DIAGNOSTIC SIGNIFICANCE OF OXIDATIVE STRESS AND ENDOGENOUS VASCULAR REGULATION MARKERS IN THE ASSESSMENT OF UNFAVORABLE OUTCOMES IN PATIENTS WITH NON-TRAUMATIC SUBARACHNOID HEMORRHAGE CAUSED BY RUPTURED CEREBRAL ANEURYSMS

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Abstract - The aim of the study was to assess the diagnostic significance of laboratory parameters in predicting unfavorable outcomes in patients with non-traumatic subarachnoid hemorrhage (SAH) caused by ruptured cerebral aneurysms. The study included 50 patients with massive basal SAH who underwent microsurgical treatment within the first 72 hours from disease onset. According to ROC analysis, on postoperative day 3, diagnostic significance was demonstrated for serum lactate dehydrogenase and albumin, as well as cerebrospinal fluid lactate dehydrogenase, lactate, albumin, malondialdehyde, and stable nitric oxide metabolites. These findings suggest that the studied parameters may be considered an additional component in assessing the risk of unfavorable outcome during the period of cerebral vasospasm and delayed ischemic brain injury.

Keywords - Subarachnoid Hemorrhage; Cerebral Ischemia; Cerebral Vasospasm; Cerebrospinal Fluid; Biomarkers.

I. INTRODUCTION

Non-traumatic subarachnoid hemorrhage (SAH) caused by ruptured cerebral aneurysms remains one of the most severe forms of acute cerebrovascular disease. It is associated with high mortality, risk of disability, and the development of secondary brain injury. One of the leading factors determining prognosis in this group of patients is delayed cerebral ischemia, which is often related to the development of cerebral vasospasm in the early postoperative period [1, 2].

Despite advances in neurosurgical treatment, early assessment of the risk of unfavorable outcome in patients with subarachnoid hemorrhage remains challenging. In recent years, increasing attention has been paid to laboratory parameters reflecting neuronal tissue damage, blood-brain barrier dysfunction, ischemic injury, oxidative stress, and endothelial dysfunction [3, 4]. In this context, serum and cerebrospinal fluid (CSF) parameters, such as malondialdehyde (MDA), stable nitric oxide metabolites (NOx), albumin, lactate dehydrogenase (LDH), and lactate, may be of particular importance.

Identification of laboratory markers associated with unfavorable outcome may complement clinical and instrumental assessment of patients with subarachnoid hemorrhage and improve the accuracy of prognosis during the period of highest risk of cerebral vasospasm. Therefore, analysis of the diagnostic significance of laboratory parameters in the early postoperative period in patients with massive basal subarachnoid hemorrhage is of particular interest.

Aim - To assess the diagnostic significance of oxidative stress and endogenous vascular regulation markers reflecting ischemia-reperfusion brain injury in predicting unfavorable outcomes in patients with SAH.

II. MATERIALS AND METHODS

A retrospective analysis was performed for the period from 2021 to 2025 and included 50 patients with massive basal SAH, defined as more than 15 points on the A. Hijdra scale, who underwent microsurgical treatment within the first 72 hours from disease onset. The median age was 54 years. The patients were divided into two groups. Group 1 included patients with a favorable treatment outcome (Glasgow Outcome Scale, GOS, scores 4-5; n=25), whereas Group 2 included patients with an unfavorable outcome (GOS scores 1-3; n=25). The study was performed before surgery (day 0) and on postoperative days 1, 3, and 7. In the present analysis, we focused on postoperative day 3, since the most pronounced changes in the studied parameters were observed during this period, and the development of cerebral vasospasm also began in these patients.
Endothelial function was assessed by measuring NOx in serum and CSF using a spectrophotometric method. Oxidative stress was assessed by measuring MDA in serum and CSF using a fluorometric method. Biochemical parameters were determined using an

Olympus AU2700 analyzer (Beckman Coulter, USA) with Beckman Coulter reagents, USA.

To assess the studied parameters as predictors of unfavorable outcomes, ROC analysis was performed with calculation of the area under the ROC curve (AUC). Statistical analysis was performed using IBM SPSS Statistics 21.0.

III. RESULTS

ROC analysis of laboratory parameters measured on postoperative day 3 identified several parameters with diagnostic significance for unfavorable outcome:

- Increased serum LDH level: AUC 0.658 [95% CI, 0.507-0.809], $p < 0.05$. An LDH level above 259.2 U/L was associated with an unfavorable outcome, with a sensitivity of 70.4% and a specificity of 62.5%.
- Decreased serum albumin level: AUC 0.736 [95% CI, 0.597-0.875], $p < 0.004$. An albumin level below 30.8 g/L was associated with an unfavorable outcome, with a sensitivity of 66.7% and a specificity of 79.2%.
- Increased CSF MDA level: AUC 0.746 [95% CI, 0.574-0.918], $p < 0.02$. An MDA level above 1.05 µmol/L was associated with an unfavorable outcome, with a sensitivity of 81.3% and a specificity of 60%.
- Increased CSF NOx level: AUC 0.750 [95% CI, 0.577-0.923], $p < 0.02$. An NOx level above 20.7 µmol/L was associated with an unfavorable outcome, with a sensitivity of 62.5% and a specificity of 80%.
- Increased CSF LDH level: AUC 0.783 [95% CI, 0.621-0.946], $p < 0.001$. An LDH level above 162.8 U/L was associated with an unfavorable outcome, with a sensitivity of 62.5% and a specificity of 86.7%.
- Increased CSF albumin level: AUC 0.713 [95% CI, 0.524-0.901], $p < 0.05$. An albumin level above 0.9 g/L was associated with an unfavorable outcome, with a sensitivity of 75% and a specificity of 73.3%.
- Increased CSF lactate level: AUC 0.773 [95% CI, 0.571-0.974], $p < 0.05$. A lactate level above 5.3 g/L was associated with an unfavorable outcome, with a sensitivity of 54.5% and a specificity of 90%.

The ROC curves are presented in Figure 1.

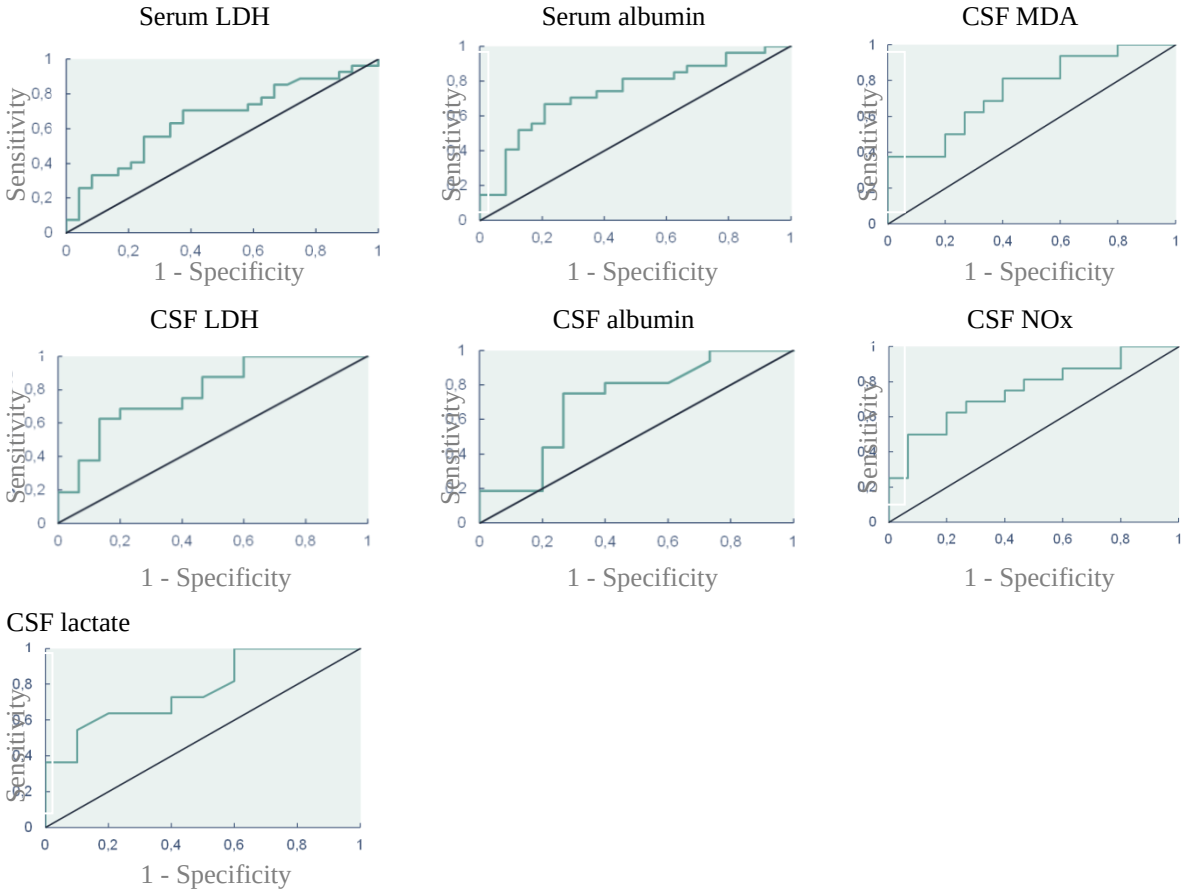

Figure 1. ROC curves of laboratory parameters for predicting unfavorable outcome in patients with subarachnoid hemorrhage on postoperative day 3.

IV. DISCUSSION

In the present study, parameters that demonstrated diagnostic significance according to ROC analysis were identified on postoperative day 3, corresponding to the onset of cerebral vasospasm and an increased risk of delayed ischemic brain injury. This is consistent with current concepts of aneurysmal subarachnoid hemorrhage, in which unfavorable outcome is largely determined by the severity of secondary brain injury [5]. The observed changes in serum and cerebrospinal fluid laboratory parameters may reflect different aspects of this process, including ischemic and hypoxic disturbances, altered blood-brain barrier permeability, oxidative stress, and endothelial dysfunction. Therefore, laboratory assessment during this period may complement clinical evaluation and contribute to more accurate prediction of an unfavorable disease course.

Increased LDH levels in serum and CSF, as well as increased CSF lactate levels, in patients with unfavorable outcome may reflect the severity of ischemic and metabolic disturbances after SAH. LDH is an intracellular enzyme, and increased activity may be related to damage to cellular structures [6], whereas lactate accumulation indicates enhanced anaerobic glycolysis under conditions of insufficient tissue perfusion. In the literature, blood and CSF lactate are considered potential laboratory markers of disease severity, vasospasm, and unfavorable outcome after aneurysmal SAH [7]. Our findings are consistent with these data and suggest that CSF LDH and lactate may be regarded as markers reflecting the severity of metabolic disturbances and tissue injury in the early postoperative period.

Opposite changes in serum and CSF albumin may reflect a combination of systemic and local disturbances in the unfavorable course of SAH. A decrease in serum albumin is probably associated with greater disease severity, inflammatory response, and impaired protein metabolism. According to the literature, hypoalbuminemia is a risk factor for unfavorable outcome in patients with SAH [8]. At the same time, an increase in CSF albumin may indicate impaired barrier function, since albumin is not synthesized intrathecally, and its increase in cerebrospinal fluid reflects increased permeability of the blood-brain barrier [9]. Thus, the observed albumin changes may characterize both the overall severity of the condition and local damage to the barrier structures of the central nervous system.

Increased CSF MDA and NOx levels in patients with unfavorable outcome may reflect the involvement of oxidative stress and impaired NO-dependent regulation of vascular tone in the development of secondary brain injury after SAH. MDA is one of the end products of lipid peroxidation; therefore, its increase in CSF may indicate activation of oxidative processes directly in the central nervous system [10]. Interpretation of CSF NOx levels is complicated by multidirectional changes in nitric oxide synthase activity: activation of inducible nitric oxide synthase contributes to increased NO production and maintenance of inflammatory and cytotoxic reactions, whereas decreased neuronal nitric oxide synthase activity is associated with impaired cerebral blood flow autoregulation and the development of delayed ischemia in the setting of cerebral vasospasm. Therefore, increased CSF NOx levels in patients with unfavorable outcome may be considered a reflection of NO-dependent mechanism imbalance in the complicated course of SAH [11].

From a practical perspective, parameters with higher sensitivity may be useful for early identification of patients with an increased probability of unfavorable outcome, as they help minimize the risk of missing a complicated disease course. In our study, these parameters included serum LDH, CSF MDA, and CSF albumin. In turn, parameters with higher specificity may be useful for confirming a high risk of unfavorable outcome; in this group, the highest specificity was demonstrated by serum albumin, CSF NOx, CSF LDH, and CSF lactate. At the same time, the obtained results should be interpreted with regard to the study limitations, including the relatively small sample size, single-center design, and assessment of diagnostic significance mainly on postoperative day 3. The identified cut-off values require further validation in larger cohorts and should be considered together with clinical findings, neuroimaging data, and instrumental assessment of cerebral vasospasm.

V. CONCLUSION

In patients with non-traumatic SAH caused by ruptured cerebral aneurysms, serum LDH and albumin, as well as CSF LDH, lactate, albumin, MDA, and NOx, demonstrated diagnostic significance for unfavorable outcome on postoperative day 3. The obtained data indicate that laboratory parameters may be used as an additional component in assessing patients during the period of increased risk of cerebral vasospasm and delayed ischemic injury. Further studies are required to confirm the diagnostic significance of the parameters used in this study.

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