

Predictive markers for new-onset atrial fibrillation in patients with non-ST-elevation acute coronary syndrome

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The aim of the study is to identify markers associated with the occurrence of new-onset atrial fibrillation (AF) in a group of patients with non-ST-elevation acute coronary syndrome (NSTEMI-ACS).

Methods. A total of 769 patients with NSTEMI-ACS participated in the observational case-control study while undergoing inpatient treatment at SSMU clinics from January 1, 2019, to January 1, 2020. The results of clinical, standard laboratory, and instrumental diagnostic methods were assessed.

Results. Patients with AF were older [73.5 [66.0; 80.0] years vs. 66.0 [59.0; 73.0] years, $p < 0.001$], had a higher incidence of prior stroke [20 [21.3%] vs. 67 [9.9%] patients, $p = 0.001$], and chronic kidney disease (CKD) [79 [84.0%] vs. 445 [65.9%] patients, $p < 0.001$]. They also exhibited a higher heart rate (HR) [86.0 [74.0; 120.0] bpm vs. 76.0 [70.0; 86.0] bpm, $p < 0.001$] and GRACE score

[151.5 [143.0; 161.0] vs. 144.0 [134.0; 153.0], $p < 0.001$], but a lower SYNTAX score [10.0 [4.0; 41.0] vs. 40.0 [24.0; 55.0], $p = 0.029$]. Patients with AF also had higher levels of creatinine [94.0 [80.0; 113.0] $\mu\text{mol/L}$ vs. 86.0 [72.0; 103.0] $\mu\text{mol/L}$, $p = 0.001$] and glucose [8.0 [6.0; 11.0] mmol/L vs. 6.0 [6.0; 8.0] mmol/L , $p = 0.001$], along with lower estimated glomerular filtration rate (eGFR, CKD-EPI) [58.0 [46.0; 73.0] ml/min/1.73 m^2 vs. 73.0 [56.0; 87.0] ml/min/1.73 m^2 , $p < 0.001$], total cholesterol [4.70 [3.45; 5.11] mmol/L vs. 5.00 [4.29; 6.00] mmol/L , $p = 0.005$], and low-density lipoprotein cholesterol [2.74 [2.00; 3.30] mmol/L vs. 3.04 [2.45; 3.79] mmol/L , $p = 0.023$].

According to the echocardiographic findings, no statistically significant differences were identified. Multivariate regression analysis revealed that age [odds ratio [OR] 1.057; 95% confidence interval [CI] 1.010–1.105, $p = 0.016$] and HR [OR 1.057; 95% CI 1.036–1.078, $p < 0.001$] were di-

rectly associated with the occurrence of AF. The area under the ROC curve for the risk stratification of AF prognosis based on logistic regression values was 0.687 (0.028) with a 95% CI of 0.631–0.742 ($p < 0.001$).

Conclusion. This study demonstrates that patients with AF were older, more likely to have comorbid conditions (stroke, CKD), higher HR, higher GRACE score, lower SYNTAX score, and more pronounced changes in laboratory parameters (lower eGFR, higher lipid spectrum concentrations, and glucose levels). The analysis identified age and HR as predictors of new-onset AF in patients with NSTEMI-ACS.

Keywords: atrial fibrillation, acute coronary syndrome, myocardial infarction, chronic kidney disease, risk factors.

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Introduction

New-onset atrial fibrillation (AF) often complicates the course of acute coronary syndrome (ACS), leading to unfavorable short-term and long-term outcomes. The prevalence of AF in patients hospitalized for ACS varies between 2% and 37%. Several factors influencing prognosis are mentioned in the literature, but they remain a topic of discussion [1, 2]. A critical aspect is the management of this patient category, as AF is associated with worsening of the underlying condition, an increased risk of thromboembolic complications, the occurrence and decompensation of heart failure. The presence of comorbid conditions acts as an additional factor determining the poor prognosis of patients with AF in the context of ACS development [3].

The aim of the study is to identify markers associated with the occurrence of new-onset AF in a group of patients with non-ST-elevation acute coronary syndrome (NSTEMI-ACS).

Methods

An observational “case-control” study included 769 patients with NSTEMI-ACS who were hospitalized in the SSMU clinics from 01.01.2019 to 01.01.2020. The diagnosis of NSTEMI-ACS was established based on current guidelines [4].

Inclusion criteria: All patients signed informed consent to participate in the trial. The time from the onset of NSTEMI-ACS to hospitalization was 2.0 (1.0; 3.0) hours: 38% of patients were admitted within 2 hours, 36% within 1 hour, 23% within 3 hours, and 3% more than 3 hours after the onset.

Exclusion criteria: ACS with ST-segment elevation, other cardiovascular diseases (pericarditis, myo-

carditis, cardiomyopathies, pulmonary embolism), decompensated comorbid conditions (liver, kidney, or blood diseases, diabetes mellitus, malignant neoplasms). The study protocol was approved by the SSMU Ethics Committee.

Two groups were identified: the group with AF (94 patients, 45 (47.9%) men, median age 73.5 (66.0; 80.0) years) and the group without AF (675 patients, 367 (54.4%) men, median age 66.0 (59.0; 73.0) years). The results of clinical, standard laboratory, and instrumental diagnostic methods were assessed.

Statistical analysis

Data analysis was performed using the SPSS software package, version 26 (USA). Non-parametric statistical methods were applied to process the results, as the distribution of quantitative data did not follow a normal distribution (presented as the median (Me) with the 25th and 75th percentiles). Qualitative parameters were expressed in absolute numbers and percentages (%).

For the analysis of independent samples, non-parametric statistical methods such as the Mann-Whitney U-test were used. Differences in qualitative variables were assessed using contingency tables: if the number of observations in any cell of the table was 10 or more, the chi-square test was applied; if the number of observations ranged from 5 to 9, Yates' continuity correction was used; and if the number of observations was <5, Fisher's exact test was applied.

To calculate sensitivity, specificity, predictive value, and diagnostic significance of parameters, ROC analysis was performed. Binary logistic regression was used to calculate the odds ratio (OR).

Differences were considered statistically significant at $p < 0.05$.

Results

During the study, a detailed analysis of clinical markers, laboratory parameters, and echocardiographic findings was conducted. The results of the assessment of pharmacological therapy showed that the prescription of antiplatelet therapy (acetylsalicylic acid, P2Y12 receptor blockers), anticoagulants, HMG-CoA reductase inhibitors, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists, beta-blockers, calcium antagonists, and nitrates were comparable between the groups.

In some cases, AF was spontaneously resolved (in 48 (51.1%) patients) within 5–30 minutes. For symptomatic patients, administration of class III antiarrhythmic drugs (amiodarone) was required (in 31 (33.0%) patients). In other cases, due to the absence of clinical symptoms associated with AF, ongoing baseline therapy contributed to the resolution of arrhythmia.

The clinical characteristics of the patients are presented in Table 1.

SYNTAX score calculations were performed in 90 (11.7%) patients due to multivessel coronary artery disease. As shown in the table, statistically significant differences were identified in terms of age, history of stroke, chronic kidney disease (CKD), heart rate (HR), GRACE risk score, and SYNTAX score. Patients with AF were older, had a higher prevalence of prior stroke, CKD, and elevated HR (evaluated in the AF group outside the arrhythmia episode), as well as higher GRACE scores but lower SYNTAX scores.

Echocardiographic studies revealed changes in the following localizations (areas of hypokinesia): the anterior wall in 163 (21.2%) patients, the posterior wall in 174 (22.6%), the lateral wall in 103 (13.4%), the anterolateral wall in 82 (10.7%), the posterolateral wall in 120 (15.6%), and unspecified localization in 40 (5.2%) patients.

Coronary angiography was performed in 265 (34.5%) patients. The findings showed atherosclerotic involvement in the following coronary arteries: the left anterior descending artery in 261 (33.9%), the circumflex artery in 139 (18.1%), the right coronary artery in 160 (20.8%), the intermediate artery in 6 (0.8%), the diagonal artery in 17 (2.2%), the obtuse marginal branch in 22 (2.9%), and the posterior interventricular artery in 8 (1.0%) patients.

Table 1. The clinical characteristics of the patients

Parameter	Absence of AF (n=675)	Presence of AF (n=94)	P
Age, years	66.0(59.0;73.0)	73.5(66.0;80.0)	<0.001
Sex (m/f), n (%)	367 (54.4 %) / 308 (45.6 %)	45 (47.9 %) / 49 (52.1 %)	0.237
History of MI, n (%)	313 (46.4 %)	59 (53.2 %)	0.215
History of stroke, n (%)	67 (9.9 %)	20 (21.3 %)	0.001
Peripheral arterial disease, n (%)	202 (29.9 %)	31 (33.0 %)	0.546
History of percutaneous coronary intervention (PCI), n (%)	112 (16.6 %)	21 (22.3%)	0.167
History of coronary artery bypass grafting (CABG), n (%)	31 (4.6 %)	8 (8.5 %)	0.127
Chronic kidney disease (CKD), n (%)	445 (65.9 %)	79 (84.0 %)	<0.001
GFR by CKD-EPI, ≥ 60 ml/min/1.73 m ²	267 (60.0 %)	39 (49.4 %)	0.003
C3a	105 (15.6 %)	23 (24.4 %)	
C3b	56 (8.3 %)	15 (16.0 %)	
C4	11 (1.6 %)	1 (1.1 %)	
C4	6 (0.9 %)	1 (1.1 %)	
Diabetes mellitus, n (%)	232 (34.4 %)	41 (43.6 %)	0.079
Arterial hypertension, n (%)	86 (52.4 %)	10 (43.5 %)	0.421
Smoking, n (%)	5 (0.7 %)	0.0 (0.0 %)	1.000
HR/min	76.0 (70.0;86.0)	86.0 (74.0;120.0)	<0.001
Systolic BP, mmHg	140.0(120.0; 160.0)	137.5 (120.0;150.0)	0.144
GRACE, score	144.0 (134.0; 153.0)	151.5 (143.0;161.0)	<0.001
SYNTAX score	40.0 (24.0;55.0)	10.0 (4.0;41.0)	0.029

Single-vessel stenting was performed in 222 (28.9%) patients, two-vessel stenting in 79 (10.3%) patients, and three-vessel stenting in 1 (0.1%) patient. Complications during the hospital stage were noted in 1 (0.1%) patient due to artery dissection and in 1 (0.1%) patient due to re-occlusion of a previously stented artery.

The distribution of coronary artery lesions by groups is presented in Table 2.

Table 2. Coronary angiography parameters in individuals with CHD

Parameter	Absence of AF (n=675)	Presence of AF (n=94)	p
Lesion of the left anterior descending artery, n (%)	236.0 (35.0%)	25.0 (26.6%)	0.108
Lesion of the circumflex artery, n (%)	115.0 (17.0%)	24.0 (25.5%)	0.045
Lesion of the right coronary artery, n (%)	138.0 (20.4%)	22.0 (23.4%)	0.508
Lesion of the intermediate artery, n (%)	5.0 (0.7%)	1.0 (1.1%)	0.544
Lesion of the diagonal artery, n (%)	17.0 (2.5%)	0.0 (0.0%)	0.249
Lesion of the obtuse marginal branch, n (%)	22 (3.3%)	0.0 (0.0%)	0.096
Lesion the posterior interventricular artery, n (%)	6 (0.9%)	2 (2.1%)	0.255

Thus, statistically significant differences between the groups were demonstrated regarding the involvement of the circumflex artery (p=0.045).

The laboratory findings are presented in Table 3.

Table 3. Laboratory parameters

Parameter	Absence of AF (n=675)	Presence of AF (n=94)	p
Creatinine, µmol/l	86.0 (72.0; 103.0)	94.0 (80.0; 113.0)	0.001
GFR by CKD-EPI, ml/min/1.73 m ²	73.0 (56.0; 87.0)	58.0 (46.0; 73.0)	<0.001
Glucose, mmol/l	6.0 (6.0; 8.0)	8.0 (6.0; 11.0)	0.001
Hemoglobin, g/l	136.0 (123.0; 146.0)	132.0 (119.0; 142.0)	0.083
Total cholesterol (TC), mmol/l	5.00 (4.29; 6.00)	4.70 (3.45; 5.11)	0.005
Low-density lipoprotein cholesterol (LDL-C), mmol/l	3.04 (2.45; 3.79)	2.74 (2.00; 3.30)	0.023
High-density lipoprotein cholesterol (HDL-C), mmol/l	1.06 (1.00; 1.40)	1.00 (0.95; 1.41)	0.543
Troponin T, ng/l	43.95 (15.0; 412.5)	75.0 (21.0; 343.5)	0.228

According to the data in the table, patients with AF had higher levels of creatinine and glucose, as well as lower levels of GFR by CKD-EPI, total cholesterol (TC), and LDL cholesterol (LDL-C).

The echocardiographic findings are presented in Table 4, with no statistically significant differences observed in the studied parameters.

The groups differed in terms of the number of hospital days: in the AF group, the median was 11.0 (8.0; 14.0) hospital days, while in the non-AF group, it was 10.0 (8.0; 13.0) hospital days (p=0.004).

Table 4. Echocardiographic parameters

Parameter	Absence of AF (n=675)	Presence of AF (n=94)	p
End-systolic dimension (ESD), mm	31.0(27.0; 35.0)	29.0(27.0;36.5)	0.847
End-diastolic dimension (EDD), mm	47.0(43.0;52.0)	47.0(44.0;52.0)	0.680
End-systolic volume (ESV), ml	38.0(31.0;50.0)	40.0(30.0;56.0)	0.765
End-diastolic volume (EDV), ml	97.0(80.0;120.0)	98.0(80.0;113.0)	0.680
Left atrium (LA), area, mm ²	38.0(35.0;42.0)	40.0(36.0;44.0)	0.013
Left ventricular mass index (LVMI), g/m ²	103.0(87.0;121.0)	106.5(95.5;123.5)	0.208
Left ventricular ejection fraction (LVEF), %	58.0(51.0;62.0)	56.0(50.0;60.0)	0.053

A risk prediction model for the development of new cases of AF based on clinical and instrumental factors was prepared using binary logistic regression. The created multifactorial regression model is statistically significant (p<0.001). Considering the value of the Nagelkerke R², 28.9% of the variance in AF risk is determined by the factors included in the model.

According to the regression coefficients, age and HR (evaluated outside the AF episode in the AF group) showed a direct relationship with the risk of AF development. The characteristics of each factor are presented in Table 5.

Table 5. Characteristics of the relationship between predictors and the probability of developing new cases of AF in patients with NSTEMI-ACS

Predictors	Univariate analysis		Multivariate analysis	
	Raw OR; 95% CI	p	Adjusted OR; 95% CI	p
Age	1.071; 1.046-1.096	<0.001	1.057; 1.010-1.105	0.016
HR	1.046; 1.034-1.058	<0.001	1.057; 1.036-1.078	<0.001

For the logistic function, the Youden's index (J) was 18.48%. At P>18.48%, a high risk of developing AF was predicted, while P<18.48% indicated a low risk of developing AF. The sensitivity was 85.7%, specificity was 52.9%, positive predictive value was 60.0%, negative predictive value was 91.0%, and diagnostic accuracy was 80.7%.

The area under the ROC curve, which determines the risk stratification of AF prognosis and the values of the logistic regression function (Figure 1), was 0.687 (0.028) with a 95% CI of 0.631–0.742. The resulting model was statistically significant (p<0.001).

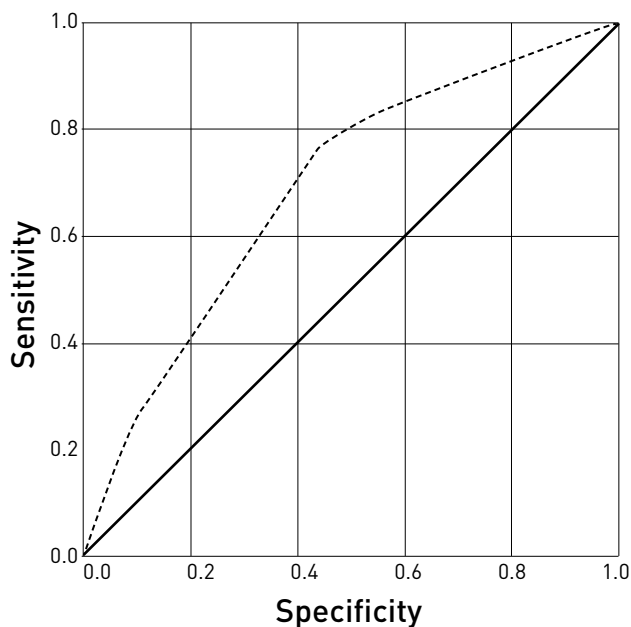


Fig. 1. The ROC curve for the logistic regression function and the risk of developing AF

Discussion

AF is one of the most common cardiovascular diseases (CVD) that impacts the quality and longevity of life for adults in various countries around the world. Its molecular, cellular, neurohumoral, and hemodynamic pathophysiological mechanisms are complex, and there is growing understanding that a wide range of comorbidities may contribute to atrial remodeling, which promotes the development of AF. Furthermore, recent studies have shown that HR is not constant, and temporary changes in comorbid conditions complicate the dynamics of AF.

In this study, the incidence of newly developed AF was 12.2%, which is consistent with the literature sources [5].

Our data demonstrate that age is a risk factor (RF) for the development of AF in NSTEMI-ACS patients, which aligns with the results of other studies. For example, Ben Halima M et al. [2022] showed that in multivariate analysis, age over 62 years ($p = 0.04$; adjusted OR = 4.83; 95% CI: 1.07-21.77) was an independent predictor for the development of AF during acute coronary syndrome, along with chronic heart failure (CHF), prior stroke, and hyperuricemia [1].

The results of this study indicate that a high HR is a significant predictor of new-onset AF development in patients with NSTEMI-ACS.

It is well known that an increased HR induces myocardial ischemia in patients with coronary heart

disease (CHD), and reducing HR is a widely accepted strategy to prevent ischemic episodes [6]. Additionally, clinical data suggest that slowing the HR alleviates symptoms of angina by improving microcirculation and coronary blood flow [7]. Elevated HR is an established risk factor for cardiovascular complications in patients with CHD and CHF [8]. Therefore, reducing HR improves prognosis in patients with heart failure, as demonstrated in the SHIFT study. HR is also an important factor determining arrhythmias; low HR may be associated with AF, while high HR after physical exertion may be associated with sudden cardiac death. Moreover, patients with AF are at higher risk for cardiovascular complications [9–12].

It has been shown that resting HR is a potential risk factor for the development of AF [13]. However, the results of this analysis have been contradictory, and the relationship between HR and AF has not been established [14, 15]. In a subsequent meta-analysis, a search in the Cochrane Library, PubMed, and Embase databases, including 10 studies, presented a total of 18,630 cases of AF in 431,432 participants [16]. The dose-effect analysis showed a non-linear relationship between resting HR and the risk of developing AF (non-linearity, $p < 0.0001$), indicating a significant J-shaped relationship between these two factors. Both low and high resting HR were associated with an increased risk of developing AF compared to the average HR (68–80 beats per minute).

The results of the present study partially align with the literature data. For example, in the study by Ben Halima M et al. [2022], multivariate regression analysis revealed, alongside age over 62 years ($p = 0.04$; adjusted OR = 4.83; 95% CI 1.07-21.77), chronic kidney failure ($p = 0.043$; adjusted OR = 6.61; 95% CI 1.06-35.80), a history of stroke ($p = 0.002$; adjusted OR = 44.51; 95% CI 3.97-498.10), and hyperuricemia ≥ 62 mg/l ($p = 0.04$; adjusted OR = 4.4; 95% CI 1.06-18.15) as independent predictors for AF development in patients with ACS [1].

Similar data are demonstrated in the study by Biccirè FG et al. [2023], where patients with AF were older ($p < 0.001$), more often suffered from arterial hypertension ($p = 0.012$), chronic obstructive pulmonary disease ($p < 0.001$), and hyperthyroidism ($p = 0.018$) [2].

As shown in our study, echocardiographic parameters were not included in the predictive model, which may be related to the mechanisms of AF devel-

opment in NSTEMI-ACS. Specifically, ischemia caused by the acute form of CHD can lead to disturbances in the electrical activity of the myocardium, promoting the development of AF. Left atrial stretch: increased pressure in the left atrium, associated with heart failure or other conditions, may predispose to AF. Inflammatory processes: ACS is accompanied by systemic inflammation, which can affect the electrical conductivity and automaticity of the atria. Stress and sympathetic nervous system activation: the acute stress reaction to sudden myocardial ischemia can lead to increased sympathetic activity, which also increases the risk of AF. Comorbidities: the presence of chronic diseases, such as hypertension or heart failure, can raise the risk of AF in patients with ACS [17–19]. These mechanisms may act independently or in combination, increasing the likelihood of AF in ACS patients. Therefore, preventive measures to correct risk factors, pharmacological treatment of comorbid-

ities, or timely treatment of ACS, including coronary angiography if necessary, can reduce the likelihood of newly diagnosed AF.

Thus, factors associated with the risk of newly occurring AF in NSTEMI-ACS require careful assessment upon patient admission to the hospital.

Conclusion

This study demonstrates that patients with AF were older, more likely to have comorbid conditions (stroke, CKD), higher HR, higher GRACE score, lower SYNTAX score, and more pronounced changes in laboratory parameters (lower eGFR, higher lipid spectrum concentrations, and glucose levels). The analysis identified age and HR as predictors of new-onset AF in patients with NSTEMI-ACS.

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