JSC "WEST KAZAKHSTAN MARAT OSPANOV MEDICAL UNIVERSITY"

ANNOTATION
The dissertation thesis
for the degree of Doctor of Philosophy (PhD)

Prediction and prevention of secondary brain damage in patients with acute vascular and traumatic lesions

Speciality 6D110100 – Medicine
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ANNOTATION on the dissertation thesis: "Prediction and prevention of secondary brain damage in patients with acute vascular and traumatic lesions", submitted for the degree of Doctor of Philosophy (PhD) in the specialty 6D110100 - Medicine

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The relevance of the problem. Currently, in the structure of acute cerebral pathology, acute vascular and traumatic brain lesions are the most common, ranking first in the world as a cause of mortality and disability along with cardiovascular and oncological diseases (Ng, Si Yun, Alan Yiu Wah Lee, 2019).

As is known, with ischemic and hemorrhagic strokes, as well as with severe traumatic brain lesions (brain bruises), the vascular cerebral blood flow suffers.

At the same time, all three pathologies, of course, have an independent pathogenesis of primary brain damage. However, regardless of the primary mechanisms of damage, the leading trigger moment in all cases of these pathologies is hypoxic-ischemic brain damage with metabolic stress (K.V. Lukashev, A.Z. Valiakhmedov et.al ., 2017).

Ischemic stroke is characterized by a sharp decrease in the rate of blood flow, or a shutdown of blood flow in cerebral vessels with the development of a cascade of pathobiochemical processes in brain tissue with the development of apoptosis of nerve cells, which is primary brain damage, and also underlies the launch of key manifestations of secondary brain damage in the form of edema, cerebral and hemodynamic dysfunction, systemic hypoxia (Robertson C.S., 2019).

In hemorrhagic stroke, cerebral blood flow also suffers with the formation of local angiospasm, leading to hypoxia – ischemia of brain tissue with the development of metabolic stress (Ng Si, Lee A. 2019; Rakhimbayeva G.S., Arifdzhanov Sh. Kh., 2018).

Severe traumatic brain injuries are accompanied by primary brain damage, leading to disorders in the vascular bed with disruption of autoregulation of cerebral blood flow. Disruption of the regulation of cerebral blood flow in these pathological processes leads to secondary brain damage (Lazaridis C., Rusin C.G., 2017).

The modern concept of brain damage significantly changes the views on the pathogenesis and clinic of cerebral lesions. Pathological processes in the form of activation of stress neuron-specific proteins with damage to the integrity of the blood-brain barrier with inflammatory reactions and vasospasm, progression of cerebral ischemia with impaired oxygenation and metabolism, which determine and enhance secondary brain damage (Busch DR, Balu R, et.al . 2019). Any of these listed mechanisms of secondary brain damage should be regarded as a potential factor in the expansion of the CNS lesion zone and predicting the outcome of the disease.

Forecasting and prevention of the listed patterns of secondary brain damage is currently an unsolved urgent problem.

There are no common points of view on the diagnosis of secondary brain damage. Registering markers of brain damage with neuromonitoring of hypoxia and ischemia episodes should be both highly specific and sensitive and represent a new concept for assessing and predicting the outcome of this pathology. Based on this concept, the problem of secondary brain lesions requires further comprehensive research.

The solution of this scientific and practical problem with the study of the prognosis and prevention of secondary brain damage in patients with acute neuropathology formed the basis of our work.

The aim of the study was to study neurobiomarkers, gas exchange, brain metabolism and hemodynamics for the prediction and prevention of secondary brain damage in patients with acute vascular and traumatic neuropathologies.

To achieve these goals, the following tasks are set:

1. To identify neuron-specific markers of brain damage in patients with acute traumatic and vascular lesions (NSE, S100β) and assess their prognostic significance.

2. To conduct a study of cerebral gas exchange, metabolism and hemodynamics with determination of hemoglobin oxygen saturation in venous blood flowing from the brain, the ratio of oxygen delivery/ consumption in the cerebral cortex ($AVDO_2$, rSO_2), lactate, glucose, LDH and ABP depending on the course of the disease and to assess their prognostic significance.

3. To develop a mathematical model for personalized prediction of the outcome and prevention of secondary brain damage in patients with acute traumatic and vascular brain lesions.

Scientific novelty:

1. For the first time, a model for predicting the outcome of the disease in patients with acute vascular and traumatic brain lesions has been developed and implemented. (Certificate of entering information into the state register of rights to objects protected by copyright No. 10456).

2. The criteria for predicting secondary cerebral injury are high levels of sensitivity and specificity of neuromarkers (S100β and NSE), indicators of cerebral gas exchange and metabolism with the ratio of oxygen delivery / consumption in the cerebral cortex, systemic hemodynamics ($SvjO_2$, $AVDO_2$, rSO_2, ABP, LDH, lactate and glucose) in patients with acute vascular and traumatic brain lesions. (Certificate of entering information into the state register of rights to objects protected by copyright No. 10487).

3. The methods of personalized early prevention of secondary brain damage are systemic and specific neuromonitoring with multimodal predictors of cerebral gas exchange, metabolism, and hemodynamic disorders with GCS correlation. (Certificate of entering information into the state register of rights to objects protected by copyright No. 22285).

Practical significance:

1. Cerebral markers (S100β, NSE) can be recommended for early diagnostic assessment of brain damage in patients with acute neuropathologies.

2. Increased activity of hypoxia markers - impaired cerebral gas exchange (rSO_2) with increased $AVDO_2$, cerebral metabolism (lactate, glucose and LDH) indicate hypoxic damage to brain tissue with a risk of death of 85.3% in patients with acute cerebral strokes and TBI.

3. A personalized mathematical model with coefficients of risk factors associated with secondary brain damage will allow predicting the outcome of the disease in patients with acute vascular and traumatic brain lesions.

Provisions for Defense:

1. Neurospecific markers make it possible to predict secondary brain damage and the outcome of the disease in patients with acute vascular and traumatic lesions.

2. Disorders of cerebral gas exchange and metabolism, systemic hemodynamics indicate hypoxic and ischemic damage to brain tissue and are criteria for early prevention of secondary brain damage.

3. A personalized model with risk factor coefficients allows you to predict secondary brain damage and the outcome of the disease with high probability.

Approbation of the work.

Publications on the topic of the dissertation. 13 scientific and pedagogical works have been published, of them 3 articles – in modifications indexed in the information bases of Web of Science, Scopus, 1 article - in Crossref, 3 articles - in modifications recommended by the committee for control in the field of education and science of the Republic of Kazakhstan; 5 abstracts in international collections conference (including indexed in the Scopus database – 1 and foreign – 3); they received a Certificate of inclusion in the State Register of rights to objects, protected author's rights – 3, acts on the introduction of results of scientific research work in the educational process and Clinical Practice-3.

All publications were written by the doctoral student personally under the leadership of the scientific director, who consulted and produced corrections. The doctoral student conducted a search and review of literary sources, selection of patients and their distribution in the research

group. The doctoral student took an irreplaceable personal part in the process of diagnostics, treatment of examined patients, conducted statistical processing and analysis of the results obtained.

1. Establishing prognostic significance of hypoxia predictors in patients with acute cerebral pathology. Journal of Neurological Research ISSN:0161-6412E-ISSN: 1743-1328, Epub 2021 Nov 10. 44(4):362-370; CiteScore 2020-4. 1., SJR 2020-0. 737; percentile-59; https://DOI: 10.1080/01616412.2021.1996981. PMID: 34758699.

2. The level of S100β in blood serum as a prognostic factor of outcome in secondary brain lesions. Journal Georgian Medical News, 2021. ISSN 1512-0112; Epub 2021 Dec; (321): 162-168.CiteScore 2020-0. 3; SJR 2020-0. 137; percentile-20; PMID: 35000928

3. Neuron-Specific Markers and their Correlation with Neurological Scales in Patients with Acute Neuropathologies. ISSN: 0895-8696E-ISSN: 1559-1166; Journal of molecular Neuroscience, 2020. CiteScore 2020-4.6; SJR 2020-0. 936; percentile-31; https://DOI.org/10.1007/s12031-020-01536-5.

4.factors for the development of pneumonia in patients with stroke. Astana medical journal No. 2/2019. - p. 349-355. KOKSON.

5. assessment of the effectiveness of intensive nutritional therapy on the dynamics of acid-slotted blood pressure indicators for patients with hemorrhagic stroke Neurosurgery and neurology of Kazakhstan No. 2. 2019. - p. 80-84. KOKSON.

6.modern aspects of etiopathogenesis, diagnosis and treatment of hemorrhagic stroke. Medical Journal of Astana. № 3(105). 2020, pp. 46-53. ISSN 1562-2940. KOKSON.

7.The problem of arterial hypertension with severe brain strokes. Anesthesiology and resuscitation of Kazakhstan. No. 1 (16)2018, p.75-78.

8. neuron-specific biomarkers: from diagnostics to prognosis of acute neuropathology. Material of the International Scientific and practical conference "topical issues of Medicine. Baku. 2019.

9. The value of neuron-specific markers in predicting severity and treatment outcomes in patients with acute Traumatic and Vascular Lesions of the Brain. TheE III International scientific and educational conference «The internationalization of continuing medical education. Prospection». Panminerva Medica. Vol.110. Suppl. I. No. 2.2019. abstract in: Current contents/ Clinical Medline, indexed EMBASE, PubMed/MEDLINE, Science Citation Index Expanded (SciSearch), Scopus (Impact Factor 2,102).

10. The role of hypoxia in the development of secondary brain damage in patients with brain strokes» Abstracts of “The first International scientific practical online conference human genetics and genetic diseases: problems and development perspectives”. Baku, Azerbaijan. 2020.

11."monitoring of thromboelastogram in intensive care in patients with acute neuropathology". Materials of the Republican scientific and practical conference with international participation " Polytrauma. Modern approaches to diagnosis and complex treatment". G. Semipalatinsk. 2020.

12. Prognostic meaning of serum NSE as the factor of bad outcome in secondary brain damage. Fifth International scientific-practical virtual conference in modern medicine "op medicine and health: prognosis, achievement and challenges". Estonia, Tallinn. 2021.

13. The level of S100β in blood serum as a prognostic factor of outcome in secondary brain lesions. Fifth International scientific-practical virtual conference in modern medicine "op medicine and health: prognosis, achievement and challenges". Estonia, Tallinn. 2021.

The validity of the entry of information into the State Register of rights to objects, protected author's rights and an application for a suitable model:

1.application for a useful model: "methods for predicting the result of secondary brain damage in patients with traumatic and vascular brain damage". Registration number No. 2021/0523. 2.Date Date 28.05.2021 .

1. Neuron-Specific Markers and their Correlation with Neurological Scales in Patients with Acute Neuropathologies. The validity of the entry of information into the State Register of rights to objects protected by author's rights No. 10456 from 02.06.2020.

2. risk factor of pneumonia in stroke patients. The validity of the entry of information into the State Register of rights to objects protected by author's rights No. 10487 from 02.06.2020.

3.Assessment of the effectiveness of intensive nutritional therapy on the dynamics of acid-slotted blood formation in patients with hemorrhagic strokes. The validity of the entry of information into the State Register of rights to objects protected by the author's right No. 6726 dated 28.11.2019.

Acts of introduction of results of scientific research work:

1. predictive value of the neuron-specific protein NSE in predicting the outcome of secondary brain damage in patients with traumatic and vascular brain damage No. 197 of 20.06.2021

2.predictive value of neuron-specific protein S100β in predicting the outcome of secondary brain damage in patients with traumatic and vascular brain damage No. 196 dated 20.06.2021 .

3.model based on the assumption of secondary traumatic and vascular brain damage No. 198 of 20.06.2021.

MATERIALS AND METHODS.

A prospective continuous cohort study included 219 adult patients. Of these, 146 patients (66.6%) who had a hemorrhagic stroke (GI), 43 (19.6%) with ischemic stroke (IS) and 30 (13.6%) with acute closed traumatic brain injuries (TBI) of mild and moderate severity, who were treated at the Emergency Hospital and Aktobe Medical Center from April 2018 to January 2020. In the group of examined -132 (60.20%) men and 87 (39.80%) women (p=0.8922). the average age of the sample was 60 years (95%CI: 52.00- 69.00); age differences by disease groups (p<0.0001, p=0.1981). According to the outcome of diseases (p=0.3904), and by age (p=0.4287) and gender, the patients were not comparable (p=0.8921).

The study was conducted in accordance with the standards of good clinical practice, the principles of the Helsinki Declaration and the principles of the Ethics Commission of the West Kazakhstan Marat Ospanov Medical University No. 12 dated 30.01.2018.

The criteria for inclusion in the study were patients with hemorrhagic stroke with an intracerebral hematoma volume of no more than 80 cm3, patients with ischemic stroke with cerebral infarction, patients with closed craniocerebral injuries (mild and moderate bruises), confirmed by clinical and computer data, the GS integral scale. All patients received written informed consent before being included in the study. The exclusion criteria from the study were patients with brain death confirmed by the EEG method; patients with GCS below 3 (18 patients), patients with open traumatic brain injuries; with severe decompensated somatic diseases (11 patients), benign and malignant neoplasms of the brain, skin and lungs (2 patients).

According to the outcome of the disease, regardless of the diagnosis, patients were divided into groups: survivors - 59.3% (n=130) and deceased - 40.6% (n=89).

The general population was 587544. P-prevalence -13.7%, the sample size was 219 people.

Research methods:

a) neuroimmunological markers of brain damage: neurospecific proteins: S100β - calcium binding protein, NSE - enolase;

b) in–depth monitoring of brain gas exchange - jagular oximetry with determination of hemoglobin oxygen saturation in the venous blood flowing from the brain in the jagular (jugular) vein ($SVJO_2$), CBS and blood gases (pH, pO_2, pCO_2) were determined by an EPOC analyzer, Canada, with a unique SmartCard technology (measuring cards with a built-in biosensor chip), the ratio of oxygen delivery/consumption in the cerebral cortex (rSO_2, $AVDO_2$) - on the device INVOS -5100, SOMANETICS, USA;

c) biochemical blood tests (LDH, electrolytes);

d) monitoring of brain metabolism (lactate and glucose), which are among the early markers of impaired brain perfusion with the development of secondary brain damage on the EPOC BGEM clinical analyzer;

e) hemodynamic monitoring, CVD monitoring systems NIHONKONDEN (Japan) and IMEC15S (Mindray, China).

e) the assessment of the neurological status of patients participating in the study was assessed on the Glasgow Coma Scale (GCS).

Statistical methods. The study of the statistical relationship between the qualitative feature and the clinical outcome was carried out using the analysis of conjugacy tables, with the calculation of the Pearson criterion. In case of non-fulfillment of the criterion applicability condition $\chi 2$ (more than 25% of the cells in the conjugacy table have an expected frequency of less than 5), the analysis was carried out in pairs according to the two-sided Fisher exact criterion (2p(F)). In the case of insufficient statistical significance of the connection of two nominal features in the multipole conjugacy table, several gradations of the feature similar in meaning were combined into one, followed by the calculation of the Pearson criterion $\chi 2$ with the achieved level of statistical significance (p) and the odds ratio (OR) with a 95% confidence interval (95% CI). The study of the relationship between the quantitative and qualitative feature was carried out using a one-factor logistic regression analysis with the calculation of statistics Вальд2 Wald with the achieved level of statistical significance and OR with 95% CI.

The construction of mathematical models for predicting the risk of an unfavorable outcome was carried out using the method of multifactorial binary logistic regression analysis with step-by-step inclusion of independent variables. The influence of the independent variable on the probability of outcome was determined using OR and 95% CI. To assess the quality of the mathematical model, the Nigelkirk determination coefficient (R2) was calculated, showing the proportion of the influence of all variables included in the model on the variance of the dependent variable, as well as the Hosmer-Lemeshov agreement criterion, which allows us to determine how much the model agrees with the initial data. The evaluation of the discriminating ability of the mathematical model was performed based on the analysis of the classification table. The predictive effectiveness of the model was evaluated using the analysis of ROC curves, with the calculation of the area under the ROC curve, called AUC (Area Under Curve). For the obtained models, we calculated the following characteristics: Se (sensitivity) – the percentage expression of the frequency of true positive results; Sp (specificity) – the percentage of true negative results; PPV (predictive value of a positive test) - the probability of having a positive result with a positive test result. NPV (predictive value of a negative test) is the probability of having a negative result with a negative test result. In the statistical analysis procedures, the achieved level of statistical significance (p) and the number of degrees of freedom (df) were calculated. The critical value of the level of statistical significance in the study was $p<0.05$. The results of the study were subjected to statistical analysis and mathematical data processing using the Statistics application software package (SPSS25).

The results of the study. To assess the prognostic values of neuron-specific proteins, we conducted studies of serum markers of brain damage - NSE and S100β, as well as their sensitivity, specificity and correlative relationships with the integral neurological scale GCS, as independent predictors of functional outcome in patients with favorable and unfavorable outcomes of the disease. Their studies were carried out at admission and in dynamics on the 3rd, 5th and 7th days of the patient's stay in the department.

Results of the study showed that peak values of NSE concentration were observed in groups of patients with traumatic brain injuries and IS already on the 1st day of the disease, followed by a decrease of 11.51% and 12.90%, respectively, in groups, but in patients in the first group, these data were not statistically significant. In patients with GI, the initial increase in NSE concentration was less pronounced. Similar changes occurred with the concentration of S100β. Its maximum increase was observed in the group of patients with IS. So, on the 1st day, its level significantly exceeded the permissible fluctuations and reached (0.78 ±2.48 mcg/l), on the 3rd

day - an increase to 0.82± 2.68 (4.37%) and it was maximum compared to patients of other groups. However, in dynamics by the 7th day of follow-up, a significant decrease was noted in all patients: with IS - by 63.54%, GI - 72.22% and TBI by 72.45%. Brain damage that causes high S100β levels, especially in patients with ischemic stroke, may be strongly associated with vasospasm and ischemia.

The determination of the correlation dependence of the concentration of neuromarkers with the neurological scale showed certain levels of their relationship with various outcomes of the disease. S100 levels in all patient groups negatively correlated with GCS values (r = -0.5, -0.48 and -0.47; p=0.0053, p<0.0001 and p=0.0033), respectively. It was noted that patients with lower GCS (<7) had significantly higher levels of S100β. Significant connections were found between the S100β and NSE markers. S100β levels were statistically significantly and positively correlated with NSE values in all groups of patients, with TBI - (r=0.39*; p=0.0320); with GI - (r=0.42**; p<0.0001) and IS - (r=0.49**; p=0.0022).

When comparing groups with favorable and unfavorable outcomes of the disease, it was found that in both groups the concentration of NSE protein increased 2-fold on the first day (14.76(95%CI:12.98-16.54) and 3-fold (20.75 (95%CI:16.10- 25.39); p=0.0010), but a statistically significant increase was noted on the 3rd day of treatment in the group of deceased patients. Similar changes were found in the study of the concentration of S100β. Its greatest increase was also observed in the group of deceased patients, where a statistically significant elevated level of 0.94 (95%CI:0.45-1.42) remained; p<0.0001 against the background of ongoing treatment, which suggested the early occurrence of an unfavorable course of the disease.

Thus, our studies showed that an unfavorable outcome was observed in patients who had higher levels of S100β and NSE compared to the group of survivors.

An analysis of the sensitivity and specificity of the differences between the studied bioneuromarkers in the diagnosis and prediction of the severity of brain tissue damage in the studied patients showed that, compared with NSE, the S100β protein demonstrates higher specificity to brain tissues and better meets the requirements for determining a serum marker for brain damage by type of GI. Its sensitivity is very high in terms of cellular brain damage. In our studies, we noted that in some patients, even with minor trauma, serum levels of S100β were elevated.

To compare the studied predictors of secondary brain damage and determine the value of their cut–off points, we analyzed the numerical indicators of the area under the ROC curve and evaluated the specificity and sensitivity in favorable and unfavorable dynamics of the disease. According to the ROC analysis study, S100β levels were significantly higher and had the largest area under the ROC curve (0.828) with a cut-off point (>0.2, p<0.0001) compared to the NSE area under the ROC curve (0.712) and a cut-off point (>12.5, p<0.0001), with sensitivity (Se) 47.46% and specificity (Sp) 91.43%. On the contrary, NSE gives sensitivity above 74.16% and specificity - 47.69%. An increased content of neurospecific proteins with statistically significant sensitivity, specificity and correlation of GCS can be considered as criteria for an unfavorable outcome of the disease. With the continuous improvement of diagnostic methods, these cerebral markers can be recommended for the diagnostic assessment of brain damage in patients.

Metabolic metabolism in the human brain has not been fully studied, even in a normal undamaged state. The resulting traumatic and vascular pathologies develop within a few hours and days and, despite treatment, can lead to a number of clinical outcomes from a good recovery to varying degrees of disability or even death. In order to study the state of brain metabolism, we investigated the activity of LDH, lactate and blood glucose markers.

The results of the studies showed that all admitted patients with acute cerebral lesions had high levels of LDH, lactate and blood glucose against the background of an initial decrease in pO_2, reflecting the presence of initial hypoxia or mitochondrial dysfunction. The obtained data on the dynamics of LDH in the groups of patients with IS, GI and TBI had no statistical significance.

In groups of patients according to the outcome of the disease (favorable and unfavorable) both at their admission and in the dynamics of their treatment, the average level of this indicator remained significantly high throughout the follow-up period ($p<0.0001$), which reflects the acute period of brain damage in patients with hypoxia. There was a tendency to decrease the initially high levels of lactate and blood glucose statistically significant with $p<0.0001$. There are significant differences in the initial lactate level between the two groups according to the outcome of the disease, 1.3 times higher in the group of deceased patients (2.88 (95% CI 2.54-3.23); $p=0.0094$) compared to survivors 2.20 (95% CI 1,97-2,42). Subsequently, significantly elevated lactate levels were maintained in patients with an unfavorable outcome: on day 3, $p = 0.0024$; on day 5, $p= 0.0012$ and on day 7, $p= 0.0013$. Serial lactate measurement can be a useful predictor of outcome in a critical patient. A similar trend was observed in the dynamics of blood glucose indicators, where on the 7th day of the disease its average values remained 1.3 times higher in the group with an unfavorable outcome (5.8 (95% CI:4.1-11.1) versus 6.8 (95%CI:6.5-18.9); $p=0.0001$). The severity of hyperglycemia correlates with the severity of the injury and can significantly aggravate the course of acute cerebral ischemia.

LDH, glucose, and lactate levels in all patient groups negatively correlated with GCS values ($r = -0.41$, -0.57, and -0.36; $p<0.0001$, $p<0.0001$, and $p=0.002$), respectively. According to the ROC analysis study, LDH, lactate and blood glucose had cut-off points ($\geq 527, p<0.0001$*), ($\geq 1.7, p<0.0001$*) and ($<8.9, p<0.0001$*), respectively, and allow predicting an unfavorable neurological outcome.

In the study of the state of cerebral gas exchange, depending on the course of the disease and the assessment of their prognostic significance, the indicators of CBS and blood gas composition in patients with an unfavorable outcome underwent more significant changes and decompensated acidosis of 7,428 (95% CI:7,31-7,48) persisted on the 3rd day in patients; $p=0.00048$. pO_2 levels starting from day 3 give statistically significant differences in hypoxia of 65.07 (95%CI 56.59-62.58) versus 53.04 (95% CI 49.36-6.71); $p=0.0095$, respectively, groups. The same changes are shown by pCO_2 41.81 (95%CI 39.14- 44.48) versus 46.24 (95% CI 44.53-47.95); $p=0.0041$, which indicates a hypoxic-ischemic process and the beginning of the mechanism of secondary brain damage. Analyzing the data obtained, it can be noted that hypoxia very quickly disrupts the normal functioning of brain cells, sometimes with irreversible functional damage and an unfavorable outcome of the disease.

The results obtained by us and the study of these predictors of hypoxia allow us to expand the existing understanding of the pathogenetic processes of hypoxic brain damage in the acute period with acute vascular and traumatic injuries, which undoubtedly has a certain scientific value and can be used as markers of cerebral damage.

Our data coincide with the opinions of many researchers, including (Lauritzen M, Strong A.J. 2017), who claim that hypoxia is an aggressive and damaging factor for patients, leading to functional disorders and damage to brain cells. In the future, this condition may be aggravated by the addition of secondary ischemic brain damage.

Upon further investigation of cerebral gas exchange, it was noted that the dynamics of the results of the ratio of brain oxygen delivery/consumption (rSO_2) compared with the initial values in all the studied groups of patients were insignificant. The indicators of rSO_2 cerebral oximetry had the same direction of changes depending on the degree of impaired consciousness (correlation analysis with GCS) and the dynamics of its development, so we found it possible to generalize the data of groups of patients with GI and IS. In these groups, there was a decrease in the average value of rSO_2: from GI - by 0.23%; IS - (8.60%), but these results were statistically unreliable. It should be noted that the rSO_2 indicators in most patients with TBI were unstable, had a large amplitude of fluctuations, changing during the follow-up by 2.14% - 5.93% were also not statistically reliable.

Against the background of a decrease in the ratio of oxygen delivery/consumption of the brain, the dynamics of the arteriovenous difference in oxygen concentration ($AVDO_2$) showed a direct negative relationship. On the 3rd day of the disease, $AVDO_2$ in patients with GI increased

by 2.44% (95% CI 49.42-52.23); with AI - by 2.07% (95% CI 44,19-49,16). The developed hypoxemia leads to a decrease in oxygen transport and the associated inhibition of hypoxic vasoconstriction, hypoxia, as factors of secondary brain damage.

There were no such changes in the group of patients with TBI, the baseline values did not decrease, but on the contrary, increased. This may be due to the fact that patients are admitted in a serious condition and in the first hours of hospitalization, ventilation begins in hyperventilation mode. To determine the relationship between gas exchange indicators and the state of neurological status according to GCS, a correlation analysis revealed a positive relationship between GCS and rSO_2 (R=0.45, p<0.0001) and a negative relationship between GCS and $AVDO_2$ (R=-0.45, p<0.0001) for all groups of patients. Similar changes were noted in the groups of patients with the disease outcome rSO_2 (42.72 (95% CI 41.18- 44.26), p<0.0001) and $AVDO_2$ (54.75 (95% CI 53.24- 56.26), p<0.0001). To assess the effectiveness of cerebral gas exchange indicators as criteria for predicting the dynamics of the disease, the specificity and sensitivity of rSO_2 and $AVDO_2$ were evaluated. According to the ROC analysis study, rSO_2 and $AVDO_2$ had the largest area under the ROC curve (0.91) and (0.88) with cut-off points (<45-48, p<0.0001) and (>54-52,p<0.0001) with sensitivity 93.9% - 95.12% and specificity 86.05% - 86.82%, respectively. Taking into account the generally accepted ideas that the indicators of high sensitivity and specificity values range from 80 to 100%, it can be noted that, in general, in the entire sample of examined patients, cerebral oximetry had high specificity and low sensitivity of 67.42% ($\chi 2$ - 73.2528) only on 1-3 days of observation. A possible explanation for the low sensitivity in the first three days is that mainly during these periods, an unfavorable outcome may occur in the most severe patients. It is obvious that a violation of brain oxygenation is most often not the cause, but the result of deterioration of cerebral metabolism due to the influence of many factors. Another possible explanation for the low sensitivity is the following: cerebral oximetry reflects local cerebral oxygenation mainly of the cortical parts of the brain, and does not reflect the nature of oxygenation of stem structures.

The prognostic value of the S100β protein.

To determine the possibility of using S100β and NSE proteins in predicting the outcome of secondary brain injuries, statistically dispersive qualitative and quantitative analyses were performed. The average protein levels for each outcome group were evaluated. With this formation, the difference became even more statistically significant (p<0.0001). The threshold value or cut-off point of S100β in blood serum for formal separation into a group of survivors and a group of deceased was 0.2 mcg/l (double the norm). Next, we constructed Kaplan-Meier survival curves for S100β<0.2 mcg/L and S100β >0.2 mcg/l. The cumulative rate of cases of a bad outcome in the group with a level of S100β >0.2 mcg/l began to diverge already in the first days of observation. The achieved level of significance according to the log Rank criterion (Mantel Cox); p<0.0001, the differences in the studied groups are significant. When further studied by the method of multiple logistic regression analysis (LRA), the results indicate the presence of a statistically significant direct relationship between

S100β >0.2 mcg/l and NSE ≥18.9 ng/ml compared to other variables 12 times more often, i.e., OR 11.95 (95% CI: 3.2927-1.6693), p<0.0001; with an increase in blood glucose above 7.4 mmol/l, OR 3.82 (95% CI: 2.1289- 0.5539), p=0.0008; GCS<13 points OR 3.69 (95%CI: 2.1316-0.4819), p=0.0019; with an increase in pCO_2<43.5, OR of 3.15 was documented (95%CI: 1.8916-0.4062), p=0.0024. The measure of certainty of the obtained model according to the criterion of pseudo R_2 Nagelkerke is 263.5; logLikelihood is 47.87.

The logistic regression equation of the model has the following form:

P = 1 / (1 + Exp(-(-4.051 + 2.481*NSE ≥18 + 1.341*Glucose ≥7 + 1.307*GCS <13 + 1.149*pCO2 <43 + 0.738))).

Where P is the probability of the risk of an increase in S100β >0.2 mcg/l; e is the base of the natural logarithm (e=2.72); -4.0511 is a constant. The cut-off point of 88.89% had the best

predictive value of the model for S100β, AuROC -0.873; Se - 91.30%; Sp - 72.09%; NPV - 93.94%; PPV - 63.64%.

To obtain a quantitative indicator of the dependent variable S100 by multiple analysis with independent indicators (NSE, GCS, patient age, glucose, rSO2 right and left, $AVDO_2$ right and left, SBP, lactate, pH, pCO_2), significant variables were identified and the final formula has the following form:

S100β = - 0,66 + 0,05* NSE - 0*LDH - 0.05*GCS + 0.01*Age + 0.04*Glucose.

Where (-0.6610) is a constant. The results of the regression analysis showed that the variables independently statistically associated with S100β were NSE, LDH, GCS, patient age and blood glucose.

Model quality: R_2 = 33.2%; R_2 (adjusted) =31.9%; p<0.0001.

The predictive value of the NSE. Also, variance qualitative and quantitative analyses assessed the level of NSE protein for each group of outcomes. Differences in the average value of protein in blood serum in patients with a favorable outcome and an unfavorable outcome significantly differ (p=0.05). According to the Kaplan-Meier survival curve, the level for NSE was >12.5ng/ml. The cumulative rate of cases of a bad outcome in the group with an NSE level>12.5ng/ml began to diverge already in the first days of follow-up. The achieved level of significance according to the log Rank criterion(Mantel Cox); p=0.0062; the differences in the study groups are significant. Variables of secondary brain damage that demonstrated a statistically significant association with NSE>12.5 ng/ml in a one-dimensional analysis were introduced into multiple LRA step by step. A direct relationship was found between NSE>12.5 ng/ml and LDH>218 with OR of 3.74(95% CI:7.25-1.93), p<0.0001; with an increase in lactate above 4.1 mmol/l, OR 3.29 (95%CI%:12.07-0.90), p=0.0719; according to GCS< 13 points, OR 1.68 (95%CI: 3.29-0.85),p=0.1337; S100≥0.2 OR 2,79 (95% CI: 5.95-1.31), p=0.0080; with an increase in pCO2 <38.5mmHg, a pH of 3.08 was documented (95%CI: 6.41-1.48),p=0.0027; at the age of <53 with aOR 2.95 (95%CI: 6.34-1.37), p=0.0055. The measure of certainty of the obtained model according to the criterion of pseudo R2 Nagelkerke is 250.6; logLikelihood is 154.04.

The logistic regression equation of the risk model of an increase in NSE has the following form:

P = 1 / (1 + Exp(-(-1.958 + 1.319*LDH ≥218 + 0.517*GCS <13 + 1.083*Age <53 + 1,026* S100β ≥0,6 + 1,124*pCO_2 ≥38 + 1,192*Lactate ≥4))).

Where P is the probability of the risk of an increase in NSE>12.5ng/ml; e is the base of the natural logarithm (e=2.72), (-1.9577) is a constant. The cut-off point of 88.89% had the best predictive value of the model, AuROC-0.809; Se-51.59%; Sp-95.06%; NPV-55.80%; PPV-94.20%.

Quantitative determination of the dependent variable NSE revealed LDH, lactate, S100β and glucose as significant predictive variables of this marker and the formula has the form:

NSE = 3,17 + 0,05*LDH + 1,7*Lactate + 4,9* S100β **- 0,63*Glucose.** Where: 3.166 is a constant. Model quality: R2 =42.9%; R2 (adjusted)= 42.1%; p<0.0001.

Thus, the threshold values or cut-off points for dividing into groups of survivors and deceased were for S100β >0.2 mcg/L and NSE >12.5 ng/ml.

The predictive value of rSO2 indicators. To determine the possibility of using the rSO2 indicator - the ratio of oxygen delivery/consumption of the brain in predicting the outcome of the disease, a threshold value or a cut-off point of rSO_2<45% was established by analysis of variance. Logistic regression analysis revealed the presence of a statistically significant direct

relationship between the dependent variable rSO_2<45% and S100β <0.6, the aOR is 4.22 (95%CI:10.76-1.66), p=0.0025; and the addition of a patient with a diagnosis of pneumonia is 6.21 (95%CI:12.0-3.21), p<0.0001; the patient's diagnosis is OR 8.13 (95%CI:25.59-2.59), p= 0.0003. The measure of certainty of the obtained model according to the criterion of pseudo R_2 Nagelkerke is 137.8; logLikelihood is 175.83.

The logistic regression equation of the model has the following form:

P = 1/(1+ Exp(-(-1,778+ 1,441*S100β<0,6+1,825*Pneumonia + 2,096*Diagnosis))).

Where P is the probability of the risk of a decrease in rSO_2 <45%; e is the base of the natural logarithm (e=2.72); -1.77777 is a constant. The best predictive value of the model had a cut-off point of 97.1%, AuROC - 0.846; Se - 68.47%; Sp - 90.16%; NPV - 61.11%; PPV - 92.68%.

Multiple regression analysis obtained a quantitative indicator rSO_2 in relation to the independent variables GCS, ABP, NSE and PH and the formula has the following form:

rSO_2 = 56.47 + 1.05* GCS - 0.09*ABP- 0.08*NSE - 0.34*pH.

Where: 56.468 is a constant; Model quality: R_2 =16.7%; R_2 (adjusted) = 15.5%; p <0.0001.

The predictive value of $AVDO_2$. Studies of the arteriovenous difference in blood oxygen as an indicator characterizing the state of oxygen transport of the brain have been carried out. The analysis of variance determined a statistically significant threshold level or cut-off point AVDO2 >52% for the formal division into groups of survivors and deceased patients. Variables of secondary brain damage that demonstrated a statistically significant association with $AVDO_2$>52% in a one-dimensional analysis were introduced into multiple LRA step-by-step: LDH ≥206, ABP<116, Glucose≥7.5 and the addition of a diagnosis of pneumonia in a patient. The results of the analysis indicate the presence of a statistically significant direct relationship between $AVDO_2$ and the diagnosis of pneumonia (if it appears in the patient) compared to other variables: OR was 2.8 (95%CI%1.53-5.11), p=0.0008; with an increase in blood LDH above 206 mmol/l - OR 2.6(95%CI:1.41-4.75),p=0.0019; with a decrease in ABP<116 - OR 1.4 (95%CI:0.75-2.66),p=0.2820.

The logistic regression equation of the model has the following form:

P = 1 / (1 + Exp(-(-1,646 + 1,028*Pneumonia + 0.955*LDH ≥206 + 0.521*Glucose ≥7 + 0.827*ABP <116))).

Where P is the probability of the risk of an increase in $AVDO_2$ >52%; e is the base of the natural logarithm (e=2.72); -1.6461 is a constant. The best predictive value of the model had a cut-off point of 83.26%, AuROC-0.753; Se-71.03%; Sp-70.64%; NPV-71.30%; PPV-70.37%.

To predict the quantitative indicator $AVDO_2$, multiple regression analysis with independent variables (LDH, GCS, NSE, pH, and ABP) determined the formula:

$AVDO_2$ = 44.05 - 0.83*GCS + 0.4*Glucose + 0.01*LDH + 0.04*NSE + 0.23*pH + 0.06*ABP.

Where: 44.046 is a constant. Model quality: R_2 =15.1%; R_2 (adjusted) = 13.1%; p<0.0001. In this part of the study, we focused on those variables that were strongly associated with the dependent variable ($AVDO_2$).

As the results of studies have shown, with an average $AVDO_2$ value>52%, the relative risk of an unfavorable outcome on the 1st day of the disease in patients increases by 2.42 (95% CI:1.77-3.31), p<0.0001.

Prognostic value of lactate. A sharp increase in the level of lactate in the blood is a constant predictor of secondary cerebral damage with ischemia and hypoxia of the brain. To divide patients into groups with favorable and unfavorable outcomes, a statistically significant threshold value or cut-off point for lactate >3.3 mmol/l was determined by analysis of variance. The results of the LRA analysis indicate the presence of a statistically significant direct

relationship between lactate and pH <7.3 - odds ratio (OR) 12 (95% CI: 3.26-42.39), p= 0.0002; with an increase in blood glucose above 8.9 mmol/l - OR 6.22 (95% CI: 2.71-14.21), p<0.0001; with an increase in ABP ≥179 mmHg, OR 3.89 (95% CI:1.60-9.43), p =0.0002; with S100ß <0.3 mcg/l, OR - 2.12 (95% CI: 0.86 - 5.24), p = 0.1025; with NSE ≥15ng/l, OR 3.43 (95% CI: 1.37 - 8.57), p=0.0083; GCS < 10 points OR 2.87 (95% CI: 1.18 - 6.99), p=0.0734.The logistic regression equation of the model has the following form:

P = 1 / (1 + Exp(-(-4,923 + 1,827*Glucose ≥8 + 1,357*ABP ≥179 + 2,464*pH <7 + 0.753* S100β ≥0,6+ 1,227* pO_2 ≥55 + 1,232*NSE ≥15 + 1,054*cSO2 <74 + 0.77*GCS <10))).

Where P is the probability of the risk of an increase in lactate >3.3 mmol/l; e is the base of the natural logarithm (e=2.72), 50,0958 is a constant. The best predictive value of the model had a cut-off point of 94.11%, AuROC-0.878; Se-78.85%; Sp-85.03%; NPV-92.81%; PPV-62.12%.

For the quantitative prediction of the rate of lactate, multiple regression analysis with independent variables (glucose, $AVDO_2$, S100β, NSE, GCS, pO_2, cSO_2) is defined by the formula:

Lactate = 2,67 + 0,24*Glucose - 0,01*$AVDO_2$ + 0,05* S100β **+ 0,02*NSE - 0,07*GCS - 0,01*pO_2 - 0,01*cSO_2.**

Where: 2.6660 is a constant. Model quality: R_2 =33%; R_2 (adjusted)= 31%; p<0.0001. As the results of studies have shown, with an average lactate value > 3.3 mmol / l, the relative risk of an unfavorable outcome on the 1st day of the disease in patients increases by 7.27 (95% CI: 4.17-12.67), p = p <0.0001.

Approaches to the prediction and prevention of secondary brain damage in patients with traumatic and vascular brain lesions with the creation of prognostic models.

Mathematical modeling methods are the most informative and promising in prediction. The ease of coding predictors of outcome, the use of a personal computer to create and maintain a database, the availability of application programs for mathematical calculations have become prerequisites for the creation of multifactor prediction models.

We have developed a formalized medical history, with the help of which the data of all patients were encoded and entered into a common database in MS Excel 2016.

The end point for the analysis of the prognosis was the indicator of the outcome of the disease (favorable and unfavorable). A discriminant analysis was carried out, predictors with statistically significant associations with the resulting feature (outcome) were left. The classification was carried out and a classification matrix was compiled for the basic model, which reflects the weights of predictors (coefficients) and constants for each group of outcomes. For any patient, using the classification matrix of the basic model, it is possible to calculate the discriminant function for each outcome using the formula presented.

At the stage of multiple LRA, we studied the relationship of the risk of an increase in the level of the target dependent variable - the outcome of the disease with the indicators or independent variables obtained during the study. The results of the analysis indicate the presence of a significant direct relationship between the outcome and the analysis of $AVDO_2$ > 52% from the left side indicates 9 times higher than other variables, or the odds ratio (OR) 9.01 (95% CI: 3.45 - 23.51), p<0.0001; $AVDO_2$, right side. with an increase of>52%, 5.71 is equal to OR (95% CI: 2.31-14.16), p=0.0002; with an increase in lactate >3.3 mmol/l, OR is equal to 4.30 (95% CI: 1.61-11.51), p=0.0036; S100ß 0.1 mcg/l >OR is equal to 3.77 (95% CI:1.63-8.73), p=0.0020; with ABP>169 mmHg, the st is 3.27 (95% CI:1.26-8.48), p=0.0146; age>65 OR is 2.43 (95% CI: 1.04-5.68), p=0.0406; NSE with an increase in ng/ml>12.5 OR 2.69 (95% CI: 1.14-6.36), p=0.0240.The measure of certainty of the obtained model according to the criterion of pseudo R2 and skills and best practices - 627.3%; logLikelihood - 112.7. The logistic regression equation of the model has the following form:

Risk=1/(1+Exp(-(-6,098+1,805*$AVDO_2$+1,336*S100β>0+2,331*$AVDO_2$+ 1,414*Lactate>3+1,358*ABP>169+0.982*NSE >12))).

Where P is the probability of the risk of an increase in the outcome of the disease, e is the base of the natural logarithm (e=2.72), -6.098 is a constant. The cut-off point of 99.33% had the best predictive value of the model, AuROC-0.915; Se - 89.77%; Sp - 78.91%; NPV - 91.82%; PPV - 74.53%. As follows, we have included a step-by-step method for selecting variables, in which the inclusion check is based on the significance of the value statistics, and the exclusion check is based on the probability of the Wald statistics

The logistic regression equation of the model is as follows:

$P=1/(1+Exp(-(-6.496+1.075*S100\beta+0.214*lactate+0.110*AVDO_2r+0.096AVDO_2l-0.005 * LDH-0.372 * GCS)))$

Thus, in the final version of several Cox proportional risk analysis, 6 variables were involved: S100β, lactate, right and left $AVDO_2$, LDH, GCS. The model was obtained by sequentially removing variables. In the second step, variable glucose was removed, in the third step - NSE, in the fourth step - young and in the fifth step - Ro2. The latest model was developed in 5 steps.

To assess the quality of the mathematical model, the Nigel-Helkerke determination coefficient (R2) was calculated, which showed the proportion of influence of all variables included in the model on the variance of the dependent variable, as well as the Hosmer-Lemeshov consent criterion, which allows us to determine how much the model corresponds to the source data. Summary of the model: -2 LL 162.997; Cox and Snell r-square=0.454, R-Nigel Square =0.612 (Nagelkerke); $\chi 2$=131.834.

The developed independent mathematical model with coefficients of risk factors makes it possible to predict with a high probability the development of secondary brain damage and the outcome of the disease in patients with acute vascular and traumatic brain diseases.The developed personalized mathematical model with risk factor coefficients allows predicting the outcome of the disease in patients with acute vascular and traumatic brain injuries and with high probability the development of secondary brain damage.

CONCLUSION

Based on the results obtained, the following conclusions were made:

1. The increased content of neurospecific markers of brain damage S100ß with OR 2.49 (95% CI: 1.71-3.64) and NSE with OR 2.48 (95%CI: 1.49-4.13) with sensitivity 72.91-79.41% and specificity 63.85-70.08% are considered as criteria for the prediction and prevention of secondary brain damage and adverse the outcome of the disease in patients with acute vascular and traumatic lesions.

2. Reduction of the ratio of brain oxygen delivery/consumption - rSO_2(dext.) by <43.1% and rSO_2(sin.)<48% with an increase in $AVDO_2$ >54% with increased activity of markers of brain metabolism - LDH ≥273.0 mmol/l OR 2.79(95%CI: 1.74-4.48), lactate at ≥3.3mmol/l OR 3.58 (95%CI: 2.32-5.53), ABP≥ 169 mmHg. OR 5.86 (95%CI: 3.82-9.00) with GCS correlation, indicate hypoxic and ischemic brain tissue damage and are criteria for early prevention of secondary brain damage.

3. Based on a comprehensive assessment of neuromarkers, cerebral gas exchange, brain metabolism and hemodynamics, models of personalized prediction of secondary brain damage and disease outcome in patients with acute vascular and traumatic brain lesions have been developed. Model Summary: - 2 LL - 162.997; Cox and Snell R-squared=0.454, Nagelkerke R-squared =0.612 (Nagelkerke); $\chi 2$=131.834. The cut-off point of 99.33%, AuROC -0.915; Se - 89.77%; Sp - 78.91%; NPV - 91.82% had the best predictive value of the model; PPV - 74.53%

PRACTICAL RECOMMENDATIONS

1. Cerebral markers (S100ß, NSE) can be recommended for early diagnostic assessment of secondary brain damage in patients with acute neuropathologies.

2. Increased activity of markers of cerebral gas exchange (rSO_2) with increased $AVDO_2$, cerebral metabolism (lactate, glucose and LDH) indicate hypoxic damage to brain tissue with a risk of death of 85.3% in patients with acute cerebral strokes and injuries.

3. A personalized mathematical model with coefficients of risk factors associated with secondary brain damage will allow predicting the outcome of the disease in patients with acute cerebral vascular and traumatic lesions.

4. The calculator of the mathematical model of the individual risk of secondary brain damage or an unfavorable outcome of the disease is recommended to be integrated into the electronic medical record of the patient upon admission to the hospital. Patients with a high coefficient of adverse outcome need individual preventive measures to correct the identified risk factors.