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Association between C-reactive protein-albumin-lymphocyte (CALLY) index and cerebral edema in acute ischemic stroke patients

Povezanost između indeksa C-reaktivni protein-albumin-limfociti (CALLY) i cerebralnog edema kod bolesnika sa akutnim ishemijskim moždanim udarom

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Abstract

Background/Aim. There is an association between brain edema and inflammation that may occur in a stroke. The aim of the study was to determine the relationship between the C-reactive protein-albumin-lymphocyte (CALLY) index and cerebral edema developed as a consequence in stroke patients. **Methods.** The retrospective study included patients aged 18 years and above who presented to the emergency department from January 2021 to December 2023 and were admitted to the neurology/intensive care unit with a diagnosis of stroke. The following hematological parameters were included in the research: the pan-immune-inflammation value (PIV), systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII), and the CALLY index. These parameters were calculated from blood samples of patients taken during admission, and neurosurgeons assessed the development of cerebral edema and the need for decompression. The parameters were compared between two groups of patients: the surgical group (SG), with patients in need of decompression, and the nonsurgical group (NSG), with patients who do not have such a need. **Results.** The study included 274 patients in total, of which 189 (68.90%) were in NSG and 85 (31.10%) in SG. It was found that the CALLY index was significantly higher in patients in NSG than in patients in SG (16.47 vs. 0.79; $p < 0.001$). SIRI and SII levels were significantly higher in SG patients compared to NSG ($p < 0.001$ and $p = 0.001$, respectively). PIV level was also significantly higher in SG than in NSG ($p < 0.001$). At a cut-off value of 4.06, the CALLY index had a sensitivity of 69.40% and a specificity of 83.00%. **Conclusion.** The CALLY index is an easily accessible and calculable marker, which can be used to predict the need for decompression that may develop in stroke patients.

Key words:
brain edema; c-reactive protein; hematologic tests; stroke.

Apstrakt

Uvod/Cilj. Postoji povezanost između edema mozga i zapaljenja koje se može pojaviti u moždanom udaru. Cilj rada bio je da se utvrdi povezanost između indeksa C-reaktivni protein-albumin-limfociti (*C-reactive protein-albumin-lymphocyte* – CALLY) i posledičnim edemom mozga kod bolesnika sa moždanim udarom. **Metode.** Retrospektivnom studijom obuhvaćeni su bolesnici stari 18 ili više godina, koji su se javili u hitnu pomoć od januara 2021. do decembra 2023. godine i bili primljeni na neurologiju/odeljenje intenzivne nege sa dijagnozom moždanog udara. U istraživanje su bili uključeni sledeći hematološki parametri: zbirni imunsko-zapaljenski količnik (*pan-immune-inflammation value* – PIV), indeks sistemskog zapaljenskog odgovora (*systemic inflammatory response index* – SIRI), sistemski imunsko-zapaljenski indeks (*systemic immune-inflammation index* – SII) i indeks CALLY. Ovi parametri izračunati su iz uzoraka krvi bolesnika uzetih prilikom prijema, a neurohirurzi su procenili razvoj cerebralnog edema i potrebu za dekompresijom. Parametri su upoređivani između dve grupe bolesnika: onih kod kojih je postojala potreba za dekompresijom, hirurška grupa (*surgical group* – SG) i onih bez takve potrebe, nehirurška grupa (*nonsurgical group* – NSG). **Rezultati.** Istraživanjem je obuhvaćeno ukupno 274 bolesnika, od kojih je 189 (68,90%) bilo u NSG, a 85 (31,10%) u SG. Utvrđeno je da je indeks CALLY bio značajno viši kod bolesnika NSG u odnosu na SG (16,47 vs. 0,79; $p < 0,001$). Nivoi SIRI i SII bili su značajno viši kod bolesnika SG u odnosu na NSG ($p < 0,001$ i $p = 0,001$,

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redom). Nivo PIV bio je takođe značajno viši kod bolesnika SG u odnosu na NSG ($p < 0,001$). Na *cut-off* vrednosti 4,06, utvrđena je senzitivnost 69,40% i specifičnost 83,00% CALLY indeksa **Zaključak.** Indeks CALLY je lako dostupan marker koji je jednostavno izračunati, kojim se može predvideti potreba za dekompresijom koja se može razviti kod bolesnika sa moždanim udarom.

Ključne reči:
mozak, edem; c-reaktivni protein; hematološki testovi; moždani udar.

Introduction

A cerebrovascular accident is a disorder of blood vessels in the brain. The main cause of this disorder is difficulty in getting oxygen and nutrients as a result of the interruption of blood flow to the brain [1]. Symptoms of a cerebrovascular accident can lead to admission to the emergency department with different symptoms, such as numbness or weakness in the face and body, imbalance or lack of coordination, loss of vision, or blurred vision, depending on the location of the affected area in the brain and the damage [2, 3]. Treatment of a cerebrovascular event may require immediate intervention and is usually carried out in an emergency department. The aim of the treatment is to minimize damage to brain tissue, restore blood flow, and prevent complications. There are a number of ways to do this, including drugs, endovascular interventions, or surgery [4, 5].

Cerebral edema (CE) is a condition caused by the build-up of excess fluid in the brain, which can put pressure on brain tissue and disrupt normal brain function [6]. CE can occur for many reasons, including brain trauma, infection, tumor, or blockage in the brain vessels. Symptoms of CE can include headache, dizziness, nausea, vomiting, visual problems, behavioral changes, and even loss of consciousness [7, 8]. Treatment may vary depending on the cause of the edema and may include medication, surgery, or other treatments. CE can be a serious condition, and it is important to seek medical attention immediately [9]. This pathological increase in intracerebral hemispheric volume can lead to a mass effect with an increase in compartment pressure, accelerating subfalcine and transtentorial herniation [10]. This type of CE is responsible for the majority of neurological impairment and carries a mortality of approximately 80% without surgical decompression. If there is a sudden deterioration in mental status, a malignant edema clinic should be prioritized [11].

Since cerebrovascular events damage brain tissue, an inflammatory response can occur. Inflammation increases the activity of immune cells in the brain to eliminate damaged cells in brain tissue [7, 11]. The effects of inflammation resulting from a cerebrovascular event can include further damage to brain tissue, the formation of edema, and deterioration in brain function [11, 12]. In addition, inflammation following a cerebrovascular event may contribute to long-term damage to brain blood vessels and an increased risk of recurrent events. Studies have shown an association between CE and the inflammation that can occur after a stroke [12, 13]. Recently, the relationship between malignancy, gastrointestinal disease, and pneumonia and the C-reactive protein (CRP)-albumin-lymphocyte (CALLY) index, calculated from albumin, lymphocyte, and CRP parameters, has been reported [14–16]. Very few studies in the literature investigate the relationship between CE, which can develop in stroke patients, and the CALLY index. Therefore, the aim of this study was to determine the relationship between the CALLY index and CE developed in stroke patients.

Methods

Patients

This retrospective study included a total of 274 patients aged 18 and above who presented to the emergency department of a tertiary teaching and research hospital from January 2021 to December 2023 and were admitted to the neurology department/intensive care unit with a diagnosis of stroke. Stroke was diagnosed using physical examination, clinical and imaging techniques, and internationally accepted guidelines.

The study was approved by the Ethics Committee of the Antalya Training and Research Hospital (from March 21, 2024).

Exclusion criteria included the following patients: those transferred to another hospital for neurological follow-up and treatment, those with chronic malnutrition, autoimmune, hematological, and renal diseases that could affect the CALLY index, those with additional pathology that could cause CE, then, patients with malignancy, patients using steroids and the like, and patients who did not accept medical treatment. They were defined as patients who did not accept medical treatment.

Laboratory and clinical data

Demographic data and laboratory parameters were collected from patients diagnosed with stroke who met the inclusion criteria for the study. The parameters were calculated from the blood drawn from the patients on admission, and neurosurgeons determined the development of CE and the need for decompression in patients under 70 years of age with a large middle cerebral artery infarct in the non-dominant hemisphere and in other patients within the first 48 hrs. Indication for surgery was based on criteria such as the shift of midline structures on tomography, and relevant parameters were compared between patients with and without the need for decompression.

According to the need for decompression, all patients were divided into two groups: surgical group (SG) with

85 patients and nonsurgical group (NSG) with 189 patients.

The pan-immune-inflammation value (PIV), one of the hematological parameters, was calculated using the following formula: neutrophil count (10^9/L) × platelet count (10^9/L) × monocyte count (10^9/L)/lymphocyte count (10^9/L). The systemic inflammatory response index (SIRI), an inflammatory marker that has been increasingly used in recent years, is calculated using the formula: neutrophil count (10^9/L) × monocyte count (10^9/L)/lymphocyte count (10^9/L). The systemic immune-inflammation index (SII) was calculated using the formula: neutrophil count (10^9/L) × platelet count (10^9/L) /lymphocyte count (10^9/L). The CALLY index was calculated using the formula: albumin value (g/dL) × lymphocyte count (/μL)/CRP value (mg/dL) × 10^4. Parameters were compared between patients in these two groups.

Statistical analysis

For statistical analysis of the data in our study, the SPSS 25.0 was used. In the analysis of demographic and laboratory data of patients who underwent decompression, frequency for categori-cal data is expressed with numbers (percentages). For the analysis of continuous variables, the mean ± standard deviation (SD) was used, while for categorical data, Pearson Chi-square and Fisher's exact test were used. The Student *t*-test and Mann-Whitney *U* test showed the effects of hematological parameters on the need for decompression. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal values of these markers for the need for decompression. The value of $p < 0.05$ was considered statistically significant.

Results

A total of 274 patients who met the inclusion criteria were included in our study, of which 189 (68.90%) were in NSG and 85 (31.10%) in SG. When both groups were compared in terms of gender, the percentage of females was higher in SG than in NSG (44.70 vs. 31.20; $p = 0.022$). Hemoglobin and albumin levels were significantly higher in NSG patients compared to SG patients. Mean neutrophil count, monocyte count, and CRP levels were significantly higher in SG patients compared to NSG patients. A comparison of demographics and laboratory values between groups is shown in Table 1.

The CALLY index, one of the parameters obtained from the combination of blood parameters, was significantly higher in NSG patients than in SG (16.47 vs. 0.79; $p < 0.001$). SIRI and SII levels were significantly higher in patients in SG than in NSG ($p < 0.001$ and $p = 0.001$, respectively). PIV level was also significantly higher in SG patients than in NSG ($p < 0.001$). The values obtained from the combination of hemogram parameters are compared in Table 1. These values were calculated by drawing ROC curves to determine the need for decompression in stroke patients (Figure 1).

The effectiveness of the CALLY index, SIRI, SII, and PIV parameters in predicting the need for decompression was statistically significant. At a cut-off value of 4.06, the CALLY index had a sensitivity of 69.40% and a specificity of 83.00% (Table 2).

Table 1

Demographic and laboratory findings for examined patients with acute ischemic stroke

Parameters	Non-Surgery Group (n = 189)	Surgery Group (n = 85)	*p*-value
Female	59 (31.20)	38 (44.70)	0.022
Age, years	64.05 ± 13.91	60.25 ± 18.01	0.092
White blood cells	8.00 ± 2.57	12.30 ± 6.52	< 0.001
Hemoglobin	12.94 ± 1.65	11.38 ± 2.55	< 0.001
Platelets	238.91 ± 80.17	240.21 ± 99.34	0.167
Neutrophils	4.89 ± 2.21	9.94 ± 6.49	< 0.001
Lymphocytes	2.17 ± 0.77	1.44 ± 0.92	0.498
Monocytes	0.68 ± 0.22	0.77 ± 0.47	< 0.001
CRP	4.0 (6.93)	41.60 (111.68)	< 0.001
Albumin	36.78 ± 6.45	30.12 ± 7.43	0.006
CALLY	16.47 (28.59)	0.79 (9.39)	< 0.001
SII	499.35 (327.40)	1,645.75 (2,120.34)	0.001
SIRI	1.39 (1.17)	4.73 (8.89)	< 0.001
PIV	320.96 (315.21)	955.44 (2,029.67)	< 0.001

CRP – C-reactive protein; CALLY – CRP-albumin-lymphocyte; SII – systemic immune-inflammation; SIRI – systemic response inflammatory index; PIV – pan-immune-inflammation value.

All values are given as mean ± standard deviation or median (interquartile range), except for Female parameter, which is expressed as number (percentage).

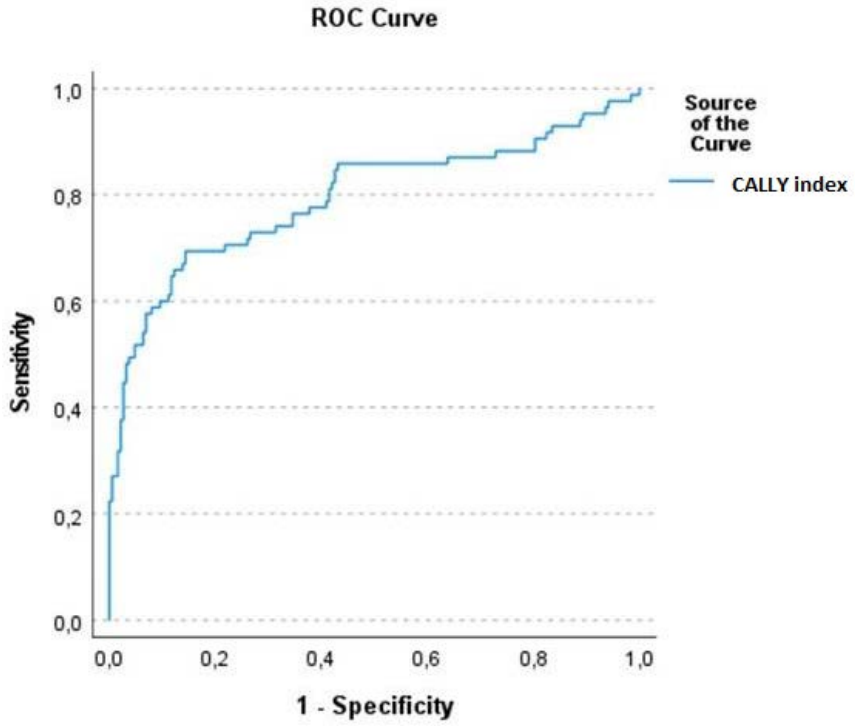

Fig. 1 – Receiver operating characteristic (ROC) curve analysis – C-reactive protein albumin-lymphocyte (CALLY) index of acute ischemic stroke patients predict cerebral edema.

Table 2

Receiver operating characteristic curves for hematologic parameters

Parameters	AUC	*p*-value	Cut-off	Sensitivity (%)	Specificity (%)
CALLY	0.795	0.001	4.06	69.40	83.00
SII	0.824	0.001	956.38	67.10	89.90
SIRI	0.775	0.001	2.96	63.50	88.40
PIV	0.765	0.001	709.68	57.60	89.40

AUC – area under the curve.

For other abbreviations, see Table 1.

Discussion

Although CE occurs approximately two to five days after stroke, the biological process that causes CE begins within hours of stroke onset [17]. A combination of cytotoxic, ionic, and vasogenic edema contributes to increased brain volume and can lead to increased pressure in this region [18]. Studies have shown that CE is associated with stroke size, National Institutes of Health Stroke Scale (NIHSS) score, and admission glucose levels with poor prognosis [14–18]. Studies have shown the prognostic efficacy of lymphocyte count as an indicator of immune competence, especially in patients with malignancies [12–16]. Acute phase reactants such as CRP and albumin are also used effectively in many diseases, especially in malignancy patients [19]. In our study, we investigated the relationship between the CALLY index and CE, which can develop in stroke patients.

The CALLY index was first shown to be prognostic in patients with malignancies and has been used effectively in the diagnosis and prognosis of many bowel diseases. In a study of oral cancer, preoperative CALLY was reported to be a simple and inexpensive prognostic marker [20]. Similarly, in another study on colorectal malignancies, the CALLY index appeared as an independently associated prognostic marker [15]. In a study of hepatocellular carcinoma patients with hepatitis C infection, the prognostic efficacy of the CALLY index was demonstrated at the optimal value of 5 [13]. A study by Yang et al. [15] demonstrated the long-term prognostic efficacy after surgery in 1,260 colorectal cancer patients and the importance of early assessment of the immuno-inflammatory response. In a study of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients, the CALLY index was reported to predict in-hospital mortality with a sensitivity of 76.15% and a specificity of 62.50% [21]. Another study demonstrated the utility of a high CALLY index, with an optimal cut-off value of 3.0, as a new prognostic biomarker and reported its effectiveness in patients suitable for postoperative adjuvant treatment with poor prognosis [15]. Recently, while conducting a study concerning the CALLY index, we found in the literature that the CALLY index can be considered an easily applicable indicator for the mortality of glioblastoma patients [22]. In a study by Gürbüzer and To-

zoğlu [23], it was found that new inflammatory, immunonutritive, and cardiovascular biomarkers SII, SIRI, atherogenic index of plasma (AIP), and CALLY index could be promising clinical tools for evaluating the severity, potential complications, and treatment response of alcohol use disorder. In a study by Fukushima et al. [24], the preoperative CALLY index < 2 was independently associated with a poor prognosis for patients after gastrectomy for gastric cancer. In our study, we found that the CALLY index could indicate the need for decompression with high sensitivity and specificity (69.40% and 83.00%), with the optimal value for the CALLY index being 4.06.

Limitations of the study

Our study has some limitations. First of all, this is a retrospective, single-center study. It is known that the parameters and the inflammatory process used for the CALLY index represent a dynamic situation, and the inability to follow the process and the changes in these parameters during the follow-up of these patients is an important limitation. In addition, the inability to compare inflammatory parameters such as CRP, interleukins (e.g., tumor necrosis factor), or white blood cells is another limitation. Although parameters such as the inflammation-related CALLY index are asso-ciated with many diseases, it may not be correct to make a surgical decision and associate mortality entirely with this parameter, representing yet another limitation. Finally, the extent to which the parameters are useful for the clinical fol-low-up of the disease is also a limitation, including the fact that the disease onset time cannot be clearly determined. A prospective multicenter study is needed so that the data in our study can be analyzed.

Conclusion

Based on the results of our study, the C-reactive protein-albumin-lymphocyte index is an easily accessible and calculable marker that can predict the need for decompression in stroke patients.

Conflict of interest

The authors declare no conflict of interest.

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