The Hemoglobin, Albumin, Lymphocytes and Platelets (HALP) Predicts Long-term Survival in Posterior Circulation Ischemic Stroke

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Abstract

The survival of posterior circulation ischemic stroke (PCIS) patients is worse. The hemoglobin, albumin, lymphocyte, and platelet (HALP) score is a novel combined index reflecting nutritional and inflammation status. We aimed to evaluate the impact of the HALP score on the prognosis of PCIS. The Kaplan-Meier method with log-rank test was used to draw the survival curves. Cox proportional hazard regression model were performed to determine the independent prognostic factors. The predictive power was evaluated by assessing the area under the receiver operating characteristic (ROC) curve. A total of 238 PCIS patients were retrospectively enrolled, and the median follow-up time was 4.3 years. Based on the Kaplan–Meier curve analysis, it was noticed that a low HALP value was significantly associated with a worse overall survival ($P < 0.001$). Multivariate Cox analysis showed that age, National Institutes of Health Stroke Scale (NIHSS), and HALP score were independent risk factors for overall survival (HR 1.059, 1.26 and 0.354). Furthermore, the combination of the HALP and NIHSS score improved the prediction performance (AUC 0.888) and appeared to has the ability to accurately identify high-risk patients with poor prognosis.

Introduction

Posterior circulation ischemic stroke (PCIS) accounts for 20–25% of all acute ischemic strokes and its prognosis is worse, with higher disability and higher mortality [1]. However, in comparison with patients with anterior circulation ischemic stroke, patients with PCIS have not been studied extensively. Exploring new predictors of long-term prognosis may help in early identification of high-risk patients with poor outcome and contribute to more effective prevention.

Nutritional status such as anemia and hypoalbuminemia are related to functional outcomes of stroke [2,3]. Immune-inflammation index such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) are also associated with the prognosis [4]. Recent studies have identified a new index called HALP, comprised of hemoglobin, albumin, lymphocytes, and platelets, which has proven to be a good prognostic indicator [5–7]. Anemia is common and independently predicts mortality of acute ischemic stroke [8,9]. Serum albumin is a multifunctional protein that plays neuroprotective roles in ischemic stroke [10]. Hypoalbuminemia is associated significantly with poor outcome [11,12]. As systemic inflammatory markers, white blood cells and their subtypes such as lymphocytes, are known to mediate the response during cerebrovascular diseases. Studies have shown that lower lymphocyte counts were associated with a poor functional outcome [13,14]. Platelet hyperactivity increases the risk of thromboembolism and atherosclerotic lesions [15]. The HALP score is a combination of nutritional status and inflammatory responses. Thus, we sought to assess the association between HALP and the long-term survival of PCIS patients.

Results

Baseline characteristics

A total of 238 PCIS patients were enrolled in the current study. The median age was 64.3 ± 11.6 years and 171 (71.8%) patients were male. The median NIHSS score and pc-ASPECTS were 3 (2–6) and 8 (8–9). The median PLR, NLR, and HALP were 123.4 (102.1–162), 2.5 (1.8–3.3), and 43.1 (31.2–54.9). The median follow-up time was 4.3 (3.7–4.5) years and 44 (18.5%) patients died during this period. 115 (48.3%) patients with basilar artery (BA) stenosis, 54 (22.7%) with posterior cerebral artery (PCA) stenosis, 37 (15.5%) with vertebral artery (VA) stenosis, and 43 (13.4%) with multiple vascular stenosis (Table 1).

Table 1
Baseline clinical data.

Variables	
Characteristics	
Age	64.3 ± 11.6
Male	171 (71.8%)
NIHSS	3 (2–6)
pc-ASPECTS	8 (8–9)
PLR	123.4 (102.1–162)
NLR	2.5 (1.8–3.3)
HALP	43.1 (31.2–54.9)
Recurrence of stroke	70 (29.4%)
Follow-up time, year	4.3 (3.7–4.5)
Mortality	44 (18.5%)
Risk factors, n (%)	
Hypertension	173 (72.7%)
Diabetes mellitus	101 (42.4%)
Coronary heart disease	36 (15.1%)
Atrial fibrillation	15 (6.3%)
Smoking	139 (58.4%)
Alcohol-drinking	80 (33.6%)
Peripheral artery disease	20 (8.4%)
Pathogenesis, n (%)	
Large vessel atherosclerosis	142 (59.7%)
Cardioembolic	37 (15.5%)
Small artery disease	31 (13%)
Other	13 (5.5%)
Undetermined	15 (6.3%)
Location of Vascular stenosis, n (%)	

Variables	
VA	37 (15.5%)
BA	115 (48.3%)
PCA	54 (22.7%)
Multiple vascular stenosis	43 (13.4%)

Data were presented as mean ± standard deviation, median (interquartile range), or n (%). NIHSS, the National Institute of Health Scale Score; pc-ASPECTS, posterior circulation Alberta Stroke Program Early Computed Tomography Score; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; HALP, hemoglobin, albumin, lymphocyte, and platelet score VA, vertebral artery; BA, basilar artery; PCA, posterior cerebral artery.

Association of HALP score with clinical characteristics

We performed ROC analysis and found that the area under the curve (AUC) of HALP score was 0.76, indicating that it was significant for predicting 5-year overall survival ($p < 0.001$, Fig. 1a). The optimal cutoff value was 42.89. Subsequently, PCIS patients were divided into low-HALP (n = 118, 49.6%) and high-HALP (n = 120, 50.4%) groups (Table 2). Patients with low levels of HALP tended to have a higher NIHSS, a lower pc-ASPECES and a higher recurrence rate (all $p < 0.05$). A low level of HALP was more likely to be present in higher age and in female patients (all $p < 0.001$). Low levels of HALP were significantly associated with high NLR and PLR levels (all $p < 0.001$).

Table 2
Association of HALP score with baseline characteristics.

Variables	Low HALP (n = 118)	High HALP (n = 120)	*p* value
Characteristics			
Age	67.1 ± 11.3	61.6 ± 11.4	0.000
Male	72 (61%)	99 (82.5%)	0.000
NIHSS	4 (2–7)	3 (1–4)	0.001
pc-ASPECTS	8 (8–9)	9 (8–9)	0.008
PLR	161.6 (137.7-200.2)	102.9 (87.4–117)	0.000
NLR	3 (2.2–4.4)	2.1 (1.7–2.7)	0.000
Recurrence of stroke	42 (35.6%)	28 (23.3%)	0.038
Risk factors			
Hypertension	94 (79.7%)	79 (65.8%)	0.017
Diabetes mellitus	57 (48.3%)	44 (36.7%)	0.069
Coronary heart disease	20 (16.9%)	16 (13.3%)	0.436
Atrial fibrillation	4 (3.4%)	11 (9.2%)	0.067
Smoking	59 (50%)	80 (66.7%)	0.009
Alcohol-drinking	32 (27.1%)	48 (40%)	0.035
Peripheral artery disease	11 (9.3%)	9 (7.5%)	0.612
Pathogenesis			0.246
Large vessel atherosclerosis	72 (61%)	70 (58.3%)	
Cardioembolic	20 (16.9%)	17 (14.2%)	
Small artery disease	12 (10.2%)	19 (15.8%)	
Other	9 (7.6%)	4 (3.3%)	
Undetermined	5 (4.2)	10 (8.3%)	
Location of Vascular stenosis			0.077
VA	19 (16.1%)	18 (15%)	
BA	65 (55.1%)	50 (41.7%)	
PCA	19 (16.1%)	35 (29.2%)	

Variables	Low HALP (n = 118)	High HALP (n = 120)	*p* value
Multiple vascular stenosis	15 (12.7%)	17 (14.2%)	

HALP, hemoglobin, albumin, lymphocyte, and platelet score; NIHSS, the National Institute of Health Scale Score; pc-ASPECTS, posterior circulation Alberta Stroke Program Early Computed Tomography Score; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; VA, vertebral artery; BA, basilar artery; PCA, posterior cerebral artery.

Association of HALP score with overall survival

we performed univariate Cox proportional hazard regression model and observed a significant association with age at diagnosis, NIHSS, pc-ASPECTS, PLR, NLR, and HALP score (all $p < 0.01$). Other factors included male, recurrence of stroke, history of alcohol drinking, and the location of vascular stenosis (all $p < 0.05$). Furthermore, multivariate analysis indicated Low HALP score (HR 0.354, 95%CI 0.146–0.86, $p = 0.022$) as an independent predictor of PCIS, along with age and NIHSS (HR 1.059, 95%CI 1.021–1.099, $p = 0.002$ and HR 1.26, 95%CI 1.148–1.383, $p < 0.001$) (Table 3). Kaplan-Meier analysis also showed that low HALP score predicted a worse overall survival ($p < 0.001$, Fig. 1b).

Table 3
Univariate and multivariate analyses for patients' overall survival with PCIS.

Variables	Univariate analysis[a]		Multivariate analysis[b]	
	HR (95% CI)	p value	HR (95% CI)	p value
Characteristics				
Age	1.103 (1.067–1.139)	0.000	1.059 (1.021–1.099)	0.002
Male	0.518 (0.284–0.944)	0.032		
NIHSS	1.297 (1.222–1.377)	0.000	1.26 (1.148–1.383)	0.000
pc-ASPECTS	0.603 (0.463–0.784)	0.000		
PLR	1.005 (1.003–1.008)	0.000		
NLR	1.223 (1.135–1.319)	0.000		
HALP (≤ 42.89 VS > 42.89)	0.161 (0.072–0.361)	0.000	0.354 (0.146–0.86)	0.022
Recurrence of stroke	1.983 (1.092–3.602)	0.025		
Risk factors				
Hypertension	1.786 (0.83–3.843)	0.138		
Diabetes mellitus	1.42 (0.787–2.565)	0.244		
Coronary heart disease	1.114 (0.497–2.499)	0.793		
Atrial fibrillation	0.689 (0.167–2.845)	0.606		
Smoking	0.769 (0.426–1.39)	0.385		
Alcohol-drinking	1.105 (1.023–1.174)	0.009		
Peripheral artery disease	1.121 (0.401–3.133)	0.828		
Pathogenesis		0.293		
Large vessel atherosclerosis	1			
Cardioembolic	1.767 (0.841–3.714)			
Small artery disease	0.768 (0.266–2.222)			
Other	2.389 (0.826–6.908)			
Undetermined	1.264 (0.379–4.21)			
Location of Vascular stenosis		0.012		
VA	1			

Variables	Univariate analysis[a]		Multivariate analysis[b]	
	HR (95% CI)	p value	HR (95% CI)	p value
BA	2.546 (0.895–7.244)			
PCA	0.333 (0.061–1.818)			
Multiple vascular stenosis	2.909 (0.896–9.446)			

HR, hazard ratio; CI, confidence interval; NIHSS, the National Institute of Health Scale Score; pc-ASPECTS, posterior circulation Alberta Stroke Program Early Computed Tomography Score; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; HALP, hemoglobin, albumin, lymphocyte, and platelet score; VA, vertebral artery; BA, basilar artery; PCA, posterior cerebral artery. a. All univariate analysis as a time-dependent variable in the model. b. Variables control in multivariable analysis including age, sex, NIHSS, pc-ASPECTS, PLR, NLR, HALP, recurrence of stroke, alcohol-drinking, and the location of vascular stenosis.

Creation of the HALPN value as a new prognostic model index

According to the multivariate Cox regression analysis, NIHSS was identified as an important predictor, in addition to the HALP score. The AUC of NIHSS was 0.825, and the optimal cutoff value was 4.5 (Fig. 2a, $p < 0.001$). Kaplan-Meier analysis showed that the high NIHSS score was associated with increased mortality ((Fig. 2b, $p < 0.001$). Thus, we combined NIHSS and the HALP score to construct a new index, HALPN. The HALPN score is defined as follows: HALPN = 0 (HALP > 42.89 and NIHSS < 5), HALPN = 1 (HALP ≤ 42.89 or NIHSS ≥ 5), HALPN = 2 (HALP ≤ 42.89 and NIHSS ≥ 5).

Kaplan-Meier analysis showed that a higher HALPN score predicted poor overall survival (Fig. 3a, $p < 0.001$) in PCIS patients. As age at diagnosis was an independent factor for overall survival, we performed further stratification analysis for the PCIS patients according to age. It showed that patients with a higher HALPN score had a worse overall survival with age ≤ 60 and age > 60 (Fig. 3b and 3c, all $p < 0.01$)

Prediction power of the combination of HALP and NIHSS

The efficacy of the combination of HALP and NIHSS score was assessed by the AUC of ROC curve. (Table 4). The AUC of the combination was 0.888 (95% CI 0.84–0.937). The prediction power of the HALPN score was significantly better than either score [HALP (AUC = 0.76, 95%CI 0.686–0.834, $p < 0.001$) or NIHSS (AUC = 0.825, 95% CI 0.751-0.9, $p < 0.001$), respectively] (Fig. 4). Moreover, the HALPN score have higher prediction accuracy than other related indices such as pc-ASPECT, PLR, NLR and Age.

Table 4
AUC analysis of various indices in PCIS patients.

	AUC	95% CI	*p* value
HALPN	0.888	0.84–0.937	0.000
HALP	0.76	0.686–0.834	0.000
NIHSS	0.825	0.751-0.9	0.000
pc-ASPECT	0.623	0.523–0.722	0.011
PLR	0.691	0.606–0.775	0.000
NLR	0.724	0.645–0.802	0.000
Age	0.785	0.707–0.864	0.000

AUC, area under receiver operating characteristic curve; CI, confidence interval; HALPN, combination of the HALP score and the NIHSS score; HALP, hemoglobin, albumin, lymphocyte, and platelet score; NIHSS, the National Institute of Health Scale Score; pc-ASPECTS, posterior circulation Alberta Stroke Program Early Computed Tomography Score; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

Discussion

This study assessed the value of the novel index HALP for predicting the long-term survival of PCIS patients. It was observed that a low level of HALP score at admission was significantly associated with a poor survival rate. Moreover, the combination of HALP and NIHSS score enabled us to create a new index, HALPN, which was observed to be an independent risk factor. HALP combined with NIHSS offered a powerful prediction effect for long-term overall survival of PCIS patients.

Increased HALP score has previously been correlated with a decreased risk of recurrent stroke and death within 90 days and 1 year in patients with acute ischemic stroke [16]. Consistent with previous findings, this study showed that HALP score was an independent factor for long-term overall survival and represented a clinically valuable prognostic tool for PCIS patients. The HALP score is a new index combined with hemoglobin, albumin, lymphocyte, and platelet. The relationship between low hemoglobin concentration and poor outcomes in patients with ischemic stroke has been well established [9,17]. Studies have shown that low hemoglobin level is a predictor of 1-year mortality for stroke patients [18]. Similarly, Barlas et. al. identified that patients with anemia have increased mortality with stroke [19]. Moreover, a prospective study demonstrated that lower hemoglobin range was related to poor outcome, regardless of when and how hemoglobin concentrations were measured [20]. Serum albumin is an indicator of the nutritional status. Recent studies have shown that decreased serum albumin levels were independently associated with poor prognosis in ischemic stroke [21,22]. The role of albumin as a neuroprotectant has been assessed in the ALIAS (albumin in acute stroke) trial. However, the Phase III clinical trial confirmed that high-dose albumin treatment was not associated with improved outcome at 90 days in acute

ischemic stroke patients [23]. Immune cells contribute to acute ischemic injury and is associated with outcomes [24]. NLR is significantly higher at admission in patients with poor 3-month outcome [25]. However, we did not observe an association between NLR, PLR and long-term mortality risk. Further studies are needed to clarify this issue.

NIHSS score was also identified as a predictor for long-term overall survival in this study. The association is easy to understand because NIHSS is the most commonly used scale to evaluate the neurologic deficit in stroke patients. Numerous studies have also confirmed the predictive effect of NIHSS on prognosis of PCIS and basilar artery occlusion patients [26–29]. In the present study, besides the NIHSS score, we also examined the predictive value of pc-ASPECTS, which has been widely studied in PCIS patients. The BASILAR study revealed that pc-ASPECTS was important for predicting mortality within 90 days in patients with acute basilar artery occlusion [30]. pc-ASPECTS ≤ 6 was independently associated with poor outcome in patients with symptomatic basilar artery stenosis [31]. However, by multivariate analysis, this study identified that it had no statistically significant association with long-term survival of PCIS patients. Accordingly, another study also failed to detect a significant association after adjusting for related confounders [8]. These discrepancies may be due to the differences in patient characteristics, treatment options among these studies.

By combining NIHSS with the HALP score, we created a new index, HALPN. The HALPN was further stratified and was found that a higher HALPN score was significantly associated with poor overall survival. The prediction power of the combination of these two factors had a better fit than both HALP and NIHSS used alone. To the best of our knowledge, this study is the first to investigate the value of HALP and NIHSS score combination. The combined scoring process is concise and would be critical in areas where resources are limited.

In conclusion, The HALP score are associated with NIHSS, pc-ASPECES, recurrence rate, age at diagnose, and NLR and PLR levels. Age, NIHSS score, and the HALP score were significantly associated with the long-term overall survival of PCIS patients. The combination of the HALP and NIHSS score, appeared to has the ability to accurately identify high-risk patients with poor prognosis.

Methods

Patients

We conducted a retrospective study with consecutive patients who diagnosed PCIS from January 1, 2016 to May 1, 2017 in the Stroke Center, Beijing Youyi Hospital Capital Medical University. PCIS was defined as a symptomatic infarct in the territory of the vertebral, basilar, or posterior cerebral artery, which was confirmed by magnetic resonance imaging. Inclusion criteria were as follows: 1) Age ≥ 18, 2) Clinical diagnosis of PCIS, 3) CT angiography (CTA) or Digital subtraction angiography (DSA) was performed to identify the location of the stenosis artery. Exclusion criteria were as follows: 1) Chronic/acute

inflammatory disease, 2) Neoplastic hematologic disorders or using immunosuppressant drugs, 3) Lack of HALP parameters; 4) Lost to follow-up.

Clinical and imaging characteristics

Patient clinical characteristics included: age, gender, smoking, alcohol-drinking, history of hypertension, history of diabetes, history of coronary heart disease, history of atrial fibrillation, history of peripheral artery disease, National Institutes of Health Stroke Scale (NIHSS) score at admission, pathogenesis, blood cell counts, and serum albumin levels.

Imaging characteristics included: location of the affected artery, posterior circulation Alberta Stroke Program Early Computed Tomography Score (pc-ASPECTS) on diffusion-weighted imaging (DWI). All the neuroimaging data were analyzed independently by two experienced neuro-radiologists not knowing the clinical information. For cases with disagreement, the final evaluation outcome was reached by consensus.

Calculation of HALP score

The HALP score was calculated according to the following formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes count (/L) / platelets count (/L). All of these blood parameters were obtained within 24 h of admission.

Follow-up

The overall survival time was the interval from the time of diagnosis to death or the last follow-up. Patients were followed up during face-to-face interviews or via telephone calls by trained research doctors unaware of the study group assignments. Patients were followed up at 3 months for the first time. Then, follow-up was conducted once a year. The last follow-up was performed in January 2021.

Statistical Analysis

Baseline characteristics were reported. Normally distributed continuous variables were presented by mean and standard deviation, while non-normally distributed continuous variables were presented by median and interquartile range. Categorical variables were presented by number and percentage. The cut-off value and prediction efficiency were calculated by the receiver operating characteristic (ROC) curve analysis. The association between the clinical features and the HALP score were analyzed using the Student *t* test for continuous variables if variables fulfilled normal distribution, the Mann–Whitney *U* test if variables violated normal distribution, and Chi-squared test for categorical variables. A univariate Cox proportional hazard regression model was used to evaluate the prognostic value of each variable for overall survival. Factors determined to be significant according to the univariate analyses were subsequently included in the multivariate Cox proportional hazard regression model. The Kaplan-Meier method with log-rank test was used to draw the survival curves for the variables tested. A two-sided *p* value of 0.05 or less was considered statistically significant. Statistical analysis was performed using

SPSS version 25 (IBM, Armonk, NY, United States) and GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, United States).

Declarations

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Author contributions

FJ Li and YB Zhang wrote the main manuscript text. D Xie, YF Han, BB Liu collected data. FJ Li, ZZ Wei, FF Zhao, YM Luo analyzed the data. All authors reviewed the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Data availability

Datasets are partly available from the corresponding author upon reasonable request after the completion of primary analyses and results dissemination.

Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki. It was approved by Ethics Committee of Beijing Friendship Hospital, Capital Medical University (2018-P2-095-02), and informed consent was taken from all individual participants.

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Figures

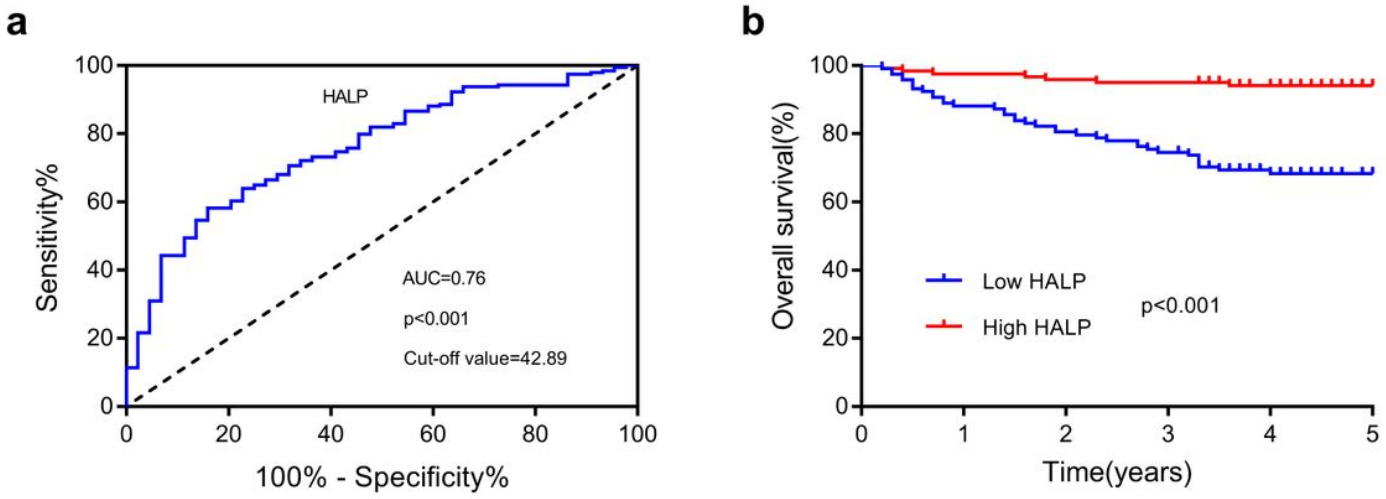

Figure 1

Receiver operating characteristic and Kaplan-Meier curves of HALP for 5-year overall survival. a. ROC curve of HALP; b. Kaplan-Meier curves of HALP. HALP, hemoglobin, albumin, lymphocytes and platelets; AUC, Area under the curve.

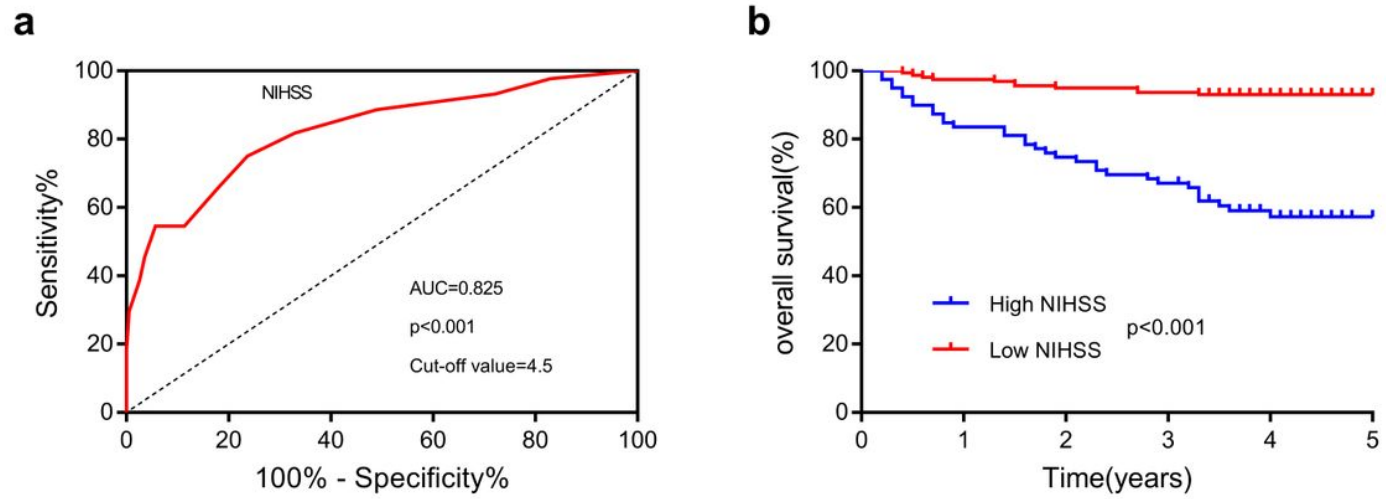

Figure 2

Receiver operating characteristic and Kaplan-Meier curves of NIHSS for 5-year overall survival. a. ROC curve of NIHSS; b. Kaplan-Meier curves of NIHSS. National Institutes of Health Stroke Scale; AUC, Area under the curve.

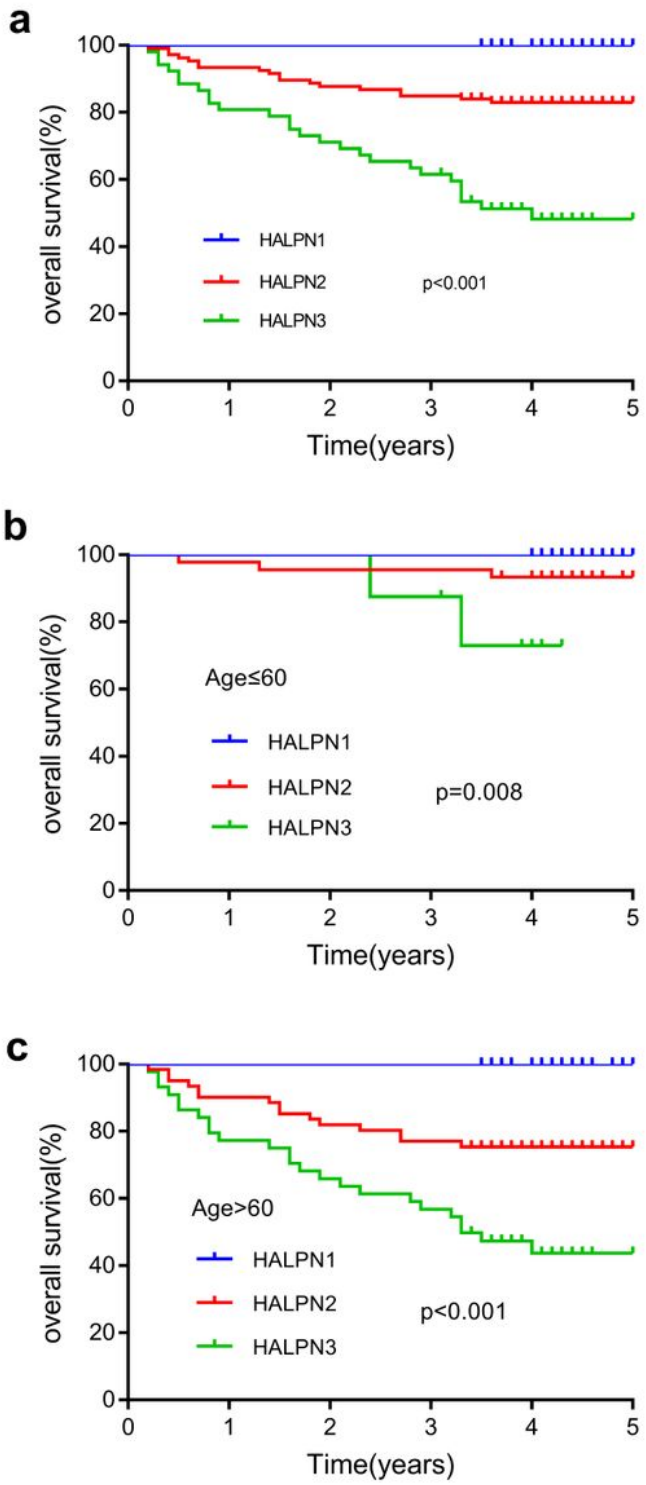

Figure 3

Kaplan-Meier curves of HALPN and its subgroups. a. Kaplan-Meier curves of HALPN. b. Kaplan-Meier curves of HALPN in the group with age≤60; c. Kaplan-Meier curves of HALPN in the group with age>60. HALPN, Combination of the hemoglobin, albumin, lymphocytes and platelets score and the National Institutes of Health Stroke Scale score.

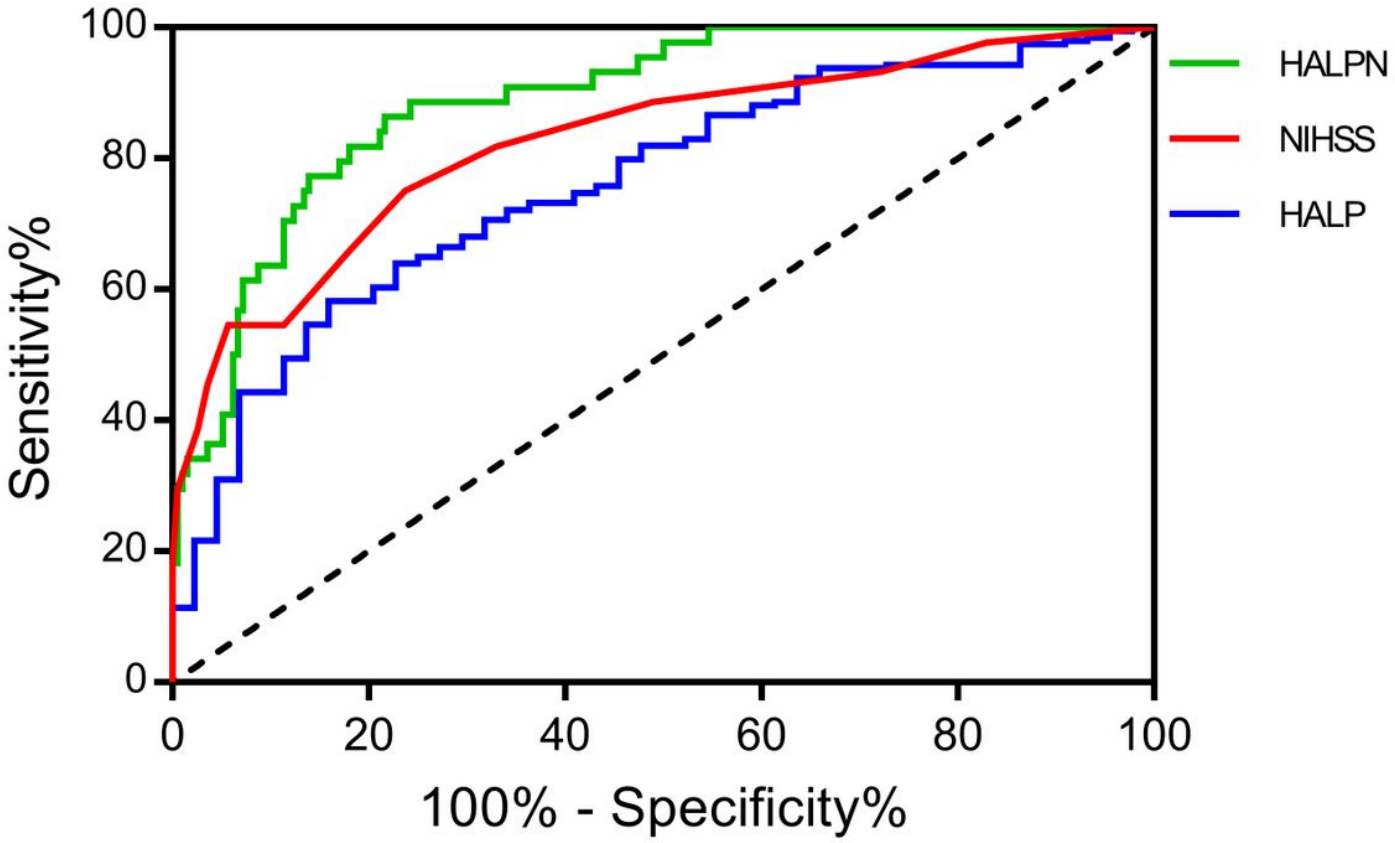

Figure 4

Comparison of predictive power among the HALPN, NIHSS, and HALP. HALP, hemoglobin, albumin, lymphocytes and platelets; NIHSS, National Institutes of Health Stroke Scale; HALPN, Combination of the HALP and NIHSS score.