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Could Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) score predict poor prognosis in patients with acute ischemic stroke?

Hemoglobin, Albümin, Lenfosit ve Trombosit (HALP) skoru akut iskemik inmeli hastalarda kötü prognozu öngörebilir mi?

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ABSTRACT

Aim: HALP (Hemoglobin, Albumin, Lymphocyte and Platelet) score was shown to have an association with prognosis in malignancies. However, the relationship between HALP score and prognosis in ischemic stroke is not clear. This study aimed to evaluate the relationship between HALP score and functional outcomes at discharge in patients with acute ischemic stroke.

Methods: A retrospective analysis was conducted on patients hospitalized with acute ischemic stroke. The HALP score was calculated. The functional status of the patients at discharge were assessed by the Modified Rankin Scale, and patients with mRS≥3 were considered to have a poor prognosis. The relationship between the HALP score, early functional results, and mortality rates of the patients was statistically evaluated. p< 0.05 was considered as significant.

Results: After exclusion criteria, data of 159 patients were analyzed. The median HALP score was 41.68. At discharge, 57 patients (35.8%) had poor prognosis. The median HALP score was significantly lower in patients with poor prognosis compared to those with good prognosis (p<0.001). The HALP score was lower in patients with mortality than patients that survive (p<0.001). The optimal cut-off value for the HALP score to predict prognosis at discharge was 37.945.

Conclusion: The HALP score may be valuable for predicting prognosis in patients with ischemic stroke. However, many variables of patients can affect prognosis. Therefore, it should be kept in mind that markers such as the HALP score should be evaluated together with other clinical parameters and the general condition of the patient.

Keywords: HALP score, prognosis, ischemic stroke

ÖZ

Amaç: Daha önce, HALP (Hemoglobin, Albümin, Lenfosit ve Trombosit) skorunun malignitelerde prognozla ilişkili olduğu gösterilmiştir. Ancak, iskemik inme hastalarında HALP skoru ile prognoz arasındaki ilişki net değildir. Bu çalışmada, akut iskemik inme hastalarında HALP skoru ile taburculuk fonksiyonel sonuçları arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Akut iskemik inme tanısıyla hastaneye yatırılan hastalar retrospektif olarak incelendi. Hastalarda HALP skoru hesaplandı. Hastaların taburculuktaki fonksiyonel durumları Modifiye Rankin Ölçeği (mRS) ile değerlendirildi ve mRS≥3 olan hastalar kötü prognoza sahip olarak kabul edildi. HALP skoru ile erken fonksiyonel sonuçlar ve hastaların mortalite oranları arasındaki ilişki istatistiksel olarak değerlendirildi. İstatistiksel anlamlılık düzeyi olarak p< 0,05 kabul edildi.

Bulgular: Dışlama kriterlerinden sonra, çalışmada 159 hastanın verisi analiz edildi. Hastalarda medyan HALP skoru 41.68 saptandı. Taburculukta 57 hasta (%35.8) kötü prognoza sahipti. İyi prognoza sahip hastalara kıyasla kötü prognoza sahip hastalarda medyan HALP skoru anlamlı olarak daha düşük bulundu (p<0.001). Ayrıca mortalite olan hastalarda hayatta kalan hastalara göre medyan HALP skoru daha düşük gözlendi (p<0.001). HALP skorunun gücü, taburculuktaki hastaların prognozu için değerlendirildi ve HALP skoru için optimum kesme değeri 37.945 olarak bulundu.

Sonuç: HALP skoru iskemik inmeli hastalarda prognozu tahmin etmede değerli olabilir. Ancak, hastaların birçok değişkeni prognozu etkileyebilir. Bu nedenle, HALP skoru gibi belirteçlerin, diğer klinik parametreler ve hastanın genel durumu ile birlikte değerlendirilmesi gerektiği akılda tutulmalıdır.

Anahtar Kelimeler: HALP skoru, prognoz, iskemik inme

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Introduction

Stroke is a significant cause of disability and death among patients, and predicting the prognosis in ischemic stroke is essential for both patients and clinicians [1]. Some specific blood biomarkers have been used for prognosis in acute ischemic stroke (AIS), but they are expensive and not widely available. Therefore, easily available and inexpensive markers have been evaluated for the prognosis in AIS [2]. Research on new markers to predict prognosis in stroke may help identify high-risk patient groups and develop effective prevention methods [1]. However, determining the prognosis in ischemic stroke remains difficult because of the inadequate capabilities of current tests.

Inflammation, poor nutritional processes, and abnormal coagulation states are thought to be associated with poor prognosis in patients with AIS. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a measurable index of inflammation and nutritional status in patients [1]. The HALP score is obtained by the combined evaluation of four parameters, and hence considered to be more stable than a single-parameter measurement. Previous studies have explored the prognostic effect of the HALP score in heart failure, coronary artery disease, and malignancy [3, 4]. However, whether the HALP score is related to prognosis in ischemic stroke is still unclear. Therefore, the present study aimed to assess and analyze the association between the HALP score and prognosis in patients who were hospitalized and monitored with AIS.

Methods

In this study, 586 patients who had AIS and were hospitalized in the neurology service and intensive care unit between July 15, 2015, and July 15, 2019, were retrospectively examined. The exclusion criteria were as follows: Those with diagnoses other than ischemic stroke at admission, patients with hemorrhagic cerebrovascular disease, patients with chronic kidney or liver disease, and those with a history of infection occurring within 1 week prior to or at the time of admission. Patients with a known malignancy or hematologic disorder, whose duration of admission exceeded 7 days after the onset of symptoms, and those with missing complete blood count and albumin test results at admission were also excluded from the study.

Stroke diagnosis was made based on the clinical signs and symptoms and confirmed by imaging findings. Also, factors posing a risk were listed, such as smoking habits and the presence of diseases (e.g., hypertension, atrial fibrillation, diabetes mellitus, coronary artery disease, and hyperlipidemia). The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was used for evaluating the subtypes of ischemic stroke [5]. The patients' National Institutes of Health Stroke Scale (NIHSS) values at admission, duration of hospitalization, mortality rates, and modified Rankin Scale (mRS) scores at the end of hospitalization were examined. Stroke severity was assessed using NIHSS [6]. mRS scores were used for assessing disability of the patients at discharge. Patients with mRS ≥3 were considered to have a poor prognosis.

Complete blood count parameters were listed. An automatic biochemical analyzer was used for assessments. Albumin, C-reactive protein, fasting glucose, and creatinine levels of patients were also listed. The HALP score was calculated in patients as follows: Hemoglobin (g/L) × Albumin (g/L) × Lymphocyte count (/L)/Platelet count (/L).

Statistical analysis: The data were processed using SPSS version 26 for Windows. The Kolmogorov–Smirnov test was conducted to assess the distribution of numerical variables. Numerical data with a skewed distribution were presented as median (25th–75th percentile), whereas numerical data with a normal distribution were reported as mean ± standard deviation. Categorical variables were expressed as frequencies and percentages. The Mann–Whitney U test was employed for skewed numerical variables, and the independent-samples t test was used for those with a normal distribution. The chi-square test was used to analyze categorical variables. Additionally, receiver operating characteristic (ROC) analysis was employed to assess the predictive ability of the HALP score in patients. A p value <0.05 indicated a statistically significant difference.

Results

After applying the exclusion criteria, data from 159 patients were reviewed. The median age of the patients was 73.00 years (range: 65.00–82.00), with 62.9% (n = 100) identified as male. A total of 33 patients (20.8%) reported a history of prior stroke. Based on the TOAST classification, 44.0% (n = 70) of the patients experienced a cardioembolic stroke. The demographic and medical characteristics of the patients are presented in Table 1.

Table 1. The demographic features and clinical characteristics of the patients with acute ischemic stroke.

	n=159
Age, years, median (25th-75th percentile)	73.00 (65.00-82.00)
Male, n(%)	100(62.9%)
Hypertension, n(%)	127 (79.9%)
Hyperlipidemia, n(%)	38(23.9%)
Atrial Fibrilation, n(%)	43(27.0%)
Diabetes mellitus, n(%)	55(34.6%)
Coronary artery Disease, n(%)	52(32.7%)
Smoking, n(%)	48(30.2%)
Previous Stroke, n(%)	33(20.8%)
Type of stroke, n(%)	
Large artery atherosclerosis	25(15.7%)
Cardioembolism	70(44.0%)
Small vessel occlusion	35(22.0%)
Stroke of undetermined etiology	28(17.6%)
Stroke of other determined etiology	1(0.6%)
NIHSS, median (25th-75th percentile)	5.00(4.00-10.00)
Duration of hospitalization, days, median (25th-75th percentile)	5.00(3.00-9.00)
mRS at discharge, n(%)	
0	36(22.6%)
1	48(30.2%)
2	18(11.3%)
3	7(4.4%)
4	27(17.0%)
5	11(6.9%)
6	12(7.5%)
Recurrent Stroke, n(%)	6(3.8%)

IQR: Interquartile Range, NIHSS: NIH Stroke Scale, mRS: Modified Rankin Scale

The admission time from the onset of symptoms ranged from 0 to 7 days. Most of the patients (n = 127) were admitted to the hospital within 48 h. The median NIHSS score of patients at admission was 5.00 (4.00–10.00), and the median duration of hospitalization was 5.00 days (3.00–9.00) (Table 1).

The median HALP score of patients was calculated as 41.68 (26.76–57.82). It was lower in women than in men, with a statistically significant difference ($p < 0.001$). A history of stroke, hypertension, diabetes mellitus, hyperlipidemia, or coronary artery disease in the patient did not cause a significant difference in the HALP scores. However, these scores were statistically significantly lower in patients with atrial fibrillation (median: 32.92 [22.67–50.22]) than in patients without atrial fibrillation (median: 44.23 [29.43–62.64]) ($p = 0.045$). Also, the median HALP score was calculated as 49.85 (37.57–65.54) in patients who smoked and 38.87 (25.83-52.18) in patients who did not smoke. This increase in HALP scores of smokers compared with nonsmokers was observed to be significantly different ($p = 0.007$). When compared based on stroke subtypes, a statistically significant difference in HALP scores was observed between the groups with stroke due to large-artery atherosclerosis and small-vessel occlusion ($p = 0.034$), but no significant difference was observed in the other group comparisons.

At discharge, 102 patients (64.2%) were in the good-prognosis group, whereas 57 patients (35.8%) had a poor prognosis. Mortality was observed in 12 patients. Patients with poor prognosis were more likely to be women and older, with higher median values of NIHSS score compared with patients with good prognosis. The hemoglobin level and leukocyte and neutrophil counts differed between patients with good and poor prognosis, and these differences were found to be statistically significant.

The median HALP score was 26.74 (18.39–37.26) for patients with poor prognosis compared with 48.35 (38.90–64.13) for those with good prognosis, revealing a statistically significant difference between the two groups ($p < 0.001$). Also, a binary logistic regression was conducted to assess whether the HALP score predicted prognosis while controlling for age. The HALP score was a significant predictor of prognosis ($\beta = 0.038$, SE = 0.010, Wald = 13.54, $p < 0.001$). The odds ratio was 1.039, with a 95% confidence interval of 1.018–1.061, while holding age constant. These

results suggested that the HALP score could be a statistically significant predictor of prognosis, even when controlling for age. Additionally, the median HALP score was significantly lower in patients with mortality (median: 21.28 [12.11–35.00]) than in those who survived (median: 43.13 [28.50–58.87]) ($p < 0.001$). The relationships between the blood test parameters and the prognosis of patients are stated in Table 2.

Table 2. The demographic features and blood test parameters according to the good and poor prognosis of patients with acute ischemic stroke.

	Patients with mRS <3 (n=102)	Patients with mRS ≥3 (n=57)	p value
Age, years, median(25th-75th percentile)	72.00(62.75-79.00)	79.00(71.00-84.50)	**0.002**
Male, n(%)	74(72.5%)	26(45.6%)	**0.001**
NIHSS, median (25th-75th percentile)	4(3.00-5.00)	12(8.00-15.50)	**p<0.001**
Duration of hospitalization, days, median(25th-75th percentile)	4(3.00-5.00)	12(6.50-17.50)	**p<0.001**
Hemoglobin, (g/l), mean ±SD	13.95±1.60	12.85±2.22	**0.001**
Leucocyte, (/l) median(25th-75th percentile)	7.63(6.52-9.35)	9.53(7.63-12.08)	**p<0.001**
Neutrophil, (/l), median(25th-75th percentile)	4.52(3.71-5.94)	7.56(5.93-9.85)	**p<0.001**
Lymphocyte, (/l), median(25th-75th percentile)	1.92(1.60-2.43)	1.31(0.99-1.76)	**p<0.001**
Platelet, (/l), median (25th-75th percentile)	220.00(178.25-261.25)	224.00(180.00-277.00)	**0.334**
Albumin, (g/l), mean ±SD	3.81±0.35	3.65±0.40	**0.007**
HALP score, median (25th-75th percentile)	48.35(38.90-64.13)	26.74(18.39-37.26)	**p<0.001**
CRP, median (25th-75th percentile)	2.80(2.00-7.00)	8.60(4.40-15.72)	**p<0.001**
NLR, median (25th-75th percentile)	2.37(1.77-2.93)	4.90(3.20-9.35)	**p<0.001**

IQR: Interquartile Range, NIHSS: NIH Stroke Scale, SD: Standard Deviation, HALP: Hemoglobin, Albumin, Lymphocyte and Platelet, CRP: C - reactive protein, NLR: Neutrophil Lymphocyte Ratio

The power of the HALP score for predicting the prognosis of patients at discharge was evaluated using ROC analysis. The optimal cutoff value for the HALP score was calculated to be 37.945. At this cutoff, the sensitivity and specificity of the score were calculated to be 77.19 and 77.45, respectively (Table 3). The ROC curve analysis for the HALP score is demonstrated in Figure 1.

Table 3. Analysis of HALP score test results for poor prognosis at discharge of acute ischemic stroke.

	HALP score
Cut-off Value	≤37,945
AUC (95% CI)	0,797(0,718-0,875)
Sensitivity	77.19(64.16-87.26)
Specificity	77.45(68.11-85.14)
Positive Predictive Value	65.67(56.52-73.79)
Negative Predictive Value	85.87(78.84-90.83)
Accuracy rate	77.36(70.06-83.61)

AUC: Area under the ROC curve

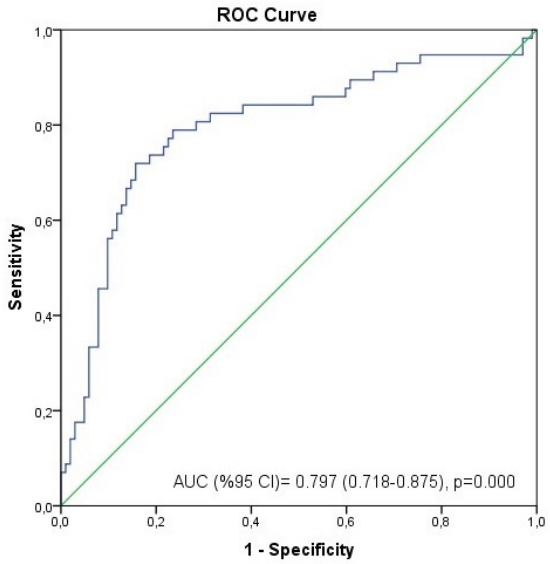

Figure 1. ROC analysis graph for HALP score

Discussion

This study evaluated the correlation between the HALP score and the prognosis of patients with AIS. We observed that lower HALP scores at admission were associated with unfavorable outcomes at discharge and in-hospital mortality.

Four variables made up the HALP score. They were individually useful for the prognosis in patients with AIS, but their combination was considered to be a better marker compared with these markers alone. The HALP score was previously found to have an association with nutritional status and inflammation in patients and

served as a novel indicator used to foresee many medical consequences in several diseases. It was associated with survival in many cancers, such as lung, gastrointestinal, and bladder cancers [4]. Some evidence shows the association of the HALP score with different types of diseases. However, the association between the HALP score and outcomes in patients with ischemic stroke remains uncertain. A few recent studies have focused on the association of the HALP score with the prognosis of patients with ischemic stroke or cerebral venous thrombosis [1, 7].

Lymphocytes play an important role in inflammation after stroke, but data about the function of lymphocytes are debatable. Previously, lymphocytes were reported to cause the release of cytokines, leading to tissue damage. However, other studies found an effect of lymphocytes on the repair of tissue damage [8]. In the present study, the lymphocyte counts were observed to be lower in patients with poor prognosis compared with patients with good prognosis, with a significant difference. Another study demonstrated an association of low lymphocyte counts with worse outcomes in patients with AIS, similar to the present study [1]. Additionally, Kim et al. noted that lower lymphocyte counts were related to poor functional recovery after 3 months in patients with AIS [9].

Platelet activation is crucial for the pathophysiology of AIS [2, 10]. It has been proposed earlier that the platelet count can serve as a predictor for the likelihood of recurrent stroke, death, and unfavorable functional results [1, 11]. Inflammation starts a few hours after stroke onset and induces thrombosis, platelet adhesion, and aggregation [1]. However, in the present study, the difference in platelet count was not significant between patients with AIS having poor and good prognoses. Similar to the findings of the present study, Du et al. and Jin et al. reported that platelet count did not differ significantly between the groups with poor and good prognosis at the time of patient evaluation [10, 12].

The association of hemoglobin levels with the prognosis of patients with stroke is still controversial. Previous studies suggested that both low and high hemoglobin levels were associated with ischemic stroke [13, 14]. Several mechanisms were suggested for the influence of hemoglobin levels on stroke prognosis. Anemia increases inflammation, reduces the oxygen transport to penumbra regions, and impairs cerebral vascular regulation [14]. A hemoglobin level of less than 11 g/dl upon admission may have a correlation with an increased risk of short-term mortality in patients experiencing an acute stroke [2]. Higher hemoglobin levels with increased viscosity can lead to a decrease in cerebral blood flow and development of carotid atherosclerosis, posing a risk for patients with AIS [1, 14]. Furlan et al. demonstrated that both elevated and reduced hemoglobin levels at the time of admission might be associated with poorer outcomes in patients with ischemic stroke [13]. Additionally, Zhang et al. discovered that both low and high hemoglobin levels, compared with normal levels, were associated with a higher likelihood of poor prognosis and increased overall mortality in patients with AIS and transient ischemic attacks [14].

In contrast, albumin exerts a neuroprotective effect and reflects the severity of inflammation [1, 15]. It is regulated by several physiological mechanisms, and a decrease in its levels can lead to decreased cellular immunity or impairment in anticoagulation mechanisms, thereby worsening the prognosis in patients with stroke [16-18]. A clinical trial by Palesh et al. showed that high-dose albumin therapy might be neuroprotective following ischemic stroke [19]. A few previous studies with small sample sizes discussed the association of albumin with stroke prognosis [16, 18, 20, 21]. Low albumin levels were associated with poor outcomes, mortality, or stroke recurrence [15, 21]. Cho et al. observed that serum albumin levels were the only predictive marker for the functional outcome and prognosis of patients after regression analysis [16]. Dziedzic et al. showed that an increase in albumin levels led to a decrease in the risk of poor prognosis in a large retrospective cohort of patients with stroke [17]. Moreover, a prospective study showed that, for every decrease in albumin level of 10 g/ l the risk of poor outcome and mortality increased by 17% and 86%, respectively [18]. A decrease in albumin levels increased the risk of complications such as infections in patients with stroke, increasing the

risk of mortality and morbidity [18].

The findings of the present study indicated that the HALP score was decreased in female patients, older individuals, and those with atrial fibrillation, which was consistent with the previous study by Tian et al. [1]. Additionally, Antar et al. noted an inverse correlation between the HALP score and age, with a 0.86-point decline in the HALP score for every year of increased age [3]. Although lower HALP scores were associated with a higher incidence of cardioembolic strokes [1], we did not observe any correlation between cardioembolic stroke and the HALP score. Instead, we identified a significant difference between strokes resulting from large-artery atherosclerosis and those caused by small-artery occlusion.

Data on the HALP score and smoking are controversial. Antar et al. observed higher scores in smokers than in nonsmokers [3]. Similarly, we observed that patients who smoked had higher HALP scores than nonsmokers. We also observed that patients who smoked had higher hemoglobin levels. Also, we thought that, apart from genetic individual differences, hemoglobin levels might contribute to this difference.

We observed that decreased HALP scores had a correlation with poor prognosis at discharge, and the optimal cutoff value was calculated as ≤37.945 for predicting poor prognosis. Similarly, a different prospective study found that a lower HALP score was correlated with an increased risk of poor outcome after 90 days and during a 1-year follow-up; scores less than 36.65 indicated the greatest risk for an unfavorable prognosis [1].

The HALP score statistically significantly decreased in patients who died compared with patients who survived in the present study. Similarly, Kurt et al. discovered considerable differences in HALP scores between survivors and nonsurvivors with ischemic stroke and concluded that the HALP score might be a reliable indicator of in-hospital mortality [22]. Also, another study observed a correlation between the HALP score and the 28-day mortality of patients aged more than 85 years who were followed up in the intensive care unit with AIS. However, the HALP score for mortality had low sensitivity and specificity [23].

Recent studies have explored the association between the HALP score and cerebrovascular diseases. Apart from functional outcome and mortality rates, the HALP score and post-stroke cognitive decline have been linked to the effects of post-stroke acute systemic inflammation and malnutrition impairment in surviving patients. In a study published last year, HALP scores of the patients with cognitive impairment in the first 2 weeks after stroke were found to be significantly lower compared with the scores of those without cognitive impairment [24]. The HALP scores were also correlated with the mini-mental state examination scores of the overall group [24]. Zuo et al. made subacute, third-month, and first-year cognitive status evaluations in patients with stroke. They reported that cognitive impairment and decreased HALP scores were associated in first-year evaluations [25].

Limitations: This study had some limitations. First, it was retrospective and conducted in a single center. Second, the sample size was insufficient for conducting detailed subgroup analyses across various stroke subtypes. Additionally, we only examined the HALP score at admission; dynamic alterations over time were not recorded. Patients with concomitant conditions, such as liver or renal disorders or malignancy, were not included in the study. Therefore, when making clinical decisions, it is important to consider the unique comorbidities of each patient. Also, the lack of long-term follow-up might have limited the ability to fully assess the prognostic value of HALP over time. Incorporating such outcomes can enhance the clinical relevance and comparability with previous studies. Future prospective studies should include extended follow-up periods to better evaluate long-term associations.

Conclusions

Ischemic stroke is a serious neurological condition with high morbidity and mortality rates. This has increased the need for reliable prognostic markers that can predict the course of the disease. Clinical, laboratory, and imaging-based biomarkers play an important role in assessing disease severity, guiding treatment strategies, and predicting both short- and long-term outcomes. In recent years, the HALP score, which reflects hematological,

nutritional, and inflammatory statuses, has become one of the remarkable parameters in this field. This study found that a low HALP score was significantly associated with worse clinical outcomes and increased mortality in patients. The findings of this study suggest that the HALP score may be useful for predicting prognosis in patients with ischemic stroke. However, many variables can influence prognosis. Therefore, markers such as the HALP score should be considered alongside other clinical parameters and the overall condition of the patient.

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