Původní sdělení | Original research article

Prognostic importance of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score in patients with acute pulmonary embolism

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ARTICLE INFO

Article history:
Submitted: 24. 11. 2023
Revised: 27. 12. 2023
Accepted: 28. 12. 2023
Available online: 27. 5. 2024

Klíčová slova:
Akutní plicní embolie
Biomarker
Nemocniční mortalita
Skóre HALP

SOUHRN

Cíl: Zhodnotit prognostickou hodnotu skóre s použitím hodnot hemoglobinu, albuminu, lymfocytů a trombocytů (hemoglobin, albumin, lymphocyte, and platelet, HALP) u akutní plicní embolie (APE).
Metody: Retrospektivně jsme vyhodnotili údaje pacientů ve věku 18 let a starších, u nichž CT angiografické vyšetření plic na oddělení urgentního příjmu v období mezi lednem 2019 a lednem 2023 prokázalo APE. Byly vyhodnoceny klinické a demografické údaje pacientů a následně vypočítán zjednodušený index závažnosti jejich plicní embolie. Skóre HALP se vypočítávalo z prvního krevního vzorku odebraného po přivezení pacienta na oddělení urgentního příjmu; přitom se používala rovnice HALP: hemoglobin × albumin × lymfocyty / trombocyty.
Výsledky: U 277 pacientů s APE, zařazených do studie, dosáhla nemocniční mortalita hodnoty 19,1 %. Skóre HALP zemřelých pacientů bylo statisticky významně vyšší než skóre přeživších ($p < 0,001$). Mezní hodnota skóre HALP na křivce ROC pro nemocniční mortalitu byla 3,21 (senzitivita: 81,13 %; specificita: 84,37 %; plocha pod křivkou ROC: 0,879; 95% interval spolehlivosti [confidence interval, CI] 0,827–0,930; $p < 0,001$). Na základě těchto mezních hodnot byla provedena logistická regresní analýza a multivariační logistická analýza prokázala, že skóre HALP (poměr šancí: 0,24; 95% CI: 0,17–0,96) je nezávislým ukazatelem mortality.
Závěr: Zjistili jsme, že skóre HALP, zahrnující čtyři hematologické parametry, může sloužit jako cenný biomarker v predikci nemocniční mortality.

Keywords:
Acute pulmonary embolism
Biomarker
HALP score
In-hospital mortality

ABSTRACT

Objective: To investigate the prognostic value of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score in acute pulmonary embolism (APE).
Methods: We retrospectively evaluated patients aged 18 years and over who were diagnosed with APE by computed tomography pulmonary angiography at the emergency department (ED) between January 2019 and January 2023. The patients' clinical and demographic data were evaluated, and their simplified pulmonary embolism severity index values were calculated. The HALP score was obtained using the first blood sample measured after the patients were admitted to the ED. The HALP score was calculated according to the formula: HALP = hemoglobin × albumin × lymphocytes / platelets
Results: The in-hospital mortality rate was 19.1% in 277 patients with APE included in the study. The HALP score of the patients who died was significantly lower than the HALP score of those who survived (p <0.001). The cut-off value of the HALP score on the receiver operating characteristic (ROC) curve for in-hospital mortality was 3.21 (sensitivity: 81.13%; specificity: 84.37%; area under the ROC curve [AUC]: 0.879, 95% confidence interval [CI]: 0.827–0.930, p <0.001). A logistic regression analysis was performed based on these cut-off values, and the multivariate logistic regression analysis revealed that the HALP score (odds ratio: 0.24, 95% CI: 0.17–0.96) was an independent indicator of mortality.
Conclusion: Our findings showed that the HALP score, which comprises four hematological parameters, can be a valuable biomarker that can be used to predict in-hospital mortality.

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DOI: 10.33678/cor.2023.099

Please cite this article as: Sert ET, Kokulu K, Mutlu H, Gönen MÖ. Prognostic importance of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score in patients with acute pulmonary embolism. Cor Vasa 2024;66:312–317.

Introduction

Pulmonary embolism (PE) is a disease characterized by increased mortality and morbidity, usually resulting from deep vein thrombosis in the lower extremities.[1] While APE progresses with mortality in 25–30% of cases if left untreated, this rate decreases to 2–8% among treated patients.[2] Therefore it is necessary to identify the patient group at risk. The risk assessment of APE and the detection of prognostic markers are very important for the closer follow-up of high-risk patients. Current guidelines recommend using the pulmonary embolism severity index (PESI) to predict prognosis in patients with APE.[3] In addition, it is recommended to perform more detailed risk grading by evaluating the echocardiographic findings of certain biomarkers, such as right ventricular (RV) overload, B-type natriuretic peptide (BNP), and troponin.[3] However, there is still an ongoing search for low-cost, simple, and easily accessible markers to be used together with the recommended risk scores for the prediction of the APE prognosis.

Previous studies have reported that markers of inflammation (such as platelet-to-lymphocyte ratio [PLR[, systemic immune inflammation index [SII], and neutrophil-to--lymphocyte ratio [NLR]) are associated with in-hospital and short-term mortality in patients with APE.[4–7] It has also been suggested that low levels of albumin, which is a negative acute phase reactant, may be a marker of inflammation and indicate an increased risk factor for venous thromboembolism.[8] In recent years, the HALP score, calculated as hemoglobin × albumin × lymphocytes / platelets, has been defined as a new biomarker of systemic inflammation.[9,10] In the literature, it has been reported that the HALP score can be used as a prognostic biomarker in various neoplasms.[11,12] Considering that venous thromboembolism resulting in APE causes a series of inflammatory reactions in the pulmonary artery wall,[3] the HALP score is also likely to be a prognostic factor for APE. Therefore, we aimed to evaluate the power of the HALP score to predict in-hospital mortality in patients with APE.

Material and methods

Study design and patient selection

In this study, patients who applied to our hospital's emergency department (ED) between January 1, 2019 and January 31, 2023 and received codes for pulmonary embolism (I26, I26.0, I26.9) according to the International Classification of Diseases-10 code system were retrospectively screened from the hospital's electronic database. Among these patients, patients aged ≥18 years and diagnosed with APE on computed tomography pulmonary angiography (CTPA) were included in the study. Ethical approval for this study was received from Aksaray University Faculty of Medicine Clinical Research Ethics Committee dated 27.04.2023 with an approval number 2023/08-03.

Patients with missing data, those whose CTPA images were without report, those with a history of hematological disease, inflammatory disease, trauma, empirical antibiotic use, active infection, and chronic renal or hepatic diseases, and those receiving immunosuppressive or anticoagulant therapy were excluded from the study.

Data collection and outcomes

Data on the clinical and demographic characteristics of the patients, physical examination findings, routine laboratory parameters, D-dimer, cardiac troponin I, and radiological imaging reports were obtained by reviewing the electronic medical records of the patients. Hemoglobin, albumin, lymphocyte, and platelet values were recorded from the first blood sample measured after the patients were admitted to the ED. HALP score was calculated as follows: hemoglobin × albumin × lymphocytes / platelets. In addition, the simplified PESI (sPESI) was calculated for all patients using heart rate, chronic cardiopulmonary disease, history of cancer, age, systolic blood pressure and O saturation parameters. CTPA was performed using a 128-slice computed tomography device (U.S.A., GE Revolution EVO). Right ventricular systolic dysfunction (RVD) was recorded from echocardiography data. The evaluated primary outcome was in-hospital mortality.

Data analysis

Statistical analysis was undertaken using the SPSS 22.0 program (SPSS Inc, Chicago, IL, USA). Frequency and percentage were used to evaluate categorical data. Chi--square test was used for the relationship between categorical variables. The Kolmogorov–Smirnov test was used to evaluate the distribution of numerical variables. Data that did not show a normal distribution were compared using the Mann Whitney-U test and presented as median (25th–75th percentile) values. The Student's t-test was used if the data distribution showed a normal distribution, and these data were presented as mean ± standard deviation. A correlation analysis was carried out to identify the linear relationship between sPESI and the investigated variables. In the correlation analysis, Pearson's correlation test was used for continuous variables and the Spearman correlation test for categorical variables. A receiver operating characteristic (ROC) curve was plotted to identify the power of HALP to predict in-hospital mortality in APE. Optimal sensitivity, specificity, and cut-off values were determined. The determined cut-off values were used in a logistic regression analysis to predict in--hospital mortality. A univariate logistic regression analysis was undertaken to identify the relationship between in-hospital mortality after APE and possible confounding factors. Variables with a p value of <0.05 in this analysis were included in a multivariate logistic regression analysis. The odds ratio (OR) and 95% confidence interval (CI) values were also determined.

Results

The mean age of the 277 patients included in the study was 63.9±8.7 years, and 175 (63.2%) were male. In--hospital mortality occurred in 53 patients (19.1%). The mean HALP score was 4.75±1.50 in the survivor group and 2.57±1.09 in the mortality group. The HALP score of the patients who died was significantly lower than of those who survived (p <0.001). Demographic data, laboratory

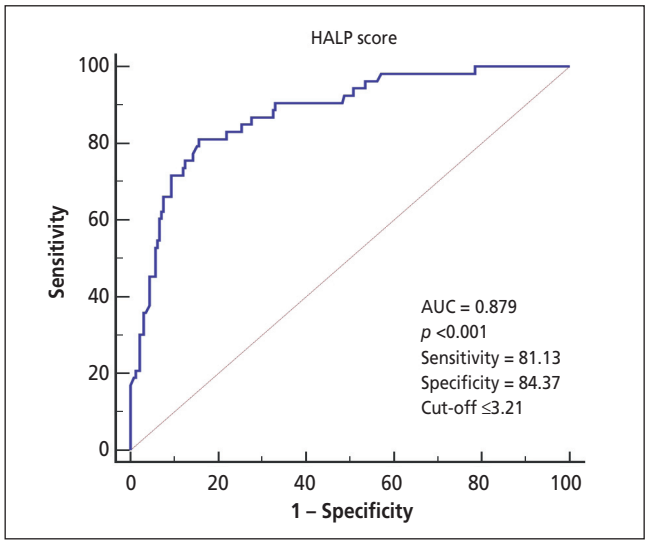

Fig. 1 – ROC curve analysis of the relationship between HALP level and in-hospital mortality.

results, and clinical outcomes of the patients are shown in **Table 1**. A statistically significant difference was found between the groups in terms of age, systolic blood pressure, hemoglobin, neutrophil count, lymphocyte count, albumin, lactate, RVD, and the sPESI score (p <0.05). The linear correlation between the HALP score and other variables is summarized in **Table 2**. In the correlation test, a significant negative correlation was detected between the HALP score and the sPESI score (r = 0.532, p <0.001).

Using the ROC curve, the cut-off value of HALP for the prediction of in-hospital mortality was determined to be 3.21 (sensitivity: 81.13%; specificity: 84.37%; area under the curve [AUC]: 0.879; 95% CI: 0.827–0.930; **Fig. 1**). The cut-off values of SII and NLR were found to be 1089.2 (sensitivity: 77.65%; specificity:79.08%; AUC: 0.809) and 3.46 (sensitivity: 74.02%; specificity: 69.11%; AUC: 0.781), respectively. A logistic regression analysis was performed based on these cut-off values. According to the multivariate logistic regression analysis, RVD (OR: 1.87, 95% CI: 1.44–3.73), sPESI (OR: 1.83, 95% CI: 1.21–3.10), SII index

Table 1 – Comparison of clinical characteristics between the groups

Variables	Mortality (n = 53)	Survivor (n = 224)	*p*-value
Age (years)	71.3±6.8	62.1±8.2	0.034
Gender, male	34 (64.2%)	141 (62.9%)	0.870
Heart rate (bpm)	115±19	109±21	0.081
Systolic blood pressure (mmHg)	97±13	114±12	0.002
Diastolic blood pressure (mmHg)	64±9	70±7	0.054
Pulse oximetry (SpO_2, %)	87 (83–91)	89 (85–92)	0.066
Hypertension	23 (43.4%)	103 (46.0%)	0.734
Diabetes	16 (30.2%)	78 (34.8%)	0.522
Coronary artery disease	7 (13.2%)	15 (6.7%)	0.115
COPD	18 (34.0%)	70 (31.3%)	0.703
Heart failure	14 (26.4%)	62 (27.7%)	0.853
Malignancy	1 (1.9%)	0 (0%)	0.191
DVT	20 (37.7%)	81 (36.2%)	0.830
White blood cell, × 10^9/L	9.18±2.54	8.60±3.09	0.205
Hemoglobin, g/dL	11.5 (10.3–12.9)	13.2 (12.3–13.9)	<0.001
Neutrophils, × 10^9/L	8.04±2.25	6.35±1.70	<0.001
Lymphocytes, × 10^9/L	1.55±0.56	2.34±0.62	<0.001
Platelet count, × 10^9/L	233 (202–259)	239 (216–268)	0.053
Glucose, mg/dL	149±47	138±46	0.113
Creatinine, mg/dL	1.04±0.23	0.99±0.21	0.138
Albumin, g/L	31.0 (28.5–36.0)	37.5 (33.0–41.7)	<0.001
D-dimer, ng/mL	1145±842	987±742	0.385
Cardiac troponin, ng/mL	10.5±3.1	8.7±2.4	0.046
Lactate, mmol/L	5.1±1.9	3.5±0.8	0.008
sPESI score	2 (1.5–3)	1 (1–2)	<0.001
RVD	26 (49.1%)	59 (26.3%)	0.001
NLR	5.84±2.62	2.97±1,34	<0.001
SII index	1421±656	829±547	<0.001
HALP score	2.57±1.09	4.75±1.50	<0.001

Data are expressed as mean ± standard deviation (SD), median (25th–75th quartile) and percentiles or n (%). COPD – chronic obstructive pulmonary disease; DVT – deep vein thrombosis; HALP – hemoglobin × albumin × lymphocytes / platelets; NLR – neutrophil-to-lymphocyte ratio; PA – pulmonary artery; RVD – right ventricular systolic dysfunction; SII – systemic immune-inflammation index; sPESI – simplified Pulmonary Embolism Severity Index.

Table 2 – Correlations between the HALP score and parameters associated with in-hospital mortality in acute pulmonary embolism

Variables	HALP score	
	r	*p*
sPESI score	–0.532	<0.001
RVD	–0.445	0.003
Hemoglobin	0.401	0.017
Lactate	–0.237	0.134
Albumin	0.458	0.006
SII index	–0.236	0.064
NLR	–0.191	0.218

HALP – hemoglobin × albumin × lymphocytes / platelets; NLR – neutrophil-to-lymphocyte ratio; RVD – right ventricular systolic dysfunction; SII – systemic immune inflammation index; sPESI – simplified Pulmonary Embolism Severity Index.

first study to examine the HALP score as a predictor of in-hospital mortality in APE. The results obtained showed a relationship between the HALP score and in-hospital mortality. The HALP score was found to be an independent predictor of in-hospital mortality in patients with APE. In addition, this score was significantly correlated with sPESI.

The localization of thrombi in the pulmonary vascular bed causes a series of inflammatory reactions that increase the release of inflammatory mediators responsible for the development and increase of systemic inflammation.[3] Inflammation that develops secondary to thrombus causes endothelial damage, promotes the release of procoagulant factors, and suppresses anticoagulant and fibrinolytic activity.[17] As a result of the acute inflammatory response, platelets are activated, and neutrophil count increases.[18] It has been shown that lymphocytes decrease with the increase in cortisol levels in acute stress condi-

Table 3 – Multivariate regression results of in-hospital mortality for acute pulmonary embolism

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (per 1 year)	1.54 (1.09–2.94)	0.034	1.31 (0.89–2.41)	0.113
SBP	0.87 (0.26–0.93)	0.002	0.98 (0.34–1.08)	0.249
Lactate	1.46 (1.19–2.12)	0.008	1.21 (0.94–1.78)	0.073
Cardiac troponin	1.13 (1.04–2.64)	0.046	1.07 (0.89–3.16)	0.376
RVD	2.01 (1.24–4.09)	0.001	1.87 (1.44–3.73)	0.015
sPESI score	1.92 (1.45–3.87)	<0.001	1.83 (1.21–3.10)	<0.001
NLR cut-off	1.14 (1.06–1.18)	<0.001	1.01 (0.55–1.16)	0.473
SII index cut-off	1.49 (1.25–2.94)	<0.001	1.23 (1.09–2.33)	0.003
HALP score cut-off	0.43 (0.22–0.98)	<0.001	0.24 (0.17–0.96)	<0.001

CI – confidence interval; HALP – hemoglobin × albumin × lymphocytes / platelets; NLR – neutrophil-to-lymphocyte ratio; OR – odds ratio; RVD – right ventricular systolic dysfunction; SII – systemic immune-inflammation index; SBP – systolic blood pressure; sPESI – simplified Pulmonary Embolism Severity Index.

(OR: 1.23, 95% CI: 1.09–2.33), and the HALP score (OR: 0.24, 95% CI: 0.17–0.96) were independent indicators of mortality in patients with APE (**Table 3**).

Discussion

Appropriate treatment of APE after an accurate risk assessment can be life-saving, while inappropriate thrombolytic treatment may cause life-threatening major bleeding, such as intracranial hemorrhage.[13] Clinical scores, such as PESI, are used in the assessment of the severity and prognosis of APE. However, previous studies have reported low positive predictive values for these tests.[14,15] Therefore it has been shown that the use of these risk models together with laboratory examination and imaging findings in the prediction of prognosis increases the effectiveness of these clinical scoring systems.[15,16] The current study aimed to investigate whether a simple and easily calculated parameter, such as the HALP score, could be used to predict mortality in APE. To the best of our knowledge, this is the

tions, such as APE.[19] These hormonal and hematological parameters detected in the serum during this process can be used to predict prognosis. Recently, it has been shown that systemic inflammation resulting from APE can be determined using a ratio, such as NLR and PLR, and this can also help predict mortality in patients with APE.[4,5,7] Wang et al. showed that NLR and PLR were associated with in-hospital and 30-day mortality in APE.[20] In another study, the authors found that low hemoglobin and lymphocyte values were parameters associated with mortality.[4] Other studies in the literature have also reported low blood hemoglobin values increase mortality in APE.[21,22] In a retrospective study of 14,276 patients with APE, Donzé et al. found that 38.7% of the patients had anemia. In the same study, the rate of 30-day mortality was determined to be 13.7% in patients with anemia and 6.3% in those without anemia. Anemia was reported to be independently associated with increased short-term mortality.[21] In anemic patients, low hemoglobin values are associated with low blood viscosity, which may increase their tendency to develop thrombosis with endothelial dysfunction and

accompanying platelet activation.[23] These findings suggest that inflammation has a significant contribution to the pathology of APE and plays or may play an important role in predicting its prognosis. In the current study, we found that the HALP score, which comprises four hematological parameters, is a valuable biomarker that can be used to predict in-hospital mortality in APE.

Serum albumin is the most abundant circulating protein and is a negative acute phase protein that decreases in response to inflammation. At physiological concentrations, it exerts an anti-inflammatory effect by inhibiting adhesion molecules in endothelial cells.[24] Several theories have been proposed to explain the association between decreased albumin and increased thrombotic risks. Albumin has been found to have anticoagulant properties by inhibiting platelet aggregation and fibrin polymerization.[25] In addition, albumin shows a heparin-like effect by increasing the effect of antithrombin III.[25] Previous studies have reported that low serum albumin levels increase the risk of venous thromboembolism.[25,26] In a study investigating the relationship between the serum albumin level and the severity of APE, lower albumin levels were detected in cases with massive APE than in those with non-massive APE, and each 1 g/dL decrease in the albumin level increased the probability of a massive APE by 75%.[8] In another study, the acute and short-term mortality rates of patients with hypoalbuminemia (<3.5 g/dL) who were hospitalized with the diagnosis of APE were found to be 2.5 times higher than those with APE who had normal serum albumin levels.[27] In recent years, the prognostic role of the HALP score, which is a new composite index calculated using hemoglobin, albumin, lymphocyte, and platelet counts, has been investigated in some malignant diseases, and it has been reported to be related to the survival of patients.[9,10] The above-mentioned findings indicate that the HALP score, which is the combination of four hematological parameters, may play an important role in predicting the prognosis of APE.

Limitations

This study has some limitations, Firstly, it has a small sample size. Secondly, it was a retrospective single center study. Thirdly, the HALP score was calculated using the blood parameters measured at the time of the patients' first presentation to the ED, and changes in these parameters over time were not evaluated, although they may be altered during the course of the disease. Fourth, diagnostic evaluations were not performed to identify the causes of anemia and hypoalbuminemia. Depending on the underlying disease, there may be other confounding variables that affect hemoglobin and albumin levels, which may have affected our findings. Finally, we examined in-hospital mortality, but we were not able to conduct a long-term follow-up of patients after their discharge from the hospital.

Conclusions

We found that the HALP score in APE was significantly lower in the mortality group compared to the survivor group. Our results showed that the HALP score was an independent predictor of mortality in APE. We consider that the HALP score can be a simple, easily calculated, and promising parameter that can be used in risk prediction for patients with APE. Large-scale, prospective, and randomized studies are needed to obtain clearer results on this subject and elucidate the pathophysiology of APE.

Author contributions

E. T. S. and H. M., M. Ö. G. researched literature and conceived the study. E. T. S. was involved in protocol development, gaining ethical approval, patient recruitment, and data analysis. E. T. S, K. K. wrote the first draft of the manuscript. All the authors reviewed and edited the manuscript and approved the final version of the manuscript.

Acknowledgements

The authors thank all the participants in this study.

Conflict of interest

No conflict of interest was declared by the authors.

Funding

The authors declared that this study has received no financial support.

Ethical statement

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. This study protocol was approved by Clinical Research Ethical Committee of Aksaray University Faculty of Medicine with a protocol number of 2023/08-03 and conducted in accordance with the Declaration of Helsinki and Good Clinical Practices.

Consent for publication

All authors have read and approved the final version of this manuscript and have consented for publication.

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