SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2025; 42 (2): 16003 DOI: 10.36141/svdld.v42i2.16003

Prognostic significance of HALP score in İdiopathic Pulmonary Fibrosis-related mortality

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Abstract. *Background & Aim:* To investigate the prognostic value of the HALP (Hemoglobin, Albumin, Lymphocyte, and Platelet) score for mortality in patients with Idiopathic Pulmonary Fibrosis (IPF). *Methods:* From November 2020, 39 patients with IPF were followed for a duration of 3 years. At the end of 3 years, the relationship between the initial HALP score and mortality was investigated. *Results:* Thirty-nine patients diagnosed with IPF were included in the study, 30 of whom were male. The average age of all patients was 68.79±7.08. At the end of the three-year follow-up period, 12 patients (33.3%) had died. When comparing patients who died and those who survived at the end of three years; significant differences were found in age, neutrophil, albumin, HALP score, $FEV_{1\%,}$ FVC%, DLCO%, GAP score, and 6 MWD. ROC analysis for the HALP score's predictive value for mortality yielded an AUC of 0.743 and p=0.011. For a cut-off value of HALP≤30.5, p=0.01, sensitivity and specificity were 61.54% and 92.31%, respectively. Multivariate analysis for predicting mortality found HALP≤30.50 as a significant risk factor (p=0.046). An increase of one monad at the HALP cut-off (≤30.50) score level reduced the risk of death by 9.57 times. It was observed that FVC%, DLCO% and 6 MWD were not risk factors in predicting mortality. (p=0.30, p=0.08, p=0.07). *Interpretation & Conclusions*: Our study suggests that the HALP score may serve as a negative prognostic biomarker that can be used to predict mortality in cases with IPF.

Key words: Idiopathic pulmonary fibrosis, HALP score, mortality, prognostic factors, biomarkers

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a progressive fibrotic lung disease with unknown etiology and poor prognosis (1). Although considered a rare disease, its incidence has been increasing worldwide due to increased awareness and an aging population (2). IPF accounts for an average of 20% of all interstitial lung disease (ILD) diagnoses (3). The incidence of IPF is reported to be 2.8-9.3 per 100,000, annually (4). The clinical management of IPF continues to be challenging due to the lack of strong indicators of disease progression and easy methods to evaluate therapeutic response (5). Despite a survival rate lower than many cancers, there is an extended range of disease courses from slow progression to rapid mortality (6). Current studies report an average survival of 3-5 years (4). Fibrosis results from exaggerated wound healing and tissue remodeling following recurrent epithelial damage, thought to be due to long-term inflammation leading to fibrosis. Both innate and adaptive immune systems play roles in the formation of fibrosis (7). The intense excessive inflammatory response see in IPF is considered multifactorial (8). The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score is calculated based on the formula: hemoglobin (g/L) x albumin (g/L) x lymphocytes (/L) / platelets (/L). The HALP score is

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Accepted: 26 October 2024
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an easily calculable indicator of systemic inflammation and nutritional status (9). A low pre-treatment HALP score has been shown to be a reliable and negative prognostic biomarker in terms of survival outcomes in cancer patients (10). A low HALP score has been connected with an increased risk of intensive care mortality in patients with acute heart failure, acute ischemic stroke, and COPD (3,9,11). Despite the HALP score has been used to estimate prognosis in various diseases, this study is the first in the literature to investigate it in IPF patients. This study aims to examine the predictive power of the HALP score for 3-year mortality in cases with IPF.

Material and methods

Our study was designed as a cross-sectional study. Patients were included in the study from the Pulmonology Clinic in November 2020, with a total of 39 IPF patients under observation. Since IPF is a rare disease, both chronically followed patients (more than 1-2 year from diagnosis) and recently diagnosed patients (within the past year) seen at the clinic within the specified dates were included for evaluation. The diagnosis of IPF was made according to the criteria set forth in the current "Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis Clinical Practice Guideline" [12]. Complete blood counts, biochemical examinations (liver and kidney function tests, albumin), comorbidities, spirometry measurements, 6-minute walk tests (6MWT), treatments, mMRC (Modified Medical Research Council) dyspnea scores, GAP (Gender, Age, Physiology) indices, and Carlson comorbidity indices were recorded during the patients' clinic visits. Biochemical parameters and blood counts were tested using an automatic analyzer. Subsequently, the HALP score was calculated with these values. Patients were followed for three years up to December 2023. The prognostic value of the initial HALP score, assessed from the start date of the study, was evaluated for three-year mortality between deceased and surviving patient. This human study was approved by X University Clinical Research Ethics Committee approval (2023/162).

Statistical analysis

Statistical analyses were performed on IBM SPSS Statistics version 23.0 (IBM Corp., USA) and MedCalc version 12.3.0.0. The Shapiro-Wilk test was used to test the normality of quantitative variables. Continuous variables with a normal distribution were expressed as mean ± standard deviation. Non-normally distributed variables were expressed as median (min-max) values. Comparisons between two independent groups, such as age, hemoglobin, albumin, lymphocytes, and HALP score, were made using the independent samples t-test when a normal distribution was observed in both groups. The Mann-Whitney U-test was used when a normal distribution was not observed. ROC curve analysis was conducted to assess the diagnostic performance of the HALP score in distinguishing survivors from non-survivors over a 3-year period. The Youden J index was used to obtain the optimum cutoff value, and the corresponding sensitivity, specificity, positive predictive, and negative predictive values were provided. A p-value <0.05 was considered statistically significant.

Results

Thirty-nine patients diagnosed with IPF were included in the study, 30 of whom were male. 28 were recently diagnosed and 11 were chronically followed patients. The mean disease duration for chronically followed patients was 32±19.8 months. The average follow-up period for all cases during the study period was 15.3±5.9 months. The mean age of cases was 68.79±7.08. At the end of the three-year follow-up period, 12 patients (33.3%) had died. The features of the patients are given in Table 1.

At the end of three years, when comparing deceased and surviving patients, significant differences were found in age, neutrophils, albumin, HALP score, $FEV_{1\%}$, FVC%, DLCO%, GAP score, and 6MWT (Table 2). When chronically followed patients and recently diagnosed patients were evaluated in terms of HALP score, no significant difference was found between the groups (p=0.11). While the mortality rate was 36.4% in recently diagnosed patients, the mortality rate was 32.1% in chronic patients. When the patient groups were compared, no significant difference was found between them in terms of mortality (p=0.54). Hemoglobin, lymphocyte, and platelet values were similar in both deceased and surviving patient groups (Table 2).

ROC analysis for the HALP score's predictive value for mortality yielded an AUC of 0.743 and

Table 1. General characteristics of the patients included in the study

		n (%)	Mean-sd	Min-max
Age (year)		**39 (100)**	**68.79±7.08**	**50-80**
Gender	Male Female	30 (76.9) 9 (23.1)		
Survey	Alive Ex	26 (66.7) 13 (33.3)		
Smoking	Smoker Ex smoker Non smoker	4 (10.3) 21 (61.5) 11 (28.2)		
Antifibrotic	Pirfenidon	27 (69.2)		
	Nintedanib	12 (30.8)		
Hemoglobin (g/L)			136.5±17.2	94-165
Lymphocyte (/μL)			2118±887	1000-5000
Platelet (/μL)			247850±86156	92000-504000
Albumin (g/dl)			3.89±0.58	2.3-4.7
HALP score			50.0±28.8	16.8-137.2
FEV_1%			83.29±17.32	45-125
FVC%			76.66±16.75	51-116
FEV_1/FVC			85.03±7.30	70-100
DLCO%			51.89±21.41	31-120
6 MWT (m)			319.42±118.65	50-594
GAP score			3.76±1.54	1-6
CCI			3.41±1.25	1-6

Abbreviations: DLCO: Diffusion capacity for carbon monoxide, FEV_1: 1. saniyedeki zorlu ekspiratuvar hacim, FVC: Forced Vital Capacity, 6 MWT: 6 min walk test, GAP: Gender-Age-Physiology, CCI: Charlson Comorbidity İndex

Table 2. Comparison of patients who lived and died due to IPF at the end of 3 years

	Survival (n:26)	Non-survival (n:13)	p
Age (year)	67±7.09	72.38±5.75	**0.023**
Hemoglobin (g/L)	137.3±15.7	134.8±20.6	0.671
Lymphocyte (/μL)	2304±957	1746±598	0.063
Neutrophil (/μL)	4816±1542	63077±2264	**0.047**
Platelet (/μL)	242580±69112	258380±115648	0.596
Albumin (g/dL)	4.17±0.29	3.33±0.63	**0.000**
HALP score	57.21±3.00	35.62±20.44	**0.012**
FEV_1%	87.73±17.64	72.77±12.34	**0.010**
FVC%	81.73±16.18	64.62±12.54	**0.002**
DLCO%	57.08±22.34	38.38±9.45	**0.007**
GAP score	3.19±1.47	4,92±0.95	**0.000**
6 MWT	351.50±96.97	200,29±122,00	**0.016**
CCI	3.19±1.26	3.85±1.14	0.125

Abbreviations: DLCO: Diffusion capacity for carbon monoxide, FEV_1: 1. saniyedeki zorlu ekspiratuvar hacim, FVC: Forced Vital Capacity, 6 MWT: 6 min walk test, GAP: Gender-Age-Physiology, CCI: Charlson Comorbidity İndex

p=0.011. The Youden J index was used to measure the predictive power of the HALP score to predict 3-year mortality. For a HALP cut-off value of ≤30.5, p=0.01, sensitivity, and specificity were found to be 61.54% and 92.31%, respectively (Figure 1).

In multivariate analysis for predicting mortality, significant variables [HALP cut-off score (HALP≤30.50), FVC%, DLCO%, 6MWT] were included in a backward conditional logistic regression analysis. In the created model (Hosmer Lemeshow p=0.254), HALP≤30.50 was found as a meaningful risk factor for predicting mortality (p=0.046, OR=9.570, 95% CI for OR=1.042-87.863). An increase of one monad at the HALP cut-off (≤30.50) score level reduced the risk of death by 9.570 times. FVC%, DLCO%, 6MWT were not found to be important parameters in predicting mortality (p=0.30, p=0.08, p=0.07) (Table 3).

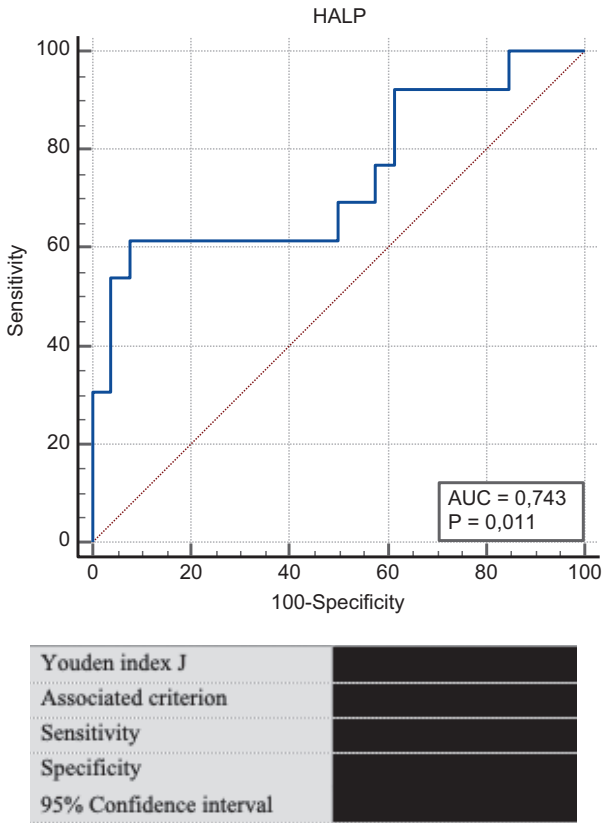

Figure 1. ROC analysis results for HALP score in assessing 3-year mortality.

Discussion

This study, to our knowledge, is the first to indicate that a low HALP score may serve as a negative prognostic biomarker that can be used to predict mortality in patients with Idiopathic Pulmonary Fibrosis (IPF). Patients with a HALP score of ≤30.50 were found to have a significantly higher mortality rate. When comparing deceased and surviving patients, although significant differences were observed in routine clinic follow-ups for DLCO, FVC, and 6MWT, these significances were not maintained in regression analysis. However, the significance of HALP≤30.50 continued to be statistically significant in regression analysis. IPF is a chronic, fibrosing interstitial pneumonia of unknown etiology, associated with the radiological and histological characteristics of usual interstitial pneumonia (12). Epidemiological studies have revealed an increase in the incidence of IPF (13). The disease is more common in men, and the average age at diagnosis is 65 (14). Consistent with the literature, our study found a higher prevalence in male patients (76.9%) with an average age of 68.79.

While the average survival time after diagnosis is 3-4 years, the course of IPF can vary significantly. While most patients progress rapidly, there are those who show a stable course or progress more slowly, surviving for more than 10 years (15). There are two anti-fibrotic drugs (pirfenidone and nintedanib) that

Table 3. Conditional logistic regression analysis results

	p	OR	95% CI for OR	
			Lower	Upper
HALP score (cut-off)	0.046	9.570	1.042	87.863
FVC %	0.301	0.964	0.899	1.033
DLCO %	0.080	0.927	0.852	1.009
6 MWT (m)	0.077	0.995	0.989	1.001

Model Summary: Nagelkerke R square:0.61, Hosmer Lemeshow Test Chi Square:10.158 p:0.254

slow the progression of IPF (16,17). Before 2010, the 3-year survival rate for patients not receiving antifibrotic treatment was 59.9%, whereas, after 2010, this rate increased to 67.4% for those receiving antifibrotic therapy (18). Similarly, our study found a 3-year survival rate of 66.7%. Compared to the general population, an increased prevalence of various comorbidities has been shown in patients with IPF, contributing to significant morbidity and early mortality (19). Our study observed multiple comorbidities among the included patients. When evaluated using the Charlson Comorbidity Index, no considerable difference was observed between the deceased and surviving patient groups. The management of IPF remains challenging due to the lack of powerful markers for disease progression and treatment response (5). The prognosis of IPF is attempted to be determined using lung function parameters (FVC, DLCO), clinical, radiological, and serological parameters (20). In recent years, multidimensional indices [GAP index, ROSE (Risk Stratification Score) scoring] have been developed to determine the most accurate prognostic factors in IPF and to predict individual mortality risk, aiming to create a method that is practical and clinically useful (21,22). Current recommendations do not encourage the systematic use of any of these scales in the treatment of IPF since there is not enough scientific evidence to support their use. In our study, although FVC, DLCO, and 6MWT were significantly lower in the deceased patient group, they were not found to be important risk factors in predicting mortality in regression analysis. The necessity for the development of a new index in IPF has been emphasized, and it has been stated that this index should emerge from studies with a reasonable number of variables and a sufficiently long follow-up period to reflect mortality. Moreover, it has been proposed that the calculation of this index should be simple, safe, inexpensive, and involve easily measurable variables (20). The HALP score is a simple, inexpensive, and easily calculable indicator. Previous studies have shown this to be a significant prognostic factor in some types of cancer (23-25). It was reported that low HALP score predicted mortality in cases treated in the intensive care unit due to COVID-19 pneumonia (26). Han et al. demonstrated that a low HALP score during the acute exacerbation phase of COPD was associated with an increase in intensive care mortality (27). Similarly, in our study, it was observed that the HALP score showed significant results in predicting 3-year mortality. With a HALP value of ≤30.50, the specificity and sensitivity in predicting 3-year mortality were found to be high, making it a useful scoring system. Our study had some limitations. It was conducted on a limited number of patients from a single center. Clinical data obtained from patient records were collected through a retrospective cross-sectional study design. It is unclear whether the current results can be adapted to other ethnic groups. Due to these limitations, multi-center, multi-regional, prospective studies are needed. In conclusion, to our knowledge, this is the first time the HALP scoring has been found to predict 3-year mortality in patients with IPF. The HALP scoring system is easy to calculate, practical, and inexpensive. According to the regression analysis results, for our study, the HALP value of ≤30.50 can predict 3-year mortality more meaningfully compared to the %FVC, %DLCO, and 6MWT parameters we use in our clinic practice.

Financial Support & Sponsorship*:* None.

Authors' Contribution: MC and HC conceived and designed the study, collected the data, and wrote the manuscript. HC contributed to the writing and critical revision of the manuscript. MC and MYS assisted in data collection. NS and FE provided supervision, critical revision, and final approval of the manuscript.

Conflicts of Interest*:* Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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