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Predictors of Adverse Outcomes in Ischemic Stroke Associated with COVID-19

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Objectives. To study predictors of adverse outcomes in ischemic stroke associated with COVID-19. **Materials and methods.** A retrospective analysis of 173 cases of ischemic stroke and COVID-19 was carried out. Mean age was 68.64 ± 11.39 years (95% CI 66.93–70.35; $M = 92$, $m = 34$). In terms of gender, there was a predominance of women (64.16%). Lethal outcomes occurred in 62 (35.84%) patients. Risk factors for lethal outcome were studied by binary logistic regression. **Results.** Univariate analysis showed that the risk of fatal stroke was associated with the patient being in a generally severe condition and a number of other factors, which included the severity of COVID-19, acute coronary syndrome, multiple organ failure, the need for a ventilator, a history of kidney disease, pneumonia, a high NIHSS score, oxygen partial pressure, respiratory rate, the number of hospitalizations, the full blood count (erythrocytes, hemoglobin, hematocrit, leukocytes, neutrophils), the coagulogram, glucose levels, liver and kidney markers (bilirubin, aspartate aminotransferase, alanine aminotransferase, creatinine, urea), and creatine phosphokinase, lactate dehydrogenase, and C-reactive protein levels. Use of a model based on multivariate analysis allowed the probability of lethal outcome to be predicted. A regression function was obtained, which included the C-reactive protein and urea concentrations and NIHSS score. Patients with values of ≥35% were at elevated risk of death, while those with values of <35% were likely to have favorable outcomes. The model was statistically significant ($p < 0.001$). The sensitivity and specificity of the model were 88.9 and 97.9%, respectively. **Conclusions.** The predictors of the likelihood of fatal outcomes of stroke identified here can serve as guidelines for physicians in selecting patient management strategies at different stages of care.

Keywords: ischemic stroke, COVID-19, death.

Diseases of the cerebral circulatory system are a problem of extreme medical and social significance [1]. Ischemic stroke (IS) is a leading cause of disability and disability. Mortality after IS in the Russian Federation for an eight-month period in 2019 was 15.5%, with 16.7% in 2020 and 17.1% in 2021. European and Chinese retrospective data show that the incidence of stroke in COVID-19 varies from 2% to 6% [2, 3]. Stroke associated with COVID-19 is more severe, has worse outcomes, and higher mortality rates than in patients without COVID-19 [4–11]. Some authors have noted that mortality ranges from 20% to 100% in patients with severe COVID-19 and cerebrovascular diseases [12]. Calmettes et al. [13] found that factors influencing lethal outcomes (LO) of IS associated with COVID-19 were C-reactive protein, platelets, obesity, age, and NIHSS score. Zhang et al. [14] found that cytokine storm, bleeding disorders, and organ dysfunction worsen prognoses of patients with stroke associated with COVID-19. Identification of factors influencing outcome plays an important role in selecting patient management strategy.

The aim of the present work was to study predictors of adverse outcomes of IS associated with COVID-19.

Materials and Methods. A retrospective analysis of 173 patients with IS associated with COVID-19 was performed. COVID-19 was confirmed in all patients using the polymerase chain reaction (PCR). IS developed at the onset of COVID-19 in 59 (34.1%) patients and on the background of COVID-19, at 3–17 days, in 143 (82.7%) patients.

Inclusion criteria: patients diagnosed with IS on the basis of clinical and neuroimaging (CT or MRI) investigations in the hyperacute or acute period; diagnosed with a new PCR-confirmed COVID-19 coronavirus infection.

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Exclusion criteria: patients with IS in the early or late recovery period; post-surgical stroke; pre-existing or currently active neurological diseases; traumatic brain injury.

Mean age was 68.64 ± 11.39 years (95% CI 66.93–70.35; $M = 92$, $m = 34$). The study included 111 (64.2%) women and 62 (35.8%) men. LO developed in 62 (35.8%) patients, with male patients predominating 36 (58.1%). On admission, 142 (82.1%) patients had community-acquired viral pneumonia, confirmed by neuroimaging data (thoracic CT) with the typical ground glass sign. Stratification by COVID-19 course was as follows: mild in 38 (22%) patients, moderate in 104 (60.1%), and severe in 31 (17.9%). Viral or bacterial pneumonia was present in 51 (29.5%) patients, of which 31 (60.8%) had LO. Concomitant somatic pathology consisted of hypertension in 172 (99.4%) patients, atrial fibrillation in 52 (30.1%), postinfarction cardiosclerosis in 39 (22.5%), and diabetes mellitus in 45 (26%). The TOAST classification identified the atherothrombotic subtype of IS in 27 (15.6%) patients, the cardioembolic in 54 (31.2%), unspecified types in 83 (48%), and lacunar strokes in nine (5.2%) patients.

Patients' levels of consciousness were assessed using the Glasgow Coma Scale. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS).

Statistically significant differences were identified using the Kruskal–Wallis and Mann–Whitney tests, as well as Student's *t* test and one-way analysis of variance (ANOVA). The median and interquartile range (Me [Q1; Q3]) were used to describe nonparametric numerical characteristics, and the mean and standard deviation *M* (SD) were determined for parametric values. Significant potential factors associated with the risk of developing LO were identified by univariate logistic regression analysis followed by the construction of curves assessing the quality of binary classifications (ROC – receiver operating characteristic) to determine sensitivity and specificity. Odds ratios (OR) were calculated for each indicator. In addition, cut-off thresholds at which sensitivity and specificity were optimal were determined for these predictors. The predictive ability of the predictors identified here was assessed in terms of the area under the ROC curve (AUC – area under ROC curve). The relationship between the probability of LO and various factors was determined by multivariate analysis using binary logistic regression with selection of factors by the elimination method. The probability of LO was calculated as $P = 1/(1 + e^{-z})\cdot 100\%$, where P is the probability of LO, $e \approx 2.72$ is the base of the natural logarithm, and z is the power of the inverse logarithm. Results were regarded as statistically significant at $p < 0.05$.

Results. The mean age of patients with favorable outcomes (FO) was 67.79 ± 11.26 (95% CI 65.67–69.91) years, while that of patients with LO was 70.16 ± 11.56 (95% CI 67, 23–73.1; $M = 90$, $m = 44$) years ($p = 0.191$). At admission, 27 patients with FO had severe COVID-19 (24.32%), compared with 51 (82.26%) patients with LO ($p < 0.001$). Assessment of the state of consciousness using the Glasgow Coma Scale showed that most patients with FO were in a state of lucid consciousness (92; 82.88%) or stupor (16; 14.41%). The LO group included significantly more patients with depression of consciousness, ranging from stupor to coma (36; 58.06%) ($p < 0.001$). NIHSS results showed that patients with mild stroke were significantly dominant in the group with FO – 27 (24.32%), only two patients (3.23%) having stroke ending with LO ($p < 0.001$). Moderate stroke was observed in 69 (62.16%) patients with FO of stroke and in 23 (37.09%) patients with LO ($p < 0.001$). Severe and extremely severe stroke was more frequent in the LO group (37 (59.68%) patients) than the FO group (15 (13.51%) patients) ($p < 0.001$). The severity of stroke depending on the subtypes of IS in FO and LO is shown in Fig. 1.

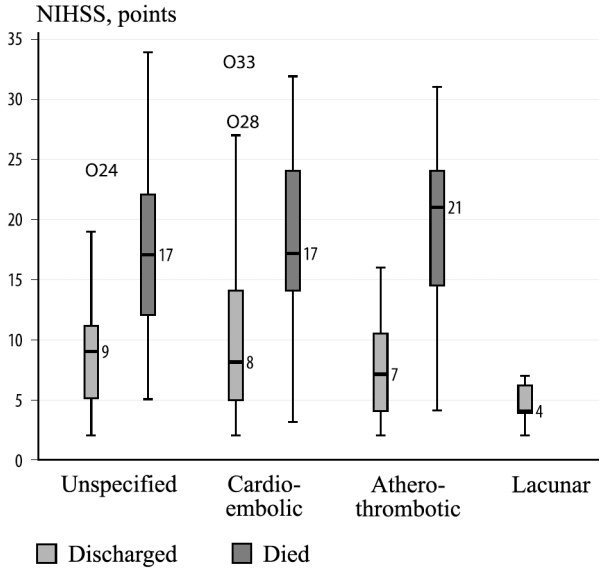

Fig. 1. Severity of stroke depending on subtypes of IS in patients with FO and LO. The numbers on the plot are single outliers (there were single cases in the groups with very high NIHSS scores that were not included in the median and CI).

Thus, LO was seen more frequently in patients with severe stroke, especially in cases of the atherothrombotic stroke subtype ($p < 0.001$).

The mean NIHSS score in patients with FO was 8 [5–11] points, which corresponded to moderate stroke severity, while the score in patients with LO was 17 [13–22.5] points, which corresponded to severe stroke ($p < 0.001$).

As part of primary prevention, antihypertensive drugs were regularly taken by a significantly greater proportion of patients with stroke with FO – 32 (18.49%), compared with LO – 24 (13.87%) ($p = 0.038$). Anticoagulants, despite the need to prescribe according to the CHA2DS2 VASc scale, were used by only 13 (25%) of 52 (30.06%) patients with atrial fibrillation. The group with LO included significantly more patients with chronic renal failure – 19 (30.65%) than the group with FO – nine (8.11%) ($p < 0.001$).

Laboratory data on hospital admission day 1 are given in Table 1. Thus, the following laboratory parameters were

TABLE 1. Mean Values of Laboratory Parameters in Groups with FO and LO

Parameter	Patients with FO (n = 111)	Patients with LO (n = 62)
Laboratory parameters, Me [Q_{25}; Q_{75}]		
leukocytes, 10^9/liter	9.25 [6.78–11.95]	12.88 [10.09–16.15]**
platelets, 10^9/liter	189.5 [149.5–274]	163.5 [139–245]*
neutrophils, abs.	5.91 [3.51–8.6]	9.38 [6.9–11.42]**
lymphocytes, abs.	1.53 [1.1–2.06]	0.93 [0.7–1.34]**
monocytes, abs.	0.65 [0.44–0.9]	0.73 [0.39–1.06]
glucose, mM	6.8 [5.76–8.89]	7.65 [6.51–9.78]*
creatinine, mM	84.5 [61–106.75]	103 [80.58–165.5]**
urea, mM	5.93 [4.37–8.9]	10.78 [6.83–20.2]**
alanine aminotransferase, U/liter	22.7 [15–36]	30.9 [18.2–51.75]*
aspartate aminotransferase, U/liter	35.5 [20.65–55.58]	63.35 [41.63–99.55]**
total bilirubin, mM	12.1 [8.85–19.25]	16.15 [10.28–25.25]*
potassium, mM	4.22 [3.85–4.59]	4.1 [3.8–4.69]
sodium, mM	140 [135.93–144]	140 [136–145]
creatine phosphokinase, u/liter	111.5 [61.25–192.25]	378 [155–864]**
ESR, mm/h	32 [18–52.75]	33 [15–53]
lactate dehydrogenase, u/liter	519 [262.5–759.7]	779.6 [510.5–1088]*
C-reactive protein, mg/liter	17.54 [4.03–48]	97.33 [34.51–144.8]**
D-dimer, μg/ml	248 [248–527]	555.5 [248–1284.25]*
aPTT, sec	29.7 [26.58–34.08]	33.7 [28.4–40.4]*
INR, units	1.09 [1–1.17]	1.17 [1.08–1.36]**
SFMC, g/liter	6.5 [5.38–8.13]	7.75 [6–11]*
VLDL, mM	0.67 [0.4–1]	0.4 [0.3–0.8]*
atherogenic index	3 [2.13–3.48]	3 [2.5–3.9]
triglycerides, mM	1.34 [1–1.92]	1.24 [0.88–2.31]
Laboratory parameters	M ± SD	M ± SD
erythrocytes, 10^{12}/liter	4.41 ± 0.69	4.59 ± 0.81
hematocrit, %	38.56 ± 6.02	40.51 ± 7.39
hemoglobin, g/liter	132.12 ± 21.27	138.94 ± 27.21
total protein, g/liter	70.47 ± 8.5	67.99 ± 8.7*
fibrinogen, g/liter	4.07 ± 1.13	4.47 ± 1.16*
cholesterol, mM	5.29 ± 1.49	5.04 ± 1.42
LDL, mM	2.81 ± 1.12	2.88 ± 1.14
HDL, mM	1.29 ± 0.47	1.24 ± 0.46

*$p < 0.05$, **$p < 0.001$; aPTT – activated partial thromboplastin time, INR – international normalized ratio, LDL – low density lipoprotein, VLDL – very low density lipoprotein, HDL – high density lipoprotein.

significantly higher in LO: leukocytosis, thrombocytopenia, lymphocytopenia, hyperglycemia, and levels of liver enzymes, creatine phosphokinase, lactate dehydrogenase, D dimer, fibrinogen, and soluble fibrin monomer complexes (SFMC).

TABLE 2. Univariate Analysis of Logistic Regression

Factor	c_r	OR	95% CI	p
Acute coronary syndrome	4.51	90.59	11.88–690.71	<0.001*
Multiorgan failure	4.1	60.5	7.89–463.62	<0.001*
Mechanical ventilation	2.68	14.59	4.09–52.04	<0.001*
Overall condition on admission	2.67	14.42	6.59–31.55	<0.001*
Chronic kidney disease	1.61	5.01	2.09–11.95	<0.001*
Viral/bacterial pneumonia	1.52	4.55	2.27–9.11	<0.001*
Viral pneumonia	1.25	3.49	1.27–9.61	0.016*
Severity of COVID-19	1.15	3.15	1.78–5.57	<0.001*
Number of readmissions	1.1	3.02	1.45–6.3	0.003*
Stroke focus size	0.95	2.59	1.55–4.33	<0.001*
Red blood cells, 10^{12}/liter	0.48	1.61	1.03–2.53	0.038*
Fibrinogen, g/liter	0.4	1.49	1.11–2.01	0.008*
Banded leukocytes	0.21	1.23	1.11–1.36	<0.001*
NIHSS score, points	0.19	1.21	1.14–1.29	<0.001*
SFMC, g/liter	0.18	1.2	1.01–1.43	0.04*
Leukocytes, 10^9/liter	0.19	1.2	1.11–1.3	<0.001*
Respiratory rate min^{-1}	0.12	1.12	1.02–1.23	0.016*
Neutrophils, %	0.11	1.12	1.07–1,17	<0.001*
Urea, mM	1.18	1.18	1.09–1.27	<0.001*
Glucose, mM	0.13	1.14	1.04–1.25	0.007*
Direct bilirubin, μM	0.09	1.09	1–1.19	0.044*
aPTT	0.05	1.06	1.01–1.09	0.008*
Hematocrit, %	0.061	1.06	1.01–1,12	0.017*
Total bilirubin, μM	0.05	1.05	1.02–1.08	<0.001*
Partial pressure of oxygen, mmHg	0.04	1.04	1.007–1.068	0.014*
Aspartate aminotransferase, U/liter	0.02	1.02	1.01–1.02	<0.001*
Hemoglobin, g/liter	0.02	1.02	1.01–1.03	0.008*
C-reactive protein, mg/liter	0.01	1.01	1.01–1.02	<0.001*
Alanine aminotransferase, U/liter	0.01	1.01	1–1.02	0.01*
Creatinine, mM	0.01	1.01	1.01–1.02	<0.001*
Creatine phosphokinase, U/liter	0.002	1	1.001–1.003	0.001*
Lactate dehydrogenase, U/liter	0.002	1	1–1.004	0.028*
Platelets, 10^9/liter	–0.004	0.99	0.99–1	0.046*
Prothrombin time, sec	–0.03	0.97	0.94–0.99	0.018*
Lymphocytes, %	–0.13	0.88	0.83–0.92	<0.001*
Monocytes, %	–0.13	0.88	0.79–0.96	0.005*
Oxygen saturation, %	–0.13	0.88	0.83–0.93	<0.001*

Factor	c_r	OR	95% CI	p
Sex	–0.63	0.53	0.28–0.99	0.047*
Eosinophils, %	–0.69	0.5	0.31–0.82	0.006*
History of antihypertensive drugs	–0.74	0.48	0.24–0.97	0.04*
Cough	–0.96	0.39	0.17–0.87	0.021*
Headache	–1.11	0.33	0.15–0.72	0.005*
General weakness	–1,16	0.31	0.16–0.6	<0.001*
Dizziness	–1.28	0.28	0.13–0.62	0.002*

c_r is the regression coefficient, *p <0.05.

TABLE 3. Factors Determining Stroke Outcome

Factor	p	OR; 95% DI
C-reactive protein, mg/l	0.006*	1.01; 1.0–1.02
NIHSS, points	<0.001*	1.2; 1.09–1.32
Urea, mmol/l	0.002*	1.16; 1.05–1.27

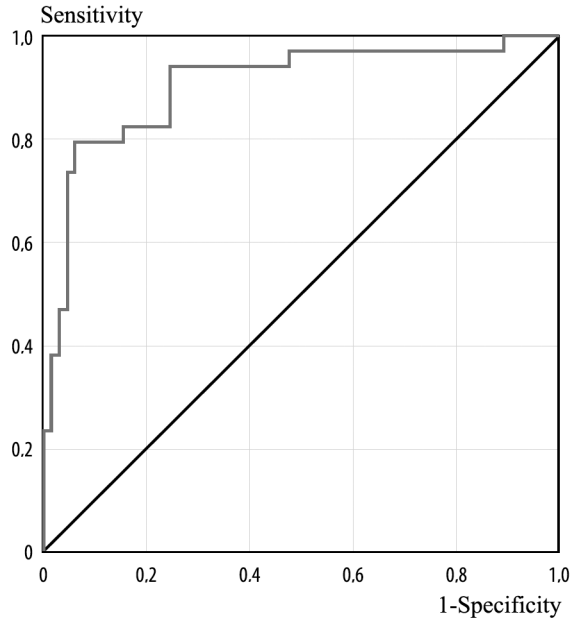

Fig. 2. ROC curve.

Among patients with LO, pulmonary embolism was also diagnosed in 31 (50%), acute coronary syndrome in 28 (3.23%), multiple organ failure in 22 (35.48%), acute respiratory distress syndrome in 22 (35.48%), disseminated intravascular coagulation syndrome in 12 (19.35%), and lower limb vein thrombosis in seven (11.29%).

Univariate analysis of the probability of LO of stroke addressed 150 different parameters. Significant results from univariate analysis of logistic regression are presented in Table. 2.

Ten predictors of LO of stroke with an odds ratio (OR) of more than 2 were identified. These included acute coronary syndrome, multiple organ failure, ventilator requirement, the severity of the patient's overall condition, chronic kidney disease, pneumonia, the severity of COVID-19, the number of hospitalizations, and the size of the stroke focus.

The following indicators were selected in multivariate analysis (Table 3).

An increase in the C-reactive protein concentration by 1 mg/liter led to an increase in the chances of LO by a factor of 1.01, an increase by 1 point on the NIHSS by a factor of 1.2, an increase in the concentration of urea by 1 mM by a factor of 1.16. The following regression function was obtained: $P = 1/(1 + e^{-z})\cdot 100\%$, $z = 0.01X_{CRP} + 0.18X_{NIHSS} + + 0.15X_{urea} - 5.32$, where X_{CRP} is the C-reactive protein concentration (mg/liter), X_{NIHSS} is the NIHSS score, and X_{urea} is the urea concentration (mM). The resulting model was statistically significant ($p < 0.001$). Assessment using the Nagelkerke determination coefficient R^2 showed that the model accounted for 58.9% of the factors influencing the probability of LO. The threshold value of the logistic function P was 50%. P values of ≥50% led to the conclusion that there was a high risk of LO, while P values of <50% indicated FO. The sensitivity and specificity of the model at the selected thresholds were 79.4% and 93.8%, respectively. The overall predictive efficiency of the model was 88.9%. Evaluation of the relationship between the probability of LO in patients with IS associated with COVID-19 and the C-reactive protein and urea concentrations and the NIHSS yielded the ROC curve shown in Fig. 2.

AUC was found to be 0.91 ± 0.04 (95% CI 0.84–0.97) and the model was statistically significant ($p < 0.001$). The outcome value at the cut-off point was defined as 0.35, or 35%. Patients with values of ≥35% had an increased risk of LO, while those with values of <35% were likely to have FO. The sensitivity and specificity of the model were 82.4% and 84.6%, respectively.

Discussion. Thus, the severity and the level of depression of consciousness on admission were significantly worse in patients with LO. Patients with LO had a significantly worse history of taking antihypertensive therapy than patients with LO ($p = 0.038$). Leukocytosis, thrombocytopenia, lymphocytopenia, hyperglycemia, elevated renal and hepatic

markers, increases in creatine phosphokinase, lactate dehydrogenase, D dimer, fibrinogen, and SFMC were significantly more common in patients with stroke with LO.

Univariate analysis showed that predictors of the likelihood of stroke with LO with an OR of >5 included the severity of overall condition at admission, acute coronary syndrome, multiple organ failure, and the need for a ventilator. Predictors of LO included chronic kidney disease, pneumonia, the severity of COVID-19, the number of hospitalizations, and the size of the stroke focus. Factors predicting the likelihood of LO with OR of 1–2 included erythrocyte and hemoglobin levels, hematocrit, and leukocyte, fibrinogen, SFMC, APTT, glucose, bilirubin, aspartate aminotransferase, alanine aminotransferase, creatinine, urea, creatine phosphokinase, lactate dehydrogenase, and C-reactive protein levels, oxygen partial pressure, respiratory rate, and the NIHSS score.

Multivariate analysis linked the risk of stroke with LO with the severity of IS on the NIHSS and increased C-reactive protein and urea levels, indicating a role for concomitant somatic pathology and multiple organ failure as predictors of IS outcomes. Increased C-reactive protein was found to be an important indicator of a systemic inflammatory response exacerbated by COVID-19. High NIHSS scores may indicate an extensive area of IS. Severe and extremely severe stroke were significantly predominant in the LO group, especially in the atherothrombotic subtype of stroke ($p < 0.001$).

The data presented here serve as the basis for timely diagnostic measures, including dynamic monitoring of laboratory parameters (C-reactive protein, urea) and neurological status (NIHSS scale), which will allow timely adjustment of treatment.

Conclusions. The predictors of the likelihood of stroke with LO identified here may serve as guidelines for doctors in selecting patient management tactics in the acute period of IS associated with COVID-19.

Patent of the Russian Ministry of Health, *Method for Predicting the Outcome of the Acute Period of Ischemic Stroke Associated with COVID-19*, priority letter dated 08.17.2021, application No. 2021124564/14 (051675).

The authors declare no conflict of interest.

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