of any provoking circumstances, or lack of explicit information about the onset of stroke. The stroke-associated neurological disorders rate at the pre-admitting time frame were divided dichotomously as sudden development of symptoms (neurological deficit did not increase) and gradual stroke symptoms evolution (consistent neurological deterioration or fluctuating course of the disease).

While patients were in the clinic, they were examined daily by their attending neurologist. The diagnosis of IS was agreed of the consent of the neurologist, the stroke department head, and the neurologist consultant. During the first three days, each patient was inspected by an internist and ophthalmologist. In the presence of indications, the patients were also provided with consulting by a cardiologist, endocrinologist, urologist, angiosurgeon, psychiatrist, surgeon, and hematologist.

Stroke score and classification

The stroke-associated neurological deficit was assessed by the observers using the National Institutes of Health stroke scale (NIHSS) [19] at the time of admission and discharge from the stroke department. Daily dynamic observation of patients made it possible to record both positive and negative changes in the patient's condition, which was reflected in the corresponding records in the medical record.

Depending on the severity of neurological symptoms of stroke, the results of the quantitative measure of stroke-related neurologic deficit of 1421 patients were divided into three groups. A mild neurological deficit was matched by the research team to the NIHSS category from 0 to 6 points, a moderate deficit - from 7 to 14 points and severe - from 15 to 42 points [11]. If the death of the patient occurred in a hospital, the final NIHSS score corresponded to 42 points. The results of the imaging tests were analyzed by experienced radiologists and neurologists to determine, by consensus, the localization of the focus of the acute ischemic brain damage responsible for the development of neurological deficit. Considering brain circulation, IS of the left anterior circulation, right anterior circulation, posterior cerebral circulation, and multifocal ischemic lesions were identified. We also classified IS into specific clinical subtypes according to the criteria of the Oxfordshire Community Stroke Project (OCSP) [20] such as total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS), and posterior circulation syndrome (POCS).

Before discharge from the hospital, taking into account the complex of examinations conducted, the author of the study (IG), together with the patients' physicians, determined the etiological variant of the stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification: large artery atherosclerosis, cardioembolism, small artery occlusion, other determined etiology, and undetermined cause [21]. The term "undetermined" designated both the cases of IS with unknown etiology and cases that might have been caused by two or more competing factors. The two last-mentioned variants of cerebral infarction (undetermined and other determined IS) in the analysis were combined into one group.

Definition of evolving IS

The development and variant of EIS were prospectively confirmed by the agreements of the patient's neurologist, the chief of the neurological department, and consultant-neurologist (IG) [10,11,22]. Evolving IS outlined as at least one of the following criteria being met within seven days after hospitalization: 1) increase in the NIHSS score since the admission of at least 2 points, 2) in-hospital lethal outcome in the same time frame [10,11]. The causes of stroke progression were the following conditions and their combinations: the cerebral infarct's hemorrhagic transformation, brain edema, re-stroke, stroke-associated pneumonia, kidney infection, cardiovascular complications, seizure, gastrointestinal disorders [11,22].

Patients were examined at discharge from the neurological department using the modified Rankin Scale (mRS) score. This scale is ranked from 0 to 6, with higher scores meaning a more severe degree of disability [23,24]. In the database, functional impairment due to IS was expressed both in points of the scale (absolute values) and in the dichotomous approach of the outcome assessment (categorical data). The stroke-related disability was represented by three sets of variables corresponding to a favorable and unfavorable functional outcome of cerebral infarction: mRS score of 0 - 2 and 3 - 6 points, mRS 0 - 3 and 4 - 6 points, and mRS 0-4 and 5 - 6 points respectively [23-25]. A final mRS score imputes a value of 6 for in-patient death case.

End points

In general, our study has three primary end points of the cohort follow-up: (1) the development of EIS during the first seven days after hospital admitting; (2) the presence of the unfavorable IS outcome at discharge from the stroke department; (3) date of death in the post-stroke period. To compare data from laboratory tests and heart rate variability parameters, 107 volunteers without acute cardiovascular and cerebrovascular diseases, matching by age and sex, were also examined.

Clinical, demographic, instrumental, laboratory data acquisition, as well as the IS course variant and the functional outcome assessment, were carried out prospectively. Further, in a post-hoc analysis, the relationship of the independent clinical variables included in

the data set with the data on the survival of patients after a stroke were analyzed. All information recorded on paper and electronic data carriers was reviewed by the first author of the article (IG). The ethics committee of RSPCNN has approved the design of the study. The informed consents were written by the patients or their representative in the inpatient hospital settings. The research was carried out according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Risk factors

In our study, the prospectively observed cohort of stroke patients consisted of 665 (46.8%) men and 756 (53.2%) women. The race of all 1421 patients with IS was defined as white. The minimal age for adult patients with IS was 30 years, the maximal - 98; the mean age of all the observed individuals was 69.5 ± 11.1 years. The age of patients when preparing data for the analysis was further categorized as four age groups with cut-off points from 30 to 44, from 45 to 59, from 60 to 74 and 75 to 98 [26].

Arterial hypertension was diagnosed according to European Society of Cardiology (ESC), the European Society of Hypertension (ESH) and the National guidelines for arterial hypertension of the Belorussian Scientific Society of Cardiologists criteria [27]. Hypertension was determined based on the anamnestic data on a high level of blood pressure in the pre-stroke period, information on the patient's treatment with antihypertensive drugs before the onset of a stroke, as well as when prescribing antihypertensive therapy to a patient with a IS before discharge. During the clinical evaluation and prescription of drug therapy, patients with acute IS were classified into four groups: without arterial hypertension, with arterial hypertension grade I, grade II, and grade III, respectively [27].

Routinely, BP was controlled every day by the attending physician during the morning rounds from 8.00 am to 10.00 am. During the first three days of hospitalization, the stroke nursing staff also repeatedly measured BP levels in the patients. Blood pressure was measured by an oscillometric method [27], in the supine position of the patient, using an appropriately sized cuff. If the patient, due to the severity of the condition, has been located in the intensive care unit of the stroke department, then we wrote out the SBP/DBP results of automatic blood pressure device at 9 am. We collected information about SBP and DBP at the time of stroke, as well as blood pressure measurement performed immediately at the time of admission in the emergency department and then subsequently on days 1, 2, 3, 7 and at the time of discharge from the clinic.

Using anamnestic information, medical documents, we obtained data about pre-existing diabetes mellitus. All patients with previously diagnosed or suspected diabetes received an endocrinologist consultation. The diagnosis of newly diagnosed diabetes mellitus was established in patients with acute IS according to the criteria of the American Diabetes Association [28]. Alcohol abuse was understood as consumption of 21 ounces or 168g of ethanol a week for men and 14 ounces, or 112g - for women [29]. Smoking status was determined as never smoker, ex-smoker (former smoker), and current smoker [30]. The research team recorded the anthropometric data of study participants: height (in meters), body weight (in kilograms), and body mass index equal to the patient's weight divided by the square of height (kg/m^2) [31]. In assessing the stroke risk factors, overweight was denoted according to the WHO data [32] as BMI ≥ 25 kg/m^2, obesity - as ≥ 30 kg/m^2.

During treatment in the stroke department, 946 (66.5%) patients were appointed to ultrasound examination of the brain vasculature. Doppler and/or duplex sonography of the extracranial and intracranial arteries was used to determine the mechanism of the IS and thereby potentially to prevent the stroke recurrence [11,33]. The following degrees of stenosis were measured: severe (70% of the artery lumen or occlusion), moderate (50 - 69%), and mild stenosis - 30 - 49%. Additionally, in 324 (22.8%) patients, the intima-media thickness of the carotid arteries was determined by imaging the vessels by duplex ultrasound scanning [11,27].

Medical history data

The diagnosis of angina, myocardial infarction, peripheral arterial diseases, previous stroke, or TIA was established according to the criteria of the ARIC study [34]. The presence of congestive heart failure was determined according to the criteria of the Framingham Heart Study [35]. The conclusion about the presence of atrial fibrillation (AF) was figured out on the anamnestic data, documentary re-

sults of the pre-stroke examination and treatment, in-patients physical evaluation, and a 12-channel ECG. According to the criteria of the European Society of Cardiology, AF was defined as cardiac arrhythmia with the following characteristics: 1. Presence on the routine ECG 'absolutely' irregular RR-intervals (cardio-intervals not following a repeating pattern). 2. Absence on the ECG distinct P waves. 3. The interval between two atrial activations on the ECG is usually variable and < 200 ms (> 300 bpm) [36]. In some cases, patients underwent additional echocardiography and Holter ECG monitoring.

The stroke-related comorbidities such as respiratory, gastrointestinal, urological, hematological disorders, thyroid pathology, diseases of the peripheral veins were determined according to the physical exam, pre-stroke medical records, counseling of various specialists interacting with the stroke department, relevant laboratory values, and instrumental examinations [37]. Infectious complications of IS (especially pneumonia and urinary tract infections) were determined as the infections diagnosed while the patients stay in the stroke department [38,39]. In the in-patient medical chart, the development of bleeding (mainly from the gastrointestinal tract) was recorded. Additionally, information about the oncological pathology of extra-cerebral localization was entered.

Laboratory investigation

In the emergency department, the following laboratory tests were performed routinely for patients with stroke: blood glucose, complete blood count, serum electrolytes, and markers of liver and kidney dysfunction [33,40]. In the complete blood count, the level of hemoglobin, as the part of the red blood cell (RBC) that carries the oxygen, was expressed in g/L. Hematocrit, as a measure of the RBC amount in the blood, was denoted as thousandths of a unit. The amount of RBC was reported as an indicator multiplied by $\times 10^{12}$/L, white blood cells (WBC) - by $\times 10^{9}$/L and platelets - by $\times 10^{9}$/L. In addition to counting the amount of erythrocytes, leukocytes and platelets, the percentage of a WBC number such as bands - immature polys (also known as stabs, segs or segmented bands; in %), polys (also known as segs, segmented neutrophils, neutrophils, granulocytes; in %), and lymphocytes (lymphs; in %) [41] were also determined.

Within the 24 hours of admission in the stroke department, from 7.30 am to 8.30 am, blood samples were collected from all patients with cerebral infarction to test the coagulation profile: the activated partial thromboplastin time (aPTT), the prothrombin time (PT), the partial thromboplastin time (PTT), the international normalized ratio (INR), the PT/INR ratio, and fibrinogen level [10,11,25]. Besides, measurements of some parameters of the blood chemistry, including total cholesterol, triglycerides, and fasting glucose level in venous blood were performed. The time frame from the stroke onset to the blood sampling did not exceed 48 hours [11,25].

Medication

When creating the computerized base, medicines assigned to patients with IS in the stroke unit were also taken into the data set. All inpatient medicines were paid for with the budget funds allocated to the health care institution. The basis for enacting therapy was the Clinical protocols for the treatment of neurological diseases, approved by the Ministry of Health from 2002 to 2018 [42].

The main groups of drugs were represented by antiplatelet agents (mainly acetylsalicylic acid, less often - clopidogrel), parenteral anticoagulants (unfractionated heparin (UFH), low molecular weight heparins (LMWH)), and vitamin K antagonist (warfarin). Sporadic patients receiving IV thrombolytic therapy with alteplase were not included in the study dataset.

If the patient received therapy for arterial hypertension in the pre-stroke period, treatment with these drugs was continued in the hospital. Also, antihypertensive drugs were prescribed according to indications in the presence of an excessive BP increase, or comorbid cardiovascular diseases. Antihypertensive drugs included several groups: angiotensin-converting enzyme inhibitors - enalapril, lisinopril, fosinopril, ramipril, perindopril; angiotensin receptor blocker - losartan; beta-blockers - metoprolol, carvedilol, bisoprolol, propranolol, atenolol, nebivolol; calcium channel blockers - amlodipine, diltiazem, verapamil; alpha-2/imidazoline receptor agonist - moxonidine. Hydrochlorothiazide predominantly presented diuretics. Less often, patients in the department were assigned indapamide, furosemide, and torsemide. Congestive heart failure was an indication for ordering an aldosterone receptor antagonist - spironolactone, or cardiac glycoside - digoxin. Amiodarone, as an antiarrhythmic drug, was given for paroxysms of atrial fibrillation or ventricular tachy-

cardia. Following the acted protocols of the Ministry of Health of the Republic of Belarus [42], patients with stroke were also treated with neuroprotective (magnesia sulfate, glycine, methyl ethylpyridinol, and carnitine chloride) and symptomatic therapy.

Statistical analysis

Statistical analyses of the computerized dataset were performed using R V.3.2.5 statistical package software [43] and IBM SPSS Statistics 26.0 for Windows. Before the comparison of the numeric parameters in groups (age, blood pressure, NIHSS score, mRS score, laboratory measurement data, *etc.*) their distributions against Gaussian distribution were validated utilizing of Shapiro-Wilk's test (Figure 1) [44,45]. For visual inspection of the conformity of parameters to the normal distribution, the distribution histograms, and the normal Q-Q plots were constructed (Figure 2) [46]. With a probability of a null hypothesis exceeding the decision level p = 0.05, and also in the absence of significant deviations from the straight line in the Q-Q plot, it was considered that there is no reason to reject the assumption that the parameter being studied corresponds to the normal distribution. With test values close to the critical value, taking into account the robustness of parametric methods, the decision on the conformity of the distribution was made based on the type of quantile graphs. With significant deviations of the distribution from the Gaussian, the attempts were made to normalize the data using reversible methods: logarithmic transformations, double logarithmic transformations, multiplicative inverse (reciprocal) transformation, and the Box-Cox technique [46,47].

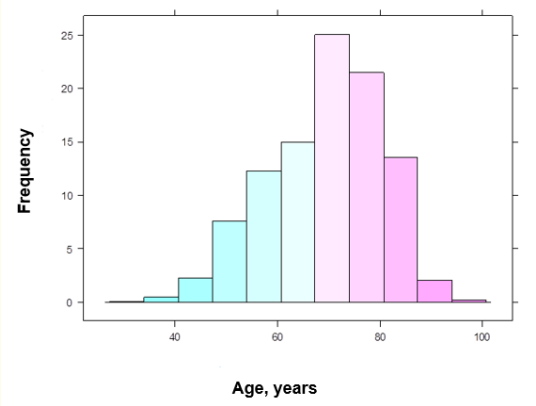

Figure 1: *Histogram of the age data of 1421 patients with ischemic stroke.*

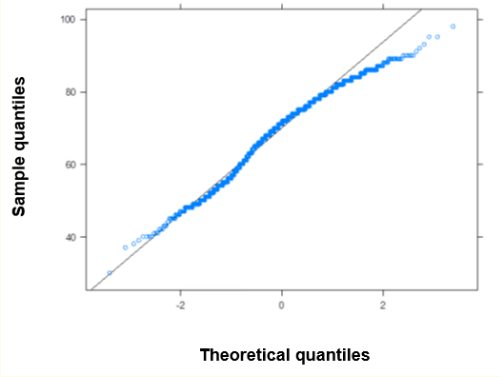

Figure 2: *The normal quantile plot of the age data of 1421 patients with ischemic stroke.*

The distribution of the obtained values was rechecked for compliance with the distribution normality. The Bartlett test was employed to weigh the variances in the groups. Depending on the results of the distribution analysis, the decision was made to use further parametric or non-parametric analysis methods [44,45]. When the distribution of the studied quantitative parameter (or its transformation) corresponded to the Gaussian distribution, the data were presented as a mean and a standard deviation. Otherwise, the data were shown as a median and quartiles [48,49]. Graphically, quantitative data were presented in the form of histograms, boxplots, and "bee swarm" plots (Figure 1 and 3). Data on the distribution of qualitative parameters (sex, localization of IS lesion, TOAST subtype, OCSP subtype, *etc.*), as well as grouped quantitative data (age group, NIHSS score ≤ 6 and > 6, mRS score 0 - 3 or 4 - 6, symptom onset-to-hospitalization time interval, etc.) were provided as frequency distributions indicating the parameter category (if the number of observations was sufficiently large) and/or as an absolute number of observations [50]. Graphically, qualitative data were presented in the form of mosaic diagrams, bar charts. While comparing numeric parameters in groups a Student test (in case of two groups) or ANOVA (in case of three or more groups) was performed if data in each group had had the normal distribution. Post hoc Tukey test was employed (TukeyHSD function) to get an estimate on differences between groups (3 or more). If the distribution was not normal Wilcoxon-Mann-Whitney test (wilcox_test function) was employed to compare two groups or Kruskal-Wallis test (kruskal_test function) for 3 or more groups. Then post hoc analysis was performed using the Kruskal test for multiple comparisons (kruskalmc function) and the BDM test (BDM.test function) [51].

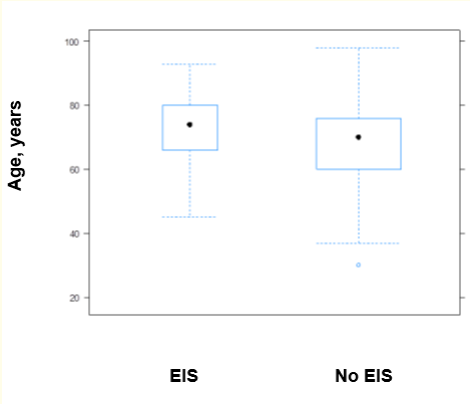

Figure 3: *The boxplot of the age data of patients with ischemic stroke (p = 0.005).*
EIS: Evolving Ischemic Stroke Group (n = 427); No EIS: Non-Evolving Ischemic Stroke Group (n = 994).

To compare the qualitative data that can be represented in the form of contingency tables 2 × 2 was applied two-tailed Fisher exact test [47]. To compare the qualitative stratified data, which can be regarded as *k* contingency tables of 2 × 2, the Cochran - Mantel - Haenszel test was practiced with the Monte Carlo estimate of p. When comparing ordinal data, a linear-by-linear association test was computed with an asymptotic estimate of p by the Monte-Carlo method (*lbl_test* function) [51]. For a quantitative assessment of the connectedness of the presence (or absence) of the unique feature and the occurrence of the event of interest, we used the odds ratio (OR). OR was calculated as one of the results of statistical evaluation, including the process of comparing frequencies in different groups.

The work assessed the overall survival of patients (Figure 4). The date of the stroke was taken as the beginning of the observation. The fact that the patient died, regardless of its cause, was taken as an event. The status of the patient (alive or dead) was evaluated at the time of reaching the deadline for observation. Depending on the objectives of the analysis, seven days, one month, three months, one year, or 5 years were taken as the completion of the study. The follow-up time t (in entire days or months) was measured from the time origin (starting of the observation - IS date) until the moment when the event of interest (here, the definition of the event is a lethal

outcome) occurred, or until the end of the study or until dropping out the patient from observation, whichever comes first. In assessing the patient's survival, the entire range of data was used to compute [52]. To compare the survival curves in groups, a log-rank test, and a stratified log-rank test was used [53]. Patients' survival was calculated using the Kaplan-Meier approach (Figure 4). The confidence interval (CI) was estimated of the cumulative hazard logarithm [47,54]. Point estimates were calculated for days or months. Additionally, the median survival time was evaluated with the 95% pointwise CI.

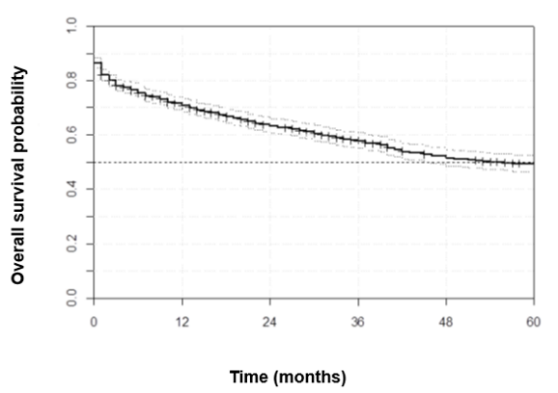

Figure 4: *Kaplan-Meier survival curve of patients with ischemic stroke.*

The relationship between the variables and survival data were computed using the Cox proportional hazards regression model (*coxph* function), and the stratified Cox model (separate baseline hazard functions are fit for each stratum) [47,53-55]. Tied events were handled by the commonly used Breslow method [56]. The proportional hazards assumption for every covariate was checked with the graphical method (Schoenfeld residuals plot for each variable) and the statistical test (*cox.zph* function) based on the scaled Schoenfeld residuals [53-55,57]. In the first instance, qualitative variables were dichotomized (coxph function). Then they were included in the regression analysis [55]. The Wald test was used to estimate the significance of the particular explanatory variables in the survival model [47]. With a probability of the corresponding Wald p-value < 0.05, the variable considered to have a significant effect on the lethal outcome. If, when testing the survival model, the maximum value of the probability p was < 0.05, then the research team concluded that the Cox regression model adequately describes the time data to the event.

ROC analysis (*ROC, prediction, performance* functions) was used to determine the threshold value of quantitative factors. The goal was to achieve maximum specificity. The value of the area under the curve (AUC) determined the quality of estimation. For the threshold obtained, the sensitivity, the specificity, the predictive power of the positive and negative outcomes were calculated [44]. When assessing the threshold for quantitative factors, when the target variable was a survival estimate, the ROC curve for survival (*survivalROC* function) was calculated using the method of calculating the nearest neighbor estimation.

To develop mathematical models predicting the progressing clinical course of IS and unfavorable functional outcome, the research team has implemented the 'decision trees' statistical methods. These methods allow evaluating the significance of the effect of the predictors included in the model, to identify the logical patterns of data and show them graphically as dendrogram [48,52]. The construction of decision trees for solving classification problems (the presence or absence of EIS, the presence or absence of an unsatisfactory IS outcome) was made on the basis of three computed algorithms: classification and regression trees (CART), trees with evolutionary learning (evolutionary algorithm), and conditional inference trees (conditional inference trees).

For the tree-structured analysis of the right-censored survival data, modules *rpart, party, randomForest, maptree, cluster, and partykit* were put forth [58,59]. A tree-structured diagram expressed the results of the time-to-event data analysis. Terminal nodes of the survival decision tree represent the Kaplan-Meier survival curves [54]. 'Bagging predictors' method by L. Breiman [60] was taken to improve the stability and accuracy of the tree-structured survival model. The integrated Brier score [58] was applied as a performance measure to assess the accuracies of the estimated survival functions. Examples of constructing tree-structured and survival decision tree models based on the variables of our computer database can be found in our previously published works [10,22,25].

The selection of variables for the subsequent multivariate analysis was carried out, taking the value $p = 0.1$ as the threshold value. If the probability of the null hypothesis was in the range of 0.05 - 0.10, the influence of the risk factor was considered marginal. Such factors were included in the model for the following evaluation. The decision to accept or reject the null hypothesis (2-sided tests) was performed using $p = 0.05$ as the threshold value. Differences were considered statistically significant at p-value < 0.05. At the p-value > 0.05, it was assumed that there was no sufficient statistical reason for rejecting the null hypothesis.

Results

Demographic and follow-up data

Among 1421 patients with acute IS, the incidence of an evolving clinical course of stroke (EIS group) has reached 30.0% (427 out of 1421 people). No increase in neurological symptoms (No EIS group) has been observed in 70.0% (994 out of 1421) cases (Table 1). Demographic characteristics of the stroke patients had significant differences in two variants of the clinical course of IS. Thus, the average age of patients with EIS reached 72.6 ± 10.2 years, which significantly exceeded the average age of patients without EIS - 68.1 ± 11.3 years; $p = 0.005$ (Figure 3). A similar pattern was maintained when comparing the frequency of stroke deterioration with the age groups of patients. The proportion of patients ≥ 75 years old reached 49.6% in the EIS group and only 32.0% - in the No EIS group; $p < 0.001$. The EIS group consisted of 177 (41.5%) men and 250 (58.5%) women. A similar gender ratio in the No EIS group was 488 (49.1%) and 506 (50.9%), respectively. That is, in patients with progressing neurological deficiency, the proportion of females significantly prevailed over the proportion of males; $p = 0.004$.

Characteristics	EIS (n = 427)	No EIS (n = 994)	p value
Demographic characteristics Age, y, n = 1421	72.6 ± 10.2	68.1 ± 11.3	0.005
Sex, n =1421			
Male	177 (41.5)	488 (49.1)	0.008
Female	250 (58.5)	506 (50.9)	
Age group, n = 1421			
25 - 44 years	0 (0%)	19 (1.9%)	
45 - 59 years	54 (12.6%)	220 (22.1%)	< 0.001
60 - 74 years	161 (37.8%)	437 (44.0%)	
≥ 75 years	212 (49.6%)	318 (32.0%)	
Clinical data			
Stroke territory, n = 1421			
Left anterior circulation	183 (42.9%)	411 (41.3%)	
Right anterior circulation	143 (33.5%)	292 (29.4%)	0.022
Posterior circulation	85 (19.9%)	267 (26.9%)	
Multifocal	16 (3.7%)	24 (2.4%)	

TOAST subtype, n = 1421			
Large artery atherosclerosis	116 (27.2%)	327 (32.9%)	
Cardioembolism	57 (13.2%)	176 (17.7%)	< 0.001
Small artery occlusion	22 (5.2%)	246 (24.7%)	
Undetermined/other determined etiology	232 (54.3%)	245 (24.6%)	
OCSP subtype, n = 1421			
TACS	210 (49.2%)	110 (11.1%)	
PACS	146 (34.2%)	400 (40.2%)	< 0.001
LACS	30 (7.0%)	303 (30.5%)	
POCS	41 (9.6%)	181 (18.2%)	
NIHSS score at admission, n = 1421	10 (6-16)	7 (5-10)	< 0.001
NIHSS score at discharge, n = 1421	12 (7-42)	3 (2-6)	< 0.001
mRS score at discharge, n = 1418	4 (3-6)	2 (2-3)	< 0.001
NIHSS score at admission, n = 1421			
≤ 6	124 (29.0%)	452 (45.5%)	< 0.001
> 6	303 (71.0%)	542 (54.5%)	
NIHSS score at admission, n = 1421			
≤ 14	284 (66.5%)	876 (88.1%)	< 0.001
> 14	143 (33.5%)	118 (11.9%)	
NIHSS score at discharge, n = 1421			
≤ 6	97 (22.7%)	767 (77.2%)	< 0.001
> 6	330 (77.3%)	227 (22.8%)	
NIHSS score at discharge, n = 1421			
≤ 14	238 (55.7%)	952 (95.8%)	< 0.001
> 14	189 (44.3%)	42 (42.2%)	
mRS score at discharge, n = 1421			
0-2	55 (12.9%)	585 (58.9%)	< 0.001
3-6	372 (87.1%)	409 (41.1%)	
mRS score at discharge, n = 1418			
0-3	129 (30.4%)	770 (77.5%)	< 0.001
4-6	296 (69.6%)	223 (22.5%)	
mRS score at discharge, n = 1418			
0-4	218 (51.3%)	921 (92.7%)	< 0.001
5-6	207 (48.7%)	72 (7.3%)	
SBP at the stroke onset (mm Hg), n = 840	177.7 ± 36.7	178.6 ± 37.4	0.953
DBP at the stroke onset (mm Hg), n = 840	99.5 ± 17.3	100.6 ± 18.4	0.385
SBP at admission (mm Hg), n = 1394	160.4 ± 25.9	159.1 ± 25.7	0.371
DBP at admission (mm Hg), n = 1394	93.6 ± 12.9	93.3 ± 12.7	0.595

SBP on the 1st day (mm Hg), n = 1350	160.2 ± 26.6	156.7 ± 27.6	0.029
DBP on the 1st day (mm Hg), n = 1350	92.8 ± 13.4	91.8 ± 13.5	0.174
SBP on the 2st day (mm Hg), n = 1247	147.5 ± 21.6	143.9 ± 12.2	0.003
DBP on the 2st day (mm Hg), n = 1247	86.4 ± 12.8	85.6 ± 10.2	0.211
SBP on the 3st day (mm Hg), n = 1237	144.4 ± 21.8	140.0 ± 19.5	<0.001
DBP on the 3st day (mm Hg), n = 1237	84.8 ± 11.9	83.8 ± 10.1	0.127
SBP on the 7st day (mm Hg), n = 1293	136.6 ± 20.8	136.1 ± 15.3	0.635
DBP on the 7st day (mm Hg), n = 1293	80.9 ± 12.1	81.2 ± 7.8	0.568
SBP on the 12st day (mm Hg), n = 1009	133.7 ± 16.8	134.3 ± 12.9	0.546
DBP on the 12st day (mm Hg), n = 1009	79.2 ± 9.6	80.6 ± 6.6	0.006
Timing of IS onset, n = 1327			
06:00 AM - 09:00 AM	99 (24.1%)	248 (27.0%)	
09:00 AM - 12:00 PM	47 (11.5%)	155 (16.9%)	
12:00 PM - 06:00 PM	115 (28.0%)	248 (27.0%)	0.034
06:00 PM - 09:00 PM	59 (14.4%)	116 (12.6%)	
09:00 PM - 12:00 AM	36 (8.8%)	60 (6.5%)	
12:00 AM - 06:00 AM	54 (13.2%)	90 (9.8%)	
Stroke provoking factors, n = 1405			
No factors	180 (42.1%)	445 (44.8%)	
Sleep, bathing, eating, bleeding	172 (40.3%)	307 (30.9%)	
Excessive alcohol drinking	8 (1.9%)	22 (2.2%)	0.006
Physical exercises, stress, BP rise	63 (14.8%)	208 (20.9%)	
Unclear	4 (0.9%)	12 (1.2%)	
Development of initial IS symptoms before admitting, n = 1421			
Suddenly	317 (74.2%)	867 (87.2%)	<0.001
Gradually	110 (25.8%)	127 (12.8%)	
Symptom onset-to-hospitalization time interval (h), n = 1417			
< 6	256 (60.4%)	465 (46.8%)	
6-24	126 (29.7%)	308 (31.0%)	< 0.001
24-48	42 (9.9%)	220 (22.2%)	
Symptom onset-to-hospitalization time (h), n = 524	4.3 (2.0-12.5)	5.8 (2.5-13.8)	0.105
Hospitalization duration (day), n = 1417	13 (10-16)	13 (11-15)	0.269
Cardiovascular risk factors: Hypertension, SBP/ DBP, n = 1421			
< 140 mm Hg / < 90 mm Hg	14 (3.3%)	24 (2.4%)	
140-159 mm Hg/ 90-99 mm Hg	11 (2.6%)	43 (4.3%)	0.301
160-179 mm Hg/ 99-109 mm Hg	253 (59.3%)	569 (57.2%)	
≥ 180 mm Hg/ ≥ 110 mm Hg	142 (34.9%)	358 (36.0%)	

Previous stroke / TIA, n = 1421	117 (27.4%)	265 (25.8%)	0.518
Diabetes mellitus, n = 1421	134 (31.4%)	260 (26.2%)	0.045
Alcohol abuse, n = 1421	62 (14.5%)	162 (16.3%)	0.396
Tobacco use, n = 1420			
Never smoker	196 (46.0%)	529 (53.2%)	0.015
Ex-smoker	173 (40.6%)	300 (30.2%)	
Current smoker	57 (13.4%)	165 (16.6%)	
Height (m), n = 734	1.66 ± 0.09	1.68 ± 0.09	0.052
Weight (kg), n = 733	77.8 ± 16.5	80.6 ± 16.4	0.556
BMI (kg / $m^{2)}$, n = 732	28.9 ± 5.9	28.7 ± 5.7	0.656
BMI ≥25 kg / m^2, n = 732	188 (44.0%)	464 (46.7%)	0.358
Carotid intima-media thickness, right (mm), n = 324	1.15 ± 0.16	1.14 ± 0.16	0.614
Carotid intima-media thickness, left (mm), n = 320	1.17 ± 0.12	1.14 ± 0.17	0.114
Medical history: Cerebral artery stenosis, n = 964			
No	86 (42.2%)	444 (58.4%)	< 0.001
< 50%	50 (24.5%)	152 (20.0%)	
50-70%	26 (12.7%)	75 (9.9%)	
> 70%	42 (20.6%)	89 (11.7%)	
Atrial fibrillation, n = 1421	210 (49.2%)	336 (33.8%)	< 0.001
Congestive heart failure, n = 1421	305 (71.4%)	517 (52.0%)	< 0.001
Angina, n = 1421	99 (23.2%)	242 (24.3%)	0.684
Myocardial infarction, n = 1421	81 (19.0%)	159 (16.0%)	0.189
Peripheral arterial disease, n = 1420	99 (23.2%)	151 (15.2%)	< 0.001
Venous disease, n = 535	35 (17.8%)	37 (10.9%)	0.035
Respiratory disease, n = 1419	200 (46.8%)	236 (23.8%)	< 0.001
Gastrointestinal disorder, n = 1420	149 (34.9%)	284 (28.6%)	0.018
Urologic disease, n = 1420	187 (43.8%)	269 (27.1%)	< 0.001
Thyroid disorder, n = 1420	24 (5.6%)	57 (5.7%)	0.960
Hematological disorders, n = 1419	18 (4.2%)	22 (2.2%)	0.052
Cancer, n = 1420	45 (10.6%)	81 (8.1%)	0.154
Stroke-associated infection, n = 535	47 (23.9%)	28 (8.3%)	< 0.001
Hemorrhages, n = 532	2 (1.0%)	2 (0.6%)	0.625
Laboratory data: Total cholesterol (mmol/L), n = 1277	5.3 (4.6-6.2)	5.5 (4.7-6.2)	0.289
Triglyceride (mmol/L), n = 1254	1.25 (0.90-1.73)	1.30 (0.84-1.91)	0.611
Creatinine (µmol/L), n = 1383	98 (82-117)	93 (80-110)	< 0.001
Glucose (mmol/L), n = 1290	6.6 (5.7-8.4)	6.0 (5.2-7.3)	< 0.001
Lactate (mmol/L), n = 464	1.61 (1.25-2.03)	1.46 (1.15-2.01)	0.140
Urea (mmol/L), n = 1391	6.5 (5.1-8.7)	6.3 (4.9-7.8)	0.001
Potassium (mmol/L), n = 1350	4.1 (3.8-4.5)	4.3 (4.0-4.6)	< 0.001

Sodium (mmol/L), n = 1354	140 (137-143)	139 (136-142)	0.025
Calcium (mmol/L), n = 430	2.25 (2.08-2.36)	2.26 (2.02-2.39)	0.535
Chloride (mmol/L), n = 404	103 (101-106)	104 (101-106)	0.302
Total bilirubin (μmol/L), n = 513	14.5 (10.6-19.6)	13.5 (10.2018.3)	0.298
Direct bilirubin (μmol/L), n = 276	4.43 (3.05-5.60)	3.79 (2.93-5.30)	0.015
Total protein (g/L), n = 519	72 (67-77)	71 (68-75)	0.193
Alanine aminotransferase (IU/L), n = 519	17 (13-23)	17 (13-24)	0.882
Aspartate aminotransferase (IU/L), n = 520	22 (18-30)	22 (17-27)	0.661
Fibrinogen (g/L), n = 514	3.74 (2.95-4.42)	3.54 (2.96-4.13)	0.170
Hemoglobin (g/L), n = 1407	139 ± 19.8	139 ± 19.1	0.919
RBC ($\times 10^{12}$/L), n = 1318	4.62 ± 0.71	4.54 ± 0.65	0.030
Hematocrit, n = 1092	0.428 ± 0.054	0.432 ± 0.053	0.348
WBC ($\times 10^{9}$/L), n = 1388	9.8 ± 4.25	8.4 ± 2.94	< 0.001
Bands (%), n = 725	5.75 ± 5.45	4.57 ± 3.30	< 0.001
Polys (%), n = 731	68.6 ± 10.4	65.7 ± 11.0	0.001
Lymphocytes (%), n = 727	21.3 ± 24.6	24.6 ± 9.9	< 0.001
Platelets ($\times 10^{9}$/L), n = 902	200 ± 86	205 ± 72	0.435
Medication after admission Antiplatelet, n = 1273	309 (76.7%)	766 (88.0%)	< 0.001
UFH or LMWH, n = 1273	215 (53.3%)	296 (34.0%)	< 0.001
Vitamin K antagonist, n = 1273	36 (8.9%)	79 (9.1%)	0.932
Antihypertensive medication Angiotensin-converting enzyme inhibitor, n = 1421	409 (96.0%)	932 (93.8%)	0.081
Angiotensin receptor blocker, n = 1421	5 (1.2%)	22 (2.2%)	0.187
Beta-blocker, n = 1420	251 (58.9%)	457 (46.0%)	< 0.001
Calcium channel blocker, n = 1420	105 (24.6%)	256 (25.4%)	0.779
Moxonidine, n = 1421	11 (2.6%)	29 (2.0%)	0.721
Diuretic, n = 1419	368 (86.4%)	801 (80.7%)	0.008
Aldosterone receptor antagonist, n = 1421	50 (11.7%)	65 (6.5%)	0.001
Cardiac glycoside, n = 1420	48 (11.3%)	82 (8.2%)	0.071
Amiodarone, n = 1417	59 (13.9%)	54 (5.4%)	< 0.001

Table 1*: Baseline characteristics of patients with ischemic stroke (n = 1421).*

Data expressed as: n (%), mean ± SD, median (Q1-Q3).

[BMI: Body Mass Index; DBP: Diastolic Blood Pressure; EIS: Evolving Ischemic Stroke; IS: Ischemic Stroke; LACS: Lacunar Syndrome; LMWH: Low-Molecular-Weight Heparins; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; No EIS: Non-Evolving Ischemic Stroke; OCSP: Oxfordshire Community Stroke Project; PACS: Partial Anterior Circulation Syndrome; POCS: Posterior Circulation Syndrome; Q1: Lower Quartile; Q3: Upper Quartile; RBC: Red Blood Cells; SBP: Systolic Blood Pressure; SD: Standard Deviation; TACS: Total Anterior Circulation Syndrome; TIA: Transient Ischemic Attack; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; UFN: Unfractionated Heparin; WBC: White Blood Cells].

At the level of the emergency department, groups of patients with EIS and without EIS have differed in the gravity of the clinical symptoms. By EIS, the stroke-associated neurological deficit at the time of admission has reached 10 (6 - 16) NIHSS points, and by favorable clinical IS course - only 7 (5 - 10) points; $p < 0.001$. The initial severity of the neurological symptoms above 14 points on the NIHSS scale was noted in 143 (33.5%) of 427 patients in the EIS group. At the same time, in the patient without EIS, a similar feature was registered significantly less frequently - in 118 (11.9%) of 994 people; $p < 0.001$. The clinical condition of patients with stroke-in-evolution could be characterized as more serious compared with patients without EIS at discharge from the hospital: 12 (7 - 42) and 3 (2 - 6) NIHSS score, respectively; $p < 0.001$. At the end of the course of treatment in the stroke department, the degree of functional insufficiency according to the mRS was evaluated as 4 (3 - 6) points by EIS and only 2 (2 - 3) points - in the absence of progressive clinical stroke course; $p < 0.001$.

In groups with EIS and without EIS, significant differences of the localization of the cerebral infarction according to brain circulation were revealed. Thus, IS of the left anterior circulation was diagnosed in 42.9% and 41.3%, right anterior circulation - 33.5% and 29.4%, posterior cerebral circulation - 19.9% and 26.9% and multifocal IS - 3.7% and 2.4%, respectively; $p = 0.022$.

The main clinical EIS subtypes according to the OCSP classification were presented as follows: TACS - 210 (49.2%) of 427 cases, PACS - 146 (34.2%), LACS - 30 (7.0%), and POCS - 41 (9.6%). The frequency of identifying of the same Oxford subtypes of stroke in the group with no progression of symptoms was different: 110 (11.1%), 400 (40.2%), 303 (30.5%), and 181 (18.2%) patients, respectively; $p < 0.001$.

The TOAST etiological variant of IS was set before discharge from the department, after assembling and analysis of the entire patient's data. In patients with the worsening course of IS, the undetermined variant of stroke was predominant in frequency - 54.3%. Large artery atherosclerosis, cardioembolism, and small artery occlusion stroke subtypes were diagnosed in fewer cases: 27.2%, 13.2%, and 5.2%, respectively. In the absence of stroke-in-evolution, large artery atherosclerosis was at the first place in frequency - 32.9%, followed by cardioembolism - 17.7%, undetermined/other determined etiology - 24.6% and small artery occlusion - 24.7%; $p < 0.001$.

According to anamnestic data, patients with EIS have indicated sleep, bathing, eating, or bleeding as the provoking factors for the development of stroke in 40.3% cases. In the group without EIS, the frequency of this factor reached 30.9%. Physical activity, stress, BP rise preceded the first symptoms of evolving stroke in 14.8% and of non-evolving IS - in 20.9%. Excessive alcohol drinking before IS onset was noticed in 1.9% and 2.2%, respectively. Provoking stroke factors were absent or unknown in 43.0% and 46.0% of patients in the compared groups; $p = 0.006$.

In 427 patients from the EIS group, a sudden onset of the disease was observed in 317 (74.2%) cases. Neurological symptoms, such as aphasia, dysarthria, muscular weakness in the limbs, coordinating, sensory disorders, and a decline in the level of consciousness were aggravated for seven days in the hospital, despite ongoing medical interventions. In every fourth follow-up (110 (25.8%) patients), a gradual, or step-like, or fluctuating progression of neurological deficit occurred in the pre-hospital stage. After admitting in the stroke department, the development of stroke-associated symptoms continued, which was assessed by the NIHSS scale as an increase in the score by 2 points or more from the emergence department level. In the group of 994 patients without EIS, the deterioration of the neurological symptoms and the level of consciousness, according to anamnesis and medical records, were noticed only in 127 (12.8%) cases. In the hospital, the severity of neurological deficit was not aggravated. In the prevailing amount of patients (867 (87.2%) cases) with the non-progressive clinical course of IS, the onset of stroke was sharp; $p < 0.001$.

Symptom onset-to-hospitalization time interval in the groups of evolving and non-evolving IS also had significant differences. Thus, 60.4% of patients with EIS were brought to the emergency department within 6 hours from the beginning of the initial symptoms. Between 6 and 24 hours, 29.7% of patients in this group were hospitalized, and from 24 to 48 hours - 9.9%. In the group without EIS, 46.8% of patients were admitted to clinic in the time interval < 6 hours from the development of stroke; 31.0% - from 6 to 24 hours, and 22.2% - from 24 to 48 hours; $p < 0.001$. The median value of symptom onset-to-hospitalization time reached 4.3 (2.0 - 12.5) hours by the evolving

clinical course of IS and 5.8 (2.5 - 13.8) hours - by non-evolving course; p = 0.105. The continuance of stay in the acute stroke department also was not significantly different in the groups with EIS and without EIS: 13 (10 - 16) and 13 (11 - 15) days, respectively; p = 0.269.

Information about all-cause mortality of IS patients was also monitored. Sources of data on patient death were medical records, autopsy results, and the official register - centralized archive of deaths of residents of the city of Minsk. For participants of the study, observation time continued from IS date until the date of death or June 30, 2015, or until the date of the last contact. The follow-up time for the survival data ranged from 1 day (with the development of death in the hospital on the first day of the stroke) to 4306 days. The median follow-up time for 1421 patients with IS was 813 (interquartile range (IQR): 99-1978) days. Kaplan-Meier survival curve of patients with stroke is presented in figure 4. The survival rate of 1421 patients during five years of follow-up after IS was 0.50; 95% CI: 0.47-0.53. The mortality rate among IS patients was extreme during the first month after stroke occurrence. Applying the Cox proportional-hazards model, we inspected EIS as the potential predictor of all-cause mortality after IS. The stroke clinical course data were fitted in the Cox model adjusted for age. Regarding the neurological worsening, mortality among patients with non-evolving IS was significantly lower (HR = 0.41; 95% CI: 0.35 - 0.49, p Wald test < 0.001) when compared to the group of subjects with EIS.

Cardiovascular risk factors and medical history data

The cardiovascular risk factors for cerebral infarction are presented in table 1. It should be noted that alcohol abuse and a history of stroke or TIA were recorded in the compared groups with a similar frequency. Smoking status was determined as never smoker, ex-smoker (former smoker), and current smoker. The smoking status was not equal in the compared groups of stroke patients. Thus, in the EIS group, "never smokers" and "current smokers" were registered more often than in the No EIS group. At the same time, among patients suffering from evolving stroke, "ex-smokers" were much more likely to meet than among patients with a favorable course of clinical symptoms of IS; p = 0.015.

The distribution of patients with stroke by groups, taking into account the degree of arterial hypertension [27], defined as the absence of arterial hypertension, presence of arterial hypertension grade I, II, or III, respectively, in EIS and No EIS groups did not show any differences. Diabetes mellitus was diagnosed in every third patient with EIS and every fourth without EIS: 31.4% and 26.2%, respectively; p = 0.045. Such anthropometric characteristics such as height, weight, BMI, and indicator of overweight (BMI ≥ 25 kg/m^2) did not have significant differences in the compared groups of patients with the various clinical course of cerebral infarction; p > 0.05.

Progression of IS was associated with the presence of stenosis of the extracranial and intracranial arteries detected by ultrasound. Thus, in the investigated patients with stroke, stenosis of less than 50% of the cerebral artery lumen occurred with a frequency of 24.5%, from 50 to 70% - 12.7%, and over 70% - 20.6%. In individuals without EIS, the above gradations of stenosis are noted with a lower frequency: 20.0%, 9.9%, and 11.7%, respectively; p < 0.001.

Permanent or paroxysmal AF (p < 0.001), congestive heart failure (p < 0.001), peripheral artery disease (p < 0.001), vein diseases (p = 0.035), respiratory pathology (p < 0.001), gastrointestinal diseases (p = 0.018), and kidney disorders (p < 0.001) were significantly more often diagnosed in patients with EIS than without EIS. According to table 1, stroke-related infections were detected in 75 (14.0%) of 535 patients with IS who have been checked for the presence or absence of the infections. In the same sample, in the individuals with evolve course of IS, post-stroke infections occurred significantly more often than in the group without EIS: 47 (23.9%) and 28 (8.3%) people, respectively; p <0.001.

However, in the compared groups of patients with IS there were no significant differences in the incidence of angina, myocardial infarction, thyroid disorders, hematological diseases, cancer, and bleeding associated with acute stroke; p > 0.05.

Laboratory data

It is noteworthy that in the first days of hospitalization, patients with the evolving clinical course of stroke compared with patients with a non-progressive IS, showed higher serum levels of such parameters of the chemical blood profile as glucose (6.6 (5.7 - 8.4) and 6.0

(5.2 - 7.3 mmol/L, respectively; $p < 0.001$), urea (6.5 (5.1 - 8.7) and 6.3 (4.9-7.8) mmol/L, respectively; $p = 0.001$), creatinine (98 (82 - 117) and 93 (80 - 110) μmol/L, respectively; $p < 0.001$), sodium (140 (137 - 143) and 139 (136 - 142), respectively; $p = 0.025$) and direct bilirubin (4.43 (3.05 - 5.60) and 3.79 (2.93 - 5.30) μmol/L, respectively; $p = 0.015$). Conversely, the level of potassium by EIS group was much lower than by No EIS group: 4.1 (3.8 - 4.5) and 4.3 (4.0 - 4.6) mmol/L, respectively; $p < 0.001$. Total cholesterol, triglyceride, lactate, calcium, chloride, total bilirubin, total protein, alanine aminotransferase, aspartate aminotransferase, and fibrinogen in the serum did not show significant differences when comparing the patients with the different clinical course of ischemic stroke; $p > 0.05$.

In the complete blood count, the levels of hemoglobin, hematocrit, and platelets count did not have any inequalities in the two groups of patients; $p > 0.05$. In patients with EIS, a higher amount of RBC and WBC was found in the blood than in patients without EIS: 4.62 ± 0.71 and 4.54 ± 0.65 ($\times 10^{12}$/L), respectively ($p = 0.030$) and 9.8 ± 4.25 and 8.4 ± 2.94 ($\times 10^{9}$/L), respectively ($p < 0.001$).

The increase in the level of leukocytes in stroke-in-evolution compared with non-progressive stroke was confirmed by the differentiation of white blood cells into the basic subtypes. In the EIS group, the relative content of immature polys reached 5.75 ± 5.45%, and in No EIS group, only 4.57 ± 3.30%; $p < 0.001$. A similar pattern was also noticed for neutrophils: 68.6 ± 10.4% and 65.7 ± 11.0%, respectively; $p = 0.001$. It should be pointed out that the progression of the IS symptoms was associated with a decrease in the lymphocytes count in the blood: 21.3 ± 24.6% and 24.6 ± 9.9%, respectively; $p < 0.001$.

Medications

In 215 (53.3%) cases, patients with evolving stroke were treated using parenteral anticoagulants - UFN or LMWH. Similar drugs were prescribed to patients with a favorable course of IS in only 296 (34.0%) cases; $p < 0.001$. It is expected that antiplatelet agents are more rarely prescribed by physicians to patients from the EIS group than from the No EIS group: 309 (76.7%) and 766 (88.0%) respectively; $p < 0.001$.

When analyzing drugs for antihypertensive, antiarrhythmic therapy, as well as treatment of comorbid congestive heart failure, certain differences were also found out. Medicaments such as beta-blockers, diuretics, aldosterone receptor antagonist spironolactone, and the antiarrhythmic medicine amiodarone were more often prescribed to the patients with EIS than without it: $p < 0.001$, $p = 0.008$, $p = 0.001$, and $p < 0.001$, respectively.

Predictors of EIS

Table 2 contains the main clinical predictors of the evolving clinical course of IS, as well as OR corresponding to each predictor with the 95% CI and the p-value. Female sex increased the odds of the progressive clinical course of stroke symptoms (OR, 1.36; 95% CI 1.08 - 1.73). The severity of neurological deficit, detected at the emergency room level, was a predictor of IS with deterioration. This was demonstrated by such parameters as the presence of TACS (OR, 7.78; 95% CI 5.91 - 10.23) according to the OCSP classification, the NIHSS score > 6 points (OR, 2.04; 95% CI 1.60 - 2.59) and also NIHSS score > 14 points (OR, 3.74; 95% CI 2.83 - 4.94). The brain infarct location in the right anterior circulation was associated with EIS (OR, 1.30; 95% CI 1.02 - 1.66).

The gradual development of initial IS symptoms before admitting of almost two and a half times increased the odds of progression of the neurological deficit during treatment in the clinic (OR, 2.37; 95% CI 1.78 - 3.15). At the same time, the odds of developing EIS were statistically significantly higher in the presence of such cardiovascular risk factors as diabetes mellitus (OR, 1.29; 95% CI 1.01 - 1.66), cerebral artery stenosis ≥ 70% (OR, 1.96; 95% CI 1.30 - 2.93), atrial fibrillation (OR, 1.89; 95% CI 1.51 - 2.39), congestive heart failure (OR, 1.90; 95% CI 1.51 - 2.39), and peripheral artery disease (OR, 1.69; 95% CI 1.27 - 2.25).

Presence of vein diseases also increased the odds of the stroke-in-evolution (OR, 1.76; 95% CI 1.07 - 2.90). Respiratory diseases (OR, 2.82; 95% CI 2.22 - 3.59), gastrointestinal disorders (OR, 1.34; 95% CI 1.05 - 1.70), and urologic diseases (OR, 2.10; 95% CI 1.65 - 2.66) were associated with the progressive clinical course of IS. Stroke-associated infection, such as pneumonia, inflammation of the kidneys and urinary tract, significantly increased the odds of EIS by three and a half times (OR, 3.47; 95% CI 2.09 - 5.76).

Variable	Univariate OR (95% CI)	p value
Female sex	1.36 (1.08-1.73)	0.008
Right anterior circulation	1.30 (1.02-1.66)	0.031
TACS	7.78 (5.91-10.23)	< 0.001
NIHSS score at admission > 6	2.04 (1.60-2.59)	< 0.001
NIHSS score at admission > 14	3.74 (2.83-4.94)	< 0.001
Gradual development of initial IS symptoms	2.37 (1.78-3.15)	< 0.001
Diabetes mellitus	1.29 (1.01-1.66)	0.044
Cerebral artery stenosis ≥ 50%	1.82 (1.29-2.54)	0.001
Cerebral artery stenosis ≥ 70%	1.96 (1.30-2.93)	0.002
Atrial fibrillation	1.89 (1.51-2.39)	< 0.001
Congestive heart failure	1.90 (1.51-2.39)	< 0.001
Peripheral arterial disease	1.69 (1.27-2.25)	< 0.001
Venous disease	1.76 (1.07-2.90)	0.027
Respiratory disease	2.82 (2.22-3.59)	< 0.001
Gastrointestinal disorder	1.34 (1.05-1.70)	0.018
Urologic disease	2.10 (1.65-2.66)	< 0.001
Stroke-associated infection	3.47 (2.09-5.76)	< 0.001

***Table 2**: Clinical predictors of the evolving clinical course of ischemic stroke.*
[CI: Confidence Interval; IS: Ischemic Stroke; NIHSS: National Institutes of Health Stroke Scale; OR: Odds Ratio; TACS: Total Anterior Circulation Syndrome].

Discussion

Deterioration of the neurologic symptoms after the initial presentation is a well-known notorious feature of the stroke [6,9,12,17,61]. The adverse clinical course of the stroke has many names - evolving stroke, progressing stroke, early neurologic deterioration, progressive stroke, stroke in progress, stroke with deterioration, stroke with worsening, stroke progression, stroke-in-progression, stroke-in-evolution and so on [8,9,61-65]. In a classic article of the causes of EIS, announced by M Fisher., *et al*. in 1996, the frequency of progression of neurological deficit ranged from 26 to 43% [61].

For predicting early deterioration of patients with cerebral infarction (that is, for the first 2-3 days), neuroimaging and clinical criteria are of prime importance [9,66]. At the same time, worsening of the IS symptoms at a later observation period is associated with systemic homeostasis disorders, the presence of infectious complications, and decompensating of comorbid somatic diseases [17,64,67,68]. The first scientific data on the frequency, pathophysiological causes, and risk factors of EIS were obtained by analyzing information from large stroke registers. We want to mention the basic research projects, as a result of which neurologists managed to obtain the research-based findings of the clinical predictors of the progressing course of cerebral infarction.

Harvard cooperative stroke registry

The Harvard Stroke Registry at Beth Israel Deaconess Medical Center began to be created under the leadership of L.R. Kaplan and a group of American researchers, enthusiasts who deal with the problem of stroke, in the 1970s. This register was the first prospective published computerized database on any medical condition [12,13]. The register contained the prospectively included data of 694

patients with stroke, among which a cerebral infarction of various etiologies was detected in 579 (83.4%) cases [14]. In approximately 50% of patients, the diagnosis of stroke was based only on carefully evaluated clinical data. At the same time, cerebral angiography was performed in 45% of patients included in the Harvard stroke register. In 4% of observations, computed tomography was performed. In 3% of cases, the adequate definition of stroke was carried out by autopsy.

According to LR Caplan [13], every fifth patient with the stroke included in the Harvard registry had a progressive increase in symptoms of the disease. At the same time, in half of the observations, the deterioration of the clinical condition developed stepwise, in the second half - gradually. The authors of the project registered the progression of IS in 37% of the patients with lacunar cerebral infarction, in 33% with the large-artery occlusive disease, and 7% with cerebral embolism.

Our IS data bank has included 1421 patients. Brain scans with CT and/or MRI, in some cases repeated, were performed in 100% of patients with IS. Worsening of stroke symptoms has been registered in 30% of the observations. The presence of intracranial hemorrhage was the non-including criteria in the database. Large-artery atherosclerosis was the etiological cause of IS in 443 (31.2%) patients, cardioembolism in 233 (16.4%), small-artery disease - in 268 (18.9%). Another etiology that was compatible with other determined rare causes of stroke or remained undetermined (further - undetermined) was recorded in 477 (33.6%). We diagnosed the evolving clinical course of IS with a frequency of 26.2% in macroangiopathy, 24.5% in cardiac embolism, 8.2% in lacunar cerebral infarction, and 48.6% in the undetermined IS. As in the Harvard Stroke Registry, we performed the prospective inclusion of the stroke patients into the data bank. With the accumulation of the survival data, we were able to carry out post-hock analysis of obtained information.

Lausanne stroke registry

The Lausanne Stroke Registry started to be created in Switzerland on the initiative of J Bogousslavsky [15,68]. The objects of the data bank were 3038 consecutive patients with first-ever cerebral infarction or hemorrhage, who were hospitalized to the community-based, primary-care center since 1982 and prospectively enrolled in the registry. The creators of the Lausanne Stroke Registry emphasize that their data bank primarily included data of patients with 100% screen by CT, which significantly increased the accuracy of stroke diagnosis [15,68]. Significant achievements of the authors of this register, in our opinion, include the organization of examination of all patients using a standard protocol, which contained, in addition to the basic neurological and laboratory tests, the ultrasound study of extracranial and intracranial arteries, 12-lead ECG, and 3-lead ECG monitoring. EIS was determined as worsening of the neurological symptoms, including the level of consciousness. The criteria for non-inclusion in the register were the recurrent stroke, as well as the deterioration due to the general condition. The authors of the Lausanne Stroke Registry did not use any established neurological scoring system for detailing the concept of stroke worsening. Thereby, worsening of the neurological condition was traced in 34% of 1968 patients with non-cardioembolic IS, and in 15% of 770 patients with cardioembolic cerebral infarction [68]. The researchers performed a univariate analysis of data from a non-cardioembolic brain infarct group (n = 1968). Patients with neurological worsening differed patients with immediately stabilized IS in such features as age, ipsilateral stenosis > 50%, decreased level of consciousness, lack of TIA before the stroke. In the group of the worsening IS, the localization of the brain infarction in the superficial anterior circulation was found in 29.2% of cases, in the posterior cerebral circulation in 32.0%, and bilateral lesion - in 16.8%. In the immediately stabilized IS group, the indicated topographic features of the infarction focus were recorded in 39.8%, 21.1% and 16.8% of observations; $p < 0.001$; $p < 0.001$; $p < 0.001$ respectively. In the Lausanne Stroke Registry, a small artery disease, as the cause of non-cardioembolic IS, was found in 37.8% of patients with worsening, and in 46.0% of patients without worsening; $p < 0.001$.

The authors of the register [68] stated the diversity of risk factors of the progression of the non-cardioembolic stroke in the groups of large-artery atherosclerosis and small-artery diseases. This circumstance was the basis for the development of two logistic multiple regression models aimed at identifying independent clinical predictors of stroke worsening. Thus, the independent risk factors of worsening by large-artery atherosclerosis were the localization of the infarct in the posterior cerebral circulation and the low level of consciousness when admitted to hospital. The predictors of evolving lacunar ischemic stroke were the age ≤ 64 years, arterial hypertension, localization of the ischemic lesion outside the superficial anterior brain circulation, absence of TIA, and reduced level of consciousness.

The main difference between our database and the results of the above Lausanne Stroke Registry is that we did not exclude patients with recurrent IS from the analysis. Repeated IS occurred in every fifth patient with a stroke - 213 (22.7%) of 1,421 people. At the same time, the stroke recurrence before hospitalization did not in itself affect the increase in the chances of worsening: OR, 1.27, 95% CI 0.98-1.66; p = 0.135. At the same time, a history of previous IS, TIA, or a combination of stroke and TIA could have occurred in the same patient before admitting. Taking into account such risk factor for the development of the IS as the presence of a stroke and/ or TIA in anamnesis (373 people, or 26.7%) also showed no significant differences in the EIS and No EIS groups. The second major dissimilarity in the methodology of our project from the Lausanne Stroke Registry consists of analyzing the data of all patients with IS, and not just those with non-cardioembolic brain infarction (Table 1). With a univariate comparison of the data, we were able to demonstrate the frequency of the evolving cardioembolic stroke in accordance with the TOAST classification. We also showed the percentage of IS with worsening in the main subtypes of stroke following the OCSP criteria. In the publications of the authors of the Lausanne Stroke Registry [15,68], the stroke location in the posterior circulation was an independent predictor of the worsening clinical course of the atherosclerotic IS. The division of strokes of the anterior cerebral circulation to the right and left carotid systems that we carried out not only had appropriate clinical support but also contributed to the selection of the right carotid topography as a predictor of IS progression (Table 2).

We revealed significant differences in age between the groups with EIS and without EIS that complies with the previously published data [15,68]. Also, we were able to identify associations of EIS with female gender, diabetes mellitus, atrial fibrillation, congestive heart failure, peripheral arteries diseases, pathology of peripheral veins, and other comorbid (Table 1). Univariate analysis of the computer database also demonstrated the lower blood concentration of potassium in the patients with EIS compared with those without EIS. The group of evolving IS had a significantly higher content in the blood of such biochemical parameters as sodium, urea, creatinine, glucose, direct bilirubin. The progression of stroke developed on the background of the general blood test alteration, which was manifested by an increase in the number of RBC and WBC.

Besançon stroke registry

The Besançon Stroke Registry represents the large hospital registry of stroke created during 1987 - 1994 in France [16]. The computer base collected data from 1776 consecutive patients with first-ever IS admitted to the Centre Hospitalier Universitaire of Besançon. All stroke patients were evaluated by the standard protocol, including neuroimaging (CT and/ or MRT), Doppler sonography, and cardiac survey. According to the logistic regression model, early (within the first 48 hours), neurological worsening was one of the independent predictors of the lethal outcome within one month [16].

As mentioned above, when creating the base of unselected patients with IS, we did not exclude individuals with a recurrent brain infarct, the proportion of which reaches 22.7%. However, it should be referred that we were not able to prospectively include in the study all patients with IS consistently hospitalized from 2002 to 2014. Therefore, in our research, we are talking about randomly selected patients with stroke. In addition, we considered deterioration in the broader time range - from the time of admission to the clinic to 7 days of inpatient observation.

European cooperative acute stroke study I

Dávalos A., *et al.* [17] published results of secondary analysis of data accumulated by ECASS I - a double-blinded, randomized multicenter trial carried out from 1992 to 1994 in 14 European countries. Trial database hold information about 615 patients with ischemic hemispheric stroke received either recombinant tissue plasminogen activator (rtPA) or placebo within 6 hours after the stroke onset.

The authors of the study [17] divided the concept of deterioration in cerebral infarction into two components: the early progressing stroke and the late one. Early progression was understood to mean a decrease of 2 or more points in the level of consciousness, or motor functions, or a decrease of 3 or more points in the assessment of speech on the Scandinavian Stroke Scale (SSS) [69] during the first 24 hours of observation. This type of neurological worsening evolved in 231 (37.6%) from 615 patients with the hemispheric brain infarc-

tion. In the group of patients who received rtPA in the first 6 hours after stroke onset, deterioration was recorded in 38.0% of cases. In the placebo group, the same indicator reached 37.0%. Late progressing IS was diagnosed in the case when one of the above signs of neurological deterioration developed in the time interval from the end of the 1st to the 7th day. With multivariate data analysis using logistic regression, five independent predictors of early progressing IS have been identified: focal hypodensity and hyperdensity of the middle cerebral artery sign on initial CT, longer delay until thrombolysis, coronary heart disease and diabetes mellitus [17]. Late progressing IS developed in 111 (20.3%) from 546 patients. Three independent prognostic criteria for this type of stroke complication were established: older age, brain swelling on initial CT, and severe neurological deficit at admission corresponding to the low SSS score. The database of our study contains information not only about 1029 (72.4%) patients with hemispheric cerebral infarction, but also about 352 (24.8%) patients with vertebral basilar IS, and 40 (2.8%) persons with acute multifocal ischemic brain damage.

According to published data [17], ECASS I was characterized by a narrow time window for the engagement of the patients in the study - up to 6 hours after the onset of IS. The primary purpose of the trial was to analyze the effectiveness of IV thrombolysis. We included patients with acute IS that occurred ≤ 48 hours before hospitalization. In 721 (50.9%) patients of our research, the symptom onset-to-hospitalization time interval was less than 6 hours. Another 696 (49.1%) patients were taken to the emergency department later than 6 hours. Direct comparison of the ECASS I data with our study seems to be inconvenient. The patients with clinical signs of TACS, including those with hemiplegia, the low level of consciousness, and the forced eye and head deviation, were excluded from the thrombolysis trial [17]. Neuroimaging criteria for excluding patients from the ECASS I were diffuse swelling of the related cerebral hemisphere and parenchymal hypodensity more than one-third of the middle cerebral artery area according to initial CT scan.

Study of H-H Geng., *et al.*

Geng H-H., *et al.* (2017) presented to the attention of the scientific community the results of observation of 1064 patients with a first-ever cerebral infarction up to 1 week old at the time of admitting to the Huai-He Hospital, Kaifeng, China [8]. Early neurological deterioration was denoted as an increase in motor weakness in the limb by 1 point or an increment in neurological symptoms by 2 or more points on the NIHSS scale within seven days of observation at the hospital. The frequency of IS progression within the designated time frame was 32%. In the univariate data comparison, the group of patients with worsening, compared with the group without neurological deterioration, was characterized by the more severe neurological deficit, the presence of arterial hypertension, diabetes, higher levels of direct bilirubin, glucose, D-dimers, C-reactive protein, homocysteine, low-density lipoprotein, lower total cholesterol. Significant differences in age, gender, BMI, smoking, and alcohol consumption H-H. Geng at al. did not observe. Diabetes, NIHSS score at admission, C-reactive protein, and homocysteine were recognized as independent clinical factors for IS progression in a multivariate logical regression model.

Our research team, as well as the authors of the study [8], defined the concept of IS progression as an elevation in the assessment of neurological symptoms by ≥ 2 NIHSS points during seven days of hospitalization. However, we included in the database only those patients who had ≤ 48 hours from the moment of the stroke to admitting. However, the frequency of recording the progression of stroke symptoms during the first week of observation in our and in the Chinese study is very close - 30% and 32% respectively. We showed the presence of significant clinical associations of the female gender, age, smoking status (ex-smoker), localization of the stroke in the right anterior circulation, TACS to OCSP criteria with a progressive clinical course of IS. In our study, not only diabetes mellitus and severe neurological deficiency are associated with the presence of EIS, but also cerebral artery stenosis, AF, congestive heart failure, pathology of peripheral arteries and veins, respiratory, gastrointestinal, and urological diseases, stroke-associated infections, as well as widespread palette of chemical profile of blood, and general blood count. Our study, as well as previous investigations [8,12-14,16,17,70], confirmed the association of EIS with a severe neurological deficit at discharge from the stroke department and the poor functional outcome.

Limitations

Our computer base reflects the real level of care for patients with IS in the clinical treatment institution in the capital city of Belarus. Brain scans were performed in 100% of patients in our registry; the frequency of the ultrasound examination of the vessels was 67.8%.

We have presented in table 1 data on the real number of observations obtained. If there were no specific data on any patient variable, then the frequency of the trait in the analyzed group was calculated based on the number of cases available. We understand quite well that it is appropriate to establish independent predictors relative to the end point of the study by mathematical construction of multiple logistic regression models, discriminant analysis, decision trees, neural networks, etc. The provided volume of one publication cannot reflect all scientific results received by the authors of the article over many years of research. In the following publications, we would like to present our data on the determination of the independent predictors of the progressive clinical course, the variant of functional outcome and post-stroke survival, obtained on the analysis of the collected dataset of the patients with IS.

Following the initially selected study protocol, we did not include in our dataset characteristics of patients who received treatment using intravenous or intraarterial thrombolysis, as well as mechanical thrombectomy. The first clinical experience of using IV thrombolysis with rtPA (alteplase) for IS was obtained in clinics of the Republic of Belarus in 2006 [71]. However, at the time of the end of our study, the use of reperfusion therapy for patients with cerebral infarction was sporadic rather than systemic. The problem was not only that the national clinical protocols for the treatment of patients with IS acted from 2005 to 2017 did not contain recommendations on the use of thrombolysis for cerebral infarction [42].

As known, in the USA, IV thrombolytic therapy with rtPA for cerebral infarction was approved by the Food and Drug Administration (FDA) in 1996. The European Medicines Evaluation Agency (EMEA) authorized thrombolysis in 2002 [72]. According to the evaluation by O Adeoye., *et al.* [73], in 2009, 3.4% to 5.2% of patients with acute IS of the USA received thrombolytic therapy, nearly double the ration of treatment in 2005. In the survey of national scientific societies and stroke experts in 44 European countries, the average frequency of the IV thrombolytic therapy among all patients with ischemic stroke was 7.3% in 2018 [74]. In the Republic of Belarus, with a population of over 9.5 million people, there are 0.4 hospitals with the capacity to administer IV thrombolysis for every 1000 patients with ischemic stroke [74].

In January 2018, the Ministry of Health of the Republic of Belarus approved a new national protocol for the treatment of patients with neurological diseases at the inpatient and outpatient stage [75]. The author of the article (IG) was granted the high honor to be at the head and coordinate a group of Belarusian specialists in the field of neurology, who worked on the new protocol in 2015-2017. The national protocol is obligatory for use in health care institutions of the Republic of Belarus that provide medical care to patients with stroke and other neurological diseases. The inclusion of the procedures of intravenous and intraarterial thrombolysis, mechanical thrombectomy in the modern version of the national protocol received acceptance from the WHO Regional Office for Europe expert group [71].

The Minsk Emergency Hospital is a large clinical center with CT, MRI and angiography equipment. The neurological department No 1 is one of the national leaders in the implementation of thrombolytic therapy for cerebral infarction. Nevertheless, in 2015, the frequency of reperfusion therapy in this department reached a level of only 2.5% in all hospitalized patients with IS. The low frequency of use of thrombolytic therapy in Belarus is also due to the high cost of drugs and angiographic instruments, insufficient equipment of clinics, especially in rural areas, by CT and MRI scanners, an ineffective system of logistics for patients with stroke, lack of the necessary level of knowledge among the population about the first signs of stroke and effective treatment option in the early hours of the disease.

Conclusion

Thus, we take the liberty to assert that our database correctly reflects information about the remaining 97.5% of all admitted patients with IS who did not receive rtPA treatment. The in-hospital dataset created by our research group contains information about the evolving clinical course frequency, the main pathogenic subtypes of ischemic stroke, patient demography, cardiovascular risk factors, comorbid pathology, clinical and laboratory support, instrumental methods of examination, medications used, severity of neurological deficit using specialized stroke scales, and post-stroke outcome. We hope that our efforts to create a database of patients with acute IS, as well as the development of a new protocol to care patients with stroke, will make a significant contribution to reducing morbidity and mortality from cerebrovascular diseases in Belarus through the use of evidence-based medical care methods.

Author Contributions

IG: search strategy design, data collection and extraction, writing and reviewing all titles, abstracts, tables, references, and full texts, data interpretation, statistical analysis, and manuscript draft. IP: search strategy design, statistical analysis.

Conflict of Interests

None stated.

Acknowledgments

In 2002-2015, the first author of the article (IG) worked at the RSPCNN (Minsk, Belarus) as a research associate, senior research associate, and principal research associate in the department of neurology; in 2015 - 2017 - as a deputy director in the same institution.

IG was the principal investigator of five research projects on the problem of ischemic stroke. These topics were financed at the expense of funds allocated by the State Committee for Science and Technology of the Republic of Belarus. The names of five research projects, information on the dates of study completion, state registration numbers, the total amount of funding, and a brief description of the results are presented on the ORHID website: https://orcid.org/0000-0001-6648-1589).

The computer database was created and filled out personally by IG while working on her doctoral dissertation on the topic "Cardiovascular predictors of clinical course, functional outcome and survival of patients with ischemic stroke" in the specialty "Neurological disorders". Since 2017, IG has resided in the USA.

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Volume 11 Issue 9 September 2019