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FACTORS ASSOCIATED WITH DEATH IN PATIENTS WITH ATRIAL FIBRILLATION

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The aim of the study was to analyze the factors influencing the mortality prognosis for atrial fibrillation (AF) among the adult population of the Kuzbass region.

Methods. 576 patients with AF were included in the study. During a three-year follow-up death was recorded in 54 (9.4%) patients. An analysis of factor s associated with mortality was carried out. Multiple logistic regression, Quasi-Newton measurement method, ROC analysis were used, the critical significance level was 0.05.

Results. According to the conducted study data, a statistically significant increase in the chance of a fatal outcome was revealed in individuals with a history stroke (odds ratio (OR) 2.47 [1.06-5.75]), with a body mass index (BMI) equal to or higher than 32.4±6.8 kg/m^2 (OR 1.07 [1.01-1.14]), with an increase in the ventricular rate (VR) of AF equal to or higher than 84.2±15.4 beats per minute (OR 1.02 [1.00-1.04]) and the risk of thromboembolic complications according to the CHA_2DS_2VASc scale equal to or higher than 4.3±2.3 points (OR 1.12 [1.04-1.21]). A decrease in creatinine clearance (CC) according to Cockcroft-Gault was associated with a high risk of adverse outcome (OR 0.99 [0.98-1.00]). At the same time, the fact of irregular intake of anticoagulant therapy was associated with a high probability of death, but did not depend on which anticoagulant was prescribed.

Conclusions. According to the results of a complex analysis it was revealed that patients with AF who have a history of stroke, high values of BMI, ventricular rate AF, CHA_2DS_2VASc were more often having an unfavorable outcome.

Key words: predictors; fatal prognosis; atrial fibrillation; stroke; body mass index

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Atrial fibrillation (AF) is the most common arrhythmia, affecting 2.04% of the population in the European part of the Russian Federation**.** While AF is observed in only 0.1% of adults aged 20–29 years, its prevalence increases to 9.6% among individuals aged 80–89 years [1]. The medical literature does not provide a definitive consensus on whether the increased risk of mortality is associated with the severity of the tachyarrhythmia itself, the underlying and/or concomitant diseases, or irregular medication intake, which has been shown to increase the risk of adverse outcomes by 1.5–2 times [2, 3]. The causes of death in patients with AF include malignancies (23.1%), infectious complications (17.3%), congestive heart failure (14.5%), with stroke accounting for only 6.5% of cases [4]. Identifying predictors of mortality and developing strategies for its prevention are therefore of significant importance. This underscores the relevance of this study, which aimed to analyse the factors influencing fatal outcomes in patients with AF among the adult population of the Kuzbass region.

METHODS

A cohort of patients diagnosed with AF (n=576) was randomly selected for this study. These patients, all aged over 18 years, were managed on an outpatient basis at the polyclinic of the Research Institute of Complex Issues of Cardiovascular Diseases between 2019 and 2022. None of the patients met the criteria for interventional treatment of arrhythmias. During a three-year prospective follow-up period, mortality was documented in 54 patients (9.4%) based on statistical records from the ARENA Medical Information System. The recorded causes of death included myocardial infarction in 26 patients, acute cerebrovascular accident (stroke) in 16 patients, and acute heart failure in 12 patients. This study was conducted in compliance with the principles outlined in the Helsinki Declaration of the World Medical Association regarding “Ethical Principles for Medical Research Involving Human Subjects”.

Statistical Analysis

For the prospective analysis of quantitative indicators, the mean value (M) and standard deviation (σ) were calculated. Differences in quantitative indicators were assessed using the Mann-Whitney test for normally distributed variables, determined by the Kolmogorov-Smirnov test.

Multiple logistic regression and the Quasi-Newton estimation method were employed to analyse factors associated with mortality in patients with AF. If logistic regression

demonstrated significance, the baseline performance parameters (sensitivity and specificity, at a threshold value of 0.5), as well as the B coefficient, standard error, p-value, odds ratio (OR) with a 95% confidence interval (CI), and Wald chi-square were calculated separately for the constant and each predictor. A mathematical formula was derived using the B coefficients of predictors and the constant to determine the probability of an adverse outcome (death) for a patient.Statistical analysis was performed using R programming language (v.4.0.3), Python (v.3.8.3), and Statistica 6.0 software.

The quality of the resulting model (classifier) was evaluated using the following indicators: sensitivity (the number of deceased patients correctly classified divided by the total number of deceased patients), specificity (the number of surviving patients correctly classified divided by the total number of surviving patients), and AUC (Area Under the Curve). AUC served as an indicator of the model's effectiveness based on ROC analysis. For AUC values, the standard error and 95% CI boundaries were determined. The critical significance level was set at 0.05.

Table 1.

Characteristics of the studied patients with atrial fibrillation (n=576)

Indicators	Deceased (n=54)	Survivors (n=522)	P-level
Age, years	69.7±8.8	67.4±8.7	0.0652
Male, n (%)	29 (53.7%)	211 (40.4%)	0.0595
Female, n (%)	25 (46.3%)	311 (59.6%)	0.0595
Body Mass Index, kg/m^2	32.4±6.8	30.3±6.0	0.0160
Heart Rate during AF, bpm	84.2±15.4	79.2±15.7	0.0260
Systolic BP, mmHg	130±19.2	128±17.5	0.4286
Diastolic BP, mmHg	81±13.4	80±12.4	0.5758
Hospitalisations, n (%)	32 (59.3%)	265 (50.7%)	0.2345
Paroxysmal AF, n (%)	20 (37.0%)	259 (49.6%)	0.0783
Persistent AF, n (%)	21 (38.9%)	144 (27.6%)	0.0803
Permanent AF, n (%)	13 (24.1%)	119 (22.8%)	0.8317
CAD, n (%)	31 (57.4%)	235 (45.0%)	0.0822
Myocardial Infarction, n (%)	10 (18.5%)	52 (9.9%)	0.0534
ACVA, n (%)	10 (18.5%)	37 (7.1%)	0.0350
Hypertension, n (%)	50 (92.6%)	484 (92.7%)	0.9726
Morisky-Green Scale, points	2.6±1.7	2.5±1.4	0.6250
CC (Cockcroft-Gault), mL/min	77.0±25.6	83.4±28.2	0.1100
CHA_2DS_2VASc Score, points	4.3±2.3	3.5±1.9	0.0041
2MACE Score, points	2.1±1.2	1.8±1.1	0.0591
Warfarin, n (%)	21 (38.9%)	176 (33.7%)	0.5442
Rivaroxaban, n (%)	14 (25.9%)	153 (29.3%)	0.6018
Apixaban, n (%)	13 (24.1%)	120 (23.0%)	0.8570
Dabigatran, n (%)	6 (11.1%)	73 (14.0%)	0.5590

Note: Hereinafter, AF - Atrial fibrillation; BP - Blood pressure; CAD - Coronary artery disease; ACVA - Acute cerebrovascular accident (stroke); CC - Creatinine clearance.

RESULTS

A comparative analysis of gender and clinical-anamnestic data between deceased and surviving patients AF was conducted, as presented in Table 1. It was found that patients with fatal outcomes were characterised by statistically significantly higher values of body mass index (BMI), ventricular rate (VR) during AF, more frequent occurrences of acute cerebrovascular accidents (stroke), and higher CHA_2DS_2VASc scores.

Clinical-anamnestic data were evaluated at the inclusion stage of the study to identify factors associated with mortality in patients with AF (Table 2). These factors included: gender, age (years), BMI (kg/m^2), VR (beats per minute), systolic and diastolic blood pressure (mmHg), history of hospitalisation, type of AF (paroxysmal, per-

Table 2.

Predictors of fatal outcomes in patients with atrial fibrillation

Indicator	Coefficient B	SE	p-level	OR	CI-	CI+	Wald Chi-Square
Gender	0.67	0.36	0.059	1.96	0.97	3.95	3.58
ACVA	0.90	0.43	0.035	2.47	1.06	5.75	4.44
CAD (MI)	0.72	0.42	0.08	2.05	0.91	4.65	2.98
Body Mass Index	0.07	0.03	0.016	1.07	1.01	1.14	5.86
Ventricular Rate	0.02	0.009	0.026	1.02	1.00	1.04	4.97
Creatinine Cleara	-0.01	0.007	0.11	0.99	0.98	1.00	2.52
CHA_2DS_2VASc Score	0.11	0.04	0.004	1.12	1.04	1.21	8.22
2MACE Score	0.22	0.12	0.059	1.24	0.99	1.56	3.59
Constant	-6.76	1.24	<0.0001	0.001	0.0001	0.013	29.62

Note: Hereinafter, B coefficient - Regression coefficient; SE - Standard error; OR - Odds ratio; CI- and CI+ - Lower and upper bounds of the 95% confidence interval for the odds ratio; MI - Acute Myocardial Infarction.

sistent, permanent), presence of coronary artery disease (CAD), cerebrovascular accident (stroke), hypertension (HTN), adherence to treatment assessed by the Morisky-Green questionnaire (points), creatinine clearance (CC) based on the Cockcroft-Gault formula (mL/min), CHA_2DS_2VASc score (points), and 2MACE score (points). Additionally, the impact of anticoagulant use on the prognosis of AF progression was also assessed.

The overall characteristics of the constructed model demonstrated its effectiveness. Pearson's Chi-Square value was 42.1, with a p-value of 0.0001, indicating statistical significance. Regression coefficients were utilised to develop a classification model for predicting patient outcomes based on the following formula:

$$Y1 = EXP(Z1) / (1 + EXP(Z1)) \quad (1)$$

$$Z1 = -6{,}76 + (X1 \times 0{,}67) + (X2 \times 0{,}90) + (X3 \times 0{,}72) + (X4 \times 0{,}07) + (X5 \times 0{,}02) + (X6 \times -0{,}01) + (X7 \times 0{,}11) + (X8 \times 0{,}22),$$

where: Y_1: The probability of a fatal outcome for a patient, ranging from 0 to 1. If the calculated value is less than 0.5, the model predicts patient survival; if the value is 0.5 or higher, the model predicts a fatal outcome; X_1: Gender (0 = female, 1 = male); X_2: History of cerebrovascular accident (stroke) (0 = no, 1 = yes); X_3: Presence of coronary artery disease (0 = no, 1 = yes); X_4: Body mass index (BMI, kg/m²); X_5: Ventricular rate (VR, beats per minute); X_6: Creatinine clearance (CC, mL/min) calculated by the Cockcroft-Gault formula; X_7: CHA2DS2VASc score (points); X_8: 2MACE score (points).

According to the analysis, patients with AF who had a history of cerebrovascular accidents (strokes), a BMI of ≥32.4±6.8 kg/m², a ventricular rate of ≥84.2±15.4 bpm during AF, or a CHA_2DS_2VASc score of ≥4.3±2.3 points were statistically significantly more likely to experience mortality (Fig. 1 and 2).

The area under the ROC curve AUC was 0.76 [0.70–0.82], indicating a good-quality classifier. Through the ROC analysis, an optimal cut-off threshold for the model was determined, with balanced levels of specificity (0.71) and sensitivity (0.70), reflecting good classification capability for predicting patient outcomes.

The study identified a statistically significant increase in the likelihood of adverse outcomes in individuals with a history of stroke (OR 2.47 [1.06-5.75]). As BMI (OR 1.07 [1.01-1.14]), ventricular rate during AF (OR 1.02 [1.00-1.04]), and CHA_2DS_2VASc score (OR 1.12 [1.04-1.21]) increased, the probability of a fatal outcome also rose.

Additionally, a non-significant direct association was observed between the dependent variable and the presence of coronary artery disease (OR 2.05 [0.91-4.65], p = 0.08), as well as the 2MACE score (OR 1.24 [0.99-1.56], p = 0.059). There was also a tendency towards increased mortality risk in male patients (OR 1.96 [0.97-3.95], p = 0.059).

Furthermore, the Creatinine Clearance by Cockcroft-Gault variable showed a negative association with adverse AF outcomes (OR 0.99 [0.98-1.00]). However, no statistically significant relationship was found between the type of prescribed oral anticoagulant and mortality.

DISCUSSION

Thus, in patients with AF and a history of cerebrovascular accidents (strokes), higher BMI values, increased ventricular rate (VR) during AF, and elevated CHA_2DS_2VASc scores were associated with higher mortality rates. Conversely, the presence of CAD and male gender were associated with a lower likelihood of adverse outcomes in patients with AF.

Numerous international and Russian studies have examined risk factors related to the likelihood of developing ischaemic stroke and other thromboembolic complications [5]. However, only a limited number of studies have focused on predictors of mortality. An analysis of the REK-VASA-AF registry (Kursk) identified factors associated with adverse outcomes through multivariate analysis, such as age, VR of 90 bpm or more, and a history of myocardial infarction (MI) [6].

In the AMADEUS study, absolute rates of stroke, systemic embolism, cardiovascular mortality, or any clin-

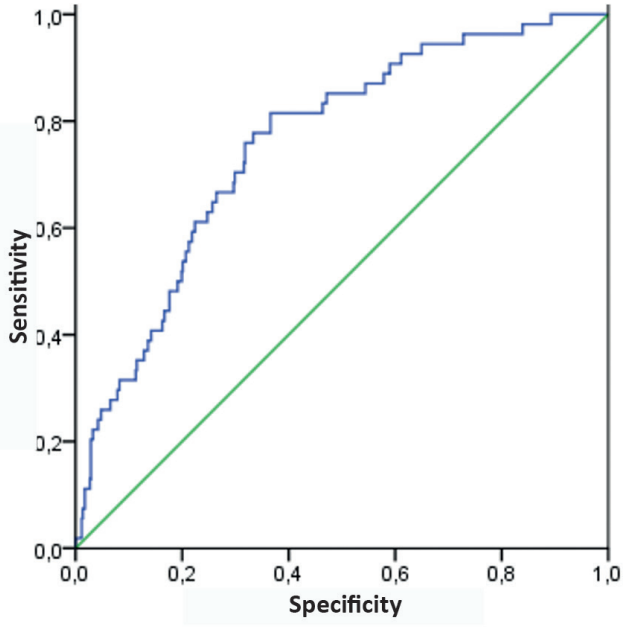

Figure 1. ROC Curve for Predicting Outcomes in Patients with Atrial Fibrillation.

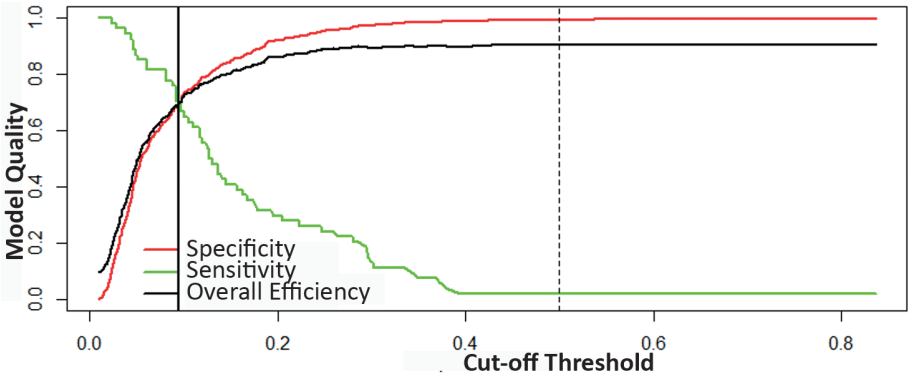

Figure 2. Dependence of the Model's Key Characteristics on the Cut-off Threshold Value.

ically significant bleeding were higher in patients aged over 75 years [7]. According to M.V.Solovieva's research [8], no specific oral anticoagulant significantly influenced mortality outcomes; however, disruptions in anticoagulant therapy regimens or discontinuation of medication were significantly associated with worse long-term outcomes, increasing the risks of composite endpoints (recurrent MI + stroke + cardiovascular mortality).

The Italian MATISS project found that VR was an independent predictor of cardiovascular and overall mortality [9]. In contrast, N.G.Vinogradova's study [10] on mortality predictors in patients with AF combined with chronic heart failure (CHF) demonstrated that tachycardia was not an independent predictor of death; instead, a higher functional class of CHF increased the mortality risk.

According to S.Wu et al. [11], in patients with AF aged 65–75 years and older, the risk of death was significantly lower in those with overweight or obesity compared to patients younger than 65 years, in whom increasing BMI was associated with higher mortality risk.

In O.P.Mamaeva's study [12], risk factors for cardiovascular mortality were evaluated in patients with persistent AF who were not on anticoagulants. Irregular anticoagulant use and failure to achieve the target INR range were associated with a high risk of thrombotic and haemorrhagic complications. The primary risk factors for mortality were tachycardia and a history of stroke, which aligns with the findings of our study.

CONCLUSION

It was found that in patients with AF, mortality occurred more frequently in those with a history of stroke, BMI of 32.4±6.8 kg/m², VR during AF of 84.2±15.4 bpm, and CHA_2DS_2VASc scores ≥4.3±2.3. It can be assumed that knowledge of these identified predictors of mortality will facilitate the development of a comprehensive set of measures aimed at preventing adverse outcomes. The correction of modifiable risk factors and adherence to prescribed therapy could help prevent severe cardiovascular complications, improve quality of life, preserve work capacity, and enhance longevity in patients with AF.

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