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Use of CALLY index to predict aneurysmal subarachnoid hemorrhage patient outcome

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Abstract

Background & Objective: Aneurysmal subarachnoid hemorrhage (aSAH) is a condition linked to elevated mortality and morbidity rates. Despite limited knowledge of the exact mechanism in aSAH patients, systemic inflammation is thought to have a significant role in cerebrovascular disease. The CALLY index is a prognostic marker utilized in many diseases, derived from parameters such as CRP, albumin, and lymphocytes. Nevertheless, there is limited research on its implementation in aSAH patients. This study aimed to investigate the CALLY index's prognostic usefulness in aSAH patients. *Methods:* The research cohort comprises patients who attended a tertiary teaching and research hospital's emergency department between January 1st, 2021, and January 1st, 2022, with a confirmed diagnosis of aneurysmal rupture. Basic demographic data and associated comorbidities of the cohort, in addition to the CALLY index derived from CRP, albumin, and lymphocyte levels, were documented. A comparison of the effects of investigations and data on in-patient mortality between the groups was conducted. *Results:* A total of 190 patients who met the inclusion criteria participated in the study. Patients with mortality were observed to have significantly lower CALLY Index scores than those in the other group (1.940 vs. 8.805). Regression analysis showed that mortality could be predicted based on the CALLY index (OR 0.393, 95% CI 0.1511-1.058, p=0.058). An AUC of 0.752, sensitivity of 78.2, specificity of 59.8 [p<0.001] was achieved by the optimal value for CALLY index. *Conclusion:* Based on the findings of this study, it can be inferred that CALLY index is a simple marker which can serve as an indicator of mortality in aSAH patients.

Keywords: Aneurysmal subarachnoid hemorrhage, CALLY index, mortality

INTRODUCTION

Aneurysmal subarachnoid haemorrhage (aSAH) is a condition with high mortality and morbidity.[1] Haemorrhage significantly impairs the functioning of cognitive processes, including language, memory, and executive functions.[2] Identifying high-risk patients is essential to ensure their well-being.[3] Although the exact mechanism in aSAH patients remains unknown, systemic inflammation may be a significant contributor to cerebrovascular disease.[4] The possibility for Systemic Inflammatory Response Syndrome (SIRS) to signal secondary damage in patients within the context of SAH pathogenesis, and thus anticipate a poorer prognosis, has been previously evidenced.[5] In the literature, several biomarkers are used to demonstrate the interplay between inflammation and aSAH, with the neutrophil-to-lymphocyte ratio, CRP, and troponin being among the crucial ones.[5-7]

Numerous biomarkers have been developed in literature using routine blood parameters, and many of them hold significant value in predicting prognosis. Hematologic indicators have demonstrated in clinical and past studies their ability to reveal the level of inflammation, nutritional status, and immunity.[8]

CRP, a significant marker of inflammation, has long been recognised as an indicator of inflammation in the literature. Albumin is also a clinically effective prognostic parameter. Moreover, the association between lymphocyte counts and immunity and inflammation has been established for many years.[9,10] Recently,

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the CALLY Index, which is derived primarily from CRP, albumin, and lymphocyte parameters, has become a prognostic marker, particularly in patients with malignancies. The CALLY index was calculated using the formula, lymphocyte (/μL) × albumin (g/dL) / CRP (mg/dL) x 10^4.[11] This study aimed to investigate the prognostic utility of the CALLY index specifically in aSAH patients.

METHODS

Patient population

The study cohort comprised patients who were admitted retrospectively to the neurosurgery clinic from the emergency department of a tertiary training and research hospital, between January 1, 2021 and January 1, 2022. These patients were treated for subarachnoid hemorrhage (SAH) caused by aneurysmal rupture. Age <18 years old, patients who had an uncertain connection between aSAH and aneurysm, co-existing immunological disorder, severe sepsis those who were transferred to another hospital, past medical history of kidney or liver dysfunction and autoimmune, used immunosuppressants; had active infection within the 2 weeks before admission and those who had incomplete laboratory data were excluded from the study. Moreover, those who were hospitalized elsewhere and those who displayed signs of infection which could have potentially impacted laboratory parameters were also excluded from the research.

Laboratory and clinical data

Upon admission to the emergency department and subsequent diagnosis of aSAH, patients' routine laboratory tests were obtained. Additionally, their demographic data and medical conditions including hypertension, diabetes, hyperlipidemia, smoking, and alcohol consumption were recorded. As per the literature, the CALLY index was computed by dividing the product of the CRP value and 104 from the result of multiplying albumin value by the lymphocyte count [(Albumin × Lymphocyte)/(CRP × 10^4)]. We determined the cut-off value for the CALLY index through Receiver Operating Characteristic (ROC) analysis to group patients accordingly. Afterwards, we compared the impact of the examinations and data on in-hospital mortality across the groups.

Statistical analysis

Statistical analysis of the study data was performed using SPSS 25.0, with a significance level of $P < 0.05$. Mean ± standard deviation was utilised for continuous variables in the analysis of data for aSAH patients. Frequencies and percentages (%) were employed in analysing other categorical data. Pearson's chi-squared and Fisher's exact tests were employed to compare suitable categorical data. The student t-test was implemented for variables displaying normal distribution, whilst the Mann-Whitney U test was utilised for those not exhibiting normal distribution when assessing parameters influencing mortality. Regression analysis was conducted to investigate factors that may impact mortality. The receiver operating characteristic (ROC) analysis was utilized to determine the optimum values indicating mortality for the CALLY index. Technical abbreviations were clarified upon their first usage. The language is objective, value-neutral, and free from biased or emotional expressions. Additionally, the text adheres to conventional structure and grammatical correctness, while presenting a clear and concise logical structure with balanced language. The citations have a consistent style and appropriate footnotes were included.

RESULTS

We included 190 patients who met the inclusion criteria in our study. Of these patients, 112 (58.9%) belonged to Group 1, while 78 (41.1%) experienced a fatal outcome and were included in Group 2. There were no significant differences observed in terms of age, gender, and average length of stay when comparing the two groups. However, comorbidities such as diabetes mellitus and coronary artery disease were significantly higher in the group that experienced a fatal outcome. White blood cell count, neutrophil count, and CRP levels exhibited higher values in the group with mortality as opposed to those without mortality. Meanwhile, the CALLY index was substantially lower in patients with mortality compared to the other group (1.940 vs. 8.805). Please refer to Table 1 for a comparison of the demographic data and laboratory values of the two groups. When split into low and high CALLY indices, the two groups had comparable age ranges. However, a notably greater proportion of males were recorded in the high CALLY index group. Comparing the groups revealed no notable difference in comorbidities. Mortality rates were significantly higher among individuals with a low

Table 1: Demographics and laboratory findings in patients with (SAH)

	Group 1 N=112	Group 2 N= 78	P value
Age (years)	61.2±13.66	62.1±14.91	0.673
Gender (Male);n(%)	53 (47.3%)	37(47.4%)	0.117
length of stay, mean (IQR)	4 (3)	5 (3.5)	0.792
Medical history			
Hypertension, n(%)	30(26.8%)	23(29.5%)	0.164
Diabetes Mellitus, n(%)"	32(28.6%)	14(17.9%)	0.034
Coronary Artery Disease, n(%)	21(18.8%)	26(33.3%)	0.010
Laboratory tests			
WBC count ($\times 10^3/mm^3$)	1107.77±557.1	1109.79±649.18	**0.013**
Neutrophil	845.89±544.18	860.98±647.79	0.006
Lymphocyt	2.19±0.99	1.71±0.95	0.922
Platelet	253.59±76.21	258.42±78.83	**0.858**
CRP (mg/dL), mean (IQR)	10.15 (24.58)	24 (56.52)	**<0.001**
Albunin	39.53±5.59	39.43±4.71	0.015
Cally index, mean (IQR)	8.805(16.38)	1.940(33.82)	**<0.001**
NLR, mean (IQR)	6.05 (17.28)	3.48 (15.3)	**0.214**

Abbreviation: WBC: white blood cell; NLR: neutrophil lymphocyte ratio ; e; CRP: C-reactive protein

CALLY index relative to those with a high index (61 (57.5%) vs 17 (20.2%), p <0.001). Analysis of demographic data and laboratory values are shown in Table 2.

The regression analysis found that mortality could be predicted by gender (OR 1.176, 95% CI 0.6191-2.253, p=1.176), age (OR 1.009, 95% CI 0.9871-1.032, p=0.425) and CALLY

Table 2: Demographics and laboratory findings in patients with aSAH

	CALLY≤6.95	CALLY >6.95	P value
Age (years)	61.01±14.77	62.27±13.39	0.512
Gender (Male);n(%)	45(42.5%)	45(53.6%)	0.037
length of stay	5(4)	4(3)	<0.001
Medical history			
Hypertension, n(%)	27(25.5%)	26(31%)	0.406
Diabetes Mellitus, n(%)"	27 (25.5%)	19(22.6%)	0.123
Coronary Artery Disease, n(%)	31(29.2%)	16(19%)	0.037
Laboratory tests			
WBC count ($\times 10^3/mm^3$)	1183.67±642.61	1013.87±517.06	**0.087**
Neutrophil	951.99±648.5	726.01±414.82	0.008
Lymphocyt	1.68±0.95	2.39±0.92	0.544
Platelet	260.56±83.14	249.28±68.76	**0.204**
CRP (mg/dL), mean (IQR)	50.66±43.5	6.77±4.72	**<0.001**
Albunin	38.93±5.56	40.19±4.72	0.069
Mortality	61(57.5%)	17(20.2%)	<0.001

Abbreviation: WBC: white blood cell CRP: C-reactive protein

Table 3: Predictors of mortality in aSAH

	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity(%)	P
WBC($\times 10^3/mm^3$)	970.5	0.526(0.437-0.615)	55.1	63.4	**0.568**
CALLY	6.943	0.752(0.683-0.821)	78.2	59.8	**<0.001**
CRP (mg/dL)	220.05	0.271(0.200-0.342)	100	1	**<0,001**

index (OR 0.393, 95% CI 0.1511-1.058, p=0.058) (Table 3). ROC curves were created to analyse the effectiveness of WBC, CALLY, and CRP parameters in distinguishing mortality (see Figure 1). For CALLY, the optimal value had an AUC of 0.752, specificity of 59.8, and sensitivity of 78.2 (p<0.001) (Table 4).

DISCUSSION

This study holds significant importance as it report the CALLY index for the first time in the medical literature regarding patients diagnosed with aSAH in the emergency department. Additionally, this index can guide emergency specialists in predicting the clinical severity of patients, as it can be easily calculated through a simple blood test taken in the emergency department. When reviewing the literature, it is known that previous investigations have focused on the effects of systemic inflammation involved in the pathogenesis process of aSAH. Therefore, some studies have investigated various new inflammatory markers used to predict the prognosis of aSAH, which has guided

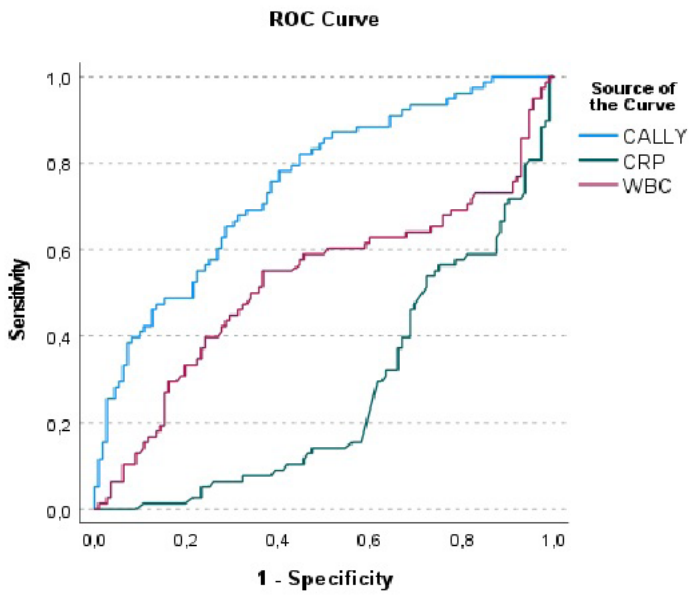

Figure 1. The ROC curve constructed.

Table 4: The receiver operating characteristic curves for aSAH

	Multivariate logistic regression		
Variable	**OR**	**95% CI**	***P*-value**
Gender	1.176	0.6191-2.253	0.622
Age	1.009	0.9871-1.032	0.425
CALLY>6.95	0.393	0.1511-1.058	0.058

Abbreviation: AUC: Area under the curve; CI: Confidence interval

our research.[12-14] Therefore, some studies have investigated various new inflammatory markers used to predict the prognosis of aSAH, which has guided our research.[12-14]

In the pathophysiological process of aSAH, the release of diverse inflammatory cytokines is increased upon bleeding initiation, resulting in escalated permeability of capillaries and disruption of the blood-brain barrier. This leads to the infiltration of neutrophils and macrophages, potentially contributing to the expansion of formed hematoma, edema formation, cell death, and enduring neurological damage.[15-17] Lymphocytes act as autoregulators against unresolved inflammation and are crucial in inhibiting cell proliferation and migration. They are a significant component of the host's tumor defense mechanism.[18,19]

Prior research has established that indicators such as leukocyte count, neutrophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, high immature granulocyte count, and other inflammatory markers are indicative of an unfavorable prognosis in individuals afflicted with aSAH.[20-23] Due to the weakening of the immune system of cancer patients and exacerbation of inflammation, albumin values and lymphocyte numbers decrease and CRP values increase. These values suggested that the CALLY index could be developed as a prognostic indicator. A study showed that the CALLY index calculated with these values can be used as a prognostic non-invasive marker in hepatocellular carcinoma patients.[24]

In a study conducted by Iida *et al*., it was shown that in 384 patients undergoing hepatectomy, the number of TNM Stage III and IV patients was significantly higher in the CALLY <5 group than in the ≥5 group, and there was a significant difference in the 5-year survival rate.[24] In a separate investigation of 280 hepatocellular carcinoma patients who underwent transarterial chemoembolization, experts evaluated the capability of the CALLY index to forecast the duration of the disease. Following the assessment, they established an optimal CALLY index cutoff point of 1 and explored the correlation between survival rates at 9 and 24 months. According to the findings, the CALLY index was established as an autonomous prognostic factor.[25] Furthermore, Liu *et al*. carried out a study on the predictive effectiveness of the CALLY index in a group of 1307 non-small cell lung cancer (NSCLC) patients. The study determined that patients with low CALLY indices experienced significantly worse overall survival than those with high CALLY indices.[26]

The clinical course and epidemiology of aSAH have not been clearly defined in the existing literature. It is important to present clear and objective evaluations of this condition, using simple sentences, logical structures, common academic sections, and consistent technical terms. The language should be formal, objective, and free from fillers, jargon, figurative language, and emotional evaluations. The text should be grammatically correct, employ precision in subject-specific vocabulary, and maintain a balanced perspective on the subject. Only a handful of case series have identified neuro-radiological signs to establish risk factors, etiopathogenesis, and prognosis relationships. For example, initial haemorrhaging may impair brain tissue via different pathways involving molecular and cellular mechanisms, and subsequently cause secondary cerebral harm. Inflammation processes significantly contribute to programmed cell death induction and triggering in the central nervous system. Nonetheless, despite considerable research into inflammation and associated events in aSAH, there is a dearth of data concerning inflammation and these events.[27] To our knowledge, there are no studies linking albumin and CRP parameters to the pathogenesis of aSAH in current literature. The purpose of this study is to examine whether the CALLY index, a parameter of critical importance, can be used as a prognostic marker in identifying mortality, one of the adverse outcomes of aSAH requiring immediate diagnosis and treatment.

Our study has several limitations. Firstly, this study is a retrospective, single-center study. We acknowledge the weaknesses associated with the small sample size and retrospective design. To obtain more conclusive findings, multicenter studies are necessary. The dynamic nature of the CALLY index and the challenge in determining the precise time elapsed until aneurysms were detected represent significant limitations in our research. As a result, the utility of the CALLY index remains limited because its predictive factor is based only on a single study per outcome. These perspectives illuminate the path for additional primary research, which should focus on a prospective multicenter approach, large samples, reduction of bias. This study ultimately forms a basis for future studies. To demonstrate the utility of the CALLY index as a predictor of mortality, multicenter and prospective studies are required.

In conclusion, CALLY index is an easily applicable marker that could serve as an indicator

for the mortality of patients with aSAH.

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