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Development of multivariate models for the verification of short-term vital and functional prognosis in patients with hemorrhagic hemispheric stroke in the onset of the disease

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The main purpose of the study was to develop multivariate models for the verification of short-term vital and functional prognosis in patients with hemorrhagic hemispheric stroke in the onset of the disease.

Materials and methods. A prospective, cohort, comparative study was conducted in 203 patients with spontaneous supratentorial intracerebral hemorrhage (SSICH) (121 men and 82 women, mean age 65.1 ± 0.8 years), who were hospitalized within the first 12 hours since the onset of the disease and received conservative therapy. National Institute of Health Stroke Scale (NIHSS) score, Glasgow Coma Scale score, Full Outline of UnResponsiveness Scale score, intracerebral hemorrhage volume, displacement of the septum pellucidum and pineal gland, white blood cell count (WBCC), neutrophil count, lymphocyte count, monocyte count, neutrophil-to-lymphocyte ratio (NLR) were detected upon admission to the hospital. The functional outcome (FO) of the acute period of the disease was assessed on the 21st day in accordance with the modified Rankin Scale (mRS), whereas >3 points on this scale were considered as an unfavourable FO, ≤3 points were considered as a favourable FO. Binary logistic regression method and ROC-analysis were used for the elaboration of prediction criteria.

Results of research. Lethal outcome (12.3 %), unfavourable FO (37.5 %) and favourable FO (51.2 %) were registered in the structure of acute period outcomes of the disease. In accordance with the data of multivariate regression analysis it was determined that admission NIHSS score >16 (Se = 68.0 %, Sp = 93.3 %), septum pellucidum displacement >3 mm (Se = 84.0 %, Sp = 74.2 %) and admission WBCC >8 600 cells/μL (Se = 84.0 %, Sp = 62.4 %) are independently associated with an increased risk of the lethal outcome of the acute period of SSICH by 12.8 (12.8–26.8) (P < 0.0001), 10.7 (3.8–29.8) (P < 0.0001) and 6.9 (2.4–19.3) (P = 0.0003) times respectively. Admission NIHSS score >9 (Se = 90.5 %, Sp = 66.3 %), septum pellucidum displacement ≥1 mm (Se = 71.6 %, Sp = 71.2 %) and ANLR >2.92 (Se = 86.5 %, Sp = 36.5 %) were independently associated with an increased risk of the unfavourable FO of the acute period of SSICH by 4.9 (2.9–8.3) (P < 0.0001), 2.9 (2.6–3.3) (P < 0.0001) and 2.4 (2.1–2.7) (P < 0.0001) times respectively.

Conclusions. Multivariate models for lethal outcome prognosis (AUC = 0.94 (0.89–0.97), P < 0.01) and unfavourable functional outcome of SSICH prediction (AUC = 0.88 (0.83–0.93), P < 0.01) were elaborated, which take into consideration the combination of clinical, neuroimaging data and the severity of inflammatory activation in the onset of the disease. Informativeness of elaborated multivariate models, which integrated independent predictors, statistically exceeds informativeness of separate predictors usage in verification of the vital and functional prognosis of SSICH acute period outcome.

Ключові слова: внутрішньомозковий крововилив, комп'ютерна томографія, запалення, смертність, прогноз.

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Розробка мультиваріантних моделей для визначення короткострокового прогнозу в пацієнтів із геморагічним півкульовим інсультом у дебюті захворювання

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Мета роботи – розробити мультиваріантні моделі для визначення короткострокового прогнозу в пацієнтів із геморагічним півкульовим інсультом у дебюті захворювання.

Матеріали та методи. Виконали проспективне, когортне, порівняльне дослідження 203 пацієнтів із ССВМК (121 чоловік і 82 жінки, середній вік – 65,1 ± 0,8 року), які були госпіталізовані в перші 12 годин від дебюту захворювання та отримували консервативну терапію. Під час госпіталізації виконали тестування за клінічними шкалами оцінювання вираженості неврологічного дефіциту (National Institute of Health Stroke Scale (NIHSS), Glasgow Coma Scale, Full Outline of Unresponsiveness), визначили об'єм осередку ураження, зсув прозорої перетинки й епіфіза, абсолютний вміст лейкоцитів (АВЛ), нейтрофілів, лімфоцитів, моноцитів у периферичній крові та нейтрофіл-лімфоцитарне співвідношення (НЛС). Функціональний вихід (ФВ) оцінювали на 21 день захворювання за модифікованою шкалою Ренкіна (мШР), при цьому значення >3 балів розглядали як несприятливий, ≤3 – як сприятливий ФВ. Для розроблення критеріїв прогнозування використали метод бінарної логістичної регресії.

Результати. У структурі наслідків гострого періоду захворювання зареєстрували летальний вихід (12,3 %), несприятливий (37,5 %) та сприятливий (51,2 %) ФВ. У результаті мультиваріантного регресійного аналізу встановили, що значення сумарного бала за NIHSS >16 (Se = 68,0 %, Sp = 93,3 %), зміщення прозорої перегородки >3 мм (Se = 84,0 %, Sp = 74,2 %) та АВЛ >8 600 кл/мкл (Se = 84,0 %, Sp = 62,4 %) в дебюті ССВМК незалежно асоційовані з підвищеним ризиком летального наслідку гострого періоду захворювання в 12,8 (12,8–26,8) (p < 0,0001), 10,7 (3,8–29,8) (p < 0,0001) та 6,9 (2,4–19,3) (p = 0,0003) раза відповідно. Значення сумарного бала за NIHSS >9 (Se = 90,5 %, Sp = 66,3 %), зміщення прозорої перегородки ≥1 мм (Se = 71,6 %, Sp = 71,2 %) та НЛС >2,92 (Se = 86,5 %, Sp = 36,5 %) у дебюті ССВМК незалежно асоційовані з підвищеним ризиком несприятливого функціонального виходу гострого періоду захворювання в 4,9 (2,9–8,3) (p < 0,0001), 2,9 (2,6–3,3) (p < 0,0001) та 2,4 (2,1–2,7) (p < 0,0001) раза відповідно.

Висновки. Розробили мультиваріантні математичні моделі для прогнозування летального (AUC = 0,94 (0,89–0,97), p < 0,01; точність прогнозування = 91,7 %) та функціонального виходу гострого періоду ССВМК (AUC = 0,88 (0,83–0,93),

p < 0,01), які враховують сукупність результатів клініко-нейровізуалізаційного дослідження та вираженість запальної активації в дебюті захворювання, при цьому інтеграція незалежних предикторів у структурі мультиваріантних моделей дає можливість підвищити точність визначення вітального та функціонального прогнозу.

Разработка мультивариантных моделей для определения краткосрочного витального и функционального прогноза у пациентов с геморрагическим полушарным инсультом в дебюте заболевания

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Ключевые слова: внутримозговое кровоизлияние, компьютерная томография, воспаление, смертность, прогноз.

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Цель работы – разработать мультивариантные модели для определения краткосрочного витального и функционального прогноза у пациентов с геморрагическим полушарным инсультом в дебюте заболевания.

Материалы и методы. Проведено проспективное, когортное, сравнительное исследование 203 пациентов с СЗВМК (121 мужчина и 82 женщины, средний возраст – 65,1 ± 0,8 года), которые были госпитализированы в первые 12 часов от дебюта заболевания и получали консервативную терапию. При поступлении проводили тестирование по клиническим шкалам оценки выраженности неврологического дефицита (National Institute of Health Stroke Scale (NIHSS), Glasgow Coma Scale, Full Outline of Unresponsiveness), определяли объем очага поражения, смещение прозрачной перегородки и эпифиза, абсолютное содержание лейкоцитов (АСЛ), нейтрофилов, лимфоцитов, моноцитов в периферической крови и нейтрофил-лимфоцитарное соотношение (НЛС). Функциональный исход (ФИ) оценивали на 21 сутки заболевания по модифицированной шкале Рэнкина (мШР), при этом значения >3 балла рассматривали в качестве неблагоприятного ФИ, ≤3 – благоприятного. Для разработки критериев прогнозирования использовали метод бинарной логистической регрессии.

Результаты. В структуре исходов острого периода заболевания зарегистрированы летальный исход (12,3 %), неблагоприятный (37,5 %) и благоприятный (51,2 %) ФИ. В результате мультивариантного регрессионного анализа установлено, что значение суммарного балла по NIHSS >16 (Se = 68,0 %, Sp = 93,3 %), смещение прозрачной перегородки >3 мм (Se = 84,0 %, Sp = 74,2 %) и АСЛ >8 600 кл/мкл (Se = 84,0 %, Sp = 62,4 %) в дебюте СЗВМК независимо ассоциированы с повышенным риском летального исхода острого периода заболевания в 12,8 (12,8–26,8) (p < 0,0001), 10,7 (3,8–29,8) (p < 0,0001) и 6,9 (2,4–19,3) (p = 0,0003) раза соответственно. Значение суммарного балла по NIHSS >9 (Se = 90,5 %, Sp = 66,3 %), смещение прозрачной перегородки ≥1 мм (Se = 71,6 %, Sp = 71,2 %) и НЛС >2,92 (Se = 86,5 %, Sp = 36,5 %) в дебюте СЗВМК независимо ассоциированы с повышенным риском неблагоприятного функционального исхода острого периода заболевания в 4,9 (2,9–8,3) (p < 0,0001), 2,9 (2,6–3,3) (p < 0.0001) и 2,4 (2,1–2,7) (p < 0,0001) раза соответственно.

Выводы. Разработаны мультивариантные математические модели для прогнозирования летального (AUC = 0,94 (0,89–0,97), p < 0,01; точность прогнозирования = 91,7 %) и функционального исхода острого периода СЗВМК (AUC = 0,88 (0,83–0,93), p < 0,01), которые учитывают совокупность результатов клинико-нейровизуализационного исследования и выраженность воспалительной активации в дебюте заболевания, при этом интеграция независимых предикторов в структуре мультивариантных моделей позволяет повысить точность определения витального и функционального прогноза.

Spontaneous hypertensive intracerebral hemorrhage (ICH) is a global problem of modern medicine. A high social significance of the disease is due to high rates of adults' mortality and disability in most countries of the world [9].

One of the ways to increase the effectiveness of treatment for patients with spontaneous supratentorial cerebral hemorrhage (SSICH) is the earliest verification of the individual vital and functional prognosis of the acute period outcome of the disease, which would serve as the basis for a differentiated choice of the optimal treatment strategy [20]. All of the above justifies the advisability of research, which is aimed at finding parameters associated with the course and outcome of the acute period of the disease.

A significant amount of data has been currently accumulated. The data confirm the predictive value of clinical-neuroimaging criteria for the assessment of the severity in patients with SSICH (severity of neurological deficit, lesion volume, etc.) [14,16].

However, SSICH is a multi-pathogenetic process. Not only primary (in the form of direct mechanical destructive effects produced by hematoma) but also secondary (thrombin-induced) mechanisms of brain damage act a part in its progress [7]. Among the latter, the leading role belongs to inflammatory activation. The response to ICH occurs in four distinct phases: (1) initial tissue damage and localization of inflammatory factors, (2) inflammation-driven breakdown of the blood-brain barrier, (3) recruitment of circulating inflammatory cells and subsequent secondary immunopathology, and (4) engagement of the tissue repair replies that promote tissue repair and restoration of neurologic function [3]. On the basis of experimental studies, it is convincingly shown that inflammatory macrophages and neutrophils in-filtrate the central nervous system after ICH, with blood-derived macrophages, the dominant phagocyte population in the ipsilateral hemisphere from 12 hours to 7 days posthemorrhage [6–8,12]. Blood-derived macrophages and neutrophils become highly activated upon recruitment to the perihematomal region after ICH in response to cytokines such as tumor necrosis factor alpha and interleukin 1 beta, as well as the inflammation-associated factors thrombin, heme, and HMGB1. These inflammatory signals bind to the cell surface receptors on myeloid cells, resulting in NF-κB activation and production of inflammatory cytokines,

reactive oxygen species, and nitric oxide that contribute to tissue damage [9,13].

A number of clinical studies revealed the relationship between some hematological markers of inflammatory activation in the onset of ICH (increasing of leukocyte count, neutrophil count, monocyte count, neutrophil-to-lymphocyte ratio) and the severity of cerebral syndrome, the lesion size, the presence of intraventricular hemorrhage, the early neurologic deterioration due to hematoma expansion [2,10,15,16].

All of the above mentioned suggests that the assessment of the severity of inflammatory activation with the use of hematological markers in combination with clinical and neuroimaging data will make possible the integration of their prognostic value and will contribute to the development of informative integral criteria for the verification of the vital and functional prognosis of SSICH acute period outcome in the very onset of the disease.

The purpose of this study

To develop multivariate models for the verification of short-term vital and functional prognosis in patients with hemorrhagic hemispheric stroke in the onset of the disease.

Materials and methods

A prospective, cohort, comparative study was conducted in 203 patients with SSICH (121 men and 82 women, mean age 65.1 ± 0.8 years). They were hospitalized within the first 12 hours since the onset of the disease and received conservative therapy at Brain circulation disorders Department of the Municipal Institution "City Clinical Hospital No.6". The diagnosis was established on the basis of clinical and neuroimaging criteria. Clinical and neurological study included an assessment in accordance with the National Institute of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS), Full Outline of UnResponsiveness Scale (FOUR) upon admission to the hospital (NIHSS0, GCS0 and FOUR0) and in the course of the disease. Neuroimaging study was carried out with the help of Computed Tomography Scan "Siemens Somatom Spirit" (Germany). The severity of the dislocation syndrome was estimated in accordance with the displacement of the septum pellucidum and pineal gland. The lesion size (ICH volume) was calculated with the help of the following formula: ICH volume (mL) = (A * B * C) / 2, where A, B, C correspond to linear lesion size (cm). Upon admission to the hospital, laboratory samples of whole blood from the ulnar veins were taken into a test tube containing EDTA. White blood cell counts were analyzed in the hematology laboratory of Municipal Institution "City Clinical Hospital No.6" as standard of care. Admission white blood cell count (AWBCC), admission neutrophil count (ANC), admission lymphocyte count (ALC), admission monocyte count (AMC), admission neutrophil percent (ANP), admission lymphocyte percent (ALP), admission monocyte percent (AMP) and admission neutrophil-to-lymphocyte ratio (ANLR) were detected.

The study excluded patients who have acute disorders of cerebral circulation (transient ischemic attacks or/and strokes) in the anamnesis, indications for neurosurgical intervention, oncological and / or decompensated somatic pathology, clinical criteria of infectious and inflammatory diseases in the onset of SSICH. The cases of extracerebral cause of death (acute myocardial infarction, pulmonary embolism, etc.) in accordance with the autopsy results were also excluded.

The functional outcome of the acute period of the disease was assessed on the 21st day in accordance with the modified Rankin Scale (mRS), whereas >3 points on this scale were considered as an unfavourable functional outcome, ≤3 points were considered as a favourable functional outcome.

Statistical analysis of the results was carried out with the help of Statistica 6.0 software (StatSoft Inc., USA, series number AXXR712D833214FAN5) and MedCalc (version 16.4). The distribution normality of studied traits was estimated on the basis of Shapiro–Wilk criterion. Descriptive statistics were presented in the form of mean and standard error of mean (M ± m) for values with normal distribution and in the form of median (Me) and interquartile range (Q_{25}–Q_{75}) for parameters with the distribution that differs from normal. To determine intergroup differences, the Mann-Whitney test was used. Binary logistic regression method was used for the elaboration of prediction criteria. To determine independent predictors, factors that had significant predictive value throughout univariate analysis were included step by step into the multivariate model. The determination of prediction criteria in the form of values of obtained binary logistic regression equations with the optimum sensitivity (Se) and specificity (Sp) was carried out on the basis of the ROC analysis. Comparison of prognostic criteria informativeness was made on the ground of ROC-analysis. For evaluation of the links between quantitative signs Fisher's exact test and Chi-square test were used. Odds ratio (OR) and relative risk (RR) were calculated. Statistically significant were the results with level $P < 0.05$.

Results of research

The values of studied indexes in patients upon admission to the hospital are presented in *Table 1*.

Secondary intraventricular hemorrhage (IVH) was verified in 127 (62.6 %) cases. Lethal outcome (12.3 %), unfavourable functional outcome in the form of >3 points according to the modified Rankin scale on the 21st day of SSICH (37.5 %) and favourable functional outcome in the form of ≤3 points (51.2 %) were registered in the structure of acute period outcomes of the disease. Lethal outcome was linked with hematoma progression which was confirmed by clinical neurological investigation (steady reduction of GCS score and FOUR score during first 3–5 days from the disease onset) and autopsy.

It was determined that patients with a lethal outcome in the acute period of SSICH had higher NIHSS score, ICH volume, septum pellucidum displacement, pineal gland displacement, AWBCC, ANC and AMC in the onset of the disease, while GCS score, FOUR score and ALP in this cohort of patients were statistically significantly lower (*Table 2*).

The frequency of the secondary intraventricular hemorrhage (IVH) was higher in patients with lethal outcome

(88.0 % versus 59.0 %, Fisher's exact test P < 0.0001). On the basis of univariate logistic regression analysis, the following indicators were associated with the risk of a lethal outcome of SSICH acute period: admission NIHSS score, admission GCS score, admission FOUR score, ICH volume, septum pellucidum displacement (SPD), pineal gland displacement, presence of the secondary IVH, AWBCC, ANC and AMC (*Table 3*).

In accordance with the data of multivariate regression analysis it was determined that independent predictors of the lethal outcome of SSICH acute period are: admission NIHSS score (OR (95 % CI) = 1.20 (1.07–1.34), P = 0.0016), septum pellucidum displacement (OR (95 % CI) = 1.30 (1.16–1.53), P = 0.0009) and AWBCC (OR (95 % CI) = 1.22 (1.03–1.44), P = 0.0234).

The optimal cut-off values of the admission NIHSS score >16 (Se = 68.0 %, Sp = 93.3 %), septum pellucidum displacement >3 mm (Se = 84.0 %, Sp = 74.2 %) and AWBCC >8 600 cells/μL (Se = 84.0 %, Sp = 62.4 %) were determined as for the lethal outcome prognosis of SSICH acute period.

The frequency distribution of lethal outcome of the SSICH acute period in terms of NIHSS score, septum pellucidum displacement and AWBCC is shown in *Table 4*.

As a result, the admission NIHSS score >16, septum pellucidum displacement >3 mm and AWBCC >8 600 cells/μL are associated with an increased risk of the lethal outcome of the acute period of SSICH by 12.8 (12.8–26.8) (P < 0.0001), 10.7 (3.8–29.8) (P < 0.0001) and 6.9 (2.4–19.3) (P = 0.0003) times respectively.

For the purpose of acute period of SSICH lethal outcome predictors prognostic value integration a multivariate mathematical model was elaborated in the form of a binary logistic regression equation, as follows: β1 = 0.181*[admission NIHSS score] + 0.266*[septum pellucidum displacement (mm)] + 0.000196*[AWBCC (cells/μL)] – 7.75.

The approximation accuracy of the interrelation between predictors and dependent variable constituted 91.7% (Chi-square = 74.6, P < 0.0001; Hosmer & Lemeshow test P = 0.72).

It was detected that informativeness of multivariate mathematic model statistically exceeds informativeness of separate predictors usage in prognosis of SSICH lethal outcome ($AUC_{\beta1}$ = 0.94 (0.89–0.97) vs AUC_{NIHSS0} = 0.85 (0.80–0.90), P = 0.0442; $AUC_{\beta1}$ = 0.94 (0.89–0.97) vs AUC_{SPD} = 0.84 (0.78–0.88), P = 0.0253; $AUC_{\beta1}$ = 0.94 (0.89–0.97) vs AUC_{AWBCC} = 0.79 (0.73–0.85), P = 0.0008).

On the basis of the ROC-analysis it was determined that the value β1 > -1.27 is the predictor of the lethal outcome of SSICH acute period with sensitivity levels 84.0 % and specificity levels 94.9 %.

It was determined that patients with an unfavourable functional outcome in SSICH acute period were statistically distinguished by the following criteria in the onset of the disease: age, admission NIHSS score, admission GCS score, admission FOUR score, ANC, ALC, ANP, ALP, ANLR. No intergroup differences were found in relation to AWBCC level (*Table 5*).

The frequency of secondary intra-cerebral hemorrhage was higher in patients with unfavourable functional outcome (71.2 % versus 51.0 %, Chi-square test P = 0.0109).

Table 1. Values of studied indexes in patients upon admission to the hospital (M ± m)

Index, Unit	Value
Admission NIHSS score	11.20 ± 0.44
Admission GCS score	13.10 ± 0.20
Admission FOUR score	14.50 ± 0.18
ICH volume, mL	20.00 ± 1.66
Septum pellucidum displacement, mm	2.80 ± 0.26
Pineal gland displacement, mm	2.30 ± 0.22
AWBCC, cells/μL	8 500 ± 210
ANC, cells/μL	6 700 ± 200
ALC, cells/μL	1 400 ± 40
AMC, cells/μL	400 ± 20
ANP, %	76.50 ± 0.64
ALP, %	17.70 ± 0.55
AMP, %	5.00 ± 0.20
ANLR	6.20 ± 0.39

Table 2. Analysis of intergroup differences between indexes in patients in the onset of SSICH versus the acute period outcome of the disease, Me (Q_{25}–Q_{75})

Indexes	Lethal outcome (n = 25)	Non-lethal outcome (n = 178)	P
Age, years	61.0 (52.0–75.0)	66.0 (58.0–75.0)	0.2004
Admission NIHSS score	20.0 (15.0–28.0)	9.0 (6.0–14.0)	<0.0001
Admission GCS score	10.0 (5.0–13.0)	15.0 (14.0–15.0)	<0.0001
Admission FOUR score	13.0 (7.0–14.0)	16.0 (15.0–16.0)	<0.0001
ICH volume, mL	55.4 (27.1–78.0)	9.6 (4.4–20.7)	<0.0001
Septum pellucidum displacement, mm	10.0 (4.0–12.0)	0.0 (0.0–4.0)	<0.0001
Pineal gland displacement, mm	5.0 (3.0–10.0)	0.0 (0.0–3.0)	<0.0001
AWBCC, cells/μL	10 400 (8 800–13 800)	7 700 (6 300–9 600)	<0.0001
ANC, cells/μL	9 000 (6 300–10 800)	5 800 (4 400–7 800)	<0.0001
ALC, cells/μL	1 400 (1 100–2 000)	1 300 (1 000–1 700)	0.2682
AMC, cells/μL	500 (300–900)	300 (200–500)	0.0008
ANP, %	82.0 (72.0–87.0)	76.0 (70.0–82.0)	0.0645
ALP, %	12.0 (9.0–18.0)	18.0 (12.0–24.0)	0.0214
AMP, %	5.0 (4.0–7.0)	4.0 (3.0–6.0)	0.2443
ANLR	7.00 (3.83–9.89)	4.19 (2.92–6.54)	0.0268

Table 3. Dependent and independent predictors of lethal outcome of SSICH acute period (univariate and multivariate logistic regression models)

Indexes	Univariate logistic regression model		Multivariate logistic regression model	
	OR (95 % CI)	P	OR (95 % CI)	P
Admission NIHSS score	1.33 (1.21–1.45)	<0.0001	1.20 (1.07–1.34)	0.0016
Admission GCS score	0.66 (0.58–0.76)	<0.0001		
Admission FOUR score	0.65 (0.55–0.76)	<0.0001		
ICH volume, mL	1.06 (1.04–1.08)	<0.0001		
Septum pellucidum displacement, mm	1.49 (1.31–1.70)	<0.0001	1.30 (1.16-1.53)	0.0009
Pineal gland displacement, mm	1.51 (1.30–1.75)	<0.0001		
Presence of the secondary IVH	3.56 (1.17–10.82)	0.0124		
AWBCC, cells/μL	1.35 (1.18–1.54)	<0.0001	1.22 (1.03-1.44)	0.0234
ANC, cells/μL	1.32 (1.16–1.51)	<0.0001		
AMC, cells/μL	8.15 (2.45–26.80)	0.0005		

Table 4. Frequency distribution of lethal outcome of the acute CHSS period in terms of NIHSS score, septum pellucidum displacement and AWBCC

Parameters	Value	Number of patients	Lethal outcome of the SSICH acute period (%)
Admission NIHSS score	>16	29	58.6
	≤16	174	4.6
Septum pellucidum displacement, mm	>3	67	32.3
	≤3	136	2.9
AWBCC, cells/μL	>8 600	88	23.9
	≤8 600	115	3.5

Table 5. Analysis of intergroup differences of studied indexes in patients in the onset of SSICH in comparison with the functional outcome of the acute period of the disease, Me (Q_{25}–Q_{75}).

Indexes	mRS score ≤3 on the 21st day of SSICH (n = 104)	mRS score >3 on the 21st day of SSICH (n = 74)	P
Age, years	63.0 (57.0–73.0)	71.0 (60.3–77.0)	0.0016
Admission NIHSS score	7.0 (5.0–9.3)	14.0 (10.3–16.0)	<0.0001
Admission GCS score	15.0 (14.0–15.0)	14.0 (12.0–15.0)	<0.0001
Admission FOUR score	16.0 (15.0–16.0)	15.0 (14.0–16.0)	<0.0001
ICH volume, mL	6.5 (2.5–14.1)	13.5 (6.2–29.7)	0.0001
Septum pellucidum displacement, mm	0.0 (0.0–1.3)	3.0 (0.0–5.0)	<0.0001
Pineal gland displacement, mm	0.0 (0.0-2.0)	2.0 (0.0-4.0)	<0.0001
AWBCC, cells/μL	7 400 (6 100–9 200)	8 000 (6 800–9 800)	0.0808
ANC, cells/μL	5 500 (4 200–7 400)	6 300 (4 800–8 300)	0.0291
ALC, cells/μL	1 400 (1 100–1 800)	1 100 (900–1 500)	0.0015
AMC, cells/μL	300 (200–500)	300 (200–500)	0.8065
ANP, %	75.0 (67.8–79.3)	79.0 (73.0–86.8)	0.0009
ALP, %	19.0 (14.0–25.0)	15.5 (10.0–21.0)	0.0006
AMP, %	5.0 (3.0–7.0)	4.0 (3.0–6.0)	0.2879
ANLR	3.92 (2.74–5.61)	5.28 (3.39–8.70)	0.0006

Table 6. Dependent and independent predictors of the unfavourable functional outcome of SSICH acute period in the form of mRS score t3 on the 21st day of the disease (univariate and multivariate logistic regression models)

Indexes	Univariate logistic regression model		Multivariate logistic regression model	
	OR (95 % CI)	P	OR (95 % CI)	P
Age, years	1.04 (1.01–1.07)	0.0044		
Admission NIHSS score	1.42 (1.28–1.57)	<0.0001	1.34 (1.20–1.50)	<0.0001
Admission GCS score	0.80 (0.69–0.93)	0.004		
Admission FOUR score	0.81 (0.66–0.99)	0.0405		
ICH volume, mL	1.04 (1.02–1.07)	0.0005		
Septum pellucidum displacement, mm	1.42 (1.23–1.64)	<0.0001	1.20 (1.02–1.41)	0.0309
Pineal gland displacement, mm	1.46 (1.24–1.72)	<0.0001		
Presence of the secondary IVH	4.22 (2.15–8.30)	<0.0001		
ANC, cells/μL	1.16 (1.03–1.31)	0.0135		
ALC, cells/μL	0.35 (0.18–0.66)	0.0013		
ANP, %	1.06 (1.03–1.10)	0.001		
ALP, %	0.92 (0.88–0.96)	0.0002		
ANLR	1.18 (1.08–1.29)	0.0004	1.10 (1.00–1.21)	0.0472

On the basis of univariate logistic regression analysis, it was determined that the following indexes are associated with the risk of unfavourable functional outcome of SSICH acute period: age, admission NIHSS score, admission GCS score, admission FOUR score, ICH volume, septum pellucidum displacement, pineal gland displacement, presence of the secondary IVH, ANC, ALC, ANP, ALP and ANLR (*Table 6*).

In accordance with the data of multivariate regression analysis it was determined that independent predictors of the unfavourable functional outcome of SSICH acute period are: admission NIHSS score (OR (95 % CI) = 1.34 (1.20–1.50), P < 0.0001), septum pellucidum displacement (OR (95 % CI) = 1.20 (1.02–1.41), P = 0.0309) and ANLR (OR (95 % CI) = 1.10 (1.00–1.21), P = 0.0472).

The optimal cut-off values of the admission NIHSS score >9 (Se = 90.5 %, Sp = 66.3 %), septum pellucidum displacement ≥1 mm (Se = 71.6 %, Sp = 71.2 %) and ANLR > 2.92 (Se = 86.5 %, Sp = 36.5 %) were determined as for the unfavourable functional outcome prognosis of SSICH acute period.

The frequency distribution of unfavourable functional outcome of the SSICH acute period in terms of NIHSS score, septum pellucidum displacement and ANLR is shown in *Table 7*.

As a result, the admission NIHSS score >9, septum pellucidum displacement ≥1 mm and ANLR >2.92 are associated with an increased risk of the unfavourable functional outcome of the acute period of SSICH by 4.9 (2.9–8.3) (P < 0.0001), 2.9 (2.6–3.3) (P < 0.0001) and 2.4 (2.1–2.7) (P < 0.0001) times respectively.

For integration of the prognostic values of predictors of SSICH acute period unfavourable functional outcome multivariate mathematical model was elaborated in the form of a binary logistic regression equation, as follows: β2 = 0.294*[admission NIHSS score] P1 + 0.179*[septum pellucidum displacement] + 0.096*[ANLR] – 4.27.

The approximate accuracy of the interrelationship between predictors and dependent variable constituted 80.9 % (Chi-square = 81.46, P < 0.0001; Hosmer & Lemeshow test P = 0.24; AUC = 0.88 (0.83–0.93), P < 0.01).

It was revealed that elaborated mathematic model is statistically informatively higher than single application of separate predictors for prognosis of SSICH acute period FO ($AUC_{β2}$ = 0.88 (0.83–0.93) vs AUC_{NIHSS0}=0.80 (0.73–0.86), P = 0.0265; $AUC_{β2}$ = 0.88 (0.83–0.93) vs AUC_{SPD} = 0.73 (0.66–0.80), P = 0.0008; $AUC_{β1}$ = 0.88 (0.83–0.93) vs AUC_{ANLR} = 0.65 (0.58–0.72), P < 0.0001).

On the basis of the ROC-analysis it was determined that the value β2 > -1.51 is the predictor of the favourable functional outcome of SSICH acute period with the sensibility levels 94.7 % and specificity levels 70.2 %.

Discussion

Thus, our study revealed higher values of admission NIHSS score, ICH volume, septum pellucidum displacement and pineal gland displacement and lower values of admission GCS score, admission FOUR score in patients with increased risks of a lethal outcome and unfavourable functional outcome of SSICH acute period. It accords with the results of other studies which prove

a high predictive value of clinical and neuroimaging parameters, reflecting the severity of primary damage of the brain tissue due to direct destructive influence of hematoma [14,16]. Among neuroimaging parameters, an independent association with a risk of death and functional disability was detected in septum pellucidum displacement, which confirms the leading role of the dislocation syndrome in the realization of unfavourable variants of SSICH acute period outcome. However, according to the results of our research the independent association between ICH volume as compared to septum pellucidum displacement and pineal gland displacement was not determined. To our opinion absence of ICH volume in the specter of independent lethal and unfavourable functional outcome predictors according to multivariate analysis testify to the limitation of the prognostic value of this parameter without taking into account the degree of perihematomal edema. The frequency of the secondary IVH was significantly higher in patients with unfavourable vital prognosis and functional prognosis of SSICH acute period outcome. However presence of the secondary IVH was not independently associated with SSICH acute period outcome.

Patients with an increased risk of lethal outcome revealed higher values of admission white blood cell count. The obtained data accord with the results of other studies. Thus, in accordance with W. Sun [et al.] (2012), leucocytosis was predictive of early neurological deterioration within the first 72 hours after ICH [16]. In a study by R. Behrouz [et al.] (2015), an inverse relationship between leukocyte count and GCS score in admission was shown. However, there was no correlation between admission leukocytosis and poor outcome at discharge, as it was not in our study [4].

On the basis of the results of our study, the up AWBCC level in patients with an increased lethal risk of SSICH acute period outcome is due to the combined ANC and AMC elevation, which accords with the results of other studies which proved the role of blood-derived neutrophils and macrophages in the course of ICH acute period. In a study by S. Lattanci [et al.] (2017), it was determined that white blood cell count, neutrophil count and neutrophil-to-lymphocyte ratio on the 1st day from ICH onset were independently associated with neurological deterioration [10]. In a study by O. Adeoye [et al.] (2014), it was determined that the higher initial white blood cell count and neutrophil count were associated with higher ICH volume, whereas AMC was not. Baseline AMC was associated with greater odds of 30-day case fatality [1]. A study by A. Morotti et al. (2016) revealed that monocyte count is associated with higher risk of hematoma expansion [11]. In a study by M.D. Hammond et al. (2014) it was discovered that after ICH, the blood-derived CCR2 + Ly6C (hi) inflammatory monocytes were trafficked into the brain, outnumbered by other leukocytes, and produced tumor necrosis factor. These findings suggest that blood-derived inflammatory monocytes and neutrophils contribute to neurological disability and secondary injury after ICH (hematoma expansion and / or cerebral edema) [6].

The results that we obtained demonstrated the interrelation between ANLR increase in patients with an increased risk of lethal outcome and an unfavourable functional outcome, which accords with the results of other studies. Thus, in a study by F. Wang [et al.] (2016), NLR on the next morning the following admission was significantly higher in the patients who died (12.53 ± 9.33) than in those who survived (5.53 ± 4.68) (P < 0.001) [17]. A study conducted by C. Tao [et al.] (2017) revealed that higher AWBCC, ANC and NLR were independently associated with mortality and worse functional outcome. These hematological markers of inflammatory activation were correlated with admission Glasgow Coma Scale score and ICH volume [16]. At the same time, in accordance with the results of our multivariate logistic regression analysis, ANLR significance as an independent predictor was demonstrated to only verify the functional prognosis of SSICH acute period outcome. The obtained data accord with the results of a meta-analysis conducted by J. Zhang [et al.] (2017), which revealed that higher NLR was associated with a poorer functional outcome at 3 months, while higher NLR was not associated with higher risk of death at 3 months [19]. A study by A. Giede-Jeppe et al. (2017) also revealed that patients with an ANLR under the 25th percentile – compared to patients with an ANLR above the 25th percentile presented with a better clinical status, lower hematoma volumes on admission and showed a better functional outcome [5]. In our study, on the basis of the ROC analysis, it was discovered that the value of ANLR >2.92 is characterized by an optimal sensitivity and specificity ratio for the identification of patients with a favourable functional outcome of the acute period of the disease (RR = 2.4 (2.1–2.7), P < 0.0001).

Table 7. Frequency distribution of unfavourable functional outcome of the SSICH acute period in terms of NIHSS score, septum pellucidum displacement and ANLR

Parameters	Value	Number of patients	Unfavourable functional outcome of the SSICH acute period (%)
Admission NIHSS score	>9	87	70.1
	≤9	91	14.3
Septum pellucidum displacement, mm	≥1	83	63.9
	0	95	22.1
ANLR	>2.92	130	49.2
	≤2.92	48	20.8

Thus, the study made it possible to confirm and clarify the diagnostic significance of some hematological markers of inflammatory activation in the onset of SSICH (increasing of AWBCC (due to the combined ANC and AMC elevation) and ANLR) for the determination of vital and functional prognosis of the acute period outcome. The most informative parameter that reflects the severity of inflammatory activation in the onset of SSICH is AWBCC for the determination of the vital prognosis of the acute period outcome of the disease, whereas ANLR is a more informative parameter for the determination of the functional outcome. Based on the research, informative multivariate mathematical models were also developed. They make it possible to identify with accuracy patients with an increased risk of a lethal outcome and an unfavourable functional outcome of the acute period of the disease in the first 24 hours from the SSICH onset. It is possible to be done on the basis of a comprehensive assessment of clin-

ical neuroimaging data and hematological markers of inflammatory activation. At the same time, mathematic models that were elaborated exceed the separate predictors on informativeness and integrate the prognostic value of them, which justifies the advisability of their use in routine clinical practice as a one of the methods of choosing the optimal treatment strategy.

Conclusions

1. Admission NIHSS score >16 (Se = 68.0 %, Sp = 93.3 %), septum pellucidum displacement >3 mm (Se = 84.0 %, Sp = 74.2 %) and AWBCC >8 600 cells/μL (Se = 84.0 %, Sp = 62.4 %) are independently associated with an increased risk of the lethal outcome of the acute period of SSICH by 12.8 (12.8–26.8) (P < 0.0001), 10.7 (3.8–29.8) (P < 0.0001) and 6.9 (2,4–19,3) (P = 0.0003) times respectively.

2. Admission NIHSS score >9 (Se = 90.5%, Sp = 66.3 %), septum pellucidum displacement ≥1 mm (Se = 71.6 %, Sp = 71.2 %) and ANLR >2.92 (Se = 86.5 %, Sp = 36.5 %) were independently associated with an increased risk of the unfavourable functional outcome of the acute period of SSICH by 4.9 (2.9–8.3) (P < 0.0001), 2.9 (2.6–3.3) (P < 0.0001) and 2.4 (2.1–2.7) (P < 0.0001) times respectively.

3. Multivariate model for SSICH acute period lethal outcome prediction was elaborated, which takes into account admission NIHSS score, septum pellucidum displacement, AWBCC (AUC = 0.94 (0.89–0.97), P < 0.01; predictive accuracy = 91.6 %) and exceeds informativeness of the predictors in case of their single use.

4. Multivariate model for SSICH acute period functional outcome prediction was elaborated, which takes into account admission NIHSS score, septum pellucidum displacement, ANLR (AUC = 0.88 (0.83–0.93), P < 0.01; predictive accuracy = 81.5 %) and exceeds informativeness of the predictors in case of their single use.

The perspective for the further scientific research is the elaboration of criteria for the prediction of the course of SSICH acute period on the basis of the evaluation of the dynamics of inflammatory activation markers.

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References

[1] Adeoye, O., Walsh, K., Woo, J. G., Haverbusch, M., Moomaw, C. J., Broderick, J. P., et al. (2014). Peripheral monocyte count is associated with case fatality after intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*, 23(2), e107-e111. doi: 10.1016/j.jstrokecerebrovasdis.2013.09.006.
[2] Agnihotri, S., Czap, A., Staff, I., Fortunato, G., & McCullough, L. D. (2011). Peripheral leukocyte counts and outcomes after intracerebral hemorrhage. *J Neuroinflammation*, 8, 160. doi: 10.1186/1742-2094-8-160.
[3] Askenase, M. H., & Sansing, L. H. (2016). Stages of the Inflammatory Response in Pathology and Tissue Repair after Intracerebral Hemorrhage. *Seminars in neurology*, 36(3), 288–297. doi: 10.1055/s-0036-1582132.
[4] Behrouz, R., Hafeez, S., & Miller, C. M. (2015). Admission Leukocytosis in Intracerebral Hemorrhage: Associated Factors and Prognostic *Implications. Neurocrit Care*, 23(3), 370–373. doi: 10.1007/s12028-015-0128-7.
[5] Giede-Jeppe, A., Bobinger, T., Gerner, S. T., Sembill, J. A., Sprъgel, M. I., Beuscher, V. D., et al. (2017). Neutrophil-to-Lymphocyte Ratio Is an Independent Predictor for In-Hospital Mortality in Spontaneous Intracerebral Hemorrhage. *Cerebrovasc Dis*, 44(1–2), 26–34. doi: 10.1159/000468996.
[6] Hammond, M. D., Taylor, R. A., Mullen, M. T., Ai, Y., Aguila, H. L., Mack, M., Kasner, S. E., et al. (2014). CCR2+ Ly6C(hi) inflammatory monocyte recruitment exacerbates acute disability following intracerebral hemorrhage. *J Neurosci*, 34(11), 3901–3909. doi: 10.1523/JNEUROSCI.4070-13.2014.
[7] Hammond, M. D., Ai, Y., & Sansing, L. H. (2012). Gr1+ Macrophages and Dendritic Cells Dominate the Inflammatory Infiltrate 12 Hours After Experimental Intracerebral Hemorrhage. *Transl Stroke Res*, 3(1), 125–131. doi: 10.1007/s12975-012-0174-9.
[8] Hammond, M. D., Ambler, W. G., Ai, Y., & Sansing, L. H. (2014). α4 integrin is a regulator of leukocyte recruitment after experimental intracerebral hemorrhage. *Stroke*, 45(8), 2485–2487. doi: 10.1161/STROKEAHA.114.005551.
[9] Keep, R. F., Hua, Y., & Xi, G. (2012). Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. *Lancet Neurol.*, 11(8), 720–731. doi: 10.1016/S1474-4422(12)70104-7.
[10] Lattanzi, S., Cagnetti, C., Provinciali, L., & Silvestrini, M. (2017). Neutrophil-to-lymphocyte ratio and neurological deterioration following acute cerebral hemorrhage. *Oncotarget*, 8(34), 57489–57494. doi: 10.18632/oncotarget.15423.
[11] Morotti, A., Phuah, C. L., Anderson, C. D., Jessel, M. J., Schwab, K., Ayres, A. M., et al. (2016). Leukocyte Count and Intracerebral Hemorrhage Expansion. *Stroke; a journal of cerebral circulation*, 47(6), 1473–1478. doi: 10.1161/STROKEAHA.116.013176.
[12] Mracsko, E., Javidi, E., Na, S. Y., Kahn, A., Liesz, A., & Veltkamp, R. (2014). Leukocyte invasion of the brain after experimental intracerebral hemorrhage in mice. *Stroke*, 45(7), 2107–2114. doi: 10.1161/STROKEAHA.114.005801.
[13] Mracsko, E., & Veltkamp, R. (2014). Neuroinflammation after intracerebral hemorrhage. *Front Cell Neurosci*, 8, 388. doi: 10.3389/fncel.2014.00388.
[14] Spina, S., Marzorati, C., Vargiolu, A., Magni, F., Riva, M., Rota, M., et al. (2017). Intracerebral hemorrhage in intensive care unit: early prognostication fallacies. A single center retrospective study. *Minerva Anestesiol*. doi: 10.23736/S0375-9393.17.12225-X.
[15] Sun, W., Peacock, A., Becker, J., Phillips-Bute, B., Laskowitz, D. T., & James, M. L. (2012). Correlation of leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia*, 19(8), 1096–1100. doi: 10.1016/j.jocn.2011.11.020.
[16] Tao, C., Hu, X., Wang, J., Ma, J., Li, H., & You, C. (2017). Admission neutrophil count and neutrophil-to-lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage. *Biomark Med*, 11(1), 33–42. doi: 10.2217/bmm-2016-0187.
[17] Walsh, K. B., Sekar, P., Langefeld, C. D., Moomaw, C. J., Elkind, M. S., Boehme, A. K., et al. (2015). Monocyte Count and 30-Day Case Fatality in Intracerebral Hemorrhage. *Stroke*, 46(8), 2302–2304. doi: 10.1161/STROKEAHA.115.009880.
[18] Wang, F., Hu, S., Ding, Y., Ju, X., Wang, L., Lu, Q., & Wu, X. (2016). Neutrophil-to-Lymphocyte Ratio and 30-Day Mortality in Patients with Acute Intracerebral Hemorrhage. *J Stroke Cerebrovasc Dis*, 25(1), 182–187. doi: 10.1016/j.jstrokecerebrovasdis.2015.09.013.
[19] Zhang, J., Cai, L., Song, Y., Shan, B., He, M., Ren, Q., et al. (2017). Prognostic role of neutrophil lymphocyte ratio in patients with spontaneous intracerebral hemorrhage. *Oncotarget*, 8(44), 77752–77760. doi: 10.18632/oncotarget.20776.
[20] Mattishent, K., Kwok, C. S., Ashkir, L., Pelpola, K., Myint, P. K., Loke, Y. K. (2015). Prognostic Tools for Early Mortality in Hemorrhagic Stroke: Systematic Review and Meta-Analysis. *J Clin Neurol*, 11(4), 339–348. doi: 10.3988/jcn.2015.11.4.339.