

Predictive Markers of Functional Outcome in Subtypes of Ischemic Stroke

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Summary

The aim of the study was to identify potential predictors of functional outcome (FO) in patients with subtypes of ischemic stroke (IS) who did not receive reperfusion therapy.

Materials and methods. A prospective study included 229 patients with ischemic stroke divided into three groups based on the IS subtype: Group 1 — 84 patients with cardioembolic IS; Group 2 — 65 patients with atherothrombotic IS; Group 3 — 80 patients with lacunar IS. Changes in the modified Rankin Scale (mRS) scores were considered as FO criteria calculated as the difference between the scores on admission and on the 21st day after IS onset — Δ mRS. In order to optimize the performance of the machine learning (ML) model, a binary FO approach was chosen for assessment on the 21st day after IS onset: mRS ≥ 3 scores corresponded to an unfavorable non-lethal outcome, and mRS = 0–2 scores corresponded to a favorable FO. We analyzed the interrelation with FO (correlation coefficient, r) and the predictive ability (ML (decision tree), information gain, i. g.) of 29 parameters, including demographic features; comorbidities; instrumental examination findings; NIHSS, BI, CDR scores; serum concentrations of cytokines on the 2nd day of hospital stay.

Results. The following significant ($P < 0.0001$) predictors of unfavorable non-lethal FO were identified: female sex (i. g. = 0.346), recurrent IS (i. g. = 0.248), diabetes mellitus (i. g. = 0.442), and CXCL2 concentration (i. g. = 0.306) in Group 1; WMHs severity (i. g. = 0.206), diabetes mellitus (i. g. = 0.340), content of CCL2 (i. g. = 0.116), CCL3 (i. g. = 0.202) and CCL23 (i. g. = 0.101) in Group 2; age (i. g. = 0.106), 2nd–3rd degree obesity (i. g. = 0.150), WMHs severity (i. g. = 0.300), CXCL5 content (i. g. = 0.143) and MIF (i. g. = 0.145) in Group 3. Concentrations of CCL25 (i. g. = 0.108) and IL-6 (i. g. = 0.401) were found as predictors of favorable FO ($P < 0.0001$) in Group 1; 1st degree obesity (i. g. = 0.118) and TNF- α concentration (i. g. = 0.211) in Group 2; arterial hypertension (AH) (i. g. = 0.113) and 1st degree obesity in Group 3.

Conclusion. Study results made evident the variances in combination of factors affecting FO, depending on IS pathogenetic subtype. Despite undoubted value of the data obtained, further research is needed to expand the potentiality in predicting acute IS outcome and confirm the relevance of identified markers.

Keywords: ischemic stroke, acute phase, functional outcome, mRS, subtypes of ischemic stroke, prognostic markers

Conflict of interest. The authors declare no conflict of interest.

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Introduction

Development of early prediction methods and identification of predictors of unfavorable functional outcome (FO) in patients with acute ischemic stroke (IS) is a crucial task in era of personalized medicine [1, 2]. There's a sound body of published data on national and international research in the field of development, evaluation, and implementation of prognostic models for ischemic stroke. However, the majority of these studies focus on longitudinal evaluation of patients' disability in the recovery period and later stages of ischemic stroke [3, 4]. Very few studies have demonstrated the potential for assessing the persistence or progression of neuro-

logical and cognitive deficits occurring in the acute phase of IS [5, 6]. The insufficient validity of risk prediction models for predicting unfavorable FO in some of them originates from the limited set of traditionally considered predictor variables, such as demographic characteristics, clinical and functional indicators, and laboratory and instrumental data. Search for potential biomarkers of functional recovery in patient's immunological status sounds promising and increases the value of stratified risk prediction models for unfavorable FO. This domain is currently in the focus of intensive research, and particularly, the role of «inducible» cytokines, such as CXCL and CC chemokines in the pathogenesis of

IS, and regulation of immune response during the acute phase of ischemia in addition to well-established interleukin (IL), interferon gamma (IFN- γ), and tumor necrosis factor (TNF- α) mechanisms of action.

There's a building up amount of data evidencing involvement of various chemokines into pathogenetic mechanisms underlying the development of cerebrovascular disorders, cell apoptosis, and neuro- and angiogenesis during the acute period of stroke. In this context, the most promising chemokines are the ligands of the CXCR1 and CCR1/2 receptors, strongly associated with the acute period of stroke and post-stroke FO [7, 8]. Of particular interest is the verification of factors affecting the dynamics of patients' functional status, depending on pathogenetic mechanisms underlying IS and patient's comorbidities [9]. Therefore, focusing research on comprehensive patient assessment in the acute period of stroke, followed by modeling of FO prognosis based on advanced mathematical algorithms, is a promising trajectory in the context of personalized medicine.

The aim of the study is to identify potential predictors of functional outcome in patients with ischemic stroke subtypes who did not receive reperfusion therapy.

Material and Methods

The prospective study was approved by the Independent Ethics Committee of the Clinical Research Center at Immanuel Kant Baltic Federal University (Minutes of Meeting No. 2 dated April 27, 2021, and No. 34 dated September 29, 2022). The study included 229 patients with a diagnosis of ischemic stroke undergoing treatment from January 2023 to February 2025 at the Neurology Department of the Emergency Medical Care Hospital and the Department of Medical Rehabilitation for Patients with Central Nervous System Disorders at the Central City Clinical Hospital of Kaliningrad. The sample size of the study was not pre-calculated. The diagnosis of IS was made based on abrupt onset (minutes, hours) of focal neurologic deficits attributable to one of the vascular territories, and lasting at least 24 hours.

Clinical signs and symptoms attributable to diagnosis of «ischemic stroke in the carotid artery territory» were set as inclusion criteria. The exclusion criteria included: reperfusion

therapy; transient ischemic attack; vertebrobasilar stroke, patient's death, and development of severe complications within 21 days. Patients were selected according to the inclusion/exclusion criteria from the initial sample ($N=508$, Fig. 1).

Patients' examinations were performed within the stroke care standards to verify IS subtype according to the TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment). Standardized procedures on admission included clinical neurological evaluation, brain CT/MRI, transcranial Doppler ultrasonography of extracranial and intracranial vessels, electrocardiography, and laboratory tests.

Stroke severity and activities of daily living were quantified on admission using the NIH Stroke Scale (NIHSS) and the Barthel Index (BI). The degree of cognitive decline was assessed using the Clinical Dementia Rating (CDR) scale on the 14th day of hospital stay.

The laboratory tests included assessment of serum concentrations of biologically active molecules (cytokines) in samples collected on the 2nd day of hospital stay, including chemokines (Gro-a/CXCL1, Gro-b/CXCL-2, GCP-2/CXCL6, ENA-78/CXCL5, MIP-1a/CCL3, MIP-1d/CCL15, MIP-1/CCL23, MCP-1/CCL2, TECK/CCL25), interleukins (IL-1b, IL-6, IL-16), interferon gamma (IFN- γ), macrophage migration inhibitory factor (MIF), and tumor necrosis factor (TNFa). Concentrations were measured by flow cytometry on a two-beam laser automatic analyzer (Bio-Plex® 200 Systems, Bio-Rad, USA) using a commercial test system (Bio-Plex Human Panel, 40-Plex Assay, Bio-Rad, USA). The results were expressed in pg/ml.

The neuroimaging parameters were assessed based on magnetic resonance imaging (MRI) data

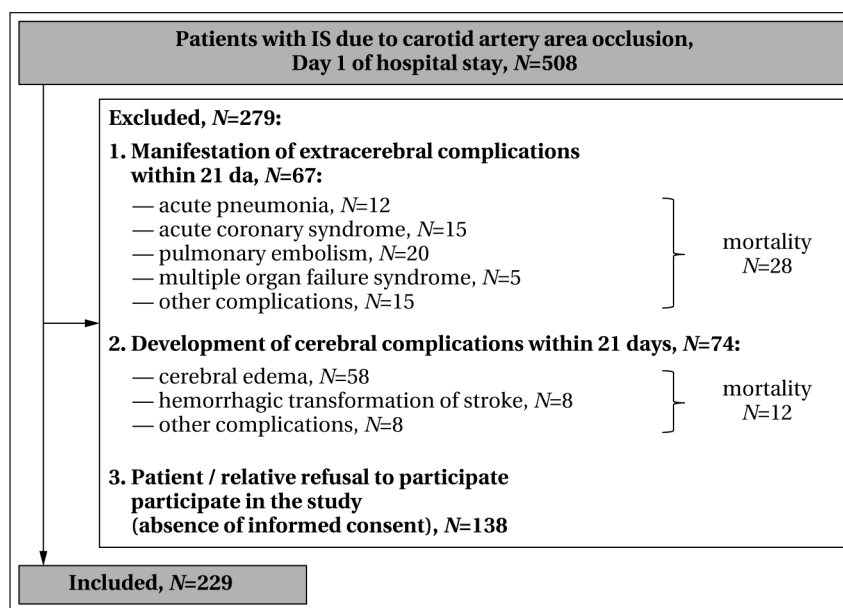


Fig. 1. Scheme of patient recruitment procedure.

(Optima MR450w 1.5T magnetic resonance scanner) using a DWI, T2* (hemo), and T2/Flair scanning protocol. White matter hyperintensity (WMH) grade was assessed using the Fazekas visual scale. The IS topography was related to the ischemic lesions in vascular territories of the anterior cerebral (ACA), middle cerebral (MCA), and anterior choroidal (AChA) arteries based on neuroimaging data.

Changes in the patient's disability index measured by the modified Rankin scale (mRS) as the difference between the mRS scores on admission and on day 21 from IS onset — Δ mRS were used as criteria of IS functional outcome (FO). In order to optimize the performance of the machine learning (ML) model, a binary FO approach was chosen for assessment on the 21st day after IS onset: mRS ≥ 3 scores corresponded to an unfavorable non-lethal outcome, and mRS = 0–2 scores corresponded to a favorable FO.

Standard SPSS Statistics V23.0 software for Windows, the Python programming language, and the Pandas and SciPy libraries were used for statistical data processing. The distribution of quantitative variables was assessed using the Shapiro–Wilk test. Quantitative variables with a normal distribution were described using arithmetic means and standard deviations ($M \pm \sigma$). Data with a normal distribution was compared using the ANOVA test for dependent and independent samples. In case of abnormal distribution, quantitative variables were described using the median (Me), lower and upper quartiles [$Q1$ – $Q3$]. The nonparametric Wilcoxon test was used when the dependent variable was not normally distributed. Quantitative variables in groups with non-normal distributions were compared using the Mann–Whitney U test. The Bonferroni correction was used for multiple comparisons to avoid false positives. Analysis of frequency differences in two independent groups was performed using the Fisher's exact test with two-sided confidence intervals and the χ^2 test with Yates's correction. The critical level of statistical significance was set at $P < 0.05$. The Z-score was not used for rating cognitive measures by CDR scale in the absence of reference values from the control group.

For mathematical analysis, 29 parameters were selected as the initial data, and grouped into the following main categories: demographic data (age and gender); comorbidities (presence or absence of arterial hypertension, recurrent stroke, and diabetes mellitus; grade of obesity based on body mass index (BMI)); instrumental examinations data (laterality of stroke and localization of lesion, lesion size, presence of multiple lesions and WMH grade); NIHSS, BI, and CDR scores; immunological indicators, such as serum concentrations of cytokines.

To optimize dataset statistical processing, all data were classified based on their nature: continuous (cytokine concentrations, age, IS lesion size, CDR,

NIHSS, and BI scores), categorical (lesion localization, WMH grade, obesity grade), and binary variables (comorbid conditions, multifocal lesions, IS lesion laterality, and gender).

The correlation coefficient (R) was calculated to assess the relationship of the functional outcome variables on the mRS scale with the studied indicators. The r value ranged from -1 to 1 , where -1 represents a complete inverse relationship, 0 represents no relationship, and 1 represents a complete direct relationship. Biserial method was used to assess Δ mRS correlation with binary variables, and Spearman test — to assess the correlation with categorical and continuous variables. The conventional value of 0.05 was chosen as the threshold. When a P -value was less than 0.05 , the significance of the correlation coefficient was considered statistically confirmed. Correlation coefficients with a P -value above 0.05 were excluded from consideration. Correlation analysis was performed separately for each group. In order to detect confounders — confusing variables, correlation coefficients between variables were calculated with subsequent exclusion from statistical analysis. Following the correlation analysis, variables with a correlation coefficient $R > 0.300$ were selected to train mathematical analysis models based on ML algorithms. For machine learning, an algorithm for predicting the target variable value — a decision tree with a maximum depth and additional selection of features using the SelectFromModel in Python Scikit-learn library was chosen. Feature importance was determined by higher values in information gain (i. g.) following the selection of the feature.

Results

The patients were distributed into three groups based on IS subtype: Group 1 — 84 patients with cardioembolic IS; Group 2 — 65 patients with atherothrombotic IS; Group 3 — 80 patients with lacunar IS. All patients were managed according to specialized medical care standards for cerebral stroke. No thrombolytic therapy was used in view of contraindications or missed therapeutic window due to late hospital admission. Based on comprehensive examination findings, the following clinical and neuroimaging signs of ischemic stroke were verified (Table 1).

Arterial hypertension was more common in group 1 patients, compared to groups 2 and 3, ($P = 0.0041$, $P = 0.0007$), while risk of recurrent stroke was higher in patients from group 3 ($P = 0.0017$, $P = 0.0025$) compared to patients from groups 1 and 2. Patients from groups 2 and 3 had higher BMI values vs patients from group 1 ($P < 0.0001$, $P = 0.009$). Neuroimaging findings showed higher prevalence of multifocal brain lesions in group 3, compared to group 2 ($P < 0.0001$), and MRI signs of grade 3 WMH according to the Fazekas scale were common in patients from groups 2 and 3, compared to group 1

Table 1. Demographic characteristics and characteristics of cerebral ischemic stroke in patients, groups 1, 2, and 3.

Parameters	Values in the groups			P
	1, N=84	2, N=65	3, N=80	
Demographic variables, N (%)				
Males, N (%)	46 (54.8)	32 (49.2)	46 (57.5)	$P_1=0.497$; $P_2=0.727$; $P_3=0.318$
Females, N (%)	38 (45.2)	33 (50.8)	34 (42.5)	$P_1=0.497$; $P_2=0.727$; $P_3=0.318$
Mean age, y, $M\pm\sigma$	66.65 $\pm$ 3.2	66.48 $\pm$ 2.9	67.03 $\pm$ 3.9	$P_1=0.738$; $P_2=0.495$; $P_3=0.305$
Comorbid conditions				
Diabetes mellitus, type 2, N (%)	29 (34.5)	16 (24.6)	26 (32.5)	$P_1=0.192$; $P_2=0.786$; $P_3=0.297$
Arterial hypertension, N (%)	75 (89.3)	46 (70.8)	54 (67.5)	$P_1=0.0041^*$; $P_2=0.0007^*$; $P_3=0.669$
Recurrent IS, N (%)	15 (17.8)	11 (16.9)	32 (40.0)	$P_1=0.887$; $P_2=0.0017^*$; $P_3=0.0025^*$
BMI, kg/m ² , $M\pm\sigma$	25.15 $\pm$ 3.8	28.14 $\pm$ 2.5	27.04 $\pm$ 3.3	$P_1<0.0001^*$; $P_2=0.009^*$; $P_3=0.0169$
Excess weight (BMI 25–30 kg/m ²)	30 (25.2)	29 (44.6)	24 (30.0)	$P_1=0.0130$; $P_2=0.491$; $P_3=0.0694$
Grade 1 obesity (BMI = 30–35 kg/m ²)	4 (4.8)	7 (10.8)	10 (12.5)	$P_1=0.165$; $P_2=0.070$; $P_3=0.715$
Grades 2–3 obesity (BMI > 35 kg/m ²)	11 (13.1)	10 (15.4)	18 (22.5)	$P_1=0.694$; $P_2=0.165$; $P_3=0.281$
Neuroimaging parameters				
Multiple lesions, N (%)	8 (9.5)	0 (0)	18 (22.5)	$P_1=0.106$; $P_2=0.023$; $P_3<0.0001^*$
Lesion size, $Me [Q1; Q3]$, mm	25 [23; 48]	23 [20; 36]	5 [3–10]	$P_1=0.567$; $P_2=0.0111^*$; $P_3<0.0001^*$
WMH (Fazekas 2), N (%)	46 (54.8)	28 (43.1)	48 (60.0)	$P_1=0.156$; $P_2=0.846$; $P_3=0.110$
WMH (Fazekas 3), N (%)	2 (2.4)	12 (18.5)	14 (17.5)	$P_1=0.0009^*$; $P_2=0.0039^*$; $P_3=0.572$
IS lesion in the right hemisphere	38 (45.2)	32 (49.2)	54 (67.5)	$P_1=0.627$; $P_2=0.004^*$; $P_3=0.026$
IS lesion in the left hemisphere	46 (54.8)	33 (50.8)	26 (32.5)	$P_1=0.627$; $P_2=0.004$; $P_3=0.026$
MCA stroke	56 (66.7)	48 (73.8)	78 (97.5)	$P_1=0.349$; $P_2<0.0001^*$; $P_3<0.0001^*$
ACA stroke	21 (25.0)	10 (15.4)	2 (2.5)	$P_1=0.152$; $P_2<0.0001^*$; $P_3=0.0051$
AChA stroke	7 (8.3)	7 (10.8)	0 (0)	$P_1=0.603$; $P_2=0.0085^*$; $P_3=0.0026^*$
Clinical scales (scores), $M\pm\sigma$				
NIHSS (on admission)	9.6 $\pm$ 1.6	7.5 $\pm$ 0.9	5.8 2.4	$P_1<0.0001^*$; $P_2<0.0001^*$; $P_3<0.0001^*$
BI (on admission)	76.18 $\pm$ 5.8	82.76 $\pm$ 8.3	86.51 $\pm$ 5.4	$P_1=0.048$; $P_2<0.0001^*$; $P_3=0.0131$
CDR (day 14)	0.64 $\pm$ 0.1	0.65 $\pm$ 0.1	0.86 $\pm$ 0.4	$P_1=0.991$; $P_2<0.0001^*$; $P_3<0.0001^*$
Functional outcome parameters				
mRS (1 st day), (scores), $M\pm\sigma$	3.6 $\pm$ 1.9	3.4 $\pm$ 1.8	2.8 $\pm$ 0.8	$P_1=0.515$; $P_2=0.0018^*$; $P_3=0.0083^*$
mRS (21 st day), (scores), $M\pm\sigma$	2.40 $\pm$ 1.3	2.17 $\pm$ 1.9	1.35 $\pm$ 0.9	$P_1=0.382$; $P_2<0.0001^*$; $P_3=0.0006^*$
Favorable outcome (mRS = 0–2 scores), N (%)	40 (47.6)	32 (49.2)	63 (78.8)	$P_1=0.846$; $P_2<0.0001^*$; $P_3=0.0002^*$
Unfavorable outcome (mRS $\geq$ 3 scores), N (%)	44 (52.3)	33 (50.8)	17 (21.2)	$P_1=0.846$; $P_2<0.0001^*$; $P_3=0.0002^*$

Notes. P_1 — the indicator of statistical significance of the difference between the parameters of the 1st and 2nd groups; P_2 — the indicator of statistical significance of the difference between the parameters of the first and third groups; P_3 — the indicator of statistical significance of the difference between the parameters 2nd and 3rd groups; * — the differences in indicators are statistically significant ($P<0.0125$ with the Bonferroni correction). ICA — internal carotid artery; IS — ischemic stroke; BMI — body mass index; WMH — white matter hyper-intensity; ACA — anterior cerebral artery; MCA — middle cerebral artery; AChA — anterior choroidal artery; CDR — Clinical Dementia Rating scale; mRS — the modified Rankin scale; NIHSS — National Institutes of Health Stroke Scale.

($P=0.0009$, $P=0.0039$). Evaluation by clinical assessment scales showed higher baseline NIHSS scores in patients from group 1 ($P<0.0001$), and higher CDR scores in patients from group 3 on the 14th day of hospital stay ($P<0.0001$). Assessment of the mRS score dynamics showed a significant ($P<0.0001$) decrease in the mRS score by the 21st day of hospital stay in all study groups. Evaluation of cytokines revealed higher concentrations of MIP-1d/CCL15 in patients from group 2 compared to group 1 ($P=0.0002$), and higher MCP-1/ CCL2 concentrations in patients from group 3 compared to group 1 ($P=0.0004$, Fig. 1). Concentrations of other evaluated cytokines did not show statistically significant differences ($P<0.0125$, Fig. 2).

Assessment of relationships between the studied parameters and Δ mRS in the groups revealed correlations of varying strength. In all groups, significant correlations ($P<0.0001$) were found between Δ mRS and presence of diabetes mellitus ($R=0.884$, $R=0.749$, $R=0.475$). In groups 1 and 3 there was a significant correlation between Δ mRS and presence

of recurrent IS ($R=0.701$, $P=0.0021$; $R=0.413$, $P=0.0001$) and IS laterality ($R=0.359$, $P=0.0071$; $R=0.454$, $P=0.001$). In groups 2 and 3, a positive correlation of Δ mRS was found with WMH grade ($R=0.625$, $P<0.0001$; $R=0.601$, $P=0.004$) and grades 2–3 obesity ($R=0.343$, $P=0.011$; $R=0.624$, $P<0.0001$), and a negative correlation with grade 1 obesity ($R=-0.427$, $P=0.0021$; $R=-0.518$, $P<0.0001$). A correlation between Δ mRS and the baseline NIHSS scores was established in patients from groups 1 and 2 ($R=0.338$, $P=0.01$; $R=0.547$, $P=0.012$). The most significant Δ mRS correlation with gender was found in patients from group 1 ($R=0.508$, $P<0.0001$), while in group 3 — with presence of arterial hypertension ($R=-0.329$, $P<0.0001$) and with age ($R=0.488$, $P=0.0001$). Assessment of correlations between immunological indicators and FO parameters in patients from group 1 revealed significant positive associations of Δ mRS with concentrations of CXCL6 ($R=0.413$, $P=0.001$), CXCL1 ($R=0.782$, $P=0.0017$), CXCL-2 ($R=0.635$, $P=0.0024$), CCL23 ($R=0.358$, $P<0.0001$) and CCL3 ($R=0.343$, $P=0.001$). A negative correlation

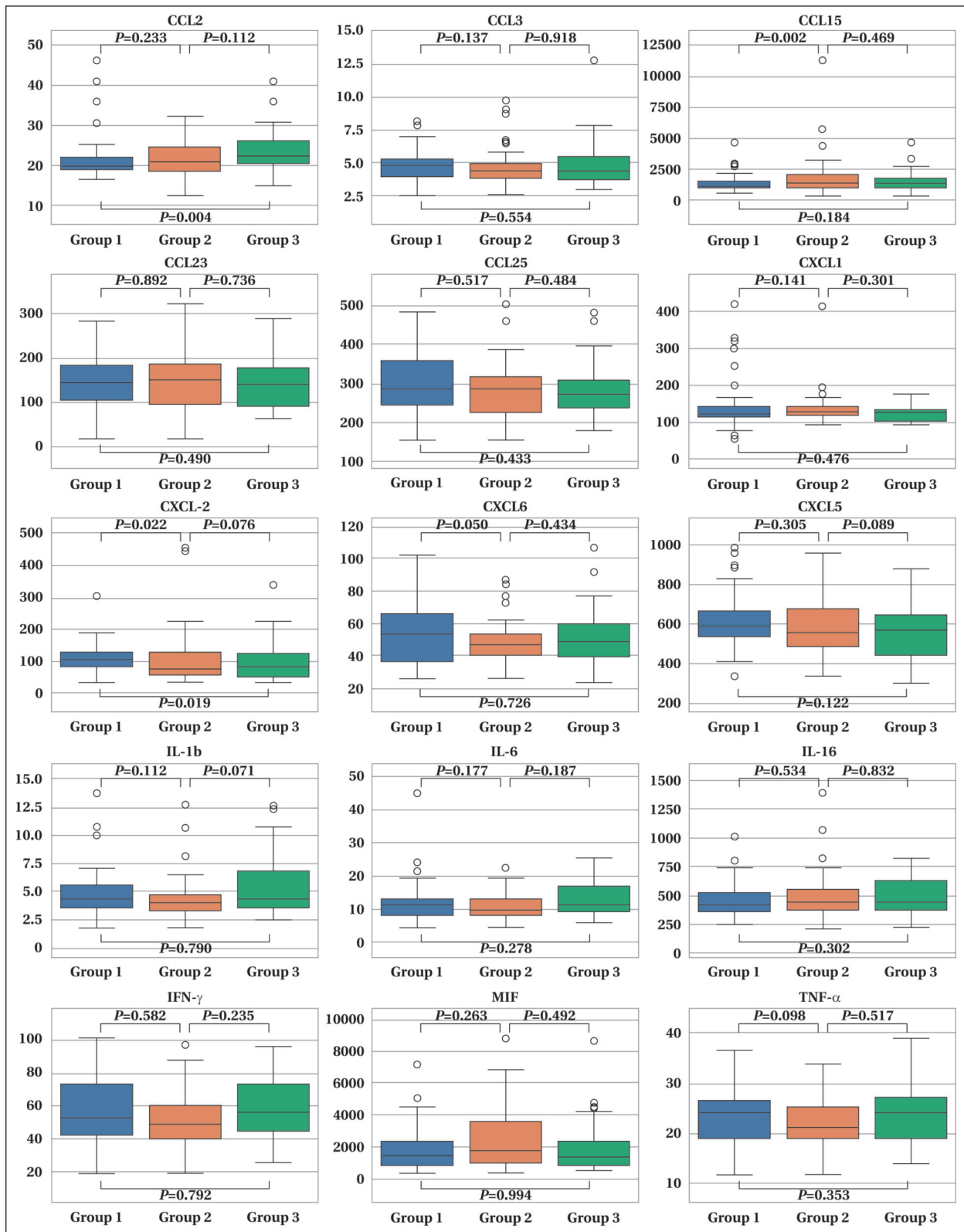


Fig. 2. Cytokine concentrations (pg/ml) in groups of patients with different subtypes of ischemic stroke ($P < 0.0125$ with Bonferroni correction).

was found between Δ mRS and IL-6 ($R = -0.474$, $P = 0.0004$), CCL2 ($R = 0.632$, $P = 0.001$), CCL3 ($R = 0.423$, $P = 0.011$), CCL23 ($R = 0.351$, $P < 0.0001$), IL-1b ($R = 0.365$, $P = 0.0213$), CXCL5 ($R = 0.341$, $P < 0.0001$), CXCL6 ($R = 0.334$, $P < 0.0001$) and IL-16 ($R = 0.328$, $P = 0.0031$).

tions of CCL2 ($R = 0.632$, $P = 0.001$), CCL3 ($R = 0.423$, $P = 0.011$), CCL23 ($R = 0.351$, $P < 0.0001$), IL-1b ($R = 0.365$, $P = 0.0213$), CXCL5 ($R = 0.341$, $P < 0.0001$), CXCL6 ($R = 0.334$, $P < 0.0001$) and IL-16 ($R = 0.328$, $P = 0.0031$).

A negative correlation was established between Δ mRS and IL-6 ($R=-0.468$, $P=0.0004$), and TNF- α ($R=-0.358$, $P=0.011$). In group 3, a significant correlation was found between Δ mRS and the concentrations of CXCL5 ($R=0.741$, $P<0.0001$), MIF ($R=0.606$, $P<0.0001$), and CXCL10 ($R=0.499$, $P=0.0074$, Fig. 3).

Performance of model in verification of binary FO reached 0.91 after training ML algorithms via feeding similar set of features for each group. Important features with higher information gain regarding an unfavorable non-fatal outcome ($mRS \geq 3$ scores) in group 1 were: female gender (i.g.=0.346; $P<0.0001$), recurrent IS (i.g.=0.248; $P<0.0001$), diabetes mellitus (i.g.=0.442; $P<0.0001$) and concentrations of CXCL2 (i.g.=0.306, $P<0.0001$). In group 1, concentrations of CCL25 (i.g.=0.108, $P<0.0001$) and IL-6 (i.g.=0.401, $P<0.0001$) were identified as predictors of favorable FO. In group 2, WMH grade (i.g.=0.206; $P<0.0001$), diabetes mellitus (i.g.=0.340; $P<0.0001$), concentrations of CCL2 (i.g.=0.116; $P<0.0001$), CCL3 (i.g.= 0.202; $P<0.0001$), and CCL23 (i.g.=0.101; $P<0.0001$) were identified as relevant indicators associated with unfavorable FO. Grade 1 obesity (i.g.=0.118, $P<0.0001$) and TNF- α concentration (i.g.= 0.211, $P<0.0001$) were associated with favorable FO. In patients from group 3, age (i.g.=0.106; $P<0.0001$), grade 2 obesity (i.g.= 0.150; $P<0.0001$), WMH (i.g.=0.300; $P<0.0001$), CXCL5 (i.g.=0.143; $P<0.0001$) and MIF (i.g.=0.145; $P<0.0001$) concentrations were indicators of unfavorable FO, while AH (i.g.=0.113; $P<0.0001$) and grade 1 obesity were indicators of favorable FO. Given the high percentage of patients with arterial hypertension and diabetes mellitus in the overall cohort, a discriminant analysis was performed to identify relevant parameters for these categories of patients in the groups. In groups 1 and 2, CXCL1 concentration was identified as a predictor of unfavorable FO in patients with AH (i.g.=0.206, $P<0.0001$; i.g.=0.105, $P<0.0001$), in patients with diabetes

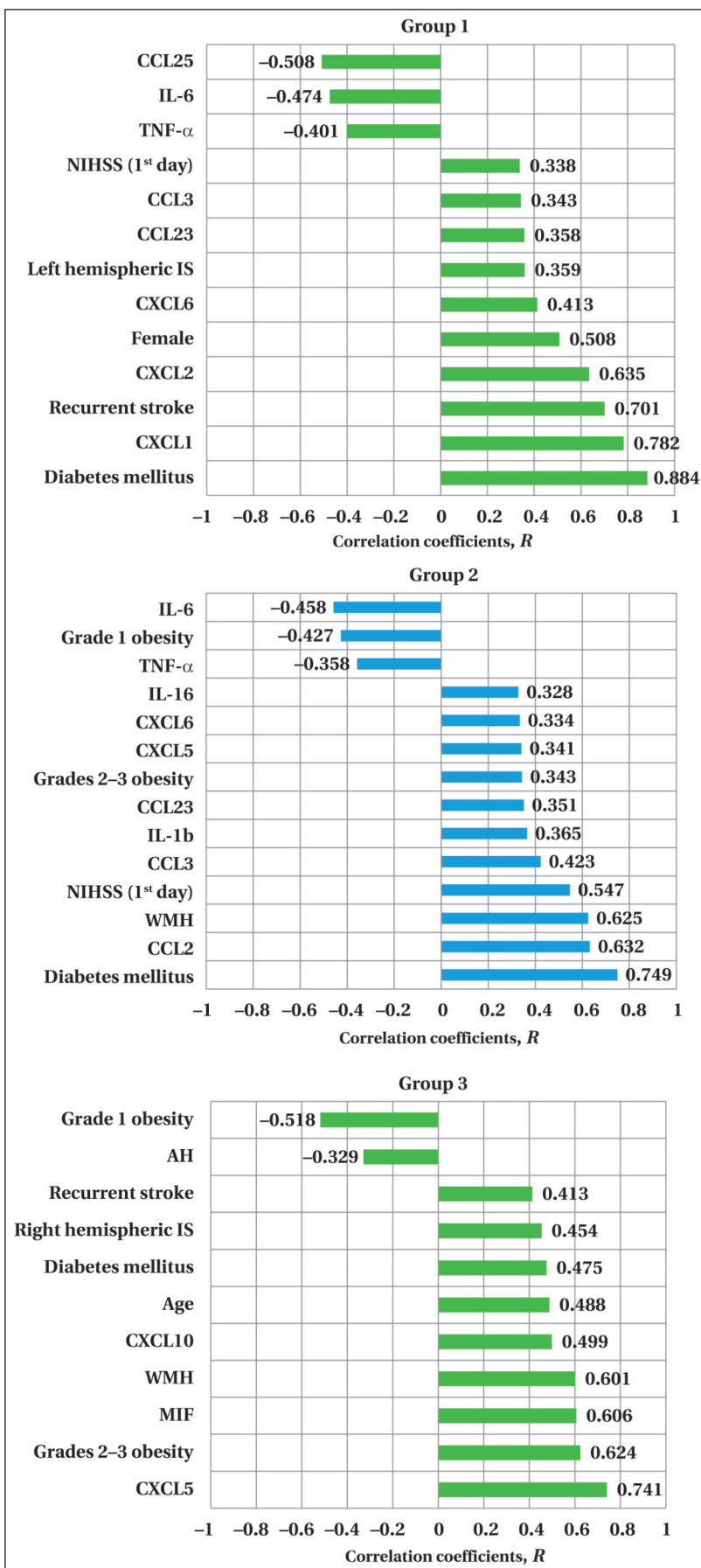


Fig. 3. Correlation of clinical parameters and cytokine concentrations (pg/ml) with Δ mRS scores in patients with different subtypes of IS.

mellitus from groups 1 and 3 it was the concentration of CXCL5 (i.g.=0.206, $P<0.0001$; i.g.=0.105, $P<0.0001$).

Discussion

An unfavorable non-lethal functional outcome in acute IS was documented in 50% of patients due to underlying atherosclerosis of large or medium-sized cerebral arteries and cerebral embolism originating from the heart. A tendency to an unfavorable outcome was established in 21.2% of patients with the lacunar IS, despite high average survival rate and a relatively good prognosis for functional recovery in this cohort. The results obtained are consistent with published evidence from other studies, which have demonstrated that early disabling functional impairments develop in 50–60% of patients with cardioembolic and atherothrombotic stroke, and in 20–30% of patients with lacunar IS [10–12]. Type 2 diabetes was identified as a predictor of unfavorable outcome, regardless of IS subtype, which is consistent with the findings of studies that contemplate the impact of carbohydrate metabolism disorders on mortality, patient recovery, frequency and timing of recurrent IS after the first-time stroke [13, 14].

Although the relationship between excessive weight and all IS subtypes has been demonstrated in cohort studies and meta-analyses [15–17], in this study, grades 2–3 obesity were significant predictors of unfavorable outcome only in patients with the lacunar IS. A favorable outcome in patients with atherothrombotic and lacunar IS who have a BMI of 30–35 kg/m² (grade 1 obesity) in this study is of interest. It can be interpreted on the context of the so-called «obesity paradox», linking extra weight and grade 1 obesity with better outcomes and reduced mortality in patients with IS [18]. However, definition of metabolic obesity as a marker of unfavorable outcome based only on BMI is insufficient, which necessitates verification of obesity significance (with thorough evaluation of central obesity, lipid profile, disorders of carbohydrate metabolism, and insulin resistance) as an important predictive factor for IS outcome in metabolic syndrome [19, 20].

Demographic characteristics were significant for prediction of IS outcome in the acute period in patients with cardioembolic (female gender) and lacunar (age) subtypes. These results are consistent with some recent studies that have demonstrated differences in non-fatal functional outcomes related to gender and age, as well as worse outcomes of cardioembolic IS in the acute period in women compared to men [21]. According to few references, these differences can be associated with higher content of molecular-genetic markers of atrial fibrillation, in particular, brain natriuretic peptide (NT-proBNP) and fibroblast growth factor-23 (FGF-23) in women compared to men [22, 23]. Age, identified as an im-

portant predictor of unfavorable outcome in lacunar IS, along with WMH and grade of cognitive decline, is most likely associated with age-dependent cerebral microangiopathy, established as the leading risk factor for lacunar stroke [24].

Severe damage to the microcirculatory vascular bed and progressive microangiopathy can lead to IS recurrence, which was a relevant indicator and marker of unfavorable outcome in patients with lacunar stroke in this study. Potential association of AH with favorable outcome in patients with lacunar IS remains controversial. Quite possible, that the obtained results prove more favorable functional outcomes of lacunar stroke in patients with hypertensive microangiopathy as compared to cases of atherosclerotic and embolic origin.

However, as there was no assessment of heterogeneity and verification of causes leading to development of this subtype of IS, the results require further confirmation in studies aimed at FO evaluation in patients with different pathogenetic subtypes of lacunar stroke. An increase in CXCL2 concentration was verified as the main immunological marker of unfavorable FO in patients with cardioembolic IS. Even though the role of CXC-chemokines in pathogenesis of cardiovascular diseases was competently investigated, nevertheless, the mechanisms of action of this family of cytokines in cerebral ischemia and hypoxia in the acute period of IS are not yet sufficiently studied.

Recent experimental studies have demonstrated the key role of the CXCR2 receptor in pathogenesis of atrial fibrillation, which is the main risk factor for development of cardioembolic stroke. In addition to its main effect of chemoattracting monocytes to the vascular endothelium and cardiac tissue, CXCL-2 expression also contributes to secretion of platelet-derived growth factor A (PDGF-A) and increase in pro-inflammatory cytokines, thereby promoting development of atrial fibrosis and heart remodeling, which are the key factors in pathogenesis of arrhythmias characterized by irregular electrical activity [25]. Clinical studies have also revealed higher concentrations of circulating CXCL-2 in patients with atrial fibrillation compared to control group patients with sinus rhythm [26]. CXCL-1 is another member from the CXC family that had been shown to be predictive, as its increased concentration was associated with unfavorable prognosis in patients with AH developing atherothrombotic and cardioembolic IS. The obtained results are consistent with the data from studies revealing higher CXCL1 levels in patients with AH compared to healthy subjects, and demonstrating that CXCL1 promotes AH by potentiating the expression of angiotensin type 1 and 2 receptors, toll-like receptor 4 (TLR4), and production of transforming growth factor β (TGF- β) [27, 28].

Ligands CCL3 and CCL2 of chemokine receptors CCR1 and CCR2, respectively, have been identified as biomarkers of unfavorable FO in patients with atherothrombotic IS. The pro-atherogenic role of these chemokines has been well-studied and demonstrated in a number of experimental and clinical studies. Increased concentrations of both CCL2 and CCL3 induce migration of leukocytes into the arterial wall, formation of foam cells, destabilization, and rupture of the atherosclerotic plaque. Studies on animal models with induced hypercholesterolemia have shown a direct correlation between CCL2/CCL3 and LDL concentrations, as well as decrease in these cytokines following intake of statins, which further supports the association between increased CCL2 and CCL3 levels and the progression of early atherosclerotic processes [29]. The CCL23 pro-atherogenic effect is enacted when it is expressed into milieu with increased LDL via stimulation of monocytes and macrophages chemotaxis into the vascular wall, increased expression of adhesion molecules and release of matrix metalloproteinase 2 (MMP-2) from monocytes [30, 31]. A favorable outcome in patients with atherothrombotic and cardioembolic IS was associated with increased concentrations of CCL25 chemokine, TNF- α and IL-6. Despite sound body of accumulated knowledge of pro-inflammatory properties of these cytokines, a number of researchers have demonstrated their opposite effect in acute IS due to mitigation of hypoxic-ischemic damage, arteriodilatation, and anti-apoptotic effects. CCL25 protection of neurons, endothelium, and microglia cells was explained by activation of NLR (NOD-like receptors) family, involved in regulation of inflammatory cascades by inhibiting the transcriptional nuclear factor-kappa B (NF- κ B) processing and mitogen-activated protein kinases (MAPK), and also by activation of apoptosis regulator Bcl-2. [32]. IL-6 and TNF- α protection after excitotoxic damage, provided via modulation of neurogenesis, angiogenesis, and revascularization processes by activating the JAK/STAT (Janus kinase/signal transducers and activators of transcription) and PI3K (phosphoinositide 3-kinase) signaling pathways, was elucidated in a number of studies [33, 34].

Concentrations of CXCL5 and MIF were identified as immunological markers of unfavorable prognosis in patients with lacunar IS. Currently, scientific experience regarding the role of CXCL5 in the pathogenesis of lacunar stroke is limited to experimental studies, demonstrating expression of astrocytic and endothelial CXCL5 in progression of chronic cerebral ischemia and WMH via modulation of microglia activity and induction of interleukin-17 expression [35, 36]. In addition, CXCL5 concentration was established as a marker of unfavorable FO in patients with diabetes mellitus. These results are consistent with CXCL5 mechanism of action, which promotes insulin resistance via potentiation

of TNF- α effects and activation of JAK/STAT (Janus kinases/signal transducer and activator of transcription) [37, 38]. Unlike CXCL5, the MIF role in development of cerebral ischemia has been extensively studied, but remains controversial. Recent studies showed that increased MIF activity in hypoxic environment, driven by expression of hypoxia-inducible factor 1 α (HIF-1- α), positively correlated with disease severity, ischemic lesion size, and neurological outcomes [39, 40]. The results of some studies show a direct correlation between the Fazekas scale score and concentration of MIF, suggesting that increase in MIF concentration may be a predictor of cerebral microangiopathy progression [41]. Given significant prevalence of patients with high BMI in the lacunar IS group, MIF expression can be associated with obesity. This is supported by studies demonstrating MIF involvement in the inhibition of hormone-sensitive lipase, which contributes to increase in triglyceride levels and exacerbation of obesity [42, 43]. MIF expression also contributes to endothelial dysfunction by regulating leukocyte trafficking into the endothelial wall, expression of adhesion molecules and TNF- α via stimulation of endothelial granular protein P-selectin [44].

Limitations. The main limitations of the study were exclusion of patients with fatal outcomes from the core data sheet, no monitoring of relevant cellular immunological parameters, and missed registration of the prospective study protocol.

Conclusion

The results of the study demonstrated differences in sets of factors affecting the functional outcome of patients with IS, depending on the pathogenetic subtype. Female gender, recurrent IS, an increase in CXCL-2F were the predictors of unfavorable outcome in patients with cardioembolic IS. For patients with the atherothrombotic subtype, WMH grade and contents of CCL2, CCL3 and CCL23 were the significant factors of unfavorable prognosis. Age, recurrent IS, BMI > 35 kg/m², and WMH grade, along with increased levels of CXCL5 and MIF, were identified as indicators of unfavorable FO in patients with lacunar IS. Type 2 diabetes mellitus was verified as an independent predictor of eventual disabling disorders, regardless of the stroke pathogenetic mechanisms.

The parameters associated with a favorable FO in patients with the cardioembolic IS were CCL25 and IL-6 expression, with the atherothrombotic subtype — grade 1 obesity along with TNF- α expression, with lacunar IS — underlying AH and grade 1 obesity. Despite the potential value of these results for improving prediction of acute stroke outcomes, further research is needed to confirm the significance of these markers by monitoring key clinical indicators, expanding the sample size, and using diverse statistical analysis methods.

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