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Original Article

The modified HALP score is associated with short-term mortality in critically ill patients with sepsis – A cohort study

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Abstract

Introduction: To systematically appraise the prognostic predictive value of the modified HALP (m-HALP) score in critically ill septic patients.
Methodology: The m-HALP scores were computed for septic patients within the initial 24 hours of admission to the intensive care unit (ICU) utilizing data from the MIMIC-IV database. The association between the m-HALP score and 30-day mortality was evaluated using restricted cubic splines and Cox regression. Kaplan-Meier (K-M) analysis was employed to estimate survival differences. Logistic regression was conducted using data from the eICU database to validate the findings. Receiver operator characteristic (ROC) curves were generated to assess predictive value.
Results: The m-HALP score exhibited an L-shaped association with 30-day mortality upon adjustment for multiple variables (HR: 0.84, 95% CI: 0.74–0.96). K-M curves revealed a favorable survival outcome in patients with high m-HALP scores ($p < 0.001$). In the validation cohort, the m-HALP score proved to be an independent factor influencing in-hospital mortality. The ROC curves suggested that the m-HALP score had a better predictive value for short-term sepsis mortality than the HALP and qSOFA score.
Conclusions: The m-HALP score demonstrated a noteworthy correlation with short-term mortality of septic patients, making it a potentially promising biomarker of prognostic relevance.

Key words: Sepsis; m-HALP score; prognostic; mortality; critically ill patients.

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Introduction

Sepsis manifests as a critical state wherein the body's immune system exhibits aberrant responsiveness to an infection, precipitating dysfunction in vital organs [1], and it is a critical factor contributing to in-hospital mortality. Septic patients' prognosis depends on the delicate balance between excessive inflammation and immune system suppression. When sepsis induces immune cell depletion, especially lymphocyte depletion, patients are at a higher risk of opportunistic infections and mortality [2]. Moreover, the prognosis of sepsis is worse in the presence of malnutrition in immunocompetent patients [3]. A thorough review and analysis revealed that 41.9% of sepsis cases admitted to the intensive care unit (ICU) died before discharge [4]. Hence, it is crucial to promptly identify septic individuals who have a high risk of mortality during their hospital stay.

The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) score, renowned for its simplicity and efficacy, serves as a prominent metric in appraising inflammation and nutritional status. It was defined as the multiplication of hemoglobin concentration (g/L) by albumin concentration (g/L) and lymphocyte count (/L), with the resultant product then divided by the platelet count (/L) [5]. A plethora of clinical investigations has consistently elucidated that a reduced HALP score emerges as an adverse prognostic determinant across various solid tumor classifications [6]. However, the unequivocal acknowledgment of the HALP score's prognostic prowess in predicting outcomes for select non-neoplastic maladies, such as acute exacerbations of chronic obstructive pulmonary disease and coronavirus disease 2019, has yet to attain uniformity in scholarly recognition [7,8]. Kocaoglu *et al.* discovered that the HALP score did not prove to be a reliable predictor of prognosis in patients receiving intensive care [9]. However, the modified HALP (m-HALP) score using the hemoglobin (g/L) × albumin (g/L) × lymphocyte count (/L) × platelet count (/L) method, rather than the classic HALP score, emerged as a noteworthy predictor of 3-month mortality in cases

with acute heart failure [10].

Currently, a dearth of research exists regarding the utilization of the HALP score as a prognostic predictive tool in septic patients. We posit a hypothesis suggesting a potential association between the HALP score and septic patients' prognosis. Considering that thrombocytopenia has been determined as a standalone risk factor for an unfavorable outcome in individuals with sepsis [11] , the combined effect of platelet count with other indicators (through multiplication) in the scoring system may better predict the outcome. We were inclined to use the m-HALP score to explore its association with short-term mortality among septic patients.

Methods

Data source

The data utilized in this investigation were extracted from the MIMIC-IV database, version 2.0, denoted as the Medical Information Mart for Intensive Care IV [12]. This expansive and openly available repository houses deidentified health records collected from patients undergoing intensive care at Beth Israel Deaconess Medical Center. Data for the validation cohort were obtained from the eICU Collaborative Research Database v2.0, which contains data from many intensive care units across the continental United States [13,14]. Noteworthy is the fact that ethical approval or informed consent was unnecessary, given the removal of all personally identifiable information from the datasets.

Study population

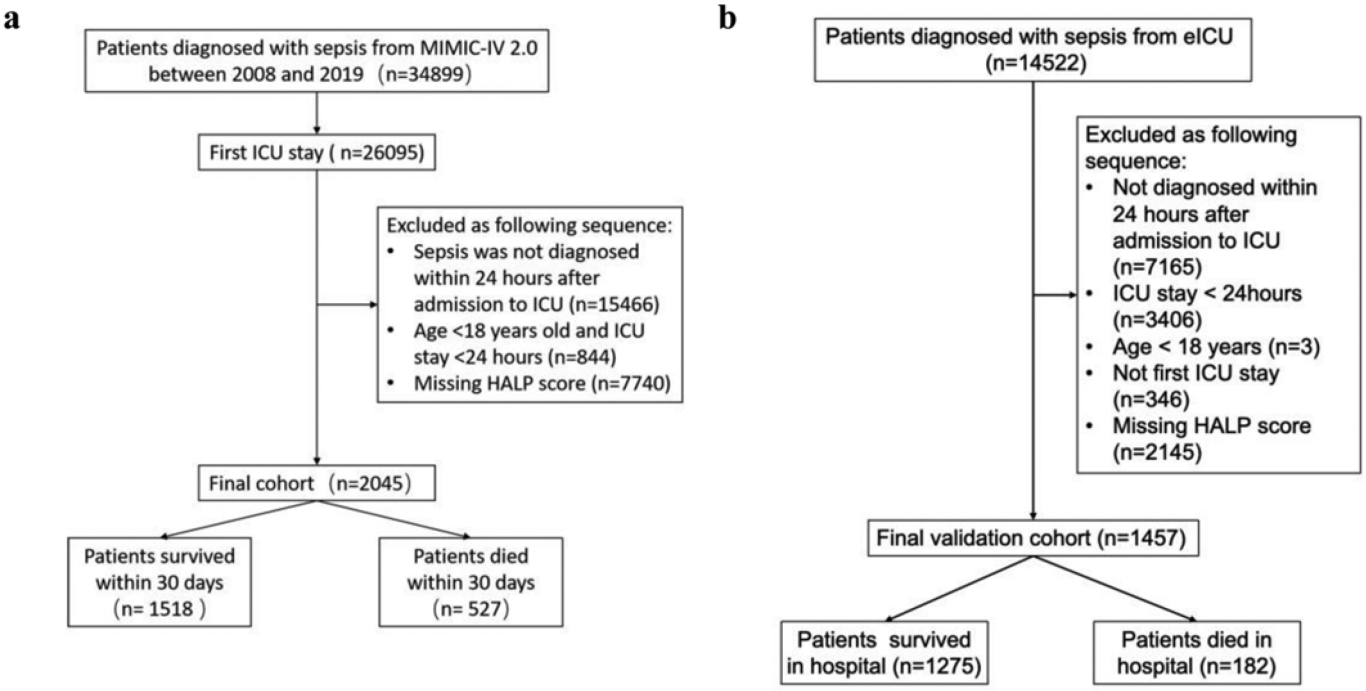
Septic patients in MIMIC-IV database were screened based on Sepsis-3.0 criteria [1], including (1) suspected or documented infection and (2) Sequential Organ Failure Assessment (SOFA) score of ≥ 2. The determination of sepsis in the eICU database was based on the ICD-9 codes A41.9 and R65.21. For patients who had been admitted to the ICU on multiple occasions, we exclusively utilized the data from their first ICU stay. We excluded patients (1) in whom sepsis was not diagnosed within 24 hours of ICU admission; (2) aged < 18 years; (3) who stayed in the ICU for < 24 hours; and (4) with missing HALP score information. The patient flowchart is depicted in Figure 1.

Data extraction

The data extraction process was facilitated using Navicat Premium software, specifically version 16.1.3. The computation of the m-HALP score involved the multiplication of hemoglobin concentration (g/L) by albumin concentration (g/L), followed by the product of lymphocyte count (/L) and platelet count (/L) [10], with the result then divided by 1000 to make it more readable.

Demographic characteristics, vital signs, and laboratory indicators were collected within a time frame

Figure 1. The process for inclusion and exclusion of septic patients.



(a) patients from MIMIC--IV database; (b) patients from eICU database; ICU: Intensive care unit; MIMIC-IV: Medical Information Mart for Intensive Care.

of 24 hours from ICU admission. The diagnosis of acute kidney injury (AKI) was undertaken according to the criteria outlined by the Kidney Disease Improving Global Outcomes organization [15]. Septic shock was recognized as International Classification of Diseases 9 code 78552. Therapeutic measures included mechanical ventilation and vasopressor use. The Charlson Comorbidity Index (CCI), qSOFA and SOFA scores were determined for every patient. The site of infection and the pathogenic microorganism are identified based on diagnoses and laboratory results of microbiological cultures.

Outcome

The main outcome of this research was the survival status within 30 days. Survival time was measured from

Table 1. Septic patients' general characteristics.

Variable	30-day mortality				
	Total (n = 2,045)	**Survival (n = 1,518)**	**Non-survival (n = 527)**	**Statistic**	***p***
Age (years), M (Q_1, Q_3)	63.00 (52.00–75.00)	62.00 (50.00–73.00)	68.00 (56.00–78.00)	Z = 27.117	**< 0.001**
Sex, n (%)				χ^2 = 2.284	0.131
Female	837 (40.93)	636 (41.90)	201 (38.14)		
Male	1208 (59.07)	882 (58.10)	326 (61.86)		
Race, n (%)				χ^2 = 12.115	**0.002**
White	1159 (56.67)	894 (58.89)	265 (50.28)		
Black	92 (4.5)	67 (4.41)	25 (4.74)		
Other	794 (38.83)	557 (36.69)	237 (44.97)		
Insurance type, n (%)				χ^2 = 15.749	**< 0.001**
Medicaid	206 (10.07)	161 (10.61)	45 (8.54)		
Medicare	874 (42.74)	610 (40.18)	264 (50.09)		
Other	965 (47.19)	747 (49.21)	218 (41.37)		
Mechanical ventilation, n (%)				χ^2 = 13.009	**< 0.001**
No	894 (43.72)	699 (46.05)	195 (37.00)		
Yes	1151 (56.28)	819 (53.95)	332 (63.00)		
Vasopressor use, n (%)				χ^2 = 97.385	**< 0.001**
No	863 (42.2)	737 (48.55)	126 (23.91)		
Yes	1182 (57.8)	781 (51.45)	401 (76.09)		
Septic shock, n (%)				χ^2 = 22.846	**< 0.001**
No	1731 (84.65)	1319 (86.89)	412 (78.18)		
Yes	314 (15.35)	199 (13.11)	115 (21.82)		
AKI, n (%)				χ^2 = 85.201	**< 0.001**
No	433 (21.17)	396 (26.09)	37 (7.02)		
Yes	1612 (78.83)	1122 (73.91)	490 (92.98)		
Heart rate (bpm), M (Q_1, Q_3)	92 (78–108)	91 (78–106)	95 (79–110)	Z = 25.104	**0.037**
Systolic blood pressure (mmHg), M (Q_1, Q_3)	120 (102–138)	121 (103–139)	116 (99–134)	Z = 22.542	**< 0.001**
Diastolic blood pressure (mmHg), M (Q_1, Q_3)	66 (56–78)	67 (57–78)	64 (53–77)	Z = 22.897	**0.003**
Respiratory rate (insp/min), M (Q_1, Q_3)	20 (16–24)	20 (16–24)	20 (16–25)	Z = 25.370	**0.007**
Temperature (°C), M (Q_1, Q_3)	36.78 (36.44–37.22)	36.83 (36.44–37.28)	36.67 (36.28–37.00)	Z = 21.246	**< 0.001**
SpO_2 (%), M (Q_1, Q_3)	97.00 (94.00–100.00)	97.00 (95.00–100.00)	97.00 (93.50–99.00)	Z = 22.628	**< 0.001**
Anion gap (mmol/L), M (Q_1, Q_3)	15.00 (13.00–18.00)	15.00 (12.00–18.00)	17.00 (14.00–21.00)	Z = 28.303	**< 0.001**
WBC (K/μL), M (Q_1, Q_3)	12.40 (8.30–18.00)	11.90 (8.20–17.00)	14.40 (8.80–20.60)	Z = 26.406	**< 0.001**
RDW (%), M (Q_1, Q_3)	15.00 (13.80–16.70)	14.80 (13.70–16.30)	15.80 (14.45–17.60)	Z = 27.870	**< 0.001**
PT (sec), M (Q_1, Q_3)	14.70 (12.90–18.20)	14.40 (12.80–17.00)	16.40 (13.40–22.50)	Z = 27.911	**< 0.001**
PTT (sec), M (Q_1, Q_3)	32.50 (28.00–40.80)	31.50 (27.60–38.90)	34.90 (29.65–48.20)	Z = 27.215	**< 0.001**
BUN (mg/dL), M (Q_1, Q_3)	24.00 (15.00–42.00)	22.00 (14.00–36.00)	34.00 (21.00–56.00)	Z = 29.133	**< 0.001**
Glucose (mg/dL), M (Q_1, Q_3)	131.00 (105.00–177.00)	128.50 (104.00–171.75)	138.00 (106.00–191.50)	Z = 25.156	**0.027**
Sodium (mEq/L), M (Q_1, Q_3)	139.00 (135.00–142.00)	139.00 (135.00–141.00)	138.00 (134.00–142.00)	Z = 23.680	0.243
Potassium (mEq/L), M (Q_1, Q_3)	4.10 (3.70–4.60)	4.10 (3.70–4.60)	4.30 (3.80–4.80)	Z = 26.158	**< 0.001**
Chloride (mEq/L), M (Q_1, Q_3)	104.00 (99.00–108.00)	104.00 (100.00–108.00)	103.00 (98.00–108.00)	Z = 22.703	**< 0.001**
Bicarbonate (mEq/L), M (Q_1, Q_3)	22.00 (19.00–25.00)	22.00 (19.00–25.00)	21.00 (17.00–24.00)	Z = 21.362	**< 0.001**
Hemoglobin (g/dL), M (Q_1, Q_3)	10.50 (9.00–12.20)	10.60 (9.10–12.30)	10.10 (8.80–11.75)	Z = 22.558	**< 0.001**
Serum albumin (g/dL), M (Q_1, Q_3)	3.00 (2.50–3.40)	3.00 (2.60–3.40)	2.80 (2.40–3.30)	Z = 22.037	**< 0.001**
Lymphocytes (10^9/L), M (Q_1, Q_3)	0.82 (0.37–1.38)	0.90 (0.42–1.46)	0.67 (0.25–1.23)	Z = 21.749	**< 0.001**
Platelets (10^9/L), M (Q_1, Q_3)	185.00 (119.00–261.00)	190.00 (127.00–261.00)	166.00 (96.50–252.50)	Z = 22.448	**< 0.001**
CCI, M (Q_1, Q_3)	6 (4–8)	5 (3–7)	7 (5–9)	Z = 28.863	**< 0.001**
SOFA score, M (Q_1, Q_3)	3 (2–5)	3 (2–5)	4 (3–7)	Z = 28.471	**< 0.001**
qSOFA score, M (Q_1, Q_3)	1.00 (1.00–2.00)	1.00 (1.00–2.00)	1.00 (1.00–2.00)	Z = 25.276	**0.007**
HALP, M (Q_1, Q_3)	13.42 (5.80–27.63)	14.60 (6.39–28.50)	10.72 (4.39–23.44)	Z = 22.341	**<.001**
m-HALP, M (Q_1, Q_3)	378.54 (120.40–895.11)	422.40 (140.59–951.74)	253.68 (82.79–658.87)	Z = 28.923	**<.001**

bpm: beats per minute; M: median; Q_1: 1st quartile; Q_3: 3rd quartile; Z: Mann–Whitney U test; χ^2: chi-square test; AKI: acute kidney injury; SpO_2: saturation of peripheral oxygen; (q)SOFA: (quick) Sequential Organ Failure Assessment; CCI: Charlson Comorbidity Index; WBC: white blood cell; RDW: red blood cell distribution width; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; (m-)HALP: (modified) hemoglobin, albumin, lymphocyte, and platelet score.

ICU admission, known as the "in time," until death or until 30 days had passed since ICU admission, whichever came first.

Statistical analyses

Continuous variables, as discerned through the Shapiro–Wilk test, demonstrated abnormal distributions and were succinctly characterized by medians and quartiles (Q_1, Q_3). It was attempted to express categorical variables numerically, particularly in the form of counts and percentages. To discern whether there would be statistical differences between the two groups, the analysis employed either the Mann–Whitney U test or the Chi-square test, contingent upon the inherent nature of the variables. Missing values were imputed using the random forest function followed by sensitivity analysis (Supplementary Table 1). However, any variable with > 10% missing values was excluded from the analysis (Supplementary Table 2).

The exploration of the intricate non-linear correlation between the m-HALP score and the hazard ratio (HR) for mortality, coupled with the identification of the inflection point, was accomplished through the application of the restricted cubic spline (RCS) function and Cox regression analysis. The RCS function incorporated four knots strategically positioned at the 5th, 35th, 65th, and 95th percentiles. The Kaplan–Meier method and the log-rank test were conducted to identify any differences in 30-day survival among patients grouped by m-HALP score. A forest plot was used to visually represent the subgroup analysis. Logistic regression was used to analyze the validation cohort due to the lack of survival data in eICU database. The area under the ROC curve (AUC) was applied to evaluate the predicted value of the scoring systems. The statistical analysis was undertaken utilizing R 4.2.1 software. Employing a two-sided approach, the presence of statistical significance was confirmed across all conducted tests when the *p* value fell below the threshold of 0.05.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Septic patients' general characteristics with different clinical outcomes

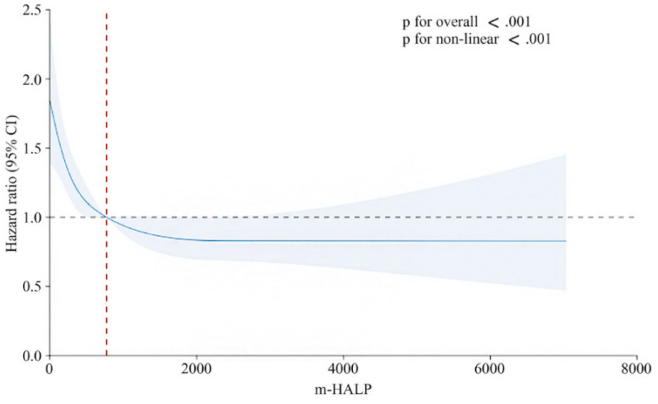
After the screening process (Figure 1), 2,045 patients with complete m-HALP score data were finally enrolled in the study cohort. Patients' mean age was 63 (52–75) years, 59.07% were male, 56.67% were White, and the 30-day mortality rate was 25.77% (Table 1).

The patients that survived up to 30 days had significantly higher m-HALP scores relative to non-survival cases ($p < 0.001$), in which median m-HALP score were 422.40 (140.59–951.74). The survival group exhibited significantly elevated values in all four components of the m-HALP score relative to the non-survival group, with all *p values* below 0.001. Noteworthy differences between the two abovementioned groups were also identified in other variables, encompassing age, race, type of insurance, utilization of mechanical ventilation, vasopressor usage, presence of septic shock, occurrence of AKI, respiratory rate, systolic and diastolic blood pressure, temperature, peripheral oxygen saturation, CCI, SOFA and qSOFA score, anion gap, red blood cell distribution width, white blood cell count, prothrombin time, partial thromboplastin time, blood urea nitrogen, glucose, potassium, chloride, and bicarbonate (all $p < 0.05$).

Non-linear relationship between the m-HALP score and 30-day mortality in septic patients

The ROC curves based on a two-piecewise Cox regression analysis showed an L-shaped association between the m-HALP score and 30-day mortality (Figure 2). The curves for the univariate and multivariate regression models shared the same shape. The m-HALP score inflection point was 774.7 in the univariate analysis and 772.9 in the multivariate analysis (covariates screened in Supplementary Table

Figure 2. Association between the m-HALP score and survival in the multivariate model with the RCS function.



The blue solid line represents the estimated values, with the 95% CI represented by the shaded area. The red dotted line indicates the inflection point of the curve. CI: confidence interval; m-HALP, modified hemoglobin, albumin, lymphocyte, and platelet score; RCS: restricted cubic spline.

Table 2. Representation of two segmented linear models examining the relationship between the m-HALP score and 30-day mortality risk in septic patients.

	m-HALP	HR (95% CI)	*p*
Model 1	Inflection point: 774.7		
	< 774.7	0.78 (0.70–0.87)	< 0.001
	≥ 774.7	1.06 (0.91–1.24)	0.45
Model 2	Inflection point: 772.9		
	< 772.9	0.83 (0.74–0.93)	0.001
	≥ 772.9	0.93 (0.77–1.11)	0.40

Model 1 constituted the univariate analysis using Cox proportional-hazards regression. Adjustment of Model 2 was undertaken for the following covariates: age, race, type of insurance, mechanical ventilation, vasopressor use, septic shock, acute kidney injury, heart rate, respiratory rate, systolic and diastolic blood pressure, temperature, peripheral oxygen saturation, Sequential Organ Failure Assessment score, anion gap, white blood cell count, red blood cell distribution width, partial thromboplastin time, prothrombin time, blood urea nitrogen, glucose, potassium, chloride, bicarbonate. CI: confidence interval; HR: hazard ratio; m-HALP: modified hemoglobin, albumin, lymphocyte, and platelet score.

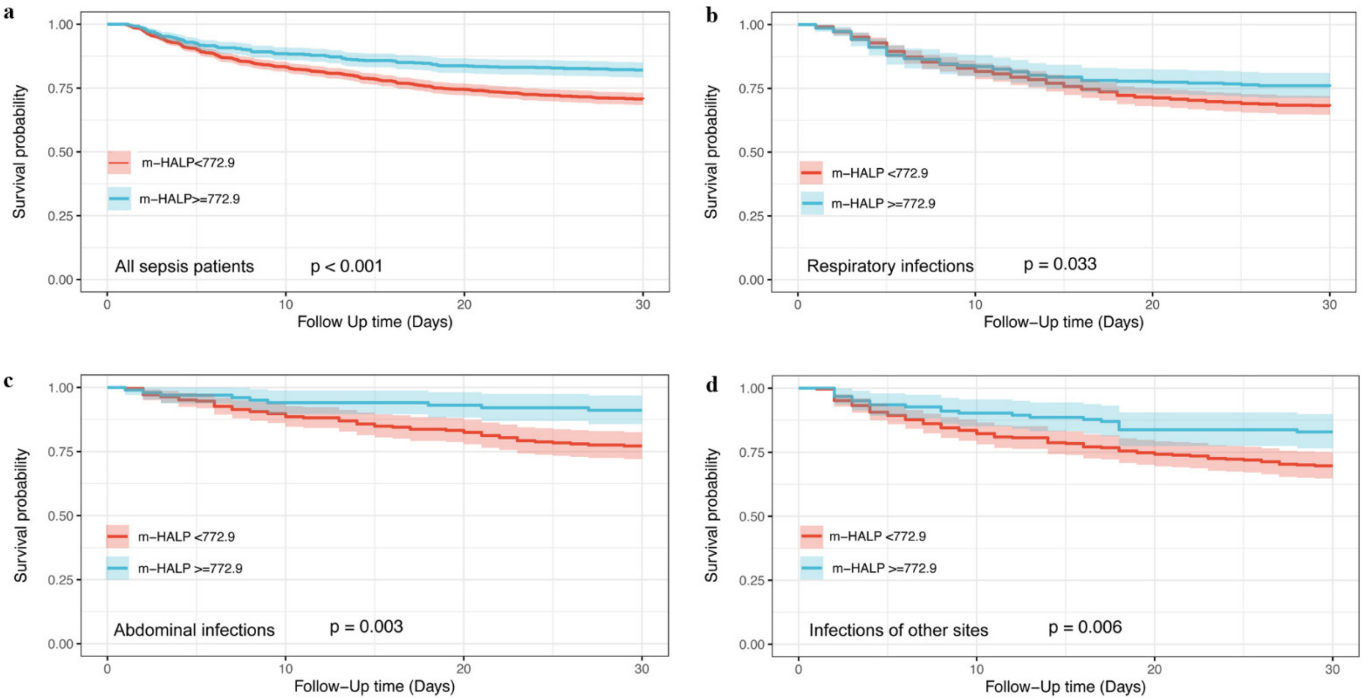
3). In instances where the m-HALP score was below the inflection point derived from the multivariate model, there was a notable 17% reduction in the risk of 30-day mortality for every incremental 1 unit in the m-HALP score (HR: 0.83, 95% CI: 0.74–0.93) (Table 2). Conversely, when the m-HALP score exceeded the inflection point, it did not exhibit a statistically significant association with mortality risk (HR: 1.06, 95% CI: 0.91–1.24). The Kaplan–Meier survival estimate, coupled with the log-rank test, illustrated that a lower m-HALP score (< 772.9) was strongly indicative of unfavorable survival outcomes ($p < 0.001$, Figure 3a). Lower m-HALP scores were similarly associated with poor prognosis for infections at various sites, including the respiratory tract, abdomen, and other sites of infection (*all* $p < 0.05$, Figure 3b-d).

When compared to patients with higher m-HALP scores, patients with lower scores had lower blood pressure, oxygen saturation, white blood cell count, sodium, bicarbonate, and higher RDW, PT, PTT, BUN, SOFA score, CCI, and 30-day mortality (all $p < 0.05$). Patients with lower m-HALP scores were more likely to experience septic shock compared to those with higher scores (16.45% vs 12.95%, $p = 0.041$). No significant differences were seen between the two groups in terms of mechanical ventilation, combined AKI, duration of mechanical ventilation, and use of vasoactive drugs (Supplementary Table 4).

Subgroup analysis and validation

To assess the strength and reliability of the correlation between the m-HALP score and 30-day

Figure 3. Kaplan–Meier (KM) survival curves of the m-HALP score over 30 days in septic patients.



(a) All sepsis patients; (b) Sepsis patients with respiratory infections; (c) Sepsis patients with abdominal infections; (d) Sepsis patients with infections in other sites; m-HALP, modified hemoglobin, albumin, lymphocyte, and platelet score.

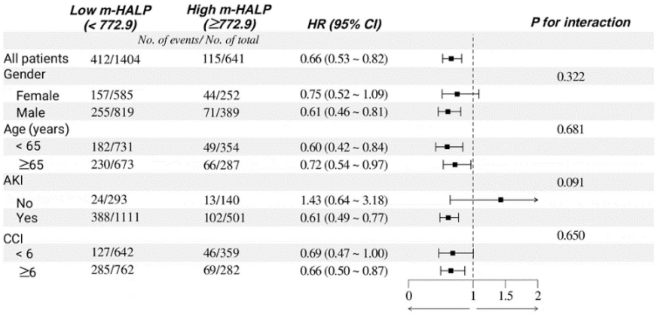
mortality, we performed a subgroup analysis with the patients stratified by age, sex, AKI, and CCI. The adverse impact of a reduced m-HALP score on septic patients' survival remained uniform across various subgroups (Figure 4). Notably, the correlation between the m-HALP score and 30-day mortality exhibited heightened strength in specific subgroups, namely those with a higher CCI (> 6), concurrent AKI, and cases of the male gender. However, all the interaction tests did not yield statistical significance (p (for interaction) > 0.05).

We performed an external validation of the prognostic value of the m-HALP score, with data extracted from eICU database. The validation cohort included 1457 patients with sepsis, having an in-hospital mortality rate of 12.49% and a mean hospital length of stay of 6 days. After data cleaning (Supplementary Table 5,6), the baseline information on patients was shown in Supplementary Table 7. Result of a multifactorial logistic stepwise regression modeling showed that m-HALP scores remained independently associated with in-hospital death (OR: 0.52, 95% CI:0.32-0.83) (Supplementary Table 8).

Predictive value of the m-HALP score in patients with sepsis

In the MIMIC-IV cohort, we conducted the ROC curves to explore the predictive value of HALP and m-HALP scores, as well as qSOFA and SOFA scoring system. As shown in Figure 5a, the m-HALP (AUC: 0.606, 95% CI: 0.578-0.634) was marginally weaker than SOFA score (AUC: 0.643, 95% CI: 0.616-0.670) in predicting 30-day mortality in septic patients (p = 0.037, DeLong's test), but better than HALP score (AUC: 0.562, 95% CI: 0.533-0.591) and qSOFA score (AUC: 0.536, 95% CI: 0.510-0.562), with p = 0.003 and p < 0.001, respectively, for DeLong test.

Figure 4. Results of the subgroup analysis depicted as a forest plot.

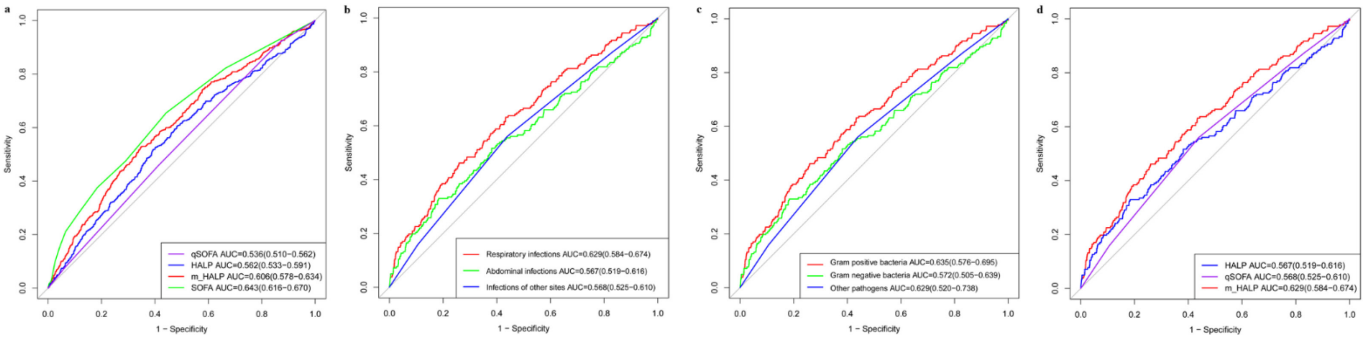


AKI: acute kidney injury; CCI: Charlson Comorbidity Index; CI: confidence interval; HR: hazard ratio; m-HALP, modified hemoglobin, albumin, lymphocyte, and platelet score.

We further explored the predictive value of m-HALP score for different sites of infection and found that it had a higher AUC for respiratory tract infections (AUC: 0.629, 95% CI: 0.584−0.674) than for abdominal (AUC: 0.567, 95% CI: 0.519−0.616) or other sites (AUC: 0.568, 95% CI: 0.525−0.610), and for DeLong test, p = 0.025 *and* p = 0.048, respectively (Figure 5b). For infections with Gram-positive, Gram-negative, and other pathogens, the m-HALP score had comparable predictive value, with AUCs of 0.635 (95% CI: 0.576−0.695), 0.572 (95% CI: 0.505−0.639), and 0.629 (95% CI: 0.520−0.738), respectively, and p > 0.05 for intergroup comparisons (Figure 5c).

In the verification queue, the m-HALP score (AUC: 0.629, 95% CI: 0.584-0.674) was still better than HALP score (AUC: 0.567, 95% CI: 0.519-0.616) and qSOFA score (AUC: 0.568, 95% CI: 0.525-0.610), with p = 0.025 *and* p = 0.042, for DeLong test, respectively (Figure 5d).

Figure 5. ROC curves for HALP, m-HALP, qSOFA, and SOFA score.



(a) ROC curves in cohort from the MIMIC-IV database; (b) ROC curves of different sites in MIMIC-IV database; (c) ROC curves of different microbiological types in MIMIC-IV database; (d) ROC curves in validation cohort from the eICU database. (q) SOFA, (quick) Sequential Organ Failure Assessment; (m-) HALP, (modified) hemoglobin, albumin, lymphocyte, and platelet score.

Discussion

In the present investigation, it was attempted to explore the prognostic utility of the m-HALP score in predicting septic patients' outcomes. Notably, a distinct correlation was identified, highlighting that a lower m-HALP score computed within the initial 24 hours of admission to the ICU was indicative of an elevated risk of short-term mortality. Furthermore, a noticeable L-shaped association was figured out between the m-HALP score and the probability of experiencing 30-day mortality.

Previous studies have shown that hemoglobin, albumin, lymphocytes, and platelets, which constitute the HALP scoring system, are implicated in the prognosis of sepsis. Sepsis is associated with a high prevalence of anemia, which can be attributed to various factors, including decreased erythropoietin secretion due to inflammatory mediators and loss of erythrocytes due to diffuse intravascular coagulation, hemolysis, and bleeding. Impaired iron metabolism may also be involved [16]. During infection, albumin synthesis in the liver is reduced to prioritize the synthesis of C-reactive protein [17]. In the context of sepsis, the inflammatory response precipitates an increase in capillary permeability, resulting in the leakage of serum albumin and consequential hypoalbuminemia. This phenomenon may cause significant association with septic patients' unfavorable prognosis [18]. Simultaneously, lymphopenia, characterized by the absence of circulating T and B lymphocytes, emerges as a distinctive manifestation indicative of impaired acquired immune responses in septic patients [19]. The persistence of lymphopenia not only elevates the susceptibility to hospital-acquired infections but also amplifies the risk of mortality in septic patients [20]. The identified correlations between these indicators and prognosis exhibited a consistent pattern not only in the context of sepsis but also extend to diverse types of cancer [21-23].

As versatile cells, platelets are involved in various pathophysiological processes, such as thrombosis, hemostasis, tumor metastasis, and the immune response [24]. In neoplastic diseases, the pro-inflammatory state of the tumor microenvironment can lead to thrombocytosis to protect tumor cells from immune surveillance. The cancer-promoting effects of platelets seem to outweigh their anti-cancer effects, and increased platelets are an unfavorable factor in tumor prognosis [25]. In ischemic stroke, platelets are involved in coagulation and thrombosis, and higher platelet counts are associated with risk of stroke recurrence, all-cause mortality, and poorer functional outcomes [26]. Thus, the HALP score, with platelet count as the denominator, provides a comprehensive assessment of a patient's immune, nutritional, and inflammatory status and is critical to the prognosis of patients with this type of disease. During the onset and progression of sepsis, immune and nutritional status similarly influence patient prognosis and treatment strategies. In inflammatory diseases, platelets interact with pathogens, leading to their activation and participation in immunomodulation, and they are involved in the development of microvascular thrombosis and subsequent organ dysfunction [27]. Thrombocytopenia is associated with elevated cytokine and complement levels and enhanced endothelial cell activation in sepsis [28]. Lower platelet counts on admission usually imply a more dysfunctional host response and an increased likelihood of mortality in septic patients [29]. Considering the potential impact of platelets in different diseases, we believe that the m-HALP score is more consistent with the pathophysiologic mechanisms of sepsis than the HALP score. Our study also fully confirms that the m-HALP score has a better prognostic value for septic patients admitted to the ICU compared with the classical HALP score.

In addition, our research identified an L-shaped nonlinear relationship between the m-HALP score and sepsis mortality. Recent investigations have demonstrated that the levels of several components comprising the m-HALP score, such as hemoglobin and albumin, exhibit a nonlinear relationship with the poor prognosis of sepsis patients [30,31]. These findings may illuminate the threshold effects observed in m-HALP scores. Furthermore, the m-HALP score was independently associated with in-hospital mortality, underscoring its utility as a powerful prognostic prediction tool. This suggested that, even after adjusting for other factors that may influence patient prognosis, the m-HALP score could significantly predict the risk of death in critically ill sepsis patients, although the optimal cutoff value may vary across different populations.

Our study also found that the AUC curve of the m-HALP score exhibits the largest area in respiratory tract infections among patients with sepsis, outperforming abdominal infections and infections from other sites. This finding has not been reported in previous studies, suggesting that the m-HALP score has significant clinical application potential for predicting the site of infection in patients with sepsis. However, additional data and further trials are necessary for validation in the future.

Strengths and limitations of study

Although our research was the first exploration into the correlation between the m-HALP score and mortality risk in critically ill septic patients, it comes with certain limitations. Firstly, it adopted a retrospective design, the missing values might lead to biased results. The absence of patient participation in the study may limit the applicability of the study in the real world, and the importance of prospective studies to validate findings across multiple centers could not be overstated. Secondly, the concentration was exclusively on the m-HALP scores of septic patients within the initial 24 hours of ICU admission, omitting an exploration into the potential significance of dynamic alterations in the scores over time. The relationship between the m-HALP score and the long-term prognosis of patients with sepsis, on the other hand, remains to be further elucidated, which is essential to understand the impact of the score on the overall prognosis of patients. Lastly, the optimal cut-off value of the m-HALP score in different subgroups of the population as well as in different pathogens deserves further exploration. The timing of this study did not cover the COVID-19 pandemic period, and therefore the score is under-explored for viral sepsis applications. Patients with COVID-19 typically present with lymphopenia, thrombocytopenia, and elevated D-dimer [32,33]. The HALP score was independently associated with adverse in-hospital overall survival in COVID-19 Omicron BA.2-infected patients [34], whereas whether the m-HALP is superior to the HALP score deserves further investigation.

Conclusions

In summary, the results elucidated a notable nonlinear correlation between the m-HALP score and short-term mortality in septic patients undergoing ICU admission. Notably, the m-HALP score exhibited enhanced prognostic efficacy relative to the conventional HALP score. Given the practical feasibility of employing m-HALP scoring, there exists a compelling rationale for further exploration and substantiation of its clinical applicability in the prognostic assessment of sepsis in future research.

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Authors' contributions

L.L.: Conceptualization, Data curation, Software, Formal analysis, Writing – Original draft preparation, Writing – Review & editing. H.H.: Conceptualization, Methodology, Writing – Review & editing. M.W.: Software, Validation, Visualization. F.C.: Conceptualization, Methodology, Supervision. C.L.: Writing – Review & editing, Supervision, Resources. All the authors read and approved the final manuscript.

Availability of data and materials

The datasets utilized and examined in the present investigation can be accessed at the following link: https://physionet.org.

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Conflict of interests

No conflict of interests is declared.

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Annex – Supplementary Items

Supplementary Table 1. Comparison of data sets before and after imputation.

Variable	After (n = 2045)	Before (n = 2045)	Statistic	*p*
Heart Rate (bpm), M (Q_1, Q_3)	92 (78–108)	92 (78–108)	Z = 27.685	0.985
Systolic blood pressure (mmHg), M (Q_1, Q_3)	120 (102–138)	120 (102–138)	Z = 27.705	0.988
Diastolic blood pressure (mmHg), M (Q_1, Q_3)	66 (56–78)	66.00 (56–78)	Z = 27.704	0.990
Respiratory Rate (insp/min), M (Q_1, Q_3)	20 (16–24)	20 (16–24)	Z = 27.630	0.708
Temperature (°C), M (Q_1, Q_3)	36.78 (36.44–37.22)	36.78 (36.44–37.22)	Z = 27.593	0.813
SpO_2 (%), M (Q_1, Q_3)	97 (94–100)	97 (94–100)	Z = 27.703	0.991
PT (sec), M (Q_1, Q_3)	14.70 (12.90–18.20)	14.70 (12.90–18.20)	Z = 27.576	0.946
PTT (sec), M (Q_1, Q_3)	32.50 (28.00–40.80)	32.50 (27.98–40.90)	Z = 27.535	0.985
Urine output (ml), M (Q_1, Q_3)	1445.00 (800.00–2375.00)	1451.00 (816.25–2381.50)	Z = 27.687	0.837

bpm: beats per minute; M: Median; Q_1:1st Quartile; Q_3:3rd Quartile; Z: Mann-Whitney test; SpO_2: Saturation of peripheral oxygen; PT: Prothrombin time; PTT: Partial thromboplastin time.

Supplementary Table 2. Distribution of missing values.

Variables	N (%)
Heart rate	2 (0.10)
Systolic Blood pressure	1 (0.05)
Diastolic Blood pressure	1 (0.05)
Respiratory rate	79 (3.86)
Temperature	69 (3.37)
SpO_2	1 (0.05)
PT	48 (2.35)
PTT	53 (2.59)
PH	316 (15.45)
Lactate	299 (14.62)
PaO_2	640 (31.30)
$PaCO_2$	640 (31.30)
Urine output	35 (1.71)

SpO_2: Saturation of peripheral oxygen; PT: Prothrombin time; PTT: Partial thromboplastin time; BUN: blood urea nitrogen; PH: Pondus Hydrogenii; PaO_2: Partial pressure of oxygen in arterial blood; $PaCO_2$: Partial pressure of carbon dioxide in arterial blood.

Supplementary Table 3. Univariate Cox proportional hazards analysis of factors associated with 30–day morality risk in patients with sepsis.

Variable	HR (95% CI)	*p*
Age	1.35 (1.24–1.48)	< 0.001
Sex		
Female	Ref	
Male	1.14 (0.96–1.36)	0.138
Race		
White	Ref	
Black	1.21 (0.81–1.83)	0.356
Other	1.38 (1.16–1.65)	< 0.001
Insurance		
Medicaid	Ref	
Medicare	1.44 (1.05–1.98)	0.023
Other	1.04 (0.76–1.44)	0.804
Mechanical ventilation		
No	Ref	
Yes	1.43 (1.19–1.70)	< 0.001
Vasopressors		
No	Ref	
Yes	2.70 (2.21–3.29)	< 0.001
Septic shock		
No	Ref	
Yes	1.69 (1.37–2.07)	< 0.001
AKI		
No	Ref	
Yes	4.06 (2.91–5.67)	< 0.001
Heart rate	1.10 (1.01–1.20)	0.028
Systolic blood pressure	0.83 (0.76–0.90)	< 0.001
Diastolic blood pressure	0.86 (0.79–0.94)	0.001
Respiratory rate	1.12 (1.03–1.21)	0.008
Temperature	0.74 (0.69–0.80)	< 0.001
SpO_2	0.87 (0.82–0.92)	< 0.001
CCI	1.55 (1.43–1.68)	< 0.001
SOFA	1.47 (1.37–1.57)	< 0.001
qSOFA	1.13 (1.03-1.23)	0.007
Anion gap	1.43 (1.34–1.52)	< 0.001
WBC	1.22 (1.14–1.32)	< 0.001
RDW	1.33 (1.24–1.43)	< 0.001
PT	1.25 (1.18–1.31)	< 0.001
PTT	1.18 (1.10–1.26)	< 0.001
BUN	1.39 (1.31–1.47)	< 0.001
Glucose	1.12 (1.04–1.20)	0.002
Sodium	0.96 (0.89–1.05)	0.414
Potassium	1.19 (1.10–1.28)	< 0.001
Chloride	0.87 (0.79–0.94)	< 0.001
Bicarbonate	0.75 (0.69–0.82)	< 0.001

HR: hazard ratio; CI: confidence interval; AKI: Acute kidney injury; SpO_2: Saturation of peripheral oxygen; CCI: Charlson Comorbidity Index; (q)SOFA: (quick)Sequential Organ Failure Assessment; WBC: White blood cell; RDW: Red blood cell distribution width; PT: Prothrombin time; PTT: Partial thromboplastin time; BUN: blood urea nitrogen.

Supplementary Table 4. Clinical characteristics grouped by m-HALP scores.

Variable	Total (n = 2045)	m-HALP < 772.9 (n = 1404)	m-HALP ≥ 772.9 (n = 641)	Statistic	*p*
Age (years), M (Q_1, Q_3)	63.00 (52.00 - 75.00)	64.00 (52.00 - 75.00)	63.00 (51.00 - 74.00)	Z = 21.486	0.073
Sex, n (%)				χ^2 = 1.008	0.315
Female	837 (40.93)	585 (41.67)	252 (39.31)		
Male	1208 (59.07)	819 (58.33)	389 (60.69)		
Insurance, n (%)				χ^2 = 1.444	0.486
Medicaid	206 (10.07)	134 (9.54)	72 (11.23)		
Medicare	874 (42.74)	606 (43.16)	268 (41.81)		
Other	965 (47.19)	664 (47.29)	301 (46.96)		
Race, n (%)				χ^2 = 1.854	0.396
White	1159 (56.67)	786 (55.98)	373 (58.19)		
Black	92 (4.5)	60 (4.27)	32 (4.99)		
Other	794 (38.83)	558 (39.74)	236 (36.82)		
Heart rate (bpm), M (Q_1, Q_3)	92.00 (78.00 - 108.00)	92.00 (79.00 - 107.25)	92.00 (77.00 - 108.00)	Z = 21.920	0.390
Systolic blood pressure (mmHg), M (Q_1, Q_3)	120.00 (102.00 - 138.00)	118.00 (101.00 - 135.00)	124.00 (107.00 - 144.00)	Z = 24.684	**< 0.001**
Diastolic blood pressure (mmHg), M (Q_1, Q_3)	66.00 (56.00 - 78.00)	65.00 (55.00 - 76.00)	68.00 (58.00 - 81.00)	Z = 24.334	**< 0.001**
Respiratory rate (insp/min), M (Q_1, Q_3)	20.00 (16.00 - 24.00)	20.00 (16.00 - 24.00)	19.00 (16.00 - 24.00)	Z = 21.817	0.279
Temperature (°C), M (Q_1, Q_3)	36.78 (36.44 - 37.22)	36.83 (36.44 - 37.22)	36.78 (36.39 - 37.22)	Z = 21.968	0.450
SpO_2 (%), M (Q_1, Q_3)	97.00 (94.00 - 100.00)	97.00 (94.00 - 100.00)	98.00 (95.00 - 100.00)	Z = 23.531	**0.008**
Anion gap (mmol/L), M (Q_1, Q_3)	15.00 (13.00 - 18.00)	15.00 (12.00 - 18.00)	15.00 (13.00 - 18.00)	Z = 22.691	0.421
WBC (K/μL), M (Q_1, Q_3)	12.40 (8.30 - 18.00)	11.20 (7.47 - 16.70)	14.90 (10.90 - 20.80)	Z = 27.369	**< 0.001**
RDW (%), M (Q_1, Q_3)	15.00 (13.80 - 16.70)	15.30 (14.10 - 17.00)	14.30 (13.50 - 15.70)	Z = 17.670	**< 0.001**
PT (sec), M (Q_1, Q_3)	14.70 (12.90 - 18.20)	15.10 (13.10 - 19.00)	14.00 (12.50 - 16.10)	Z = 19.119	**< 0.001**
PTT (sec), M (Q_1, Q_3)	32.50 (28.00 - 40.80)	32.90 (28.40 - 41.10)	31.10 (27.10 - 40.10)	Z = 21.002	**0.005**
BUN (mg/dL), M (Q_1, Q_3)	24.00 (15.00 - 42.00)	27.00 (16.00 - 47.00)	20.00 (13.00 - 32.00)	Z = 18.896	**< 0.001**
Glucose (mg/dL), M (Q_1, Q_3)	131.00 (105.00 - 177.00)	130.50 (104.00 - 174.00)	131.00 (105.00 - 181.00)	Z = 22.978	0.155
Sodium (mEq/L), M (Q_1, Q_3)	139.00 (135.00 - 142.00)	138.00 (135.00 - 142.00)	139.00 (136.00 - 142.00)	Z = 23.245	**0.045**
Potassium (mEq/L), M (Q_1, Q_3)	4.10 (3.70 - 4.60)	4.10 (3.70 - 4.60)	4.10 (3.70 - 4.70)	Z = 22.929	0.187
Chloride (mEq/L), M (Q_1, Q_3)	104.00 (99.00 - 108.00)	104.00 (99.00 - 109.00)	104.00 (100.00 - 108.00)	Z = 22.390	0.877
Bicarbonate (mEq/L), M (Q_1, Q_3)	22.00 (19.00 - 25.00)	22.00 (18.00 - 25.00)	23.00 (20.00 - 26.00)	Z = 24.836	**< 0.001**
GCS, M (Q_1, Q_3)	13.00 (8.00 - 14.00)	13.00 (8.00 - 14.00)	13.00 (8.00 - 14.00)	Z = 22.627	0.500
CCI, M (Q_1, Q_3)	6.00 (4.00 - 8.00)	6.00 (4.00 - 8.00)	5.00 (3.00 - 7.00)	Z = 20.151	**< 0.001**
SOFA score, M (Q_1, Q_3)	3.00 (2.00 - 5.00)	4.00 (2.00 - 6.00)	3.00 (2.00 - 4.00)	Z = 18.614	**< 0.001**
qSOFA score, M (Q_1, Q_3)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	Z = 21.772	0.204
Mechanical ventilation, n (%)				χ^2 = 0.624	0.429
No	894 (43.72)	622 (44.30)	272 (42.43)		
Yes	1151 (56.28)	782 (55.70)	369 (57.57)		
Vasopressor use, n (%)				χ^2 = 0.840	0.359
No	863 (42.2)	583 (41.52)	280 (43.68)		
Yes	1182 (57.8)	821 (58.48)	361 (56.32)		
AKI, n (%)				χ^2 = 0.249	0.618
No	433 (21.17)	293 (20.87)	140 (21.84)		
Yes	1612 (78.83)	1111 (79.13)	501 (78.16)		
Septic Shock, n (%)				χ^2 = 4.159	**0.041**
No	1731 (84.65)	1173 (83.55)	558 (87.05)		
Yes	314 (15.35)	231 (16.45)	83 (12.95)		
Infection Site, n (%)				χ^2 = 14.039	**0.015**
Respiratory	918 (44.89)	626 (44.59)	292 (45.55)		
Abdominal	346 (16.92)	245 (17.45)	101 (15.76)		
Other sites	433 (21.17)	311 (22.15)	122 (19.03)		
Uncertain sites	348 (17.02)	222 (15.81)	126 (19.66)		
Microbiological Type, n (%)				χ^2 = 5.595	0.232
Gram-positive bacteria	422 (20.64)	293 (20.87)	129 (20.12)		
Gram-negtive bacteria	378 (18.48)	259 (18.45)	119 (18.56)		
Virus	22 (1.08)	18 (1.28)	4 (0.62)		
Fungus	95 (4.65)	73 (5.20)	22 (3.43)		
Uncertain	1128 (55.16)	761 (54.20)	367 (57.25)		
Mechanical ventilation time (hours), M (Q_1, Q_3)	30.00 (0.00 - 125.00)	29.00 (0.00 - 127.28)	30.45 (0.00 - 120.92)	Z = 22.303	0.972
30-day mortality, n (%)				χ^2 = 29.919	< 0.001
Survival	1518 (74.23)	992 (70.66)	526 (82.06)		
Non-survival	527 (25.77)	412 (29.34)	115 (17.94)		

M: median; Q_1: 1st quartile; Q_3: 3rd quartile; Z: Mann–Whitney U test; χ^2: chi-square test; m-HALP: modified hemoglobin: albumin: lymphocyte: and platelet score; bpm: beats per minute; SpO_2: saturation of peripheral oxygen; WBC: white blood cell; RDW: red blood cell distribution width; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; GCS: Glasgow coma scale; CCI: Charlson Comorbidity Index; (q)SOFA: (quick) Sequential Organ Failure Assessment; AKI: acute kidney injury.

Supplementary Table 5. Distribution of missing values in validation cohort.

Variables	N (%)
Heart rate	1 (0.07)
Systolic Blood pressure	3 (0.21)
Diastolic Blood pressure	3 (0.21)
Respiratory rate	3 (0.21)
Temperature	26 (1.78)
SpO_2	1 (0.07)
PT	828 (56.83)
PTT	1056 (72.48)
RDW	39 (2.68)
Anion gap	261 (17.91)
Bicarbonate	158 (10.84)
Glucose	2 (0.14)
BUN	3 (0.21)
GCS	8 (0.55)

SpO_2: Saturation of peripheral oxygen; PT: Prothrombin time; PTT: Partial thromboplastin time; RDW: Red blood cell distribution width; BUN: blood urea nitrogen; GCS: glasgow coma scale.

Supplementary Table 6. Comparison of data sets of validation cohort before and after imputation.

Variable	After (n = 1457)	Before (n = 1457)	Statistic	*p*
Heart Rate (bpm), M (Q_1, Q_3)	94 (81 - 110)	94 (81 - 110)	Z = 23.388	0.988
Systolic blood pressure (mmHg), M (Q_1, Q_3)	106 (92 - 127)	106 (92 - 127)	Z = 23.382	0.952
Diastolic blood pressure (mmHg), M (Q_1, Q_3)	60 (50 - 72)	60 (50 - 72)	Z = 23.340	0.948
Respiratory Rate (insp/min), M (Q_1, Q_3)	20.00 (17.00 - 25.00)	20.50 (17.00 - 25.00)	Z = 23.396	0.962
Temperature (°C), M (Q_1, Q_3)	37 (37- 37)	37 (37 - 37)	Z = 23.289	0.988
SpO_2 (%), M (Q_1, Q_3)	97 (95 - 99)	97 (95 - 99)	Z = 23.369	0.980
BUN (mg/dL), M (Q_1, Q_3)	26 (15 - 43)	26 (15 - 43)	Z = 23.402	0.953
RDW (%), M (Q_1, Q_3)	15 (14 - 17)	15 (14 - 17)	Z = 23.189	0.930
Glucose (mg/dL), M (Q_1, Q_3)	125 (99 - 161)	125 (99 - 160.5)	Z = 23.367	0.984
GCS, M (Q_1, Q_3)	14 (12-15)	14 (12-15)	Z = 23.365	0.979

bpm: beats per minute; M: Median; Q_1:1st Quartile; Q_3: 3rd Quartile; Z: Mann-Whitney test; SpO_2: Saturation of peripheral oxygen; BUN: blood urea nitrogen; RDW: Red blood cell distribution width; GCS: Glasgow Coma Scale.

Supplementary Table 7. Patients' general characteristics in validation cohort.

Variable	Total (n = 1457)	Survival (n = 1275)	Non-survival (n = 182)	Statistic	*p*
Age (years), M (Q_1, Q_3)	67.00 (56.00 - 79.00)	66.00 (55.00 - 78.00)	75.00 (63.25 - 83.00)	Z = 27.474	< **0.001**
Gender, n (%)				χ^2 = 0.002	0.961
Male	755 (51.82)	661 (51.84)	94 (51.65)		
Female	702 (48.18)	614 (48.16)	88 (48.35)		
Race, n (%)				χ^2 = 3.688	0.158
White	1124 (77.14)	990 (77.65)	134 (73.63)		
Black	149 (10.23)	132 (10.35)	17 (9.34)		
Other	184 (12.63)	153 (12.00)	31 (17.03)		
Heart rate (bpm), M (Q_1, Q_3)	94.00 (81.00 - 110.00)	94.00 (81.00 - 109.00)	97.00 (82.00 - 113.00)	Z = 26.344	0.127
Systolic blood pressure (mmHg), M (Q_1, Q_3)	106.00 (92.00 - 127.00)	108.00 (93.00 - 127.50)	97.00 (82.00 - 113.00)	Z = 24.052	< **0.001**
Diastolic blood pressure (mmHg), M (Q_1, Q_3)	60.00 (50.00 - 72.00)	61.00 (51.00 - 72.00)	57.00 (46.25 - 66.00)	Z = 24.576	< **0.001**
Respiratory rate (insp/min), M (Q_1, Q_3)	20.00 (17.00 - 25.00)	20.00 (17.00 - 25.00)	21.00 (18.00 - 26.00)	Z = 26.350	0.122
Temperature (°C), M (Q_1, Q_3)	37.00 (37.00 - 37.00)	37.00 (37.00 - 37.00)	37.00 (36.00 - 37.00)	Z = 23.549	< **0.001**
Spo2 (%), M (Q_1, Q_3)	97.00 (95.00 - 99.00)	97.00 (95.00 - 99.00)	97.00 (93.00 - 99.00)	Z = 25.075	**0.019**
WBC (K/μL), M (Q_1, Q_3)	13.00 (8.00 - 19.00)	12.00 (8.00 - 18.00)	15.00 (10.00 - 21.00)	Z = 26.790	**0.004**
RDW (%), M (Q_1, Q_3)	15.00 (14.00 - 17.00)	15.00 (14.00 - 17.00)	17.00 (15.25 – 21.00)	Z = 28.697	< **0.001**
BUN (mg/dL), M (Q_1, Q_3)	26.00 (15.00 - 43.00)	25.00 (15.00 - 41.00)	41.00 (24.00 - 59.50)	Z = 28.291	< **0.001**
Glucose (mg/dL), M (Q_1, Q_3)	125.00 (99.00 - 161.00)	125.00 (100.00 - 159.00)	128.50 (91.25 - 173.75)	Z = 25.810	0.930
Potassium (mEq/L), M (Q_1, Q_3)	4.00 (4.00 – 5.00)	4.00 (4.00 – 5.00)	4.00 (4.00 - 5.00)	Z = 27.149	< **0.001**
Chloride (mEq/L), M (Q_1, Q_3)	105.00 (101.00 - 110.00)	105.00 (101.00 - 110.00)	106.00 (100.00 - 111.00)	Z = 26.182	0.300
Albumin (g/dL), M (Q_1, Q_3)	3.00 (2.00 - 3.00)	3.00 (2.00 - 3.00)	2.00 (2.00 - 3.00)	Z = 23.548	< **0.001**
Hemoglobin (g/dL), M (Q_1, Q_3)	10.00 (9.00 - 12.00)	10.00 (9.00 - 12.00)	10.00 (9.00 - 12.00)	Z = 25.680	0.627
Lymphocytes (10^9/L), M (Q_1, Q_3)	0.88 (0.52 - 1.40)	0.90 (0.54 - 1.43)	0.70 (0.38 - 1.21)	Z = 24.777	**0.001**
Platelets (10^9/L), M (Q_1, Q_3)	183.00 (124.00 - 251.00)	185.00 (129.50 - 253.00)	160.00 (85.50 - 239.00)	Z = 24.721	< **0.001**
Mechanical ventilation, n (%)				**χ^2 = 92.615**	< **0.001**
No	1058 (72.61)	980 (76.86)	78 (42.86)		
Yes	399 (27.39)	295 (23.14)	104 (57.14)		
Vasopressor use, n (%)				**χ^2 = 46.519**	< **0.001**
No	1085 (74.47)	987 (77.41)	98 (53.85)		
Yes	372 (25.53)	288 (22.59)	84 (46.15)		
AKI, n (%)				**χ^2 = 13.179**	< **0.001**
No	1157 (79.41)	1031 (80.86)	126 (69.23)		
Yes	300 (20.59)	244 (19.14)	56 (30.77)		
Septic shock, n (%)				**χ^2 = 34.625**	< **0.001**
No	983 (67.47)	895 (70.20)	88 (48.35)		
Yes	474 (32.53)	380 (29.80)	94 (51.65)		
LOS (days), M (Q_1, Q_3)	2.00 (1.00 - 3.00)	2.00 (1.00 - 3.00)	2.00 (1.00 - 3.00)	Z = 24.861	**0.002**
qSOFA, M (Q_1, Q_3)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	2.00 (1.00 - 2.00)	Z = 26.815	**0.002**
HALP, M (Q_1, Q_3)	12.68 (6.91 - 24.25)	12.94 (7.15 - 24.70)	9.96 (4.74 - 22.13)	Z = 24.866	**0.003**
m-HALP, M (Q_1, Q_3)	406.56 (181.44 - 812.74)	423.70 (193.83 - 854.73)	249.09 (107.08 - 547.88)	Z = 23.975	< **0.001**

bpm: beats per minute; M: median; Q_1: 1st quartile; Q_3: 3rd quartile; Z: Mann–Whitney U test; χ^2: chi-square test; SpO_2: saturation of peripheral oxygen; WBC: white blood cell; RDW: red blood cell distribution width; BUN: blood urea nitrogen; AKI: acute kidney injury; LOS: length of unit stay; qSOFA: quick Sequential Organ Failure Assessment; (m-)HALP, (modified) hemoglobin, albumin, lymphocyte, and platelet score.

Supplementary Table 8. Logistic regression of the relationship between m-HALP score and in-hospital mortality risk in validation cohort.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Age	1.03 (1.02–1.04)	< 0.001	1.03 (1.01–1.04)	< 0.001
Sex				
Male	Ref			
Female	1.01 (0.74-1.38)	0.961		
Race				
White	Ref			
Black	0.95 (0.54-1.59)	.0856		
Other	1.50 (0.96-2.27)	0.064		
Heart rate	1.01 (1.00-1.01)	0.072		
Systolic blood pressure	0.98 (0.97-0.99)	< 0.001	0.98 (0.97-0.99)	< 0.001
Diastolic blood pressure	0.98 (0.98-0.99)	0.001		
Respiratory rate	1.01 (0.99-1.03)	0.101		
Temperature	0.56 (0.48-0.65)	< 0.001	0.67 (0.57-0.80)	< 0.001
Spo2	0.93 (0.90-0.96)	< 0.001	0.94 (0.91-0.97)	< 0.001
WBC	1.02 (1.01-1.03)	0.003	1.01 (1.00-1.02)	0.110
RDW	1.26 (1.20-1.33)	< 0.001	1.26 (1.18-1.34)	< 0.001
BUN	1.02 (1.01-1.02)	< 0.001	1.01 (1.00-1.01)	0.058
Glucose	1.00 (1.00-1.00)	0.417		
Potassium	1.56 (1.30-1.86)	< 0.001		
Chloride	1.01 (0.99-1.04)	0.180		
Mechanical ventilation				
No	Ref			
Yes	4.43 (3.22-6.12)	< 0.001	4.93 (3.39-7.23)	< 0.001
Vasopressors				
No	Ref			
Yes	2.94 (2.13-4.04)	< 0.001	1.67 (1.13-2.47)	0.001
AKI				
No	Ref			
Yes	1.88 (1.32-2.64)	< 0.001		
Septic shock				
No	Ref			
Yes	2.52 (1.84-3.45)	< 0.001	1.58 (1.08-2.32)	0.019
m-HALP				
< 772.9	Ref			
≥ 772.9	0.53 (0.35-0.78)	0.002	0.49 (0.30-0.78)	0.004
qSOFA	1.31 (1.10-1.57)	0.002	0.74 (0.58-0.94)	0.013

OR: Odds ratio; CI: confidence interval; SpO_2: saturation of peripheral oxygen; WBC: white blood cell; RDW: red blood cell distribution width; BUN: blood urea nitrogen; AKI: acute kidney injury; m-HALP: modified hemoglobin: albumin: lymphocyte: and platelet score; qSOFA: quick Sequential Organ Failure Assessment.