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Predictors of atrial fibrillation in patients with ischemic stroke of undetermined etiology

Aim	To identify a complex of predictors and to create a mathematical model for prognosis of atrial fibrillation (AF) in patients with ischemic stroke of undetermined etiology.
Material and methods	The study included 981 patients with ischemic stroke. Effects of the following factors were evaluated: gender, a history of stroke, a history of thromboembolism, presence of diabetes mellitus, grade of arterial hypertension, functional class (FC) of chronic heart failure (CHF), age, data of blood biochemistry, and data of coagulogram. The prognostic model was constructed using the binary logistic regression. The value of area under the ROC curve for the proposed prognostic model was calculated.
Results	The main predictors of AF in patients with ischemic stroke of undetermined etiology were CHF FC, a history of stroke, age, gender, values of cholesterol and prothrombin index, which were included into the final prognostic model. The sensitivity of the developed model was 83.5% and the specificity was 85.5%. The area under the ROC curve corresponding to the interrelation between the prognosis of AF and the regression function value was 0.921±0.012 with 95% confidence interval: 0.898–0.944.
Conclusion	According to the results of the study, the probability of AF in patients with ischemic stroke increased with CHF progression, recurrent stroke, older age, female gender, and reduced prothrombin index and cholesterol level.

Keywords	Atrial fibrillation; stroke of undetermined etiology; cryptogenic stroke; prognostic model
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Introduction

According to the World Stroke Organization, cerebrovascular accident (CVA) has reached epidemic proportions. Stroke remains the second leading cause of death and the third leading cause of death and disability worldwide. The absolute number of stroke cases increased significantly between 1990 and 2019. The increase in the number of cases was 70%. The number of deaths of stroke increased by 43% [1, 2]. There is a trend towards an increase in disability adjusted life years (DALY), i.e., the number of years of life with disability in patients from 20 to 64 years old due to history of CVA. The highest DALY values have been reported in East Asia [3]. Despite the fact that this age group is at a lower risk of cerebral accidents than older people, they form an active working class. In their case, stroke causes immense social and economic damage to the country as a whole [4].

Between 2000–2008, the incidence of stroke in low and middle-income countries exceeded the incidence in high-income countries by 20%. More than 60% of patients with CVA are residents of low and middle-income countries [1]. According to the World Health Organization (WHO), Kazakhstan is the leading country in stroke-related mortality among 128 reporting countries in 2003 [5]. Stroke-related mortality in East Kazakhstan Region is one of the highest in Kazakhstan and amounts to 85.9 per 100 thousand people [6].

Ischemic stroke constitutes an absolute majority of all types of stroke, with a percentage of about 80% [7]. Despite the progress in the diagnostic search for the causes of this cerebrovascular circulation disorder, up to 40% of patients are diagnosed with stroke of uncertain origin [8].

Paroxysmal atrial fibrillation (AF) can cause ischemic stroke of uncertain origin in every third patient. This is due to the formation of clots in the heart chambers [9]. However, such forms of arrhythmias often remain undiagnosed due to short duration and silent nature [10].

Improved technology allows the use of various devices for long-term heart rate monitoring [11–14]. However, the largest percentage of silent AF can be detected in case of preliminary stratification of patients by risk factors [15].

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Administration of antiarrhythmic drugs and switching from antiplatelet therapy to anticoagulants taking into consideration the pathophysiology of clotting is an important therapeutic outcome of detecting AF in patients.

Objective

To identify predictors of AF and construct a mathematical model for predicting AF in patients with ischemic stroke of uncertain origin.

Material and Methods

A retrospective study was conducted in Emergency Care Hospital (Semey, Kazakhstan) from 01.01.2018 to 31.12.2018. The study included 981 patients with ischemic stroke.

Inclusion criteria: patients with history of ischemic stroke treated in the stroke management center (ICD-10 diagnosis codes: I63.1 Cerebral infarction due to embolism of precerebral arteries and I63.3 Cerebral infarction due to thrombosis of cerebral arteries).

Exclusion criteria: patients with valvular AF due to chronic rheumatic heart disease.

Ischemic stroke was diagnosed, if a patient presented with clinical manifestations such as focal and/or non-focal cerebral disorders with sudden onset [16]. All patients underwent CT scanning on a 64-slice Siemens Definition AS CT scanner or magnetic resonance imaging (MRI) of the brain on a Siemens Magnetom Essenza scanner to verify the diagnosis.

The presence of the following comorbidities was assessed: arterial hypertension (AH); chronic heart failure (CHF); diabetes mellitus (DM); and AF. AH is determined by office systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg [17].

CHF was diagnosed in the presence of characteristic symptoms and signs of heart failure: echocardiographic evidence of systolic and/or diastolic dysfunction; and laboratory abnormalities (elevated levels of natriuretic peptide) [18].

DM type 2 can be verified by the WHO criteria, according to which normal fasting blood glucose concentration is ≥7.0 mmol/L (126 mg/dL) [19].

Atrial fibrillation was defined as arrhythmia confirmed by electrocardiogram and demonstrating a typical pattern of AF: irregular RR intervals and a lack of clear P-waves. According to the generally accepted rule, an episode registered by a standard 12-lead ECG or a single-channel ECG of at least 30 seconds long is considered significant for diagnosis [20]. Standard ECG was recorded using a 12-lead Cardipia 400H Trismed device (South Korea). ECG was recorded at least 3 times during hospital stay (an average of 7–10 days): at admission; on the third day of hospital stay; and before discharge. Additional ECG records were made if indicated.

The presence or absence of a history of stroke was also established. Blood chemistry analysis was performed. Urea, creatinine, glucose, cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL–C), low-density lipoprotein cholesterol (LDL–C), potassium, and sodium were estimated using a biochemistry turbidimetry analyzer BioSystems BA400 (Spain). Peripheral venous blood was collected, in order to determine activated partial thromboplastin time (aPTT), prothrombin time, prothrombin index, international normalized ratio (INR), and fibrinogen. The analysis was performed using an automatic coagulometer Sysmex CA-620 (Japan).

All patients were managed by a multidisciplinary team consisting of a neurologist, a cardiologist, a rehabilitologist, a nurse, a physical therapy instructor, a speech therapist, a psychologist, and other specialists when necessary.

Statistical processing

In order to identify factors affecting the probability of AF, unadjusted odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for the following factors: binary categorical factors (sex, history of stroke, history of thromboembolism, presence of DM); ordinal categorical factors (grade of AH, CHF FC (NYHA)); quantitative factors (age, blood chemistry (urea, creatinine, glucose, cholesterol, TG, HDL–C, LDL–C, potassium, sodium); and coagulation indicators (aPTT, prothrombin time, prothrombin index, INR, fibrinogen). Factors with the significance of $p<0.05$ were used for further analysis. Binary logistic regression was used to develop a prediction model. Stepwise multivariate analysis was used in the logistic regression model, in order to construct the prediction model. The ROC curve analysis was conducted to evaluate the area under the characteristic curve corresponding to the correlation between the prognosis of AF and the value of the regression function. The significance threshold for the statistical hypotheses was equal to 0.05. Nominal data was presented as the absolute number (n) and percentages. The quantitative data was expressed as the median and interquartile range (Me (Q1; Q3)), since they were non-normally distributed. The groups were compared by categorical criteria using Pearson's chi-squared test and Fisher's exact test when the expected value was less than 5 in at least one cell of the contingency table. The Mann-Whitney test was used to compare the groups by quantitative indicators. Statistical analysis was conducted in SPSS v.20.

The study was approved by the ethics committee of Semey State Medical University (Minutes #10 dated 30.05.2019).

Results

The data of 981 patients with the primary diagnosis of ischemic stroke was analyzed in this study. The subjects' age

was 66 [59; 75], and more than half of the patients (52.7%) were male. All patients had AH of any grade. Clinical and laboratory characteristics of patients are provided in Table 1.

Thus, the intergroup comparison detected statistically significant differences in sex, age, history of stroke, CHF FC, the levels of urea, total cholesterol, TG, LDL–C, and coagulation parameters. The final prediction model includes six factors: CFH FC (NYHA), history of stroke, age, sex, cholesterol, and prothrombin index.

The assessment of the dependence of the probability of AF on numerous factors using the binary logistic regression allowed the following prediction model (1) to be constructed:

$$P=1/(1+e^{-z})$$
$$z=-3,51+1,709*X_{CHF\ FC}+0,526*X_{rep}+0,053*X_{age}-0,016*X_{PI}-0,382*X_{chol}-0,888*X_{sex},$$

Where P is the probability of the presence of AF, $X_{CHF\ FC}$ is chronic heart failure functional class according to the NYHA classification (0 – no CHF, 1 – FC I, 2 – FC II, 3 – FC III, 4 – FC IV), X_{rep} is a history of stroke (0 – absence, 1 – presence), X_{age} is age (years), X_{PI} is prothrombin index (%), XTC is total cholesterol (mmol/L), and X_{sex} is sex (0 – female, 1 – male). The resulting prediction model was statistically significant (p=0.001). The Nagelkerke coefficient of determination R2

Table 1. Clinical and laboratory characteristics of patients with and without atrial fibrillation

Factor	All patients (n=981)	Patients without AF (n=828)	Patients with AF (n=153)	p
Male, n (%)	517 (52,7)	462 (55,8)	55 (35,9)	<0,001
Age, years, Me (Q1; Q3)	66 (59;75)	65 (57,5;72,0)	74 (66;81)	<0,001
History of stroke, n (%)	254 (25,9)	199 (24,0)	55 (35,9)	0,002
History of PE, n (%)	4 (0,4)	2 (0,2)	2 (1,3)	0,057
AH, n (%)	981 (100)	–	–	–
AH grade 1, n (%)	15 (1,5)	13 (1,6)	2 (1,3)	0,401
AH grade 2, n (%)	60 (6,1)	47 (5,7)	13 (8,5)	
AH grade 3, n (%)	906 (92,4)	768 (92,8)	138 (90,2)	
CHF, n (%)	275 (28,0)	146 (17,6)	129 (84,3)	<0,001
CHF FC I, n (%)	81 (8,3)	58 (7,0)	23 (15,0)	<0,001
CHF FC II, n (%)	170 (17,3)	85 (10,3)	85 (55,6)	
CHF FC III, n (%)	21 (2,1)	3 (0,4)	18 (11,8)	
CHF FC IV, n (%)	3 (0,3)	0	3 (2,0)	
DM, n (%)	226 (23,0)	192 (23,2)	34 (22,2)	0,794
Urea, mmol/L, Me (Q1; Q3)	5,4 (4,3;7,0)	5,4 (4,2;6,8)	6,4 (4,8;8,5)	<0,001
Creatinine, mmol/L, Me (Q1; Q3)	79 (64;99)	79 (64;98)	80 (66;104)	0,232
Glucose, mmol/L, Me (Q1; Q3)	6,6 (5,8;8,6)	6,5 (5,7;8,4)	7,3 (6,2;9,0)	0,001
Cholesterol, mmol/L, Me (Q1; Q3)	5,3 (4,4;6,1)	5,3 (4,5;6,1)	4,9 (3,9;5,7)	0,001
TG, mmol/L, Me (Q1; Q3)	1,2 (0,86;1,87)	1,22 (0,88;1,94)	1,04 (0,76;1,47)	0,001
HDL-C, mmol/L, Me (Q1; Q3)	1,24 (1,0;1,46)	1,23 (1,0;1,46)	1,25 (1,01;1,45)	0,643
LDL-C, mmol/L, Me (Q1; Q3)	2,72 (2,1;3,31)	2,73 (2,11;3,36)	2,65 (1,92;3,03)	0,019
Potassium, mmol/L, Me (Q1; Q3)	4,0 (3,7;4,3)	4,0 (3,7;4,3)	3,9 (3,7;4,3)	0,336
Sodium, mmol/L, Me (Q1; Q3)	139 (137;141)	139 (137;141)	139 (136;141)	0,247
aPTT, sec, Me [Q1; Q3]	32,3 (28,9;35,9)	32,1 (28,8;35,7)	32,8 (29,8;37,3)	0,064
PT, sec, Me (Q1; Q3)	16 (14,3;18,5)	15,9 (14,2;18,3)	16,9 (15,0;20,1)	<0,001
PI, %, Me (Q1; Q3)	88,1 (76,1;98,2)	89,1 (76,9;99,0)	84,2 (69,3;93,5)	<0,001
INR, units Me (Q1; Q3)	1,16 (1,02;1,36)	1,15 (1,02;1,34)	1,24 (1,07;1,51)	<0,001
Fibrinogen, g/L, Me (Q1; Q3)	4000 (3300;4800)	4000 (3300;4800)	4050 (3400;4800)	0,759

The data is expressed as the median and interquartile range (Me [Q1; Q3]) or a number of patients (n (%)); PE, pulmonary embolism; AH, arterial hypertension; CHF, chronic heart failure; CHF FC, functional class of chronic heart failure; DM, diabetes mellitus; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; aPTT, activated partial thromboplastin time; PT, prothrombin time; PI, prothrombin index; INR, international normalized ratio.

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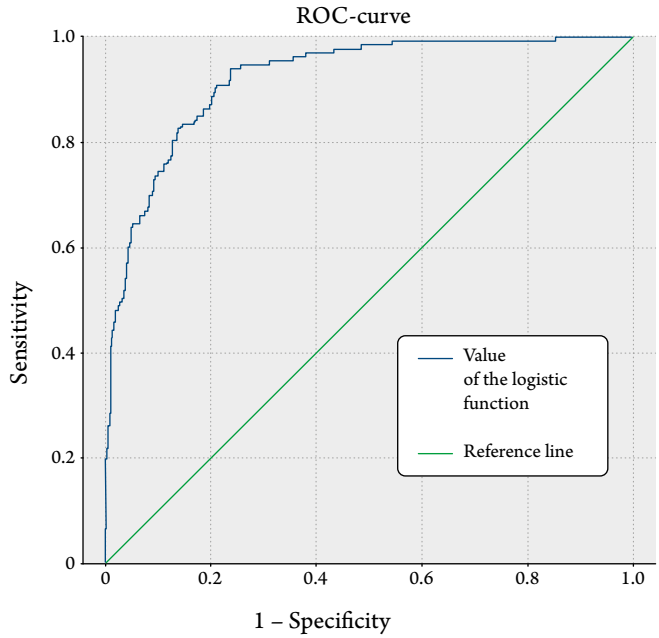
was 53.8%. Given the regression coefficient, higher CHF FC, a history of stroke, and older age were associated with an increased risk of AF. Factors such as prothrombin index, total cholesterol levels, and male sex were inversely related to the risk of AF.

The estimated odds ratios for AF and statistical significance for each of the factors are presented in Table 2.

The ROC curve analysis showed that the logistic function P at the cut-off point, with the highest sensitivity and specificity, was 0.133. Function values equal to or higher than this value corresponded to the prediction of the presence of AF. The sensitivity and specificity of the method were 83.5% and 85.5%, respectively. The positive predictive value (PPV) of the model was 49.3% (111 correctly predicted cases of AF of 225 predicted cases of AF), while the negative predictive value (NPV) of the model was 96.8% (672 correctly predicted cases of the absence of AF of 694 predicted cases of the absence of AF). The diagnostic efficacy of the model was 85.2%. Patients with insufficient data for the analysis were excluded from the calculations (n=62).

The area under the ROC curve, corresponding to the correlation between AF and the regression function, was 0.921 ± 0.012 with 95% CI: 0.898–0.944 (Figure 1).

Figure 1. ROC curve of the dependence of AF probability on the value of the logistic function (1)



Discussion

The retrospective analysis of clinical and laboratory data of 981 patients with ischemic stroke allowed the prediction model of the risk of AF to be developed.

Several papers were found during the search for data on existing predictors of atrial fibrillation However, there was no data from patients with ischemic stroke.

The 70+ age was a powerful predictor of AF in the study which included patients with cryptogenic stroke and implanted cardiac monitors [21]. In the population-based prospective cohort study FINRISK conducted in Finland every 5 years since 1972, researchers have shown the predictive role of age and increased levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) in the development of AF. In this study, elevated levels of NT-proBNP, which is an indicator of the presence of CHF, increased the risk of AF 4.77-fold, while age increased the risk 16.7-fold [22]. In the next study, the role of NT-proBNP in predicting AF in patients with AH was demonstrated, as well as the roles of other biomarkers such as P-wave duration, left atrial dimensions, and left ventricular hypertrophy [23].

Female sex was associated in our study with the increased risk of AF. However, there is no universal statement on the sex of patients with AF in world literature. Westerman et al. [24] showed that only one predictor intrinsic to the female sex, such as pregnancy parity, was associated with

Table 2. Odds ratio and statistical significance of the factors during selection and within the prediction model

Factor	Univariate analysis; 95% CI	p	Multivariate analysis; 95% CI	p
Male	0,45; 0,31–0,64	<0,001	0,41; 0,24–0,71	0,001
Recurrent stroke	1,77; 1,23–2,56	0,003	1,69; 0,98–2,93	0,06
Age, years	1,07; 1,06–1,09	<0,001	1,05; 1,03–1,08	<0,001
CHF FC (NYHA), %	5,18; 4,14–6,49	<0,001	5,52; 4,2–7,26	<0,001
Urea, mmol/L	1,05; 1,01–1,09	0,028	–	–
Cholesterol, mmol/L	0,77; 0,66–0,89	<0,001	0,68; 0,56–0,84	<0,001
TG, mmol/L	0,66; 0,52–0,85	0,001	–	–
LDL-C, mmol/L	0,74; 0,59–0,91	0,005	–	–
Prothrombin index, %	0,98; 0,97–0,99	<0,001	0,99; 0,97–0,99	0,02

CHF FC, functional class of chronic heart failure according to the New York Heart Association Classification; TG, triglycerides; LDL, low-density lipoprotein cholesterol; CI, confidence interval.

the increased risk of AF. Wu et al. successfully used the traditional stroke risk scores of patients with pre-existing AF (CHADS2 and CHA2DS2VASc) to predict the new onset of AF. These scores include factors such as cardiac failure, AH, DM, history of stroke, age, and female sex. These data are mainly consistent with our findings [25].

The decrease in prothrombin index was associated in our study with the increased risk of AF. In other words, hypocoagulation predicted the presence of AF. This contradicts existing data [26] and is of major concern. Further research is required to investigate this relationship in a larger number of patients.

Triglyceride levels are directly related to the risk of AF in this model, and total cholesterol is inversely related to the risk of AF in our model. Analysis of the literature revealed a greater heterogeneity of data on this issue. Certain papers provide evidence of a direct relation of lipid profile with AF and inverse relation of total cholesterol and LDL-C to AF, or the absence of any relation to AF [27–30]. Thus, relevant large, randomized studies are required to clarify the presence and direction of the relation of AF with blood lipid profile in patients with ischemic stroke.

Our model is a cost-effective, versatile tool for identifying the risk of AF, since all factors included in the model are assessed within the standard examination of patients with ischemic stroke. The model is implemented by means of a convenient and simple Excel calculator. However, despite the benefits, this study was limited mainly by the retrospective design.

Conclusion

Detecting atrial fibrillation in patients with ischemic stroke plays a significant role in the prevention of recurrent cerebrovascular accidents with frequent unfavorable outcomes. The issue of selecting patients for long-term heart rate monitoring after ischemic stroke remains relatively understudied. Patients can be selected based on the presence of AF predictors in patients with ischemic stroke of uncertain origin, such as functional class of chronic heart failure, history of stroke, age, sex, total cholesterol, and prothrombin index.

No conflict of interest is reported.

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