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D-DIMER LEVEL AS A PREDICTOR OF ADVERSE OUTCOMES IN PATIENTS WITH ISCHEMIC STROKE

DOI 10.25789/YMJ.2021.74.02

The level of D-dimer is associated with the severity of stroke. The objective of this study was to test the hypothesis that the D-dimer level measured in the first 96 hours of hospitalization has prognostic value for mortality in patients with acute ischemic stroke (AIS) in the acute and early recovery periods.

This retrospective study included 54 patients with AIS. The patients were divided into 2 groups: the survivors after 65 days of observation (n = 37) and those who died during observation (n = 17). The level of D-dimer in blood plasma was determined in the first 96 h after hospitalization and expressed in terms of the number of upper normal levels (UNL). Its prediction of mortality was evaluated.

The D-dimer level was significantly higher in patients with an adverse outcome: 5.53 (2.8-7.84) versus 1.84 (1.2-3.06) UNL, p = 0.00035. Logit regression model of outcomes showed that the probability of death was 30% with 4 UNL, 40% with 5 UNL, and 50% with 7 UNL. Statistically, the lethality was significantly higher in patients with a D-dimer level ≥5 UNL (odds ratio 5.813 [95% CI 1.596-21.174], p = 0.05).

Measured in the first 96 hours from the start of hospitalization, D-dimer level ≥5 UNL was the predictor of an adverse outcome in patients with AIS in the acute and early recovery periods. Therefore, the use of anticoagulants needs to be modified.

Keywords: D-dimer level; acute ischemic stroke; mortality predictor; adverse outcome.

Introduction. Cardiovascular diseases are the main cause of death worldwide [6]. Ischemic stroke, along with ischemic heart disease, is the leading disease of the cardiovascular system and makes a significant contribution to the lethality and disability of the population. In the Russian Federation, the incidence rates of stroke in 2009 and 2010 were 3.5% and 3.27%, respectively, and the mortality rates were 1.19% and 0.96%, respectively [2]. During stroke, the following periods are distinguished: the peracute period (the first 3 days), the acute period (up to 28 days), early recovery (up to 6 months), late recovery (up to 2 years), and the period of residual effects (after 2 years) [1].

In the past two decades, the approach to the treatment and prevention of acute cardiovascular diseases has changed significantly in Russian and worldwide practice [27]. One of the main "extra-cerebral" causes of mortality in stroke is the development of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). The unsatisfactory results of prevention and treatment, as well as the asymptomatic course in the majority of patients [29] are of great importance. Therefore, searching for new methods of anticoagulant therapy is reasonable and relevant [31].

The existing standards and recommendations for the prevention and treatment of thromboembolism of the pulmonary artery in patients with stroke are regularly updated due to the presence of a range of risk factors [1,13,15,22]. However, anticoagulant use is associated with the risk of bleeding, including hemorrhagic transformation (HT) of the ischemic focus [12,29].

A promising predictive index of the coagulogram is the D-dimer level. According to published data, this indicator has prognostic significance in terms of outcomes and mortality in various diseases, including stroke (ischemic [24,32,33] and hemorrhagic [18]), myocardial infarction [17], mesenteric thrombosis [7], and infective endocarditis [9]. D-dimer is one of the few markers of thrombosis that can be determined directly in standard samples of citrated plasma. It does not require specific biomaterial processing, and its determination is quick. D-dimer is also an indicator of the effectiveness of anticoagulant therapy [3,5,8,30].

The results of determining the D-dimer level, in contrast to other markers of activation of the hemostasis system, are practically not affected by the admixture of platelets in the blood plasma [14] but are influenced by factors such as the size of the thrombus, the time from the beginning of clinical signs to the prescription of anticoagulant therapy, the intake of anticoagulants (affected by which the level of D-dimer gradually decreases), and thrombolytic therapy, which causes an increase in its level [11]. Individual differences in the rate of D-dimer increase in some patients can be explained by the different rates of activity of the fibrinolytic system [26]. Thus, in clinical practice, D-dimer can be used as a marker of the body's ability for hypercoagulability and endogenous fibrinolysis, the elevated levels of which are typical for thrombosis [32].

The purpose of this study was to test the hypothesis that the D-dimer level, measured in the first 96 hours of hospitalization, was a prognostically important predictor of mortality in patients with acute ischemic stroke in the acute and early recovery periods.

Methods and Study Design. This study included 54 men and women aged

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40 years and older. An acute ischemic stroke was determined according to the World Health Organization criteria [16]. This study was approved by the Local Ethics Committee.

All patients admitted in the first 40 minutes after hospitalization underwent a Multislice Spiral CT Scan to exclude hemorrhagic stroke or an intracranial malignant neoplasm.

If the patient's age was between 40 and 59 years, the additional criteria for enrolment in the study were: D-dimer level ≥ 2 upper normal levels (UNL) and a history of VTE or cancer (with the exception of non-melanoma skin cancer). If the patient's age was between 60 and 74 years, an additional criterion for enrolment in the study was the D-dimer level ≥ 2 × UNL. Patients aged 75 years and older were included in the study without additional factors.

Exclusion criteria were: high risk of bleeding, inability to undergo a proper bilateral compression ultrasound, contraindication for anticoagulant therapy, pregnancy, intake of oral anticoagulants for 96 hours before the start of therapy with the test drug, heparin therapy lasting longer than 96 hours, and concomitant antiplatelet treatment with two medications [16].

All patients underwent treatment in accordance with the standard for cerebral infarction treatment [25]. The patients received antiplatelet therapy. The drug intake lasted for 14 days, but with continued true immobilization, it was prolonged to 35 days.

The following risk factors were analyzed: age, smoking, diabetes, arterial hypertension, atrial fibrillation, history of an infarction, laboratory indicators, and body mass index. To assess the neurological deficit in the acute period of ischemic stroke, the National Institutes of Health Stroke Scale (NIHSS), the Rivermead mobility index, and the Rankin Scale were used. When assessing the severity of the stroke, the following gradation of the NIHSS was used: mild (0-5 points), medium (6-13 points), and severe (14 points or more) [19,25,28]. For the retrospective analysis, the patients were divided into 2 groups: the survivors during 65 days of observation (n = 37) and those who died during observation (n = 17).

In the early periods (the first 96 hours) after hospitalization, the level of D-dimer in the blood plasma obtained from the cubital vein was determined once. The D-dimer concentration was determined by the immunoturbidimetric method (microlatex agglutination) on a calibrated BCT analyzer (DadeBehring), the INNOVANCE D-Dimer kit (Siemens). In two cases, the analysis was performed on an automatic analyzer ACL TOP 700 (Instrumentation Laboratory, USA) with a reagent D-Dimer (Instrumentation Laboratory, USA). To obtain plasma, the blood was centrifuged at 1500-2000 g for 15 minutes.The results of the D-dimer level determination were reported in mg/l FEU (fibrinogen-equivalent units). The reference range was 0-0.49 mg/L for 52 patients and 0-0.286 mg/L for 2 subjects.

The data were processed using nonparametric tests. Quantitative variables such as age, D-dimer level, body mass index, time interval from hospitalization to D-dimer level determination, NIHSS, Rivermead, and Rankin scales were presented as median, upper and lower quartiles - Interquartile range (IQR). The statistical significance of differences was determined using the Mann-Whitney criterion (U). Correlation analysis was performed using the nonparametric Spearman test (R). Risk factors such as smoking, history of infarction, diabetes, atrial fibrillation, and lower urinary tract infections were presented as odds ratio (OR) with a 95% confidence interval (CI).

Linear and logistic regression analyses of lethality were performed depending on the level of the D-dimer expressed in terms of UNL. The accuracy of the model was verified by analyzing the frequency characteristics (receiver operating characteristic [ROC] curve), and the area under the curve (AUC) was determined to estimate the accuracy of the model. The Yates' correction for multiple comparisons was applied for the comparative analysis of lethality, depending on the level of the D-dimer. Statistical significance was defined as $p<0.05$. The statistical analysis was carried out using the Statistical 6.0 software for Windows.

Results. 3.1 Baseline Characteristics of Study Samples. The mean age of the patients included in the study was 78 years (range: 75-82 years), and 66.7% of the patients were women. The value of the NIHSS at admission was 9 (range: 5-16). Adverse outcome was revealed in 17 patients (31.5%), whose life span was 22 days (range: 14-33 days) of observation.

The two groups did not differ in terms of sex (pF = 1.0) and the presence of risk factors, such as smoking (OR = 0.66, CI 0.1-4.4, pF = 0.65), myocardial infarction in the anamnesis (OR = 0.51, CI 0.1-2.2, pF = 0.44), diabetes (OR = 1.3, CI 0.4-4.5, pF = 0.76), atrial fibrillation (OR = 0.8, CI 0.3-2.95, pF = 1), and lower urinary tract infection (OR = 1, CI 0.3-3.6, pF = 1). However, there was a statistically significant difference in body mass index between the dead and the survivors (23.7 [range: 23.1-26.4] vs. 27.3 [range: 26-29.4] kg/m^2; pU = 0.0097). (Figure 1).

The severity of ischemic stroke, assessed using the Rivermead scale and NIHSS upon hospitalization, was significantly higher in patients with adverse outcomes. A correlation was found between the NIHSS and the D-dimer level (r = 0.41, $p<0.001$).

There was no statistically significant difference in the time between hospital-

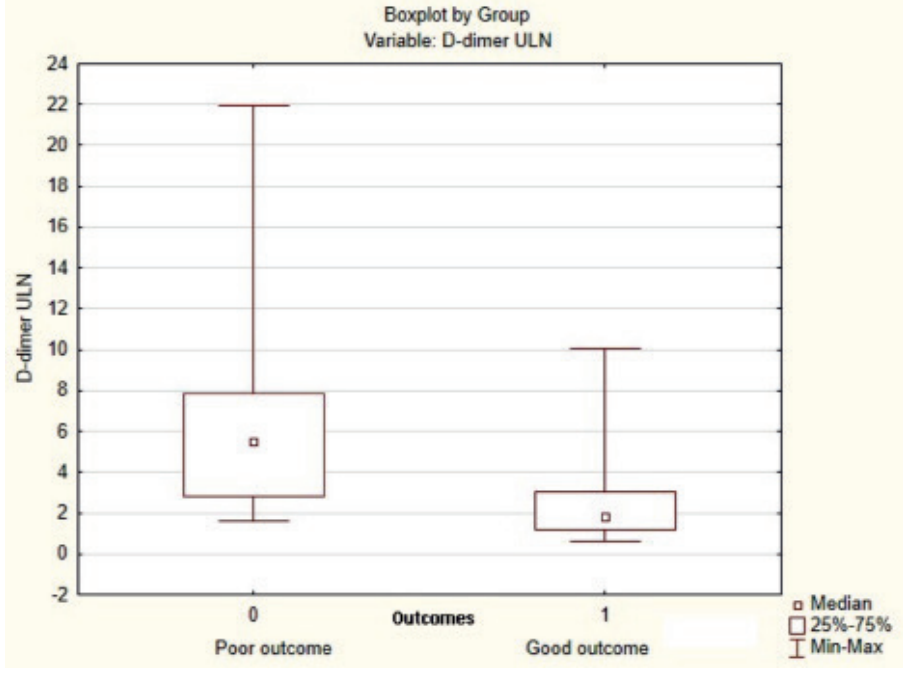

Fig. 1. D-dimer level, expressed in the upper limits of the norm, depending on the outcome

ization and the D-dimer level determination between the two groups. HT of the ischemic site was detected only in two patients from the survivor group; in the group of dead patients, HT was not revealed. In 47.1% of cases, the cause of death was a breakdown of stroke progression—an increase in cerebral edema and the progression of cardiovascular insufficiency. In another 47.1% of cases, the cause was not detected (death occurred in the nursing hospital), and in 5.8% cases (one observation), the cause of death was an acute vascular intestinal disease.

In the group of patients who survived, a severe neurological deficit (NIHSS 14 or more) was present in four patients (10.8%). In three patients, the D-dimer level was lower than 5 UNL, and one patient had a D-dimer level more than 5 UNL. In the group of patients who died, an intense neurological deficit was found in 17 patients (100%). Nine of them (52.9%) had a D-dimer level higher than 5 UNL, and eight of them (47.1%) had a D-dimer level lower than 5 UNL.

A logit regression model based on the obtained data showed that the probability of death was 30% at 4 UNL, 40% at 5 UNL, and 50% at 7 UNL (Figure 2).

The constructed ROC curve with an AUC of 0.79 corresponded to a good quality model with suitability for practical use of the obtained data (Figure 3).

Lethality was significantly higher in patients with a D-dimer level of ≥5 UNL.

Discussion. The level of D-dimer was significantly higher in patients with an adverse outcome: 5.53 (2.8, 7.84) versus 1.84 (1.2, 3.06), p = 0.00035. Logit regression model of outcomes showed that the probability of death is 30% with 4 UNL, 40% with 5 UNL and 50% with 7 UNL. Statistically, the lethality was significantly higher in patients with a D-dimer level ≥5 UNL; OR 5.813 (1.596-21.174), p = 0.05.

Yang et al. showed that a high level of plasma D-dimer is a predictor of mortality in patients with ischemic stroke [24]. Our study has shown the reasonability of the D-dimer level calculation (in UNL), and the criteria of adverse outcome risk, which increases with the level of D-dimer exceeding 5 UNL within 96 hours of hospitalization, have been refined. The informative value of the D-dimer level in predicting lethality during the 65-days observation period in patients with acute ischemic stroke with involuntary immobilization for more than 1 day has also been confirmed. Furthermore, the relationship between the increase in the D-dimer level and the neurological deficiency

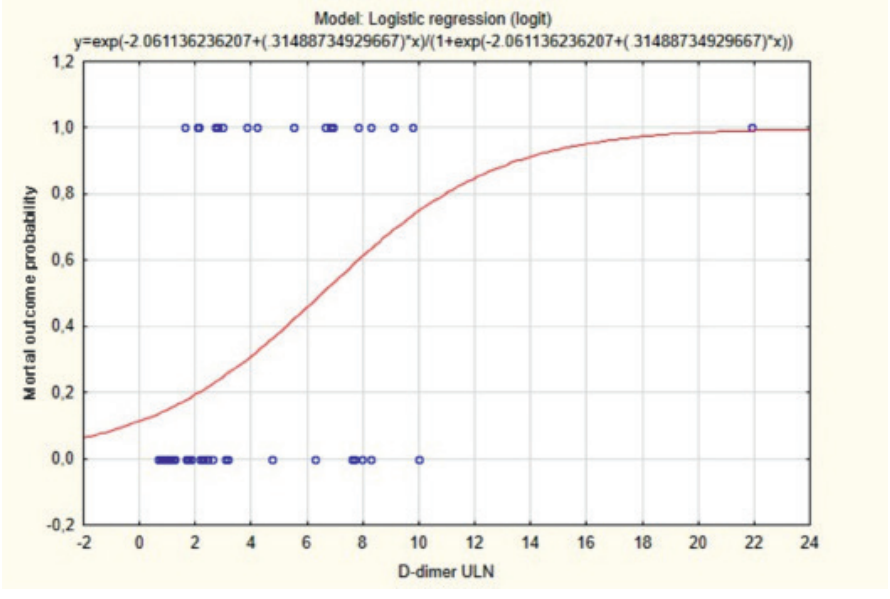

Fig. 2. Logistic regression model of the probability of death depending on the level of D-dimer, expressed in the upper limits of the norm

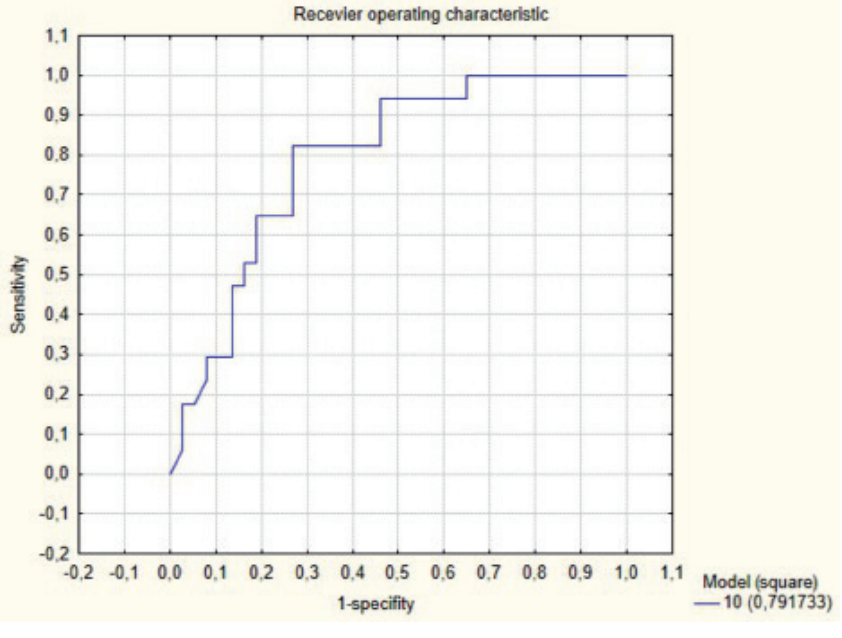

Fig. 3. Receiver operating characteristic (ROC) -curve, showing the adequacy of the model of using the level of D-dimer, expressed in the upper limits of the norm, as a predictor of mortality

level assessed by the NIHSS has been shown. Our results conform to those of other studies, showing that higher D-dimer levels are associated with a high severity of neurological deficits, major ischemic lesions, and poor prognosis in stroke patients [4,23,32].

In accordance with the Russian standard for cerebral infarction treatment [21], all patients hospitalized with a stroke spend 24 hours in the resuscitation department or intensive care unit, i.e., they have strict immobilization, and in the early recovery period of stroke, no more than half of the patients are able to live without outside help [20]. Thus, the results of our study can be applied to the bulk of patients hospitalized with ischemic stroke.

The level of D-dimer not exceeding 1 UNL is a rare phenomenon in patients with thrombosis. This may be due to a small thrombus size and late determination with false-positive results due to a mistake at the pre-analysis stage (such as storage of plasma samples for more than 6 hours), which results in a decrease in fibrinolytic activity due to either deficiency of tissue plasminogen activator (t-PA) or a high level of plasminogen activator inhibitor (PAI-1). A false increase in the level of this indicator can be caused by a violation of the blood sampling technique;

excessive and prolonged application of a tourniquet above the site of venipuncture activates the coagulation system and the release of the tissue plasminogen activator into the bloodstream, which increases the level of D-dimer in the laboratory study [10].

The probability of death, estimated using logistic regression, with a D-dimer level equal to or higher than 5 UNL was 40% (Figure 1). We have confirmed the significance of this value as a cut-off point with respect to the mortality prognosis in patients with acute ischemic stroke. Further, the results of this study may indicate the advisability of applying therapeutic dosages of anticoagulants at a D-dimer level ≥5 UNL.

However, if a high level of D-dimer is a predictor of death, and its decrease during treatment reduces the likelihood of adverse outcomes, then a dynamic control of the D-dimer level in blood plasma should accompany the therapeutic doses of direct anticoagulants. Thus, moving from anticoagulant therapy to preventive dosages is advisable when the D-dimer level is lower than 5 UNL. This hypothesis needs to be verified by further studies.

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