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Original Article *Özgün Araştırma*

THE PERFORMANCE OF HALP SCORE IN PREDICTING IN-HOSPITAL MORTALITY RISK AMONG VERY ELDERLY PATIENTS WITH RESPIRATORY-RELATED HOSPITALIZATION

HALP Skorunun Solunum Problemiyle Yatışı Yapılan Çok Yaşlı Hastalarda Hastane İçi Mortalite Riskinin Tahminindeki Rolü

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ABSTRACT

Objective: This study aimed to investigate the performance of the novel score combining hemoglobin and albumin levels and lymphocyte and platelet count (HALP) in predicting in-hospital mortality risk in very elderly patients with respiratory-related hospitalization.

Material and Methods: A total of 2011 very elderly (over 80 years) patients with respiratory-related hospitalization were included in this single-center retrospective cohort study. Reason for hospitalization, comorbidities, complete blood count and biochemistry findings on the first day of hospital admission, length of hospital stay (LOS), and in-hospital mortality were recorded. Factors predicting in-hospital mortality risk were analyzed via the univariate and multivariate Cox regression analyses. The ROC curve analysis was performed to determine the performance of HALP score in predicting the in-hospital mortality risk.

Results: The median age was 83 years (range, 80 to 108 years) and males comprised 51.6% of the study population. The in-hospital mortality rate was 7%. The lower HALP score (HR 0.693, 95% CI: 0.549 to 0.875, p=0.002), male gender (HR 0.654, 95% CI: 0.453 to 0.945, p=0.024), and higher C-reactive protein (CRP) values (HR 1.004, 95% CI: 1.002 to 1.006, p<0.001) were found to predict the increased risk of in-hospital mortality on multivariate analysis. The median LOS was 7 days. There was a significant negative correlation between HALP scores and LOS (r=-0.153, p<0.001). ROC analysis revealed the HALP score to be a potential marker of in-hospital mortality risk in very elderly patients with respiratory-related hospitalization, at a cut-off value of ≤13.7 (AUC: 0.706, 95% CI: 0.685 to 0.726, p<0.001) and with a sensitivity of 60.7% and specificity of 69.8%.

Conclusion: As an independent prognostic factor of in-hospital mortality risk in very elderly patients with respiratory-related hospitalization, the use of the HALP score may aid clinicians in timely recognition of at-risk patients and in making strategic decisions for interventions.

Keywords: *HALP score, respiratory-related hospitalization, in-hospital mortality, very elderly patients*

ÖZ

Amaç: Bu çalışmada hemoglobin ve albümin düzeyleri ve lenfosit ve trombosit sayımını birlikte içeren yeni bir skor olarak HALP skorunun solunum problemiyle yatışı yapılan çok yaşlı hastalarda hastane içi mortalite riskinin tahminindeki rolünün incelenmesi amaçlandı.

Gereç ve Yöntemler: Bu tek-merkezli retrospektif kohort çalışmasına solunum problemi ile yatışı yapılan toplam 2011 çok yaşlı (80 yaş üzeri) hasta dahil edildi. Hospitalizasyon nedeni, komorbiditeler, yatışın ilk günü yapılan tam kan sayımı ve biyokimya testi sonuçları, hastanede kalış süresi (HKS) ve hastane içi mortalite verileri kaydedildi. Hastane içi mortalitenin belirleyicileri tek-değişkenli ve çok-değişkenli Cox regresyon analizi ile saptandı. HALP skorunun hastane içi mortaliteyi tahmin etmedeki performansı ROC eğrisi analizi ile belirlendi.

Bulgular: Medyan hasta yaşı 83 yıl (80-108 yaş aralığında) olup, çalışma popülasyonundaki erkek hastaların oranı %51,6 idi. Hastane içi mortalite oranı %7 olarak bulundu. Çok-değişkenli analizde, düşük HALP skoru (HR 0,693, %95 GA: 0,549-0,875, p=0,002), erkek cinsiyet (HR 0,654, %95 GA: 0,453-0,945, p=0,024) ve yüksek C-reaktif protein (CRP) değeri (HR 1,004, %95 GA: 1,002-1,006, p<0,001) hastane içi mortalite riskinin anlamlı belirleyicileri olarak bulundu. Medyan HKS 7 gün idi. HALP skorları ve HKS arasında anlamlı negatif korelasyon (r=-0,153, p<0,001) tespit edildi. ROC analizi sonuçları HALP skorunun ≤13,7 kesim değerinde (AUC: 0,706, %95 GA: 0,685-0,726, p<0,001) ve %60,7 sensitivite ve %69,8 spesifisite ile solunum problemi ile yatışı yapılan çok yaşlı hastalarda hastane içi mortalitenin potansiyel bir belirteci olduğunu gösterdi.

Sonuç: Solunum problemi ile yatışı yapılan çok yaşlı hastalarda hastane içi mortalitenin bağımsız prognostik bir faktörü olarak, HALP skorunun kullanılması, klinisyenlere risk altındaki hastaların zamanında tespitinde ve girişimlere yönelik stratejik karar almada yardımcı olabilir.

Anahtar Kelimeler: *HALP skoru, solunum problemi ile hospitalizasyon, hastane içi mortalite, çok yaşlı hastalar*

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INTRODUCTION

While the global population is aging due to increased life expectancy, elderly (over 65 years of age) remain at high risk of multiple comorbidities with adverse health outcomes and mortality in both outpatient and inpatient settings.[1,2]

The very elderly patients (over 80 years of age) are particularly prone to disability and illness and are at higher risk of multi-morbidity and functional impairment, besides the frequent hospitalization, intensive care unit (ICU) admission, and mortality.[3,4] Predicting the risk of in-hospital mortality is critical for the timely recognition of at-risk patients and the therapeutic planning of targeted interventions to reduce mortality.[2-4] However, few studies have investigated the risk factors and predictors of in-hospital mortality in elderly patients, particularly in the very elderly hospitalized population.[3-5]

The HALP score is a novel index calculated based on readily available laboratory parameters including hemoglobin, albumin, lymphocyte, and platelet, reflecting both the systemic inflammation and the nutritional status of a patient.[6,7] In the setting of infectious diseases, HALP score was found to be associated with adverse clinical outcomes in sepsis patients admitted to the intensive care unit, and to be independently related to in-hospital mortality among COVID-19 patients, particularly for age ≥70 and severe disease groups.[8,9] However, the scarce amount of evidence exists regarding in-hospital mortality rates in elderly patients.[3-5,10] Also, there are few studies demonstrating the predictive value of the HALP score in lung diseases.[11,12] No studies to date have investigated the prognostic value of the HALP score in very elderly patients with respiratory-related hospitalization. Therefore, this study aimed to investigate the performance of the HALP score to predict the in-hospital mortality risk of very elderly patients with respiratory-related hospitalization.

MATERIALS AND METHODS

Study population

A total of 2011 very elderly (over 80 years) patients with respiratory-related hospitalization at a tertiary care chest disease center were included in this single-center retrospective cohort study conducted between January 2021 and December 2023. Of 3061 very elderly patients were hospitalized at our clinic within the study period, 2011 patients were included in the study, after the exclusion of 1050 patients due to incomplete medical records (n=952), less than 1 day of hospital stay (n=32), presence of abnormal lymphocyte counts or any malignancy (n=38), dialysis therapy (n=18), and previous history of COVID-19 disease or ongoing treatment for chronic comorbidities likely to affect the HALP scores (n=10) (Figure 1).

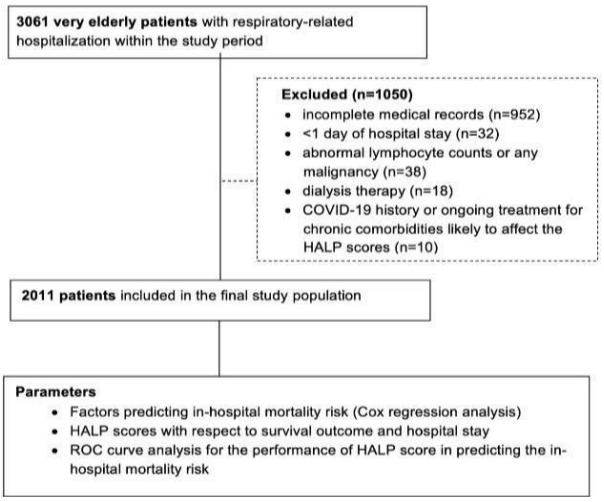

Figure 1: Study flowchart

This study was conducted following the ethical principles stated in the "Declaration of Helsinki" and approved by the University of Health Sciences Istanbul Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee (Date of Approval: 13.05.2024, Protocol no: 2024-4). The informed consent was waived by the University of Health Sciences Istanbul Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee considering the retrospective nature of the study.

Assessments

Data on patient demographics, reason for respiratory-related hospitalization, comorbid diseases, complete blood count, and biochemistry analysis findings on the first day of hospital admission, as well as the length of hospital stay (LOS), and in-hospital mortality were collected from hospital records. The HALP score was calculated using the formula: HALP Score= hemoglobin (g/dL)×albumin (g/L)×lymphocytes (10^3/μL)/platelets (10^3/μL)].[6]

Overall, the factors predicting in-hospital mortality risk were analyzed via the univariate and multivariate Cox regression analyses. HALP scores were evaluated in terms of in-hospital mortality and LOS. The receiver operating characteristic (ROC) curve analysis was performed to determine the performance of HALP score in predicting the in-hospital mortality risk.

Statistical analysis

Statistical analysis was performed using MedCalc® Statistical Software version 22.009 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023). Normal distribution was investigated via Shapiro Wilks test. Mann-Whitney U test was used to analyze two independent non-normally distributed variables. ROC analysis was used to investigate the performance of the

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HALP score in identifying in-hospital mortality risk with the calculation of area under curve (AUC) values and optimal cut-off value. The factors predicting in-hospital mortality were analyzed via the univariate and multivariate Cox regression analyses. Pneumonia, chronic obstructive pulmonary disease (COPD), respiratory failure, chronic heart failure, other comorbidities, HALP score, gender, neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) were the parameters included in the univariate analysis, while the multivariate analysis was based on the parameters with significance in the univariate analysis (HALP score, gender, and CRP). Data were expressed as mean (standard deviation, SD), median (minimum-maximum), 95% confidence interval (CI), and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Patient demographics, reason for hospitalization, comorbidities, and in-hospital mortality

A total of 2011 patients were enrolled in this study (median age 83 years, range 80 to 108 years; 51.6% were males) (Table 1).

Pneumonia (63.8%), respiratory failure (55.3%) and COPD; 26.5%) were the leading causes of respiratory-related hospitalization. The most common comorbidities were hypertension (67.9%), chronic heart failure (49%) and atherosclerotic cardiovascular disease (45.5%) (Table 1). Median LOS was 7 days, while in-hospital mortality rate was 7% (n=140) and (Table 1).

Table 1: Patient demographics, reason for hospitalization, comorbidities and in-hospital mortality

Patient demographics	
Age (year), median (min-max)	83 (80-108)
Gender, n (%)	
Female	973 (48.4)
Male	1038 (51.6)
Reason for hospitalization, n (%)	
Pneumonia	1284 (63.8)
Respiratory failure	1113 (55.3)
Chronic obstructive pulmonary disease	532 (26.5)
Pulmonary emboli	166 (8.3)
Comorbidities, n (%)	
Hypertension	1365 (67.9)
Chronic heart failure	986 (49)
Atherosclerotic cardiovascular disease	915 (45.5)
Diabetes mellitus	558 (27.7)
Chronic kidney disease/acute renal failure	211 (10.5)
Dementia	174 (8.7)
Asthma	122 (6.1)
Intracranial atherosclerotic disease	106 (5.3)
Cerebrovascular event	15 (0.7)
Length of hospital stay (day), mean (SD; median)	8.1 (14.9; 7)
In-hospital mortality, n (%)	
Yes	140 (7)
No	1871 (93)

Table 2 summarizes laboratory findings on the day of hospital admission.

Table 2: Laboratory findings on the day of hospital admission

	n	Median (min-max)
Complete blood count		
WBC (10^3/μL)	2011	8.8 (1.4-43)
Hemoglobin (g/dL)	2011	11.4 (6-18.6)
RBC (million/mm^3)	2011	4.1 (1.6-6.6)
Hematocrit (%)	2010	35.7 (19-57.2)
Platelet (10^3/μL)	2011	241 (43-667)
Lymphocyte count (10^3/μL)	2010	1.1 (0.1-8.1)
Lymphocyte (%)	2011	13.5 (1-56.3)
Monocyte count (10^3/μL)	2010	0.6 (0.03-4.1)
Monocyte (%)	2011	7.4 (0.3-32.4)
Eosinophil count (10^3/μL)	2010	0.04 (0-3.4)
Eosinophil (%)	2010	0.4 (0-39.1)
Basophil count (10^3/μL)	2010	0.02 (0-0.3)
Basophil (%)	2010	0.3 (0-2.4)
Neutrophil (%)	2011	76.6 (27.7-97.2)
Neutrophil count (10^3/μL)	2011	6.6 (0.4-38.5)
MCV (fL)	2011	88.4 (58.7-119)
MPV (fL)	1986	10.2 (7.8-14.1)
NLR	1865	5.8 (0.5-102)
Blood biochemistry		
CRP (mg/L)	1940	20.8 (0.2-404.4)
Procalcitonin (ng/mL)	1517	0.1 (0.02-37.6)
ProBNP (pg/mL)	664	1099 (24.4-31784)
Glucose (mg/dL)	2001	126 (45-687)
Urea (mg/dL)	1999	53 (0-320)
Creatinine (mg/dL)	2007	1 (0.2-4.3)
Albumin (g/L)	2011	36 (19-53)
AST (U/L)	1634	20 (6-520)
ALT (U/L)	1622	15 (0-341)
Calcium (mg/dL)	1994	8.9 (5.9-14.7)
LDH (U/L)	1779	214 (103-3592)

WBC: White blood cell, RBC: Red blood cell, MCV: Mean cell volume, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, ProBNP: Pro-B-type natriuretic peptide, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

In the univariate analysis, the lower HALP score (HR 0.640, 95% CI: 0.527 to 0.777, $p<0.001$), and higher NLR (HR 1.021, 95% CI: 1.01 to 1.032, $p<0.001$) and CRP (HR 1.005, 95% CI: 1.003 to 1.007, $p<0.001$) values were associated with increased risk of in-hospital mortality. Females vs. males were associated with lower risk of in-hospital mortality (HR 0.675, 95% CI: 0.481 to 0.949, $p=0.024$) (Table 3).

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Table 3: Univariate and multivariate Cox regression analyses for factors associated with in-hospital mortality risk

	Univariate analysis			Multivariate analysis		
	p value	**HR**	**95%CI (LB-UB)**	**p value**	**HR**	**95%CI (LB-UB)**
Variables						
Pneumonia	0.315	0.840	0.598-1.18	-	-	-
COPD	0.253	0.809	0.563-1.163	-	-	-
Respiratory failure	0.360	1.172	0.835-1.644	-	-	-
Chronic heart failure	0.350	1.174	0.839-1.643	-	-	-
Other comorbidities[a]	0.075	1.378	0.968-1.960	-	-	-
HALP score	**<0.001**	0.640	0.527-0.777	**0.002**	0.693	0.549-0.875
Gender (female vs. male)	**0.024**	0.675	0.481-0.949	**0.024**	0.654	0.453-0.945
NLR	**<0.001**	1.021	1.01-1.032	0.957	1	0.985-1.016
CRP	**<0.001**	1.005	1.003-1.007	**<0.001**	1.004	1.002-1.006

COPD: Chronic obstructive pulmonary disease, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, HR: Hazard ratio, CI: Confidence interval, LB: Lower bound; UB: Upper bound

[a] having at least 2 of the following comorbidities: hypertension, atherosclerotic cardiovascular disease, diabetes mellitus, chronic kidney disease/acute renal failure, dementia, pulmonary emboli, asthma, intracranial atherosclerotic disease and cerebrovascular event

The multivariate analysis confirmed the association of the lower HALP score (HR 0.693, 95% CI: 0.549 to 0.875, p=0.002), male gender (HR 0.654, 95% CI: 0.453 to 0.945, p=0.024) and higher CRP values (HR 1.004, 95% CI: 1.002 to 1.006, p<0.001) with the increased risk of in-hospital mortality (Table 3).

HALP scores with respect to reasons for hospitalization and comorbidities

No significant difference was noted in HALP scores with respect to different reasons for hospitalization and presence of comorbidities (Table 4).

Table 4: HALP scores with respect to reasons for hospitalization and comorbidities

	HALP score, median(min-max)		
Reason for hospitalization	**Absent**	**Present**	**p value**
Pneumonia	18 (1.6-130.6)	18.6 (1.1-132.1)	0.987
Respiratory failure	18.5 (1.6-132.1)	18.4 (1.1-129.4)	0.687
Chronic obstructive pulmonary disease	18.5 (1.6-132.1)	18.4 (1.1-130.6)	0.602
Pulmonary emboli	18.5 (1.1-132.1)	17.1 (4.6-130.6)	0.674
Comorbidities	**Absent**	**Present**	**p value**
Hypertension	17.4 (1.9-13.06)	18.8 (1.1-132.1)	0.013
Chronic heart failure	18.4 (1.6-13.06)	18.4 (1.1-132.1)	0.491
Atherosclerotic cardiovascular disease	18.4 (1.6-13.21)	18.2 (1.1-130.6)	0.450
Diabetes mellitus	18.7 (1.6-132.1)	17.6 (1.1-130.6)	0.479
Chronic kidney disease/acute renal failure	18.4 (1.1-130.6)	18.2 (4.8-132.1)	0.703
Dementia	18.5 (1.1-132.1)	17.2 (2.9-116.1)	0.687
Asthma	18.3 (1.1-132.1)	19 (3.5-102)	0.163
Intracranial atherosclerotic disease	18.4 (1.1-132.1)	17.7 (1.6-80.4)	0.242
Cerebrovascular event	18.4 (1.1-132.1)	19 (7.3-68.3)	0.927

HALP scores with respect to mortality and LOS

HALP score was found to be significantly lower in patients with in-hospital mortality than in those without in-hospital mortality (median (min-max)13 (1-47) vs. 19 (4-132), p<0.001) (Table 5).

There was a significant negative correlation between HALP scores and LOS (r=-0.153, p<0.001) (Table 5).

Table 5: HALP scores with respect to in-hospital mortality and length of hospital stay

	HALP score	
In-hospital mortality	**median(min-max)**	**p value[a]**
No (n=1870)	19 (4-132)	**<0.001**
Yes (n=140)	13 (1-47)	
	HALP score	
Length of hospital stay	**r**	**p value[b]**
	-0.153	<0.001

r: Correlation coefficient

[a]Mann-Whitney U test; [b]Spearman correlation analysis

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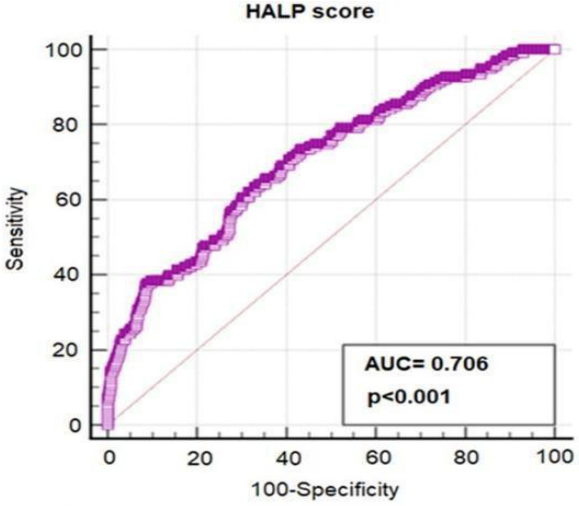
ROC analysis for the performance of HALP score in predicting in-hospital mortality risk

ROC analysis revealed the HALP score to be a potential marker of in-hospital mortality risk in very elderly patients with respiratory-related hospitalization, at a cut-off value of ≤13.7 (AUC: 0.706, 95% CI: 0.685 to 0.726, p<0.001) and with a sensitivity of 60.7% and specificity of 69.8% (Figure 2).



Area under the ROC curve (AUC)	0.706
Standard Error	0.0236
95% Confidence interval	0.685 to 0.726
z statistic	8.712
Significance level p (area=0.5)	<0.001
Youden index J	0.3055
Associated criterion	13.74315789
Sensitivity	60.7
Specificity	69.8

Figure 2: ROC curve analysis of the role of HALP score in prediction of respiratory-related hospitalization.
AUC: Area under curve

DISCUSSION

Our findings in a retrospective cohort of very elderly patients with respiratory-related hospitalization revealed the association of lower HALP scores (a cut-off value of ≤13.7) on admission with a significantly greater risk of in-hospital mortality. Besides, HALP scores were negatively correlated with the LOS. In-hospital mortality risk was lower for females (vs. males) and higher for increasing CRP values, while the in-hospital mortality risk and HALP scores were similar across the respiratory causes of hospitalization and the comorbidities.

Pneumonia, as a common and serious infection in the elderly population, is considered a leading cause of hospitalization and mortality in these patients.[13] On-admission pneumonia was reported to be associated with the highest risk of mortality in very elderly (over 80 years of age) patients.[5,10] Acute exacerbation of COPD (AECOPD) is also a frequent cause of hospital admission with a relatively better survival outcome in very elderly patients, while respiratory failure is a complication strongly associated with high mortality and poor prognosis.[3,4,14] In our cohort, pneumonia, respiratory failure, and COPD were the primary causes of respiratory-related hospitalization, while the overall in-hospital mortality rates (7%) are in line with the previously reported in-hospital mortality rates (range, 7.8 to 12.7%) for very elderly patients with respiratory-related hospitalization in Turkey.[3,4]

In geriatric hospitalized patients, increasing age (>80 years) and malnutrition are considered risk factors for mortality, while prolonged LOS is associated with increased risk of hospital readmission, progressive worsening of functional state and mortality.[2,15,16] In this regard, HALP score at hospital admission, as a readily available measure of systemic inflammation and nutritional status, seems to be a simple and favorable marker in predicting prolonged hospitalization and in-hospital mortality risk among very elderly hospitalized patients.[6]

Our findings indicate, for the first time in the literature, the predictive value of the HALP score in assessing the in-hospital mortality risk in very elderly patients with respiratory-related hospitalization.

A number of available studies in patients with respiratory diseases also indicated the association of low HALP scores with mortality or adverse clinical outcomes.[11,12] Low HALP scores were associated with an increased risk of ICU mortality in patients with AECOPD.[11] In bronchiectasis patients, HALP score was reported to be significantly lower in the exacerbation period than in the stable period, besides its negative correlation with infectious (CRP, leukocytes and neutrophils) parameters and positive correlation with pulmonary functional (FEV1% and FVC%) parameters.[12]

Previous studies reported the prognostic value of low HALP scores among elderly hospitalized patients with many other diseases. The lower HALP score was correlated with the increased risk of post-stroke cognitive impairment and frailty in patients with stroke, particularly in male patients and those aged ≥60 years old.[17] In elderly patients with small-cell lung cancer, the low HALP score was reported to be an independent predictor of poor progression-free survival.[18] In elderly patients with coronary heart disease, a low HALP score was negatively associated with all-cause.[19]

Also, decrease in serum albumin levels (as a marker of impaired nutritional status, inflammation, and disease severity) was associated with morbidity and mortality in hospitalized patients.[20,21] Anemia was associated with adverse outcomes and all-cause and cardiovascular mortality in different settings (i.e. cancer, diabetic nephropathy and kidney disease).[22,23] Although the inflammation may be exacerbated by anemia and thrombosis, lymphocytes decrease the inflammation.[12,24] Accordingly, the HALP score, reflecting both malnutrition (i.e., hemoglobin and albumin levels), and

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inflammatory response (i.e., lymphocyte and platelet counts) parameters, is considered a comprehensive index that reflects the inflammation-nutritional status of patients.[7,23]

Our findings emphasize the growing trend of malnutrition mortality reported in older adults, which is notable given that aging and hospitalization are strong risk factors for malnutrition, while the respiratory-related hospitalization specifically predicts mortality in the very elderly.[25,26] Hospitalized older adults with malnutrition, when compared to non-malnourished counterparts, exhibit an increased likelihood of decline in multiple physiological systems, while frailty and sarcopenia, as the significant determinants of mortality in elderly, often coexist with malnutrition in hospitalized older adults.[27,28]

In geriatric patients hospitalized with acute medical illness, the clinical diagnosis of malnutrition, hypoalbuminemia, and lymphocytopenia were reported to independently predict in-hospital mortality.[16,29] Indeed, malnutrition risk was related to an increased risk of 90-day mortality in elderly patients with acute respiratory failure, while nutritional (hemoglobin levels, albumin levels) and inflammatory (lymphocyte counts, and platelet counts) parameters, as well as concomitant pneumonia, are considered critical for survival in COPD.[11,30,31] Accordingly, given its correlation with both the inflammation-nutrition status and the pulmonary function, the HALP score can be considered as a valuable prognostic biomarker in respiratory clinical practice to monitor the risk of in-hospital mortality in very elderly patients with respiratory-related hospitalization.[11,12]

Besides the HALP score, higher CRP values were also associated with an increased risk of in-hospital mortality in our study. Although NLR was significantly associated with increased in-hospital mortality in the univariate analysis, our multivariate analysis did not confirm this association. Previous studies also reported the association of higher CRP values, as well as the concurrently high values of NLR and CRP/albumin ratio, with the increased risk of in-hospital mortality in very elderly hospitalized patients.[4,15] Indeed, activation of inflammatory pathways is suggested to play an important role in the mechanism linking malnutrition to all-cause mortality, possibly by increasing catabolic demand in patients with already poor nutritional status, particularly in terms of cardiac events. Also, hypoalbuminemia, reflecting a poor nutritional state, was related to cardiac cachexia and extremely poor prognosis.[32,33]

The significant gender influence on in-hospital mortality risk in our cohort supports the previously reported association of male gender with adverse clinical outcomes secondary to pneumonia, while the HALP score is also considered likely to show a possible sex bias in relation to a greater risk for mortality in males than females.[15,34,35] Notably, in a study with hospitalized COVID-19 patients, males had higher mortality than females despite a higher prevalence of pulmonary disease in females, emphasizing the possible role of sex hormones in immune response, and the effect of age on sex hormone concentration in identifying higher odds of mortality in males.[36,37]

Our findings revealed similar survival outcomes and in-hospital mortality risk across the reasons for respiratory-related hospitalization (pneumonia, respiratory failure, or COPD) as well as the comorbidities (i.e., hypertension, chronic heart failure, atherosclerotic cardiovascular disease). Similarly, in a study on the risk indices that predict in-hospital mortality in a hospitalized elderly cohort, ≥65 years of age and LOS were reported to be the significant risk factors, while no specific comorbidity predicted in-hospital mortality.[3] However, many studies indicated the association of higher comorbidity burden (i.e., a cardiovascular diagnosis, congestive heart failure, acute or chronic renal failure, cerebrovascular accident) with increased risk of in-hospital mortality in very elderly hospitalized patients.[4,5,10,16,29]

Increasing age is considered the strongest indicator of the in-hospital mortality risk in elderly hospitalized patients, while the frailty scores and comorbidity were found to have a moderate ability to predict in-hospital and long-term mortality in patients hospitalized with pneumonia.[2,38-40] Notably, the likelihood of age-specific in-hospital mortality predictors (i.e., hemoglobin in the elderly population but comorbidity index in non-elderly) has been noted in respiratory-related hospitalizations.[35]

This study has potential limitations. First, the retrospective single center design of the study prevents establishing the temporality between cause and effect and generalization of our findings to the overall patient population. Second, certain limitations are inherent to the retrospective design, particularly in controlling for potential confounding factors due to data collection constraints based on existing hospital records alongside the potential selection bias due to exclusion of the patients with missing data. Second, the lack of data on other outcomes of interest such as nutritional status is another limitation. Third, studying the effectiveness of the HALP score across various age groups, comorbidity profiles and course of hospital stay could enhance the generalizability of findings, while there is a need for prospective and randomized studies to confirm the predictive power of the HALP score.

In conclusion, our findings in a retrospective cohort of very elderly patients with respiratory-related hospitalization indicate the potential utility of the HALP score as an immune nutritional biomarker in targeting

high-risk patients in terms of in-hospital mortality and prolonged hospital stay. Accordingly, the use of the HALP score in respiratory clinical practice may aid clinicians in timely recognition of at-risk patients in need of particular attention and care and to make decisions regarding the intervening strategies to minimize adverse outcomes. Nonetheless, further investigation on the clinical relevance of the HALP score in larger prospective observational studies is needed in the setting of respiratory-related hospitalizations.

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