Original Article

DOI: 10.7860/NJLM/2025/76339.2900

Internal Medicine Section

Prognostic Significance of the HALP Index in Predicting Mortality in COVID-19 Hospitalisations: A Retrospective Cohort Study from a Tertiary Care Hospital in Northern India

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ABSTRACT

Introduction: Early identification of critically ill Coronavirus Disease-2019 (COVID-19) patients is crucial for recognising those at high-risk of poor outcomes. Both inflammation and nutritional status play pivotal roles in the prognosis of COVID-19 patients. Systemic inflammatory markers derived from peripheral blood cells, such as the Neutrophil-to-Lymphocyte Ratio (NLR), derived NLR (dNLR), and the Systemic Immune-Inflammation Index (SII), have been widely studied and shown to predict the prognosis of COVID-19. The Haemoglobin Albumin Lymphocyte Platelet (HALP) index, a novel biomarker, combines indicators of systemic inflammation and nutritional health-both essential in forecasting mortality risk in patients with COVID-19.

Aim: To assess the prognostic significance of the HALP index in predicting mortality in COVID-19 hospitalisations.

Materials and Methods: This retrospective cohort study was conducted in the Department of General Medicine, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Jammu and Kashmir, India for a period of three months from May 2021 to July 2021 and involved 129 patients hospitalised with COVID-19. Key laboratory values-namely HALP were recorded upon admission. Chi-square test and Cox proportional hazards regression models were used to evaluate the impact of HALP on survival in COVID-19 patients.

Results: Out of a total of 129 patients, the majority of the patients in present study were males, accounting for 66.6%. The mean age of the cohort was 60.9±12.02 years, and the average duration of hospitalisation was 12.15±8.04 days. A 72% of the cases recovered from the illness. A notably high in-hospital mortality rate of 27% was observed. An analysis of hospital stay durations revealed a notably extended length of stay for patients in the low HALP group compared to those in the high HALP group, with a t-value of 5.312 and a p-value of <0.001. Significant associations were also found with lymphocyte, platelet, and neutrophil counts, with p-values of 0.036, 0.016, and <0.001, respectively.

Conclusion: The findings of present study highlight the prognostic significance of the HALP index in patients hospitalised with COVID-19. A low HALP index was associated with prolonged hospital stays and higher in-hospital mortality, emphasising its utility as a predictor of poor outcomes.

Keywords: Coronavirus disease-2019, Haemoglobin albumin lymphocyte platelet biomarkers, Risk stratification, Survival analysis

INTRODUCTION

The Coronavirus Disease-2019 (COVID-19) pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), profoundly disrupted global life until it was officially declared over by the World Health Organisation on May 5, 2023 [1]. At the height of the pandemic, many health systems were on the verge of collapse due to overwhelmed facilities, including shortages of Intensive Care Unit (ICU) beds and ventilators, which rendered them incapable of meeting the surging healthcare demands. Previous studies have indicated that managing patients with severe or critically severe COVID-19 was particularly challenging and associated with a high mortality rate, even within ICUs [2-4]. Early identification of risk factors that can forecast patient outcomes and inform treatment decisions for severely infected COVID-19 patients is crucial [5]. Laboratory markers, along with assessments of inflammation and nutritional status, are vital for the diagnosis, prognosis, and mortality assessment of COVID-19 [6-10]. Various scoring systems and algorithms have been developed to predict critical care needs among COVID-19 patients [11]. Systemic inflammatory biomarkers derived from peripheral blood cells- such as the dNLR, NLR, SII, HALP, and Albumin (ALB) levels- have been identified as useful indicators for predicting the prognosis of patients with moderate-to-severe COVID-19 [12-17]. The HALP score is an index designed to evaluate patients' nutritional and immune status [18-20]. Literature suggests that a low HALP score may be predictive of mortality in patients with malignancies and inflammatory diseases [21-24].

Despite its potential importance, the relationship between HALP levels and COVID-19 mortality remains inadequately explored. Given the scarcity of data on this association and the absence of similar studies in India, we conducted this research with the aim of assessing the prognostic significance of the HALP Index in predicting mortality in COVID-19 hospitalisations and thus contributing to the existing body of literature.

MATERIALS AND METHODS

The present retrospective cohort study was conducted in the Department of General Medicine at the Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Kashmir, India, for a period of

three months. Convenience sampling was done and the clinical data of 129 patients were obtained from May 2021 to July 2021. The study was planned in July 2024 and received approval from the institutional ethics committee under IEC/SKIMS Protocol (#215/2024), after which we proceeded with the data analysis and interpretation. The Committee waived the requirement for informed consent. The research adheres to the ethical guidelines of the Declaration of Helsinki.

Inclusion criteria: Patients of both genders and age groups ranging from 30 to 80 years, who were hospitalised and tested positive for Severe Acue Respiratory Syndrome Coronavirus-2 (SAR-CoV-2) by real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR), were included in the study, which counted a total of 129 patients over three months.

Exclusion criteria: Patients with positive results for other respiratory viruses or bacterial infections were excluded from the study.

Study Procedure

The diagnosis of COVID-19 was based on the detection of SARS-CoV-2 using rRT-PCR, and the patients were classified as having mild, moderate, severe, or critical COVID-19 according to WHO guidelines [25]. The demographic, clinical, and laboratory data collected included age, gender, co-morbidities, laboratory findings, disease severity, length of hospital stay, treatments, and patient outcomes. The HALP score was calculated using the formula: Haemoglobin (HB) (g/L)×ALB (g/L)×Lymphocyte Count (LYMPHO) (10^9/L)÷Platelet Count (PLT) (10^9/L). A HALP score of ≥18.06 was categorised as the high HALP group, serving as the reference for the low HALP group (HALP <18.06) [26].

STATISTICAL ANALYSIS

The statistical analysis of present research was performed using Statistical Package of Social Sciences (SPSS) software version 20.0. Statistical differences were considered significant at p-value of <0.05. An independent t-test was used to compare the continuous variables, which included parameters like age, length of hospital stay, and laboratory investigations. To compare the categorical variables, like age categories, gender, habitat, patient outcomes, signs, symptoms, co-morbidities, treatment received, and severity of disease with HALP, a Chi-square test was used. The Cox regression analysis was conducted to assess the effect of the HALP (cut-off of 18.06) on the length of hospital stay, with the outcome of interest being the time to event (hospital discharge or death). The analysis included various variables, such as age, gender, Haemoglobin (HB), Albumin (ALB), Lymphocyte count (LYMPHO), Platelet count (PLT), HALP cut-off, Monocyte count (MONOS), neutrophil count, C-reactive protein (CRP), D-dimers, Hypertension (HTN), Type 2 Diabetes Mellitus (T2DM), Chronic Obstructive Pulmonary Disease (COPD), asthma, hypothyroidism, malignancy, and disease severity.

RESULTS

In present research analysis, 129 COVID-19-positive patients were examined. The majority of these patients (66.6%, n=86) were male. The mean age was 60.9±12.02 years, and the average length of hospital stay was 12.15±8.04 days. Out of the total, 93 (72%) survived the disease, while a high in-hospital mortality rate of 27% was observed. Notably, all deceased patients had a low HALP index. The demographic and clinical characteristics of patients stratified by HALP index has been depicted in [Table/Fig-1]. A comparison of hospital stays between low and high HALP groups revealed that the length of stay was significantly longer in the low HALP group, with a t-value of 5.312 and a p-value of <0.001. Statistically significant associations were also observed with lymphocyte, platelet, and neutrophils, with p-values of 0.036, 0.016, and <0.001, respectively (see [Table/Fig-1]). Although there was no significant difference in HALP levels across age categories (p=0.27), patients aged 51-60 had a higher percentage of low HALP (34 out of 38, 89.5%) compared to high HALP (4 out of 38, 10.5%). Males had a notably higher proportion of low HALP (96.5%). Among patients who survived, the majority (94.6%) had low HALP. A significant difference was also observed regarding dyspnea: all patients with high HALP reported no dyspnea (5 out of 5, 100%), while a substantial portion of those with low HALP experienced dyspnea (60 out of 64, 93.8%), with a p-value of 0.033. Furthermore, a statistically significant association was found between headaches and HALP levels (p=0.007), with 66.7% (2 out of 3) of those with headaches having low HALP.

Parameters	Low HALP Mean±SD	High HALP Mean±SD	t-value	p-value
Age (years)	60.93±12.2	60.4±6.95	0.096	0.924
Hospital stay (days)	12.45±8.12	6.4±1.95	5.312	<0.001
Haemoglobin (HB) (gm/dL)	12.69±1.84	12.82±1.23	-0.16	0.873
Albumin (ALB) (gm/dL)	3.34±0.47	3.51±0.21	-0.79	0.431
Lymphocytes (x10^3/µL)	14.52±8.82	43.4±20.88	-3.082	0.036
Platelet count (PLT) (x10^3/µL)	146.92±62.86	78±33.59	2.431	0.016
Monocyte (x10^3/µL)	5.49±3.33	4.4±1.67	0.724	0.47
Neutrophil (x10^3/µL)	78.93±10.39	49.8±19.77	5.906	<0.001
CRP (mg/L)	21.16±35.82	23.53±24.53	-0.131	0.896
IL6 (pg/mL)	35.23±139.07	2.8±1.41	0.464	0.643
D-Dimers (ng/mL)	1317.28±4205.65	202.2±132.83	0.591	0.556

[Table/Fig-1]: Demographic and laboratory characteristics of the study population viz a viz HALP.

The use of face masks was significantly associated with HALP levels (p=0.013). Most patients requiring a face mask had low HALP (89 out of 90, 98.9%), whereas 80% (4 out of 5) of those with high HALP did not use a face mask. Other variables, including gender, habitat, patient status, various symptoms (such as abdominal pain, Per Rectum (PR) bleed, haemoptysis), and clinical interventions {such as use of Non invasive Ventilation (NIV), Invasive Mechanical Ventilation (IMV), baricitinib}, did not show statistically significant associations with HALP levels (all p-values >0.05) (see [Table/Fig-2].

Parameters	Categories	HALP (cut-off 18.06) Low HALP n=124 (96%)	HALP (cut-off 18.06) High HALP n=5 (4%)	Chi-square	p-value
Age categories	<30	2 (1.6)	0	7.591	0.27
	31-40	6 (4.8)	0		
	41-50	16 (12.9)	0		
	51-60	34 (27.4)	4 (80)		
	61-70	44 (35.5)	0		
	71-80	17 (13.7)	1 (20)		
	>80	5 (4)	0		
Gender	Female	41 (33.1)	2 (40)	0.104	0.747
	Male	83 (66.9)	3 (60)		
Habitat	Rural	41 (33.1)	2 (40)	0.104	0.747
	Urban	83 (66.9)	3 (60)		
Patient status	Alive	88 (71.5)	5 (100)	1.958	0.376
	Dead	35 (27)	0		
	Left against medical advice	1 (0.8)	0		
Symptoms					
Abdominal pain	No	120 (96.8)	5 (100)	0.166	0.683
	Yes	4 (3.2)	0		
Per rectal bleed	No	123 (99.2)	5 (100)	0.041	0.84
	Yes	1 (0.8)	0		

Haemoptysis	No	123 (99.2)	5 (100)	0.041	0.84
	Yes	1 (0.8)	0		
Diarrhoea	No	121 (97.6)	5 (100)	0.124	0.725
	Yes	3 (2.4)	0		
Vomitting	No	122 (98.4)	5 (100)	0.082	0.775
	Yes	2 (1.6)	0		
Fever	No	22 (17.7)	0	1.069	0.301
	Yes	102 (82.3)	5 (100)		
Sore throat	No	115 (92.7)	5 (100)	0.39	0.532
	Yes	9 (7.3)	0		
Cough	No	35 (28.2)	1 (20)	0.162	0.688
	Yes	89 (71.8)	4 (80)		
Headache	No	122 (98.4)	4 (80)	7.153	0.007
	Yes	2 (1.6)	1 (20)		
Breathlessness/ dyspnoea	No	64 (51.6)	5 (100)	4.523	0.033
	Yes	60 (48.4)	0		
Myalgias/arthralgias	No	100 (80.6)	4 (80)	0.001	0.971
	Yes	24 (19.4)	1 (20)		
Examination findings					
Encephalopathy	No	119 (96)	5 (100)	0.21	0.647
	Yes	5 (4)	0		
Respiratory failure	No	8 (6.5)	0	0.344	0.558
	Yes	116 (93.5)	5 (100)		
Tachypnea	No	73 (58.9)	5 (100)	3.401	0.065
	Yes	51 (41.1)	0		
Tachycardia	No	101 (81.5)	5 (100)	1.129	0.288
	Yes	23 (18.5)	0		
Crepitations	No	88 (71)	4 (80)	0.192	0.662
	Yes	36 (29)	1 (20)		
Shock	No	123 (99.2)	5 (100)	0.041	0.84
	Yes	1 (0.8)	0		
Co-morbidities					
Hypertension (HTN)	No	42 (33.9)	2 (40)	0.08	0.777
	Yes	82 (66.1)	3 (60)		
Type 2 Diabetes Mellitus (T2DM)	No	72 (58.1)	5 (100)	3.513	0.061
	Yes	52 (41.9)	0		
Chronic Obstructive Pulmonary Disease (COPD)	No	117 (94.4)	5 (100)	0.298	0.585
	Yes	7 (5.6)	0		
Asthma	No	120 (96.8)	5 (100)	0.166	0.683
	Yes	4 (3.2)	0		
Hypothyroid	No	103 (83.1)	4 (80)	0.032	0.858
	Yes	21 (16.9)	1 (20)		
Maliganacy	No	118 (95.2)	5 (100)	0.254	0.614
	Yes	6 (4.8)	0		
Treatments needed					
Nasal prong	No	8 (6.5)	0	0.344	0.558
	Yes	116 (93.5)	5 (100)		
Face mask	No	35 (28.2)	4 (80)	6.108	0.013
	Yes	89 (71.8)	1 (20)		
Reservoir bag	No	62 (50)	4 (80)	1.731	0.188
	Yes	62 (50)	1 (20)		
High flow nasal cannula	No	79 (63.7)	4 (80)	0.556	0.456
	Yes	45 (36.3)	1 (20)		
Non invasive ventillation	No	101 (81.5)	5 (100)	1.129	0.288
	Yes	23 (18.5)	0		
Invasive mechanical ventillation	No	113 (91.1)	5 (100)	0.485	0.486
	Yes	11 (8.9)	0		
Received baricitinib	No	48 (38.7)	0	3.082	0.079
	Yes	76 (61.3)	5 (100)		
High dose Methyl prednisolone 1 gm 3 days	No	116 (93.5)	5 (100)	0.344	0.558
	Yes	8 (6.5)	0		
Remdesivir	No	42 (33.9)	2 (40)	0.08	0.777
	Yes	82 (66.1)	3 (60)		
Antibiotics	No	0	0	.	.
	Yes	124 (100)	5 (100)		
Clinical characteristics of COVID-19	Mild covid	5 (4)	0	7.312	0.063
	Moderate covid	19 (15.3)	3 (60)		
	Severe covid	68 (54.8)	2 (40)		
	Critical covid	32 (25.8)	0		

[Table/Fig-2]: Clinical characteristics and treatments needed for the study population viz-a-viz HALP.

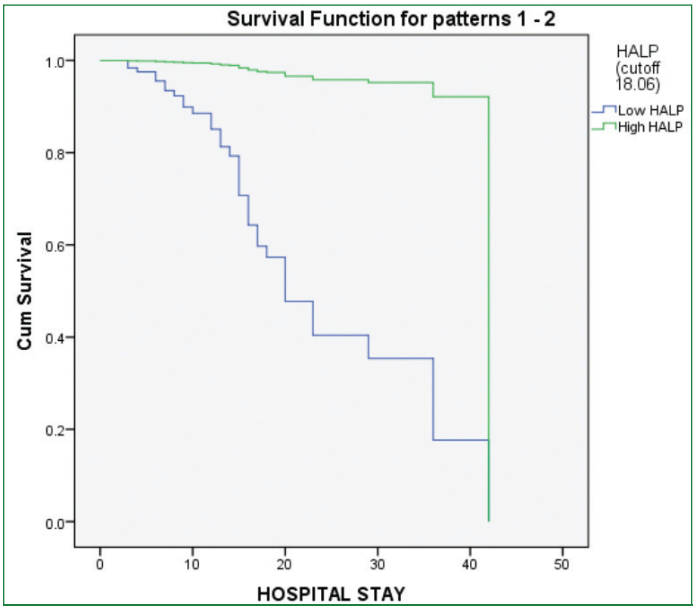
A Cox regression analysis was performed to evaluate the impact of HALP (with a cut-off value of 18.06) on hospital stay duration, where the event of interest was either hospital discharge or death. The case processing summary revealed that out of an initial 129 cases, 127 were included in the final analysis (98.4%). Among these, 34 cases (26.4%) represented events (either discharge or death), while 93 cases (72.1%) were censored. Two cases (1.6%) were excluded due to missing data. In the Cox regression model, HALP was categorised into low HALP (122 cases) and high HALP (5 cases). The analysis yielded a Hazard Ratio (HR) of 21.106 for high HALP, accompanied by a broad 95% Confidence Interval (CI). Despite this notable hazard ratio, the result was not statistically significant (p=0.721), as determined by the Wald test. This suggests that there is no significant association between HALP levels and the length of hospital stay in this dataset. The extensive CI indicates substantial uncertainty in the estimate, likely attributable to the small number of cases with high HALP.

A Cox regression analysis incorporating multiple covariates was performed to investigate the factors influencing hospital stay duration, with the primary outcome being time to event (hospital discharge or death) [Table/Fig-3,4]. The analysis encompassed a range of variables, including age, gender, HB, ALB, LYMPHO, PLT,

Variables		p-value	Hazard Ratio (HR)
Demographics	Age	0.616	0.975
	Gender	0.291	0.340
Laboratory findings	Haemoglobin (HB)	0.752	0.932
	Albumin (ALB)	0.404	0.483
	Lymphocyte	0.064	1.274
	Platelet	0.530	0.994
	Monocyte	0.085	1.323
	Neutrophil	0.055	1.338
	CRP	0.022	1.018
	D-dimers	0.575	1.000
Co-morbidities	HTN	0.575	0.635
	T2DM	0.950	1.048
	COPD	0.020	49.850
	Asthma	0.994	0.000
	Hypothyroid	0.699	0.687
	Malignancy	0.660	1.776
Disease severity	Moderate COVID	0.085	1.0887
	Severe COVID	0.571	1.770
	Critically severe COVID	0.702	2.018

[Table/Fig-3]: Association between baseline variables and hospital stay.
CRP: C-reactive protein; T2DM: Type 2 diabetes mellitus; COPD: Chronic obstructive pulmonary disease

MONOS, NEUTROPHIL, CRP, D-dimers, HTN, T2DM, COPD, asthma, hypothyroidism, malignancy, and the severity of the diagnosis. The results identified CRP (HR=1.018, 95% CI: 1.003-1.034, p=0.022) and COPD (HR=49.850, 95% CI: 1.873-1326.994, p=0.020) as significant predictors of hospital stay. Elevated CRP levels were positively correlated with a prolonged hospital stay, indicating that higher CRP levels are associated with an increased risk of extended hospitalisation. Like-wise, patients with COPD had a markedly higher hazard ratio, signifying a considerably longer hospital stay compared to those without COPD.



[Table/Fig-4]: Cox regression analysis curve comparing HALP and hospital stay with outcome being discharge or death.

Conversely, other variables such as age (HR=0.975, p=0.616), gender (HR=0.340, p=0.291), HB (HR=0.932, p=0.752), ALB (HR=0.483, p=0.404), and HTN (HR=0.635, p=0.575) did not exhibit significant associations with the length of hospital stay. NEUTROPHIL (HR=1.338, p=0.055) and LYMPHO (HR=1.274, p=0.064) approached but did not achieve statistical significance, suggesting a potential influence on the duration of hospital stay that remains inconclusive. The HALP cut-off did not demonstrate a significant effect (HR=14,029.147, p=0.992), primarily due to an extremely wide confidence interval, which reflects considerable uncertainty in the estimate.

DISCUSSION

Several investigations have explored the role of the HALP index in various inflammatory conditions, such as myelodysplastic syndrome [27], coronary heart disease [28], and stroke [29]. However, its potential for predicting the prognosis of viral infections, particularly those causing pandemics like COVID-19, remains underexplored, with limited data available [26]. To the best of authors' knowledge, the present study represents the first investigation of this kind from the region. Inflammatory responses significantly impact the prognosis of patients with COVID-19 [30-32].

The study revealed a high in-hospital mortality rate of 27%, which was higher compared to that observed in a study conducted by Wu W et al., All deceased patients had low HALP levels [26]. This finding aligns with existing literature linking low HALP to poor outcomes in various clinical settings, as HALP reflects a composite of nutritional and inflammatory status. Low HALP likely signifies malnutrition and heightened systemic inflammation, both of which can compromise immune response and exacerbate disease severity. The absence of deaths in the high HALP group suggests that higher HALP may have protective effects, though this conclusion requires confirmation in larger cohorts due to the limited number of high HALP cases (n=5). Wu W et al., have shown that lower HALP levels are independently associated with higher mortality in COVID-19 patients, particularly those with severe disease [26]. This aligns with our findings that low HALP correlates with adverse outcomes.

The mean hospital stay was significantly longer in patients with low HALP, with a t-value of 5.312 and a highly significant p-value (<0.001). This indicates that low HALP is associated with prolonged recovery times, possibly due to impaired immune function and greater disease severity in present group. These findings suggest that HALP may serve as a valuable prognostic marker for hospital resource utilisation.

Zuo L et al., also reported that patients with low HALP experienced extended recovery times due to heightened inflammatory responses and impaired immune function [33]. Despite this, the Cox regression analysis for the association of HALP with hospital stay duration did not achieve statistical significance (HR=21.106, p=0.721). The broad confidence interval reflects substantial uncertainty in the hazard ratio, likely due to the small sample size of the high HALP group.

The study highlighted several significant associations between HALP levels and specific clinical characteristics. Patients with low HALP were significantly more likely to experience dyspnea (93.8%) compared to those with high HALP (0%), with a p-value of 0.033. Dyspnea is often a marker of severe respiratory involvement, and its strong association with low HALP further supports the hypothesis that low HALP correlates with worse disease outcomes. Although not a common symptom, the significant association between headaches and HALP levels (p=0.007) suggests that low HALP may exacerbate inflammatory pathways or vascular changes leading to headaches. Nearly all patients requiring face masks had low HALP (98.9%), whereas 80% of those with high HALP did not use face masks. This disparity likely reflects differences in disease severity, with low HALP patients needing more intensive respiratory support. Carfì A et al., noted similar trends, where systemic inflammation (low HALP or high CRP) correlated with more pronounced respiratory symptoms and neurological complaints [34].

These adjustments enhance the overall readability and accuracy while maintaining the original meaning.

Impairments in both innate and acquired immunity observed in COVID-19 patients can lead to lymphocyte activation and dysregulation [35,36]. Additionally, platelet activation contributes to inflammatory factors that play a crucial role in modulating immune responses and inflammation during the illness [37,38]. Our study identified a statistically significant association between low HALP levels and CRP, lymphocyte, neutrophil, and PLTs. Many studies, including Fara A et al., have identified CRP as a reliable marker of systemic inflammation and disease severity in COVID-19 patients. High CRP levels correlate with a hyperinflammatory state, often resulting in extended recovery periods or complications such as Acute Respiratory Distress Syndrome (ARDS) [39]. The present study found COPD to be a significant predictor of prolonged hospitalisation (HR=49.850, p=0.020), consistent with existing literature. A study by Alqahtani JS et al., identified COPD as a major risk factor for severe COVID-19, likely due to pre-existing respiratory compromise and heightened susceptibility to secondary infections [40]. Although low Hemoglobin (HB) levels did not reach statistical significance (p=0.752), they exhibited a high hazard ratio of 0.932, consistent with previous research indicating that low HB levels are associated with poor outcomes in COVID-19 patients [41].

The precise causes and pathophysiological mechanisms linking HALP to poor prognosis remain unclear. However, HALP values represent a comprehensive measure of body reserves, including nutritional status, liver function, inflammation, and coagulation. This multifaceted index may provide a more accurate assessment of disease outcomes than individual variables. Furthermore, HALP is straightforward to calculate and clinically convenient. Its application can serve as a cost-effective method for early identification of COVID-19 patients at high risk of mortality, potentially guiding

timely interventions to improve survival rates. HALP score has been studied mostly in cancer patients; future studies may investigate the combination of the HALP score with other scores to obtain clearer information about the prognosis of various diseases.

Limitation(s)

The results of present study align well with the broader body of research highlighting the prognostic value of HALP and other inflammatory markers in COVID-19. However, the retrospective nature of the study and the differences in statistical significance for certain variables, such as co-morbidities and HALP levels in regression analysis, underscore the limitations of smaller sample sizes and emphasise the need for larger, more diverse datasets to refine and validate these findings. Future research should incorporate multimarker models and longitudinal designs to enhance the predictive utility of HALP in clinical practice.

CONCLUSION(S)

The present study concludes that a low HALP index is an independent risk factor for in-hospital mortality among COVID-19 patients. A lower HALP index was linked to extended hospitalisations and increased in-hospital mortality, highlighting its potential as a marker for adverse outcomes. Considering the elevated mortality rate, integrating the HALP index into standard clinical evaluations could help identify high-risk patients early, facilitating prompt and tailored interventions.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 17, 2024
- Manual Googling: Dec 16, 2024
- iThenticate Software: Dec 19, 2024 (14%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 16, 2024**
Date of Peer Review: **Nov 15, 2024**
Date of Acceptance: **Dec 20, 2024**
Date of Publishing: **Jan 01, 2025**