

Clinical Prognostic Factors for One Year Survival in Patients after Ischemic Stroke

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Abbreviations: BMI: Body Mass Index; CT: Computer Tomography; DBP: Diastolic Blood Pressure; IQR: Interquartile Range; IS: Ischemic Stroke; LACS: Lacunar Syndrome; MRI: Magnetic Resonance Imaging; MRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; OSCP: Oxfordshire Community Stroke Project; PACS: Partial Anterior Circulation Syndrome; POCS: Posterior Circulation Syndrome; RSPCNN: The Republican Scientific and Practical Center for Neurology and Neurosurgery of the Ministry of Health of the Republic of Belarus; SBP: Systolic Blood Pressure; TACS: Total Anterior Circulation Syndrome; TIA: Transient Ischemic Attack; TOAST: Trial of ORG 10172 in Acute Stroke Treatment.

ABSTRACT

Introduction: The goal of the study was to identify the most significant prognostic clinical criteria for the survival of patients with Ischemic Stroke (IS) within 1 year of observation.

Materials and Methods: The object of the clinical prospective study was 1421 patients with IS hospitalized in 2002-2015 in the neurological (stroke) departments of the 5th Minsk City Clinical Hospital and the Minsk Emergency Hospital. Analyzing the obtained data, we adhered to the prospective specimen collection, retrospective evaluation design of the study. The primary endpoint of the study was the patient's death from any reason within one year of the development of IS. Information on post-stroke all-cause mortality was obtained through linkages to the official source the centralized archive of deaths of residents of the city of Minsk. Patients without a confirmed death date were censored at the date last known alive. All patients that were alive at one year are assumed to be censored at that time. The collection of clinical, demographic, neuroimaging, laboratory data, as well as the final determination of the stroke outcome, was performed blindly with respect to survival data.

Results: To build the model, 22 multivariate clinical indicators were used that demonstrated the relationship with post stroke survival at the stage of preliminary data analysis: stroke subtype according the Oxfordshire Community Stroke Project, age, gender, the severity of the neurological deficit according to the NIHSS scale at hospitalization, previous stroke or TIA, the presence of arterial hypertension, atrial fibrillation, myocardial atherosclerosis, congestive heart failure, diabetes mellitus, peripheral arterial diseases, alcohol abuse, level of creatinine, glucose, urea, potassium, sodium in blood, amount of hemoglobin, erythrocytes and leukocytes on the 1st day of treatment, the level of systolic and diastolic blood pressure in the hospital admission department.

In the construction of a survival decision tree of patients with IS, of the 22 initially embedded parameters, only 6 independent predictors were finally included in the prognostic model the stroke subtype according to the OSCP, the presence of a lacunar infarction, the severity of neurologic deficit at hospitalization according NIHSS, level of urea and glucose in the blood, and the presence of congestive heart failure.

INTRODUCTION

Cardiovascular diseases are the major contributors to the mortality of the population of the Republic of Belarus, making the structure of the total mortality of 55.2% in 2014 (52.4% in 2012, 52.7% in 2013)^[1]. According to a WHO expert review on the organization of emergency care and rehabilitation for myocardial infarction and stroke in Belarus (2017) cardiovascular diseases are responsible for 63% of mortality among non-communicable diseases. In this case, ischemic heart disease occupies 57% of the causes of years of life lost due to premature death, and stroke 32%^[2].

The single population study, including 671 patients with acute stroke, was conducted in the Republic of Belarus in 2001 in the conditions of the regional city Grodno^[3]. For all the subtypes of the stroke, the lethality within 1 year of observation was 37.4% (95% CI:33.0%–42.3%). As the authors of this population study point out, due to the low frequency (37.1%) of confirming the diagnosis of stroke by methods of neuroimaging and or autopsy, stratification of outcomes for various subtypes of a stroke was not carried out. Data on clinical features of first-ever-in-a-lifetime stroke were not registered; the analysis of the functional outcome of a stroke was limited to an estimate of MRS in 5 follow-up years^[3].

Present neurologists underline the need of developing prognostic scales and models based on the evaluation of those clinical parameters that can be measured in the first minutes of the patient's stay in the admission department. The scale of assessing the risk of an IS adverse outcome could be a valuable clinical and research tool in the first day of a stroke if it combines fast mathematical calculation, simplicity and reliability of biological endpoints prediction^[4].

The goal of the study was to identify the most significant prognostic clinical criteria for the survival of patients with Ischemic Stroke (IS) within 1 year of observation.

MATERIALS AND METHODS

Study design

The object of the clinical prospective study was 1421 patients with IS hospitalized in 2002-2015 in the neurological (stroke) departments of the 5th Minsk City Clinical Hospital and the Minsk Emergency Hospital the clinical bases of the Republican Scientific and Practical Center for Neurology and Neurosurgery of the Ministry of Health of the Republic of Belarus (RSPCNS). Patients were randomly selected for inclusion in the study^[5]. Information about each patient was included in a specially designed paper form and a computer database. Individual informed consent was received by all patients with IS or their official representatives.

Analyzing the obtained data, we adhered to the prospective-specimen-collection, retrospective evaluation design of the study, informal consent form, and study protocol approved by the local ethical committee of the RSPCNS. Individual informed consent was received by all patients with IS or their official representatives.

Study population

We included patients who met the following inclusion criteria: the presence of an acute IS developed less than 48 hours prior. In patients with cerebrovascular disease admitted to the emergency department of our clinical hospitals, an immediate differential diagnosis of IS with Transient Ischemic Attack (TIA), intracerebral hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage (aneurysmal, traumatic and another etiology) subdural and epidural hematoma, venous sinus thrombosis, meningoencephalitis, brain tumor, hypoglycemia, epilepsy, decompensated chronic stroke, neurodegenerative and autoimmune diseases. Detection of the cerebral pathology mentioned above after providing the differential diagnosis was a criterion for non-inclusion of the patient in the cohort of acute IS. The clinical manifestations of IS in all patients were confirmed by a neuroimaging investigation CT and or MRI of the brain.

All 1421 patients underwent a physical examination, ECG recording, chest x-ray, complete blood count, coagulation tests, blood chemistry profile, and urinalysis. Particular patients underwent ultrasound examination of extra and

intracranial arteries (n=964, 67.8%), transthoracic echocardiography (n=130, 9.1%). All patients with cerebral infarction were examined daily by neurologists in the stroke department. In the first 3 days, each patient was consulted by a therapist, and if necessary, by a cardiologist, endocrinologist, ophthalmologist, urologist, psychiatrist and other

Additional information recorded includes: age, gender, BMI, history of hypertension, coronary artery disease, myocardial infarction, peripheral arterial disorders, atrial fibrillation, congestive heart failure, diabetes mellitus, prior stroke or TIA, other somatic diseases, also alcohol consumption, and smoking. The levels of systolic and diastolic blood pressure at the stroke onset and at the time of hospitalization were also entered. The race of all of the patients was categorized as white.

Total Anterior Circulation Syndrome (TACS), Partial Anterior Circulation Syndrome (PACS), Lacunar Syndrome (LACS) and Posterior Circulation Syndrome (POCS) of the IS were determined using the criteria of the Oxfordshire Community Stroke Project^[6]. According to the TOAST criteria such ischemic stroke subtypes were defined: large artery atherosclerosis, cardioembolism, small artery occlusion and other or unknown cause of stroke^[7].

The neurological deficit was assessed using the National Institutes of Health Stroke Scale (NIHSS) at the time of admission to the stroke department and at discharge. Progressive IS was understood as a stroke with an increase in neurological symptoms by 2 or more NIHSS scores in the first 7 days of the hospitalization, or death of the patient in a given period of time^[8,9].

Thrombolytic therapy was not prescribed for the patients included in the study. The treatment of patients with IS included anti-thrombotic (acetylsalicylic acid, clopidogrel, unfractionated heparin, low molecular weight heparins, warfarin), anti-hypertensive (angiotensin converting enzyme, angiotensin-receptor blockers, diuretics, β -blockers, calcium channel blockers), neuroprotective (magnesium sulfate, methyl ethylpyridinol, carnitine chloride, glycine), symptomatic medications in compliance with the acted clinical protocol for the treatment of neurological diseases of the Republic of Belarus^[10]. The time from the development of a IS to the blood sampling on the first day of treatment did not exceed 48 hours^[8]. A complete blood count, coagulation profile, and blood chemistry profile were performed in the clinical laboratories of hospitals.

Serum biomarkers, that have been identified in patients with IS, were presented as a median and Inter Quartile Range (IQR): total cholesterol 5.4(4.6-6.2) mmol/L, glucose 6.2(5.3-7.6) mmol/L, urea 6.3(5.0-8.0) mmol/L, creatinine 95(80-110) μ mol/L, potassium 4.2(3.9-4.6) mmol/L, and sodium 139(137-142) mmol/L. The level of hemoglobin reached 141(128-152) g/L, erythrocytes 4.6(4.2-5.0) $\times 10^{12}$ /L and leukocytes 8.1(6.6-10.0) $\times 10^9$ /L.

The endpoint of the study was the patient's death from any reason within one year of the development of IS. Information on poststroke all cause mortality was obtained through linkages to the official source the centralized archive of deaths of residents of the city of Minsk. The collection of clinical, demographic, neuroimaging, laboratory data, as well as the final determination of the stroke outcome (totally more than 36 parameters) were performed blindly with respect to survival data. The records of all patients with IS were reviewed by one of the authors (IG).

The average length of stay in the hospital was 12 {10;14} days. 295 people who did not have a complete list of clinical and routine laboratory tests were excluded. Thus, for the construction of a prognostic survival model after IS, the results of the survey and observation of 1126 people were used (79.2% of the study cohort).

Statistical analysis

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 normal distribution. To get an estimate on differences between groups (3 or more) a post hoc Tukey test was used. Distributions of the numeric parameters against Gauss distribution were validated by means of Shapiro-Wilk test^[11,12]. If the distribution was not normal Wilcoxon-Mann-Whitney test was employed to compare 2 groups or Kruskal-Wallis test for 3 or more groups following post Kruskal-Wallis for multiple comparison post hoc tests.

For statistical data analysis, a non-commercial package R V.3.2.5^[13,14] (modules rpart (<https://cran.r-project.org/web/packages/rpart/index.html>) and tree (<https://cran.r-project.org/web/packages/tree>) was introduced. Libraries base, car, epicalc, and Rcmdr were obtain to study the quantitative parameters. Libraries coin, presence absence were applied for comparison of the quality parameters. To build decision trees based on the R V.3.2.5 statistical package, we put on the libraries rpart (<https://cran.r-project.org/web/packages/rpart/index.html>), party, random Forest, rpart.plot, maptree, cluster, partykit.

Formation a survival model for patients with stroke using the tree based method makes it possible to estimate the significance of the influence of the predictors included in the model on the disease outcome, to identify the logical patterns of data and display them in the form of dendrogram^[15,16]. Building the survival decision tree begins at the root

node (Figure 1 Node 1: OCSF). The root node is the top of the dendrogram comprising of all data in the bootstrap sample^[16]. As can be seen from the picture, the survival tree contains 6 internal nodes (Figure 1 Nodes 1,2,4,5,9,11) and 7 terminal nodes (Figure 1 Nodes 3,6,7,8,10,12 and 13). Terminal nodes (also called leaves, final nodes, solution nodes, decision leaves) represent the Kaplan-Meier one year survival curves^[18] where “n” is the number of patients with IS that are distributed as a result of classification into corresponding leaves.

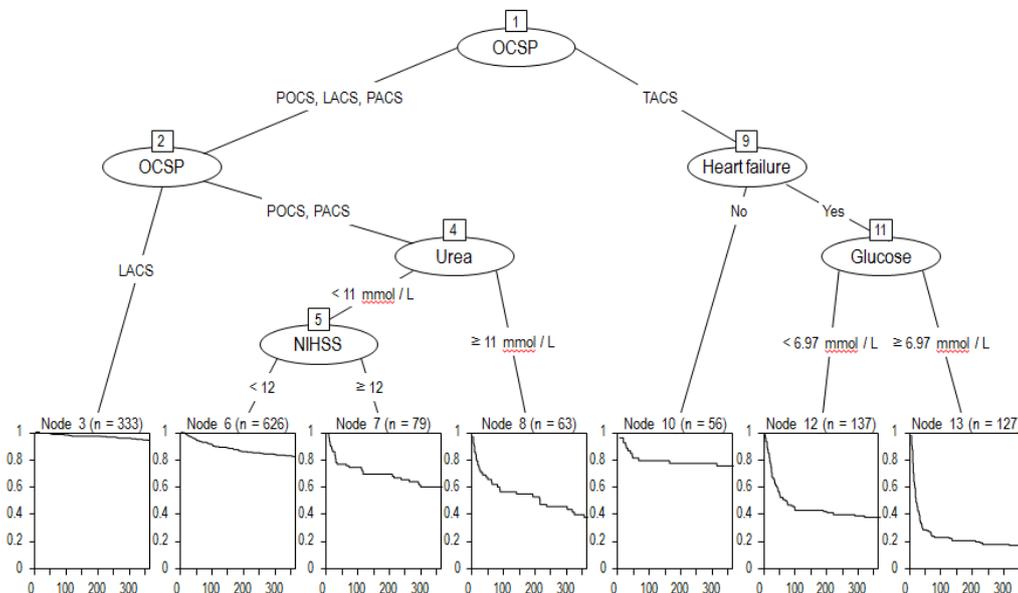


Figure 1. Tree-structured survival model for the clinical data and the distribution of survival times in the terminal nodes. The median survival time is displayed in each terminal node of the tree.

Each node of the decision tree carries some information necessary to efficient composition of the model of patient survival. Bagging predictor’s method by L. Breiman^[19] was put on to improve the stability and accuracy of the survival model. Bagging procedure included 16 bootstrapping replications of survival tree. The conclusive prediction was received by averaging the prognosis from each individual tree^[20]. The integrated Brier score^[21,22] was applied for evaluation the expected patient survival during 365 days after IS. In consideration of the Brier score, in its contemporary formulation^[23] it takes on a quantity betwixt zero and one, so far as this is the greater possible distinction between a predicted probability (which must be between zero and one) and the factual outcome (which can get values of only 0 and 1). Thus, the lower the Brier score is for the possible outcome’s series, the superiorly the predictions are calibrated. In our case, out of bag estimate of Brier’s score reached 0.1357. This indicates a sufficient accuracy of the constructed survival model.

The date of IS was set as the start point of follow-up. The end of follow-up was defined as date of death independent of the reason, last contact date or 1 year after start point whatever was early. Patient’s without a confirmed death date within one year after the start point were censored.

RESULTS

Study patients and follow up

During one year of observation 320 people died. The main causes of death were due to cardiovascular pathology. Baseline characteristics of the patients are included in **Table 1**.

Table 1.Demographic and baseline characteristics (n=1126).

Characteristics	Survivals (N = 806)	Dead (N = 320)	p-value
Age, years (mean ± SD)	68.2 ± 11.1	74.8 ± 9.2	< 0.0001
Male sex, N (%)	388 (48.1)	124 (38.8)	0.0043
NIHSS at admission, median	6.0 (4.0-9.0)	14.0 (8.0-19.0)	< 0.0001

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(IQR)			
NIHSS at discharge, median (IQR)	4.0 (2.0-7.0)	15.0 (7.0- 42.0)	< 0.0001
OCSP subtype, N (%)			
POCS	150 (18.6%)	36 (11.2%)	< 0.0001
LACS	227 (28.2%)	13 (4.1%)	
TACS	101 (12.5%)	172 (53.8%)	
PACS	328 (40.7%)	99 (30.9%)	
TOAST subtype, N (%)			
Large artery atherosclerosis	281 (34.9%)	67 (20.9%)	< 0.0001
Cardio-embolism	134 (16.6%)	55 (17.2%)	
Small artery occlusion	188 (23.3%)	10 (3.1%)	
Other or unknown cause of stroke	203 (25.2%)	188 (58.8%)	
Progressive clinical IS course, N (%)	175 (21.7%)	181 (56.6%)	< 0.0001
Carotid / vertebral stenosis, N (%)*			
No	332 (54.7%)	60 (44.4%)	0.0302
< 50%	141 (23.2%)	31 (23.0%)	
50-70%	62 (10.2%)	16 (11.9%)	
> 70%	72 (11.9%)	28 (20.7%)	
Medical history			
Prior stroke or TIA, N (%)	191 (23.7%)	103 (32.2%)	0.0035
Myocardial infarction, N (%)	112 (13.9%)	73 (22.8%)	0.0003
Atrial fibrillation, N (%)	265 (32.9%)	202 (63.1%)	< 0.0001
Congestive heart failure, N (%)	412 (51.1%)	273 (85.3%)	< 0.0001
Blood pressure, SBP/DBP, N (%)			
< 120 mm Hg/< 80 mm Hg	21 (2.6%)	10 (3.1%)	0.0906
120-139 mm Hg/80-89 mm Hg	34 (4.2%)	9 (2.8%)	
140-159 mm Hg/90-99 mm Hg	480 (59.6%)	170 (53.1%)	
≥ 160 mm Hg/≥ 100 mm Hg	271 (33.6%)	131 (40.9%)	
Peripheral artery disease, N (%)	126 (15.6%)	90 (28.1%)	<0.0001
Diabetes mellitus, N (%)	215 (26.7%)	113 (35.3%)	0.004
Alcohol consumption, N (%)	117 (14.5%)	48 (15.0%)	0.836
Smoking, N (%)			
No	322 (40.0%)	105 (32.8%)	0.0732
Prior	365 (45.3%)	166 (51.9%)	
Current	119 (14.8%)	49 (15.3%)	
BMI ≥ 25 kg/m ² , N (%)	396 (49.1%)	131 (40.9%)	0.013

Patients who survived during the observation year were characterized by a younger age, a less pronounced initial neurological deficit, or a lesser degree of stenosis cerebral artery disease. Surviving patients were significantly less likely to be diagnosed with atrial fibrillation, congestive heart failure, peripheral arterial disease and diabetes mellitus **Table 1**. It should be noted that the Body Mass Index (BMI) of surviving patients was significantly higher than the BMI of the deceased patients 396 (49.1%) and 131 (40.9%) kg/m², respectively; p=0.0130.

To build the model, 22 clinical indicators were used that demonstrated the relationship with post-stroke survival at the stage of preliminary data analysis: stroke subtype according the Oxfordshire Community Stroke Project (**Figure 1**- OCSP) age, gender, the severity of the neurological deficit according to the NIHSS scale at hospitalization (**Figure 1**-NIHSS), previous stroke or TIA, the presence of arterial hypertension, atrial fibrillation, myocardial atherosclerosis, congestive heart failure (**Figure 1**-Heart failure), diabetes mellitus, peripheral arterial diseases, alcohol abuse, level of creatinine, glucose (**Figure 1**-Glucose), urea (**Figure 1**-Urea), potassium, sodium in blood, amount of hemoglobin, erythrocytes and leukocytes on the 1st day of treatment, and the level of systolic and diastolic blood pressure in the hospital admission department.

A characteristic feature of node 1 is that when the condition "presence of the posterior circulation syndrome or lacunar syndrome or partial anterior circulation syndrome" (POCS, LACS, PACS respectively) is satisfied, the tree branches left to node 2. The realization of the condition in node 2 "presence of LACS" results in terminal node 3, or solution node (Node 3), reflecting the Kaplan-Meier curve of the survival of patients with lacunar stroke for 1 year of follow up. The presence of the Posterior Circulation Syndrome (POCS) or Partial Anterior Circulation Syndrome (PACS) at node 2 leads to the right to node 4 (Node 4).

In node 4, if there is a urea level in the blood ≥ 11 mmol/L, the decision tree leads to terminal node 8 (Node 8). Node 8 contains the Kaplan-Meier survival curve of patients with POCS or PACS with a high urea blood level. If urea level in the blood is less than 11 mmol/L, the tree branches out from node 4 to the left, to node 5 (Node 5). The node 6 reflects the survival curve of patients with POCS or PACS, urea level <11 mmol/L and initial neurological deficit < 12 NIHSS points.

Survival during the year of follow up of similar patients who had a neurological symptom score ≥ 12 on admission is reflected in the Kaplan-Meier curve at terminal node 7. Non-completion of the condition "presents of POCS, LACS, PACS" in node 1, that is the Total Anterior Circulation Syndrome (TACS) leads to the right to node 9 (Heart failure). Survival of patients with TACS in the absence of congestive heart failure is presented in terminal node 10. In node 9, the presence of heart failure with total stroke in the carotid basin leads to node 11 (Glucose).

When the condition "glucose level <6.97 mmol/L" is satisfied at node 11, branching of the decision tree towards the node 12 is observed. That is, the terminal node 12 reflects graphical information on the survival of patients with TACS, congestive heart failure and glucose level less than 6.97 mmol/L at admission. Accordingly, the implementation of the rule "glucose level ≥ 6.97 mmol/L" leads to terminal node 13 (Node 13), which presents the Kaplan-Meier survival curve for patients with ischemic stroke during the observation year.

In the survival model construction of patients with IS, of the 22 initially embedded parameters, only 6 independent predictors were finally included in the prognostic model: the stroke subtype according to the Oxfordshire Community Stroke Project classification (1-OCSP: POCS, LACS, PACS/TACS), the presence of a lacunar infarction (2-OCSP: LACS/POCS, PACS), severity of neurologic deficit at hospitalization (5-NIHSS), level of urea (4-Urea) and glucose (11-Glucose) in the blood, the presence of congestive heart failure (9-Heart failure). 6 independent clinical predictors of survival of patients after stroke are internal nodes of the dendrogram. 7 terminal nodes contain specific graphical information on the survival of stroke patients during the year of observation, depending on specific clinical characteristics.

One of the most attractive features of decision trees data analysis is the ability to determine threshold values of quantitative indicators. In our study, this was a blood glucose level of < 6.97 mmol/L and ≥ 6.97 mmol/L and blood urea level < 11 mmol/L and ≥ 11 mmol/L.

The algorithm for creating the decision tree model showed a statistically significant difference in the survival of patients with total stroke in the anterior circulation, depending on the severity of the initial neurological deficit. The point of separation was the NIHSS score of <12 points and ≥ 12 points at the time of hospitalization.

DISCUSSION

On the basis of clinical characteristics, many models and scores of post stroke survival were created^[24,25]. At the same time, in the Republic of Belarus there have been no scientific studies aimed at detection of the independent clinical predictors of long-term survival of patients who suffered an IS. According to the regression model authors from Grodno (2001)^[3], the prognostic factors of the risk of death of patients with stroke for 5 years were age, previous stroke, arterial

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hypertension, diabetes mellitus, atrial fibrillation, myocardial infarction in the anamnesis. Existing differences in the long term survival of patients with ischemic and hemorrhagic stroke subtypes are shown. At the same time, the factors determining the risk of developing a lethal outcome with a cerebral infarction, as the most common variant of a stroke, were not determined in this study.

In the population based study of Vernino et al.^[26] survival after first IS (n=444) measured up 83% at first month, 71% at 1 year and 28% at 10 years. After cerebral infarct patients have a higher mortality rate than exceeded that of a control group comparable in age and sex. Cox's multi variant model of proportional hazards allowed authors of the study^[26] to identify such independent risk factors for death after the first IS as age, cardiac comorbid conditions, severity of stroke symptoms according to MRS, development of recurrent stroke, seizures, respiratory and cardiovascular complications in both acute and reconstructive period of a stroke.

In connection with the epidemic of cerebrovascular diseases in low-income countries, a number of epidemiological studies were conducted^[27-30]. The survival of patients with IS varies widely according to the data of different researchers^[31-34]. While analyzing the data of more than 170 thousand patients with acute ischemic stroke, American neurologists^[35] convincingly demonstrated that correctly organized care^[36] can significantly improve the results of hospitalization. Thus, the strict adherence to the program "Get With The Guidelines (GWTG) Stroke", developed by the American Heart Association, makes it possible to significantly improve the functional state of patients with IS on discharge from the hospital, as well as improve short-term (1 month) and long term (1 year) post discharge survival. The most accessible for analysis are the clinical criteria that can be determined in the acute period of a stroke. They do not require additional laboratory studies or the use of complementary diagnostic equipment.

iScore

Canadian researchers^[37-39] developed the ischemic stroke risk score (iScore) based on a logistic regression model that predicts short term and long term survival after an acute IS. Also, this scale can be successfully used to predict an unsatisfactory IS functional outcome, including systemic thrombolysis^[39]. As independent predictors, each with a certain number of points, iScore includes sex, the age of the patient, a variant of ischemic stroke (lacunar, non-lacunar and undeterminate etiology), the severity of the initial neurologic symptoms on the NIHSS or on the Canadian Neurological Scale (CNS), smoking, hyperglycemia on admission to the clinic ≥ 7.5 mmol/L (≥ 135 mg%), atrial fibrillation, heart failure, previous myocardial infarction, cancer, renal failure (with baseline creatinine ≥ 400 mg/L), requiring dialysis. The predictive value of the iScore was confirmed by analyzing the data of a large group of IS patients from two registers: the Registry of the Canadian Stroke Network, the regional stroke center (n=3818) and the Registry of the Canadian Stroke Network Ontario Stroke Audit (n=4635)^[37,38].

Our prognostic model of patient survival in the one year of follow up initially has included 22 clinical and laboratory indicators. In the model we constructed, the decision on the risk of death should be taken not by summing up the scores, as in the iScore scale, but by moving along the decision tree to 7 terminal nodes containing the Kaplan Meier curves of different subgroups of patients with IS having significant differences in one year survival rates.

In our opinion, there are no fundamental differences between the iScore scale and our model. Both of these include, as independent predictors of death, the clinical subtype of IS, the severity of neurological disorders in the stroke onset, heart failure, and hyperglycemia. Blood glucose concentration was included in the iScore as a qualitative variable with a cutoff of ≥ 7.5 mmol/L. In our case, the mathematical analysis of the data allowed to determine a lower glucose level associated with poor post stroke survival under certain conditions (the presence of TACS and heart failure).

PLAN score

O'Donnell et al.^[40] performed data analysis of 9847 persons with IS, included in the Registry of the Canadian Stroke Network from 2003 to 2008. Researchers used regression coefficient based scoring method, developed from estimates generated by the multivariate model. The PLAN score includes 9 clinical indicators, each of which corresponds to a specific number of points: preadmission comorbidities, cancer, congestive heart failure, AF, level of consciousness, age, focal neurologic deficit: weakness of the leg, arm, aphasia, neglect. Depending on the final total score, a forecast is made for a 30-day and 1 year survival rate, as well as for in-hospital death or a severe functional condition for discharge.

ASTRAL

ASTRAL score (Acute Stroke Registry and Analysis of Lausanne) was initially developed to identify predictors of an unfavorable functional outcome 90 days after the stroke (MRS > 2)^[41]. This scale includes a number of clinical and laboratory parameters determined at the time of admission to the stroke department, such as the age of the patient with IS, NIHSS value, impaired consciousness, visual field defect, blood glucose level > 7.3 mmol/L (131 mg/dL) or < 3.7 mmol/L (66 mg/dL) and period > 3 hrs from IS symptom onset to hospitalization (or last proof of good health if stroke onset is unknown). It is noteworthy that the prognostic value of independent predictors included in the ASTRAL score was

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evaluated later with respect to the long-term prognosis of the unsatisfactory functional IS outcome of stroke and 5 year survival^[4]. Using data of 323 patients with acute IS, Wang et al. were compared the iScore, the PLAN Score and the ASTRAL Score, using the clinical parameters as the basis for the prognosis^[42].

All three scales showed comparable prognostic sensitivity and accuracy of the prognosis for an unfavorable functional outcome (3-6 MRS points, including lethal outcome, 6 months after the stroke).

SOAR

The stroke subtype (ischemic or hemorrhagic) the Oxfordshire Community Stroke Project classification, age, and pre-stroke MRS assessment are the basic clinical parameters of the SOAR scale. This scale allows doctors to predict in-patients death, as well as a lethal outcome within the first 7 days after stroke^[43].

The SOAR gives also the opportunity to forecast the duration of hospital stay. According to the authors of the study^[44], this clinical scale is helpful for doctors, patient's family members, and service providers.

mSOAR

English researchers attempted to modify SOAR by adding to the univariate and multivariate logical regression models an estimate of the initial severity of stroke on the NIHSS scale at the time of hospital admission^[45]. A modified SOAR (mSOAR) score would improve the prognostic accuracy of the previous scale by assessment of post stroke mortality within 90 days follow-up. The predictive value of the mSOAR score was analyzed on the data of 1012 patients with stroke from the Anglia Stroke and Heart Clinical Network data (2008 to 2011). Within 90 days 121 (12.0%) patients died. The mSOAR score indicated the risk of early death ranging from 3% to 42%. The area under the Receiver Operating Curve (ROC) measured up to 0.84 (95% confidence interval, 0.82–0.88) for a 3 month lethal outcome. SOAR and mSOAR scales were developed for ischemic and hemorrhagic types of stroke based on logistic regression models. Our model, which is a decision tree, is designed to separate the probability of a one year lethal outcome of patients with different types of cerebral infarction. Common to the three models under consideration is their construction on the basis of the clinical parameters that are always available for a neurologist who provides medical care for an acute cerebrovascular accident.

It is noteworthy that the models discussed include, as independent predictors of post-stroke mortality, the subtype of stroke according to the Oxfordshire Community Stroke Project classification and the severity of neurologic symptoms of stroke in the admission department of the clinic. The age and sex of patients with IS, of course, were originally included in our study in the survival model based on the decision tree. However, these demographic characteristics did not confirm their prognostic significance with respect to long-term survival after IS as independent predictors.

Study of CARTER AM

The investigation of AM Carter et al.^[46] allowed establishing risk factors for the death in a cohort of 545 patients with IS compared with a cohort of 330 age-matched healthy control persons. The duration of observation was more than 7 years. Hazard ratios for post-stroke mortality were established using univariate and multivariate Cox proportional hazards regression analyses. The independent predictors of the long-term lethal outcome were old age, IS subtype according to the Oxfordshire Community Stroke Project criteria, atherosclerosis of the cerebral arteries, AF, previous TIA or stroke, as well as laboratory parameters measured when entering the stroke department: albumin, creatinine, thromboglobulin and von Willebrand factor.

At the same time, in determining the risk of long-term death, the authors^[46] excluded from analysis the data of 32 IS patients who died within the first 30 days. In our opinion, this may be the main reason for the difference between the results obtained in the Carter AM et al. study and in our work. According to prospective, population-based Northern Manhattan Stroke Study^[47], lethality in the first month of stroke makes the main contribution to the cumulative risk of death in the first year of follow-up.

Therefore, in our work, we assessed the risk of all-causes death within 365 days of the post-stroke period. Initially, we did not set ourselves the goal to determine the level of albumin, thromboglobulin and Von Willebrand factor in association with post-stroke survival. We supplemented the list of clinical and demographic characteristics with routine laboratory biochemical parameters available in each case of hospitalization of a patient with a stroke. Such parameters were glucose level in the blood, urea, creatinine, sodium, potassium, total and direct bilirubin, total protein and so on. In addition, we included data from a general blood test and coagulation examinations (fibrinogen, activated partial thromboplastin time, thrombin time, international normalized ratio).

By the univariate data analysis, the blood creatinine level of patients who died was significantly higher than that of the survivor group. Nevertheless, by creating a mathematical model based on decision trees that takes into account the interaction and mutual influence of a variety of factors, creatinine level was not an independent prognostic factor for the

long-term survival of patients after IS. Statistically significant predictive value was demonstrated by laboratory parameters such as hyperglycemia ≥ 6.97 mmol/L in patients with TACS plus heart failure and urea level ≥ 11 mmol/L in patients with non-total stroke in the anterior circulation.

Limitations

The analysis of the data is based on the group of hospitalized patients; they were randomly selected. Since the study was organized and conducted at the expense of personal funds by the author of the publication, it was not possible to ensure the inclusion of each of the patients with IS by the sequential series method for 14 years. Currently, there is no national stroke register in the Republic of Belarus. A single register of patients who have suffered a stroke in the city of Minsk with a population of almost 2 million people is also not conducted for organizational and financial reasons.

Our study did not include patients with IS who received thrombolytic therapy, since their real number in real clinical practice does not yet reach the European average of 20%^[2]. Intravenous thrombolysis with alteplase has been used in selected hospitals in the Republic of Belarus since 2006.

According to the personal data of one of the authors of the article (IG), in 2015, 511 people with acute IS were admitted into the neurological department no. 1 of the Emergency Hospital of Minsk. This hospital is equipped by CT and MRI, and has an angiographic department. Thrombolysis has been performed for various reasons by only 11 (2.5%) of 511 patients.

CONCLUSION

Our research has shown the prognostic value of determining the survival rate of patients after IS, on the basis of a new mathematical method of constructing predictive models the method of decision trees. Among the previously published studies of other authors, we have not found work assessing the risk of survival of stroke patients using the biostatistical model of decision trees.

The decision tree model can be used in the practice of a neurologist, not only to stratify the risk of long term mortality in the post-stroke period. The creation of a mathematical model allows the doctor to consider the risk of death for each patient differentially, depending on the IS subtype and the presence of specific clinical characteristics. The undeniable advantage of using the decision tree method is not only the accuracy of the prediction, but also the simplicity and clarity of the obtained model, which gives an instant possibility for the doctor to obtain information about the patient survival forecast.

The mathematical apparatus of decision trees provides an opportunity for specialists, during the implementation of the main task, to calculate specific threshold values of the quantitative indicators associated with the long-term survival of patients after ischemic stroke, such as severity of the initial neurologic deficit ≥ 12 NIHSS points, blood urea level ≥ 11 mmol/L, and glucose level ≥ 6.97 mmol/L. Post hoc analysis of survival data of a prospective cohort study of 1421 patients with IS showed that the independent clinical characteristics of patients, along with the laboratory parameters determined in the admission department, are associated with a high risk of fatal outcome within one year of observation ($p < 0.001$).

The obtained results testify to the advisability of conducting further studies using the method of decision trees in determining the role of coagulation, electrocardiographic, echocardiographic and other parameters in long term stratification of the risk of death in patients undergoing IS.

AUTHOR'S CONTRIBUTION

IG: search strategy design, data extraction, reviewing all titles, abstracts and full texts, data interpretation, statistical analysis, and manuscript draft. IP: search strategy design, statistical analysis, contributing to the writing of manuscript.

CONFLICT OF INTERESTS

None stated.

In 2002–2015, the first author of the article (IG) worked at the RSPCNN 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. The computer database of the study 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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