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CALLY index, but not HALP score, is associated with mortality in cirrhosis patients

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ABSTRACT

Background: Cirrhosis is a chronic liver disease that is characterized by inflammation and fibrosis, as well as liver dysfunction. The CALLY index and HALP score have recently provided crucial data in the diagnosis, follow-up, and prognosis of numerous diseases, particularly those of a malignant nature and those affecting the gastrointestinal system. The objective of this study was to ascertain whether the CALLY index and HALP score are appropriate indicators of mortality in patients with cirrhosis.

Methods: This study was conducted retrospectively in patients with liver cirrhosis between 01.01.2022-01.10.2024. The HALP and CALLY scores were calculated from the blood samples taken from the patients at the time of admission. The in-hospital mortality status of the patients was recorded. The effects of the parameters on mortality were compared.

Results: The study cohort comprised 235 participants, of whom 23 died. The median CALLY value was found to be 0.44 in patients who died and 1.19 in surviving patients. A significant decrease in the CALLY score was observed in patients who died (p=0.019). However, the HALP score did not show a significant difference in mortality between the two groups (p=0.262).

Conclusions: Based on the results of our study, CALLY index is an easily applicable index that can be used as an indicator of mortality in cirrhosis patients, but the HALP score is not a suitable marker for this purpose.

Keywords: CALLY index, cirrhosis, HALP score, mortality

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INTRODUCTION

Cirrhosis is a chronic liver disease that is characterized by inflammation and fibrosis, as well as liver dysfunction. A substantial body of evidence indicates that inflammation is a key factor in the progression of cirrhosis over an extended period. Cirrhosis complications include acute decompensation and acute-chronic liver failure [1]. The inflammatory response in cirrhosis is complex, involving systemic inflammation and immune dysfunction that can exacerbate liver damage and affect patient prognosis [2]. Immune dysfunction associated with cirrhosis encompasses both systemic inflammation and immunoparesis, which are evident across the disease spectrum, from compensated to decompensated cirrhosis [3]. Systemic inflammation is a principal factor in the development of acute decompensation and the progression to acute-to-chronic liver failure, which results in organ dysfunction and failure [4]. The predictive value of inflammatory markers in patients with newly diagnosed cirrhosis has been demonstrated, indicating their potential as prognostic tools. The use of biomarkers may enhance patient outcomes by facilitating the early detection and management of these complications [5].

Acute kidney injury (AKI) represents a significant complication in cirrhosis. In this context, studies have employed biomarkers such as urinary neutrophil gelatinase-associated lipocalin (uNGAL), interleukin-18 (IL-18), and liver-type fatty acid binding protein (L-FABP) to indicate kidney damage [6,7]. Similarly, Interleukin-6 (IL-6) and C-reactive protein (CRP) have been demonstrated to serve as biomarkers associated with inflammation in patients with cirrhosis [8]. As is widely recognized, IL-6 has been demonstrated to stimulate the production of CRP by the liver in patients with cirrhosis, which is associated with gastrointestinal bleeding [9]. This has been linked to the disease itself and its subsequent management. Furthermore, recent evidence indicates that biomarkers such as IL-6, CRP, NGAL, and L-FABP can provide valuable insights during the course of the disease and its subsequent monitoring [10].

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In recent years, the CRP-Albumin-Lymphocyte (CALLY) index and HALP score have provided important data in the diagnosis, follow-up and prognosis of many diseases, especially malignancy and gastrointestinal diseases [11,12]. Since inflammation is also important in the pathophysiology of cirrhosis, we aimed to determine whether the CALLY index and HALP score are suitable indicators for mortality in patients with cirrhosis.

METHODS

This study was conducted retrospectively on patients who had been diagnosed with liver cirrhosis and followed up at the emergency department of a tertiary education and research hospital. Following the granting of ethical approval, patients with a diagnosis of liver cirrhosis between the dates of 01/01/2022 and 01/10/2024 were identified through the hospital information management system. The study population consisted of individuals aged 18 years and above with a diagnosis of cirrhosis who had sought care at the emergency department. A diagnosis of cirrhosis was made using a combination of radiological imaging methods, abdominal ascites and related complications, biopsy, endoscopic or radiological evidence of portal hypertension or cirrhosis, and signs of hepatic decompensation. The exclusion criteria for this study included patients with chronic diseases that may affect complete blood count (CBC) parameters, those with systemic infection findings and findings suggestive of sepsis at the time of admission, patients with human immunodeficiency virus, patients with uncertain cirrhosis diagnosis, patients who had transplants, those using drugs such as steroids that may affect CBC parameters, those who did not accept hospitalization or were referred to different hospitals, and those with missing data.

The demographic data, chronic diseases, biochemical data, and mortality status of the patients were recorded and subjected to analysis. The data pertaining to cirrhosis patients in the present study were obtained from the hospital information system and patient files. The study included CBC and biochemistry parameters at the time of admission. The CBC parameters were obtained and analyzed during the initial hour of emergency room admission. Additionally, the study form was expanded to include basic parameters such as white blood cell, neutrophil, lymphocyte, monocyte, immature granulocyte, platelet, hemoglobin, and hematocrit levels. CRP was recorded in the albumin form and analyzed in conjunction with the aforementioned parameters. The SII and SIRI values of the patients were obtained from the CBC values and calculated by dividing the multiplication of the neutrophil and monocyte counts by the lymphocyte count. SII values were calculated by dividing the multiplication of platelet and neutrophil counts by lymphocytes. The pan-immune inflammation rate (PIH), a hematological parameter, was calculated by dividing the multiplication of neutrophil and platelet counts by monocyte count. The HALP score was calculated according to the following formula: haemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)/platelets (/L). The CALLY index was defined by multiplying the albumin value by the lymphocyte count and dividing it by the value obtained by multiplying the CRP value by 10,000. This is represented by the following equation: (Albumin × Lymphocyte)/(CRP×10^4). The neutrophil-lymphocyte-platelet ratio (NLPR) was calculated using the formula [neutrophil count / (lymphocyte count × platelet count)]. The SII was calculated by multiplying the peripheral platelet count by the neutrophil count and dividing the result by the lymphocyte count. SIRI was calculated by the following formula: (monocyte counts × neutrophil counts)/lymphocyte counts. The in-hospital mortality status of the patients was recorded, and the effects of the parameters on mortality were compared.

Statistical analysis

The data evaluated in the study were recorded in the database after being compiled from the hospital record system and analyzed with SPSS version 27. GraphPad Prism 9 program was used in graphic designs. After the data were classified, categorical data were stated as percentage and frequency values. Among the numerical data for which distribution analysis was performed, those that conformed to normal distribution were defined as mean ± Standard deviation. Data that did not conform were defined as median and interquartile range (IQR). While the chi-square test was performed between categorical data, the parametric test t-test was applied between data conforming to normal distribution. Mann-Whitney u test was used for data that did not conform to normal distribution. Receiver operator characterization (ROC) test was used in the evaluation of independent variables and multiple logistic regression analysis was performed in the evaluation of the relationship between variables. Results with a p-value below 0.05 were considered significant.

RESULTS

The study cohort comprised 235 individuals, of whom 23 died. No significant differences were observed in the comparison of demographic data, including age, gender, and additional diseases. The mean neutrophil count of patients who died was $12.74\times10^3 \pm 10.33\times10^3$, while the mean neutrophil value of surviving patients was found to be $5.98\times10^3 \pm 5.13\times10^3$. The neutrophil values were found to be significantly higher in the deceased patients. Table 1 presents the demographic data of the patients, a comparison of biochemistry and CBC values according to

Table 1. Comparison of demographic and labratory parameters for cirrhosis patients

	Live (n=212)	Exitus (n=23)	*p* value
Female	83 (39.2%)	8 (34.8%)	0.433
Age (years)	61.18 ± 14.32	63.17 ± 18.7	0.471
Congestive heart failure	7 (3.3%)	0	0.376
Arterial hypertension	13 (6.1%)	0	0.222
Diabetes mellitus	6 (2.8%)	1 (4.3%)	0.684
Alcoholism	31 (14.6%)	4 (17.4%)	0.723
White blood cell (×10³/µL)	8.33 ± 6.59	15.03 ± 10.78	<0.001
Hemoglobin (g/dL)	9.85 ± 2.15	8.62 ± 1.80	0.072
Hematocrit (%)	29.67 ± 6.21	26.86 ± 5.24	0.108
Platelets (×10³/µL)	130.72 ± 82.11	153.57 ± 121.86	0.024
Neutrophil (×10³/µL)	5.98 ± 5.13	12.74 ± 10.33	<0.001
Lymphocyte (×10³/µL)	1.05 (0.56-1.76)	1.04 (0.72-1.21)	0.677
Monocyte (×10³/µL)	0.62 (0.52-0.88)	0.92 (0.62-0.98)	0.084
Basophil (×10³/µL)	0.04 ± 0.04	0.05 ± 0.04	0.241
Eosonophil (×10³/µL)	0.09 (0.06-0.14)	0.06 (0.04-0.12)	0.161
Immature granulocyte (%)	0.5 (0.4-0.6)	1.7 (1.5-2.4)	<0.001
Immature granulocyte (×10³/µL)	0.04 (0.03-0.06)	0.27 (0.1-0.52)	<0.001
C-reactive protein (mg/L)	23.15 (18.26-44.18)	51.5 (44.52-61.2)	0.007
Albumin (g/L)	27.86 ± 5.83	25.60 ± 6.07	0.716

mortality status, and a summary of the statistical analysis. The median CALLY value was 0.44 in patients who died, while the median value was 1.19 in surviving patients, indicating a significant decrease in CALLY score in the deceased (p=0.019). Table 2 presents a comparison of hematological indices. The ROC analysis revealed that the area under the curve for the CALLY score was 0.656 (p=0.009). The optimal cutoff value was determined to be 0.842. At this value, the sensitivity was 73.9%, and the specificity was 59.4%. The results of the ROC analysis are presented in Table 3 (Figure 1). The results of the multiple logistic regression analysis indicate that hematological indices are not an independent risk factor for mortality. Table 4 shows the results of the multiple logistic regression analysis of hematological indices according to mortality.

Table 2. Comparison of hematological indices

	Live (n=212)	Exitus (n=23)	*p* value
SII	465.26 (322.26-845.64)	1305.28 (1024.42-1808.88)	0.018
SIRI	2.74 (2.12-4.96)	9.94 (6.62-13.20)	0.002
PIV	313.82 (212.64-707.62)	1266.12 (1012.62-2263.33)	0.009
NPLR	0.036 (0.02-0.06)	0.058 (0.10-0.07)	0.019
CALLY	1.19 (1.02-1.35)	0.44 (0.24-0.93)	0.014
HALP	2.39 (2.12-2.52)	2.06 (1.81-2.24)	0.262

Values are expressed as median with (interquartile range). Abbreviation: NLPR- neutrophil-lymphocyte-platelet ratio, PIV- pan-immune inflammation value, SII- systemic immuno-inflammation index, SIRI- systemic inflammatory response index.

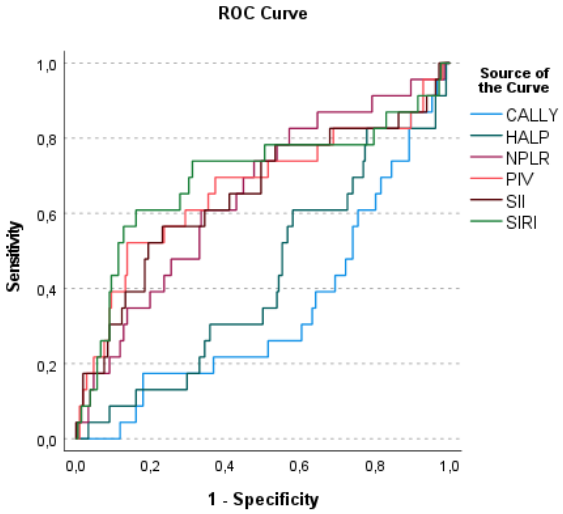

Figure 1. ROC curve analysis of mortality

Table 3. ROC analysis of mortality

	AUC	p value	Cut-off	Sensitivty (%)	Specificity (%)
SII	0.650	0.030	1131.17	47.8	81.6
SIRI	0.696	0.006	8.45	60.9	84
PIV	0.665	0.020	1261.97	52.2	85.8
NPLR	0.650	0.014	0.0557	60.9	67.5
CALLY	0.656	0.009	0.842	73.9	59.4
HALP	0.571	0.246	2.406	69.6	50

Abbreviation: NLPR- neutrophil-lymphocyte-platelet ratio, PIV- pan-immune inflammation value, SII- systemic immuno-inflammation index, SIRI- systemic inflammatory response index.

DISCUSSION

In this study, we investigated the relationship between two new inflammatory markers, the CALLY and HALP scores, and mortality in patients with cirrhosis. According to the results of our study, we found that a low CALLY index was associated with mortality in cirrhosis patients, while the HALP score was not. We also found that haematological parameters such as SIRI, SII, PIV, and NLPR were associated with mortality.

Cirrhosis is a chronic liver disease that is characterized by the replacement of normal liver tissue with fibrotic tissue. It is a significant disease that progresses with a course associated with liver dysfunction and related morbidity and mortality [13]. The disease may manifest with no symptoms or may progress to a level associated with serious complications, including hepatic encephalopathy, ascites, and variceal hemorrhage [14]. Hepatic encephalopathy, as well as complications such as acute chronic liver failure and hepatorenal syndrome, have been linked to increased mortality and morbidity in patients with decompensated cirrhosis. They have also been identified as key indicators of in-hospital mortality [15]. Furthermore, research has demonstrated that the etiology of cirrhosis, encompassing alcohol-related liver disease and viral hepatitis, can influence mortality [16]. Notably, alcohol consumption, particularly when coupled with viral hepatitis, can be a substantial contributor to mortality. Similarly, age and racial differences in mortality are also observed in older adults. It has been observed that increased mortality rates are more prevalent among males and young females, particularly within non-Hispanic white and Hispanic populations [17]. Recent studies have concentrated on numerous parameters that can inform the management and prognosis of patients with cirrhosis. Among these biomarkers, IL-6 was identified as a valuable indicator of mortality, exhibiting superior performance compared to numerous scoring models [18]. Similarly, the relationship between mean platelet volume and red cell distribution width and mortality was examined, and these parameters were identified as prognostic useful models with high sensitivity and specificity [19]. In our study, we focused on a new parameter, the CALLY index and HALP score, and examined their relationship with mortality. Our findings revealed a correlation between low CALLY index and mortality in these parameters. Our findings may guide physicians in clinical practice in determining the relationship between low CALLY index and mortality, initiating rapid follow-up and treatment, and closely monitoring patients. The widespread use of scores such as the CALLY index, which are obtained from simple parameters, in clinical practice may be important in critically ill patients.

The CALLY index has been employed in both diagnostic and prognostic contexts across a range of diseases, with particular relevance in oncological settings [20]. In one study, the CALLY index was examined in terms of mortality and morbidity rates in gastric cancer patients who underwent gastrectomy [21]. In this study, the CALLY index was used as a biomarker with higher sensitivity and specificity rates compared to many inflammatory markers [21]. In a separate investigation, the impact on survival in patients with ovarian cancer was assessed [22]. This study revealed that a CALLY index ≥3.00 was linked to more favorable survival outcomes [22]. In a study conducted by Takeda et al., it was highlighted that a preoperative CALLY index score <2.00 was associated with a poor prognosis in patients with colorectal cancer, and that the CALLY index was a valuable prognostic marker [23]. In a study conducted by Zhuang et al. on patients with breast cancer, it was demonstrated that a CALLY index ≥2.28 was associated with high survival rates [24]. In a study conducted on patients with SARS-CoV-2 infection, the CALLY index was employed. In comparison to albumin or lymphocyte count, CRP demonstrated superior predictive ability for in-hospital mortality. A CALLY index value <2.72 has been associated with a higher risk of in-hospital mortality [25]. Similarly, the HALP score has been investigated as a prognostic biomarker for mortality and disease outcomes in various medical conditions and it has provided valuable information in predicting mortality in many diseases [26]. The role of HALP score as a mortality predictor in stroke patients has been investigated and a negative correlation was found between HALP score and mortality [27]. Similarly, although the Pulmonary Embolism Severity Index (PESI) and its simplified version (SPesi) are effective predictors, the effectiveness of the HALP score has been examined but it was concluded that it is not associated [28]. In ad-

Table 4. Multiple logistic regression analysis by mortality

	B	S.E.	Wald	Sig.	Odds Ratio
SII	0.000	0.000	2.843	0.092	1.000
SIRI	0.067	0.038	3.181	0.075	1.069
PIV	0.000	0.000	2.610	0.106	1.000
NPLR	-0.849	2.707	0.098	0.754	0.428
CALLY	-0.092	0.098	0.888	0.346	0.912
HALP	-0.004	0.058	0.005	0.946	0.996

Abbreviation: NLPR- neutrophil-lymphocyte-platelet ratio, PIV- pan-immune inflammation value, SII- systemic immuno-inflammation index, SIRI- systemic inflammatory response index.

dition, the prognostic role of a low HALP score in rheumatological diseases has been reported in the literature [29]. In our study, we showed that there is a relationship between low CALLY index and mortality in patients with cirrhosis, but there is no relationship between HALP score and mortality that may develop in patients with cirrhosis.

It should be noted that our study is subject to certain limitations. Primarily, it is a retrospective, single-center study. The CALLY index and HALP score are parameters related to inflammation. While studies on mortality have been conducted, the dynamic nature of inflammation presents a significant challenge in determining the effects of disease onset, exacerbation, and additional diseases on these parameters. Although the parameters used in inflammatory systems such as the CALLY index can be parameters that can help predict diseases, mortality or hospital stay, we accept that it would not be correct to associate disease-related conditions entirely with them. Similarly, comparisons could not be made with inflammatory parameters such as interleukins, tumor necrosis factor, and integrin. Prospective multicenter studies are necessary to fully validate the value of the data in our study.

CONCLUSION

The findings of our study indicate that the CALLY index is a readily applicable index that can be utilized as an indicator of mortality in cirrhosis patients. Conversely, the HALP score is not an appropriate marker for mortality in cirrhosis patients.

ABBREVIATIONS

AKI- acute kidney injury

CALLY- CRP-Albumin-Lymphocyte (index)

CBC- complete blood count

CRP- C-reactive protein

IQR- interquartile range

L-FABP- liver-type fatty acid binding protein

NGAL- neutrophil gelatinase-associated lipocalin

SII- systemic immuno-inflammation index

SIRI- systemic inflammatory response index

AUTHORS' CONTRIBUTION

GY: conceptualization, methodology, data collection, writing.

CB: conceptualization, methodology, writing, review and editing, supervision.

ÖZ: methodology, data analysis, writing, review and editing, supervision.

FS: methodology, writing, review and editing.

YK: supervision.

CONFLICT OF INTEREST

None to declare.

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