Effect of prealbumin level on mortality in heatstroke patients

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Abstract. This study investigated whether serum prealbumin level is associated with mortality in heatstroke patients. A retrospective study of 102 heatstroke patients admitted to the ICU in the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University from June 2010 to November 2017 was performed they were divided into normal serum prealbumin group (n=79) and low prealbumin group (n=23) according to the difference in PA expression. The clinical data, laboratory inspection data, invasive positive pressure ventilation (IPPV), co-infection, shock and length of ICU stay during the ICU were compared between the two groups of patients. The study endpoints, deaths at admission, were recorded, and the survival curve plotted. Cox regression analysis was performed based on the clinical data of patients, and ROC curve plotted based on Cox multivariate independent prognostic indicators. There were significant differences in clinical variables PLT, ALT, AST, TBIL, ALB, TCH, LDH, TNI, BNP, creatinine, PT, APTT, FBG and D-dimer (P<0.05). The incidence of infection, shock and IPPV was significantly lower in normal serum prealbumin group of patients than those in low prealbumin group (P<0.05). There was a statistically significant difference in short-term survival rate between the groups of patients (χ^2=29.101, P<0.001). Prognostic factors for heatstroke patients were IPPV, heart rate, WBC count, PLT count, ALB, PA, TBIL, LDH, CPK, Cr, PCT, PT, APTT, D-dimer, co-infection and shock at admission. Independent prognostic-related factors for heatstroke patients were IPPV, PA level, PLT level, ALB level, CPK level and PT level. When prealbumin <17.95 mg/dl was used as the death threshold for predicting at 28 days, the sensitivity was 77.8%, and the specificity was 85.7%. Significantly associated with the prognosis of heatstroke patients, prealbumin level can be used as an important predictive indicator of the disease progression and worse clinical outcomes.

Introduction

Heat stroke has a high incidence and fatality rate (1), which will continue to increase with global warming (2). Results of epidemiological survey show that the average fatality rate of heat stroke is between 10 and 15%. Once developing into severe heat stroke, it is easy to be complicated by multiple organ dysfunction syndrome (MODS), with a fatality rate >40%. Of the survivors, over 30% of patients suffer from long-term nervous system diseases (2,3). The cluster treatment strategy of 'early rapid cooling, early rapid expansion, early anticoagulation, and active support of organ function' can effectively prevent multiple organ dysfunctions and shorten the length of ICU stay, so as to improve prognosis (4). Heatstroke is further divided into typical heatstroke and exertional heatstroke according to whether there are fatigue factors in thermal exposure process (5). Due to its high fatality rate, possibly determining relevant factors for the prognosis of patients reduce the long-term effects on their outcomes.

Prealbumin (PA), synthesized by the liver, the level of which is related to protein metabolism, can sensitively reflect the body's nutrition and liver synthesis function, associated with the inflammatory response in the body (6). Widely used in clinical practice, it has been confirmed to predict the mortality and re-hospitalization rate in patients with acute heart failure (7), mortality in patients with acute kidney injury (8,9), mortality in patients with peritoneal dialysis (10) and mortality in burn patients (11). It can also predict infectious complications after gastric operation (12) and the prognosis of patients in the medical department ICU (13).

At present, the determination of prognostic risk factors for heatstroke patients worldwide, mainly based on the analysis of the relationship between multiple univariates and outcomes in clinical data, ignores the interactive relationship among multiple univariates. In addition, whether prealbumin can predict the prognosis of heatstroke has not been studied. Therefore, in this study, a multivariate analysis of the relationship between clinical parameters and disease outcomes of heatstroke patient at admission in the past 10 years was performed, to determine whether the serum prealbumin level was associated with short-term (28 days) mortality, so as to provide a theoretical basis for guiding their rational treatment and improving the prognosis.

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Patients and methods

Subjects. A retrospective study of 118 heatstroke patients admitted to the ICU in the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University (Changzhou, China), from June 2010 to November 2017, was performed. Except for 1 case of age <18 years, 2 cases of chronic hepatic insufficiency, 2 cases of chronic renal insufficiency and 11 cases with incomplete data caused by dying or discharging within 24 h of admission, 102 patients were eventually included. Among them, 61 male patients and 41 female patients, aged from 20 to 89 years, were divided into normal serum prealbumin group (n=79) and low prealbumin group (n=23) according to the difference in PA expression. In normal serum prealbumin group, there were 50 male patients and 29 female patients, aged from 20 to 73 years, and in low prealbumin group, 11 male patients and 12 female patients, aged from 25 to 89 years. All patients were diagnosed in accordance with China's Diagnostic Standards and Treatment Principles of Occupational Heatstroke (GB11508-89). Exclusion criteria were: Patients aged <18 years, knowing liver and kidney dysfunction and with incomplete data caused by death or discharging within 24 h of admission, were excluded.

This study was approved by the Ethics Committee of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University. Patients and their family members were informed and consented to all treatments and examinations.

Grouping scheme. A COBAS8000 analyzer (Roche Diagnostics, Indianapolis, IN, USA) was used to determine serum prealbumin content by immunoturbidimetry. Patients were divided into normal serum prealbumin group (>15 mg/dl) and low prealbumin group (≤15 mg/dl) according to serum prealbumin level.

Observation indicators. Main observation indicators: i) General clinical data and vital signs on admission, including age, sex, body mass index (BMI), systolic blood pressure, heart rate and respiratory rate; ii) major underlying diseases such as hypertension, diabetes mellitus, chronic obstructive pulmonary disease, stroke and tumor and iii) laboratory inspection data, including white blood cell (WBC) count, hemoglobin, platelet (PLT) count, blood sodium, blood potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), total cholesterol (TCH), lactic dehydrogenase (LDH), phosphocreatine kinase (CPK), forebrain natriuretic peptide (BNP), troponin I (TNI), serum creatinine (Cr), albumin (ALB), prealbumin (PA), C-reactive protein (CRP), procalcitonin (PCT), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FBG) and D-dimer. Blood samples from all patients were obtained within 24 h of admission, used for the determination of the above indicators.

Secondary observation indicators: i) Invasive positive pressure ventilation (IPPV), co-infection, shock, length of ICU stay and outcome during the ICU were compared between two groups of patients; ii) the study endpoints, deaths at admission, were recorded, and the survival curve plotted; iii) Cox regression analysis was performed based on the clinical data of patients and iv) ROC curve was plotted based on Cox multivariate independent prognostic indicators.

Statistical analysis. SPSS 20.0 (IBM Corp., Armonk, NY, USA) software was used for data processing, Shapiro-Wilk for the normality test. The measurement data in accordance with the normal distribution were expressed as mean ± standard deviation (SD), and t-test was used for the comparison between two groups. That not in accordance with the normal distribution were expressed as median (quartile) [M (QL-QU)], and Mann-Whitney U test was used for the comparison between two groups. The χ^2 test was used for comparison among count data, Kaplan-Meier survival curves for the analysis of survival rates of two groups and Mantel-Cox was the log-rank test. Univariate Cox regression analysis was performed to determine the association between each potential variable and the mortality in patients, and multivariate Cox regression analysis to identify independent variables predicting the mortality in patients. The receiver operating characteristic (ROC) curve was plotted for statistically significant indicators of multivariate regression analysis. The area under the ROC curve (AUC) was calculated to assess the ability of indicators to predict the mortality. P<0.05 was considered to indicate a statistically significant difference.

Results

Comparison of clinical data of patients. The clinical data of the groups were compared, and it was found that there was no statistically significant difference between them in age, sex, BMI, heart rate, respiratory rate, history of hypertension, history of diabetes mellitus, COPD, history of stroke, history of tumor and number of typical heat stroke (P>0.05), and in NA, K, hemoglobin, WBC CPK, PCT and CRP (P>0.05), but there were significant differences in clinical variables PLT, ALT, AST, TBIL, ALB, TCH, LDH, TNI, BNP, creatinine, PT, APTT, FBG and D-dimer (P<0.05) (Table I).

Comparison of adverse conditions in the course of treatment, length of stay in the hospital, IPPV times and length of ICU stay between two groups of patients. The adverse conditions, length of stay in the hospital and IPPV times in two groups of patients were counted. It was found that the incidence of infection, shock and IPPV was significantly lower in normal serum prealbumin group of patients than those in low prealbumin group, with a statistically significant difference (P<0.05). There was no statistically significant difference between two groups of patients in the length of stay in the hospital and length of ICU stay (P>0.05) (Table II).

Length of survival of patients at admission. The length of survival of two groups of patients at admission was calculated. It was found that altogether 8 patients died in normal serum prealbumin group of 79 patients, with the length of survival of 26.177±0.649 days, and 13 patients died in low prealbumin group of 23 patients, with the length of survival of 16.130±2.559 days. By comparison, it was found that there was a statistically significant difference in short-term survival rate between the groups of patients (χ^2=29.101, P<0.001) (Fig. 1).

Cox regression analysis. A univariate Cox regression analysis of the collected data was performed. It was found that prognostic factors for heatstroke patients were IPPV, heart rate,

Table I. Characteristics of study cohort.

Characteristics	All (n=102)	Normal serum prealbumin group (n=79)	Low prealbumin group (n=23)	P-value
PA (mg/dl), median (IQR)	19.56±6.21	22.05±4.51	10.99±2.38	-
Age (years), median (IQR)	66 (50-77.25)	66 (52.50-77.50)	73 (49-77)	0.916
Male, n (%)	61 (59.80)	50 (63.29)	11 (47.83)	0.229
BMI (kg/m^2), median (IQR)	24.55 (20.58-26.93)	24.60 (20.60-26.80)	22.80 (20.50-26.35)	0.819
SBP (mmHg)	120.39±22.93	123.86±21.67	108.47±23.60	0.004
Heart rate (bpm), median (IQR)	102.5 (80-124.5)	96 (79-117.5)	113 (94.5-138)	0.017
Respiratory rate (bpm), median (IQR)	21 (18-27.25)	21 (18-26.50)	24 (18.50-28.50)	0.572
Previous disease				
Hypertension, n (%)	29 (28.43)	26 (32.91)	3 (13.04)	0.071
Diabetes mellitus, n (%)	11 (10.78)	9 (11.39)	2 (8.69)	0.714
COPD, n (%)	5 (4.90)	3 (3.79)	2 (8.69)	0.315
Stroke, n (%)	8 (7.84)	7 (8.86)	1 (4.35)	0.679
Tumor, n (%)	4 (3.92)	2 (2.53)	2 (8.69)	0.218
NA (mmol/l), median (IQR)	137.20 (131.35-140.15)	137.70 (131.00-140.20)	136.90 (132.40-138.80)	0.788
K (mmol/l)	3.56±0.67	3.60±0.62	3.41±0.78	0.267
Hemoglobin (g/l)	124.22±17.72	124.97±16.21	121.60±22.34	0.425
WBC (10^9/l), median (IQR)	12.84 (9.96-15.99)	12.17 (9.02-15.26)	13.88 (12.10-18.19)	0.070
PLT (10^9/l), median (IQR)	121.10 (80-172.25)	132 (92-179.20)	87 (51-117.50)	0.006
ALT (U/l), median (IQR)	100.50 (51.18-152.95)	95 (50-139.50)	127 (95.90-267)	0.016
AST (U/l), median (IQR)	140.55 (90.13-213.63)	118 (83.30-180.70)	185.30 (141.50-430)	<0.001
TBIL (umol/l), median (IQR)	17 (10.35-24.10)	15.60 (10-20.90)	22.60 (17.60-27.55)	0.004
ALB (g/l)	34.08±4.81	35.22±4.43	30.15±3.96	<0.001
TCH (mmol/l), median (IQR)	3.45 (2.79-4.11)	3.59 (3.05-4.21)	3.20 (2.60-3.66)	0.006
LDH (U/l), median (IQR)	416.80 (316.15-643.40)	394 (308.45-566.60)	503.40 (394.65-915.90)	0.020
CPK (U/l), median (IQR)	754.55 (290.90-2,059.78)	688.80 (289.15-1831.45)	1,109 (495.15-3,081.60)	0.172
TNI (ng/ml), median (IQR)	0.15 (0.04-0.58)	0.10 (0.02-0.36)	0.57 (0.16-0.84)	<0.001
BNP (pg/ml), median (IQR)	488 (178-2633)	394 (170-1,970)	2480 (255-6505)	0.037
Creatinine (umol/l), median (IQR)	93.25 (73.83-127.15)	87 (72.05-117.90)	108.40 (88.30-138.10)	0.036
PCT (ng/ml), median (IQR)	3.42 (0.90-13.39)	3.10 (0.81-10.66)	5.85 (2.79-25.30)	0.054
CRP (mg/l), median (IQR)	4.45 (1.38-14)	4.20 (1.62-12.95)	8.50 (0.75-25)	0.680
PT(s), median (IQR)	15.10 (12.78-18.93)	14.10 (12.40-16.75)	24 (17.20-27.65)	<0.001
APTT(s), median (IQR)	29.55 (25.35-36.58)	27.80 (24.95-31.60)	37.50 (34.50-43.85)	<0.001
FBG (g/l), median (IQR)	2.16 (1.70-2.61)	2.22 (1.81-2.78)	1.80 (1.31-2.40)	0.015
D-dimer (mg/l), median (IQR)	1.87 (1.03-4.64)	1.76 (0.76-4.37)	3.11 (1.75-10.99)	0.010

PA, prealbumin; BMI, body mass index; SBP, systolic blood pressure; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; TCH, total cholesterol; LDH, lactic dehydrogenase; CPK, creatine phosphate kinase; TNI, troponin; BNP, brain natriuretic peptide; PCT, procalcitonin; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; FBG, fibrinogen.

WBC count, PLT count, ALB, PA, TBIL, LDH, CPK, Cr, PCT, PT, APTT, D-dimer and co-infection and shock at admission. Then, a multivariate Cox regression analysis of indicators with differences in univariates was performed. It was found that independent prognostic-related factors for heatstroke patients were IPPV (OR: 7.111, 95% CI: 1.977-25.574, P=0.003), PA level (OR: 1.204, 95% CI: 1.068-1.357, P=0.002), PLT level (OR: 1.010, 95% CI: 1.002-1.019, P=0.017), ALB level (OR: 1.159, 95% CI: 1.021-1.316, P=0.022), CPK level (per 1,000 U/l) (OR: 1.152, 95% CI: 1.052-1.262, P=0.002) and PT

Table II. Adverse conditions in the course of treatment, length of stay in the hospital and length of ICU stay in both groups.

Index	Normal serum prealbumin group (n=79)	Low prealbumin group (n=23)	P-value
Typical heatstroke, n (%)	54 (68.36)	15 (65.22)	0.803
Infection, n (%)	45 (56.96)	17 (73.91)	0.156
Shock, n (%)	18 (22.78)	15 (65.22)	<0.001
IPPV, n (%)	19 (24.05)	13 (56.52)	0.005
Days of ICU (days)	8 (6-12)	7 (3-10)	0.161

IPPV, invasive positive pressure ventilation; ICU, intensive care unit.
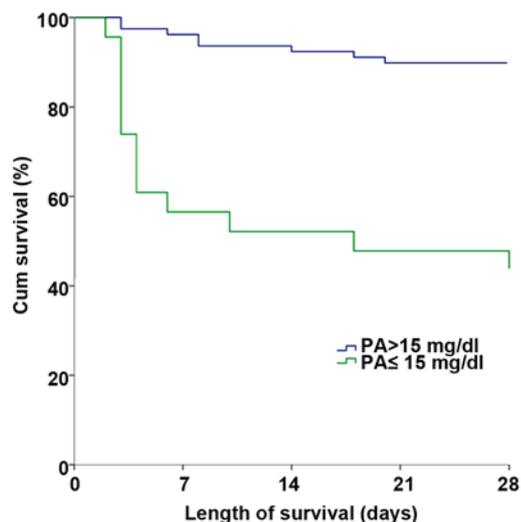

Figure 1. Kaplan-Meier survival curves according to prealbumin (cut-off 15 mg/dl) at admission. Patients with prealbumin ≤15 mg/dl had significantly poorer survival than those with higher prealbumin.

level (OR: 1.096, 95% CI: 1.032-1.164, P=0.003) (Tables III and IV).

ROC curve analysis. ROC curve was plotted to further compare the role of these six indicators in predicting patient mortality. It was found that IPPVAUC=0.842 (95% CI: 0.743-0.941), PAAUC=0.845 (95% CI: 0.760-0.931), PLTAUC=0.780 (95% CI: 0.668-0.892), ALBAUC=0.652 (95% CI: 0.527-0.777), CPKAUC=0.694 (95% CI: 0.558-0.829) and PTAUC=0.862 (95% CI: 0.771-0.953). When prealbumin <17.95 mg/dl was used as the death threshold for predicting at 28 days, the sensitivity was 77.8%, and the specificity was 85.7% (Fig. 2 and Table V).

Discussion

In this study, the relationship between serum prealbumin and mortality in heatstroke patients was shown. The total in-hospital mortality was (20.6%) in this study cohort, lower than that in other reports (14,15). Possible reasons are: First, all heatstroke patients were admitted to the ICU for standard treatment. Secondly, a certain degree of clinical experience was accumulated in the early stage of this group, that is, the cluster treatment strategy of 'early rapid cooling, early rapid expansion,

early anticoagulation, and active support of organ function' was proposed, effectively reducing the mortality. Finally, some critically ill patients were not included due to their incomplete data, as a result of failure of admission or admission to hospital in <24 h, which affected the calculation of mortality. In this study, prealbumin has been shown to be a predictor of mortality in heatstroke patients. The cumulative survival rate of patients with prealbumin >15 mg/dl is significantly better than that of patients with prealbumin ≤15 mg/dl. The results of multivariate Cox regression analysis have confirmed that low serum prealbumin level on admission is an independent risk factor for the poor prognosis of heatstroke patients. ROC curve analysis has shown that the AUC of prealbumin is greater than that of albumin, with the sensitivity and specificity of it higher than those of albumin, indicating that it is satisfactory for judging the prognosis of heatstroke patients, and that prealbumin may be clinically useful. This is the first clinical study at home and abroad of serum prealbumin level in heatstroke patients.

Composed of the same four subunits, the main function of serum prealbumin is to transport thyroxine and vitamin A, which promotes lymphocyte maturation and immunity enhancement. Due to its small base and shorter half-life (2 days), prealbumin can effectively reflect the synthesis of protein in the body, which has become an internationally recognized indicator of nutritional status. Moreover, as a negative acute phase reaction protein, the expression of serum prealbumin has a significant decrease in tumor, cirrhosis and inflammatory response (16). According to the Nutritional Health Consensus Group, serum prealbumin >15 mg/dl indicates a lower risk of malnutrition (17). Therefore, in this study, 15 mg/dl of serum prealbumin was selected as the cut-off value, 23 patients had ≤15 mg/dl, accounting for 22.5%. In low prealbumin group of patients, the levels of PLT, ALB and TCH were lower, PT and APTT significantly prolonged, and there was no significant difference in PCT and CRP reflecting the inflammatory state.

Cardiac dysfunction is the leading cause of death in patients with heat-related diseases (18). Experimental studies have confirmed that under heat stress conditions, severe damage to myocardial cells is characterized by vacuolar changes and partial necrosis of cells (19). Clinical studies have found that myocardial markers are significantly elevated after heat stress, the elevated levels of which can better predict the severity of myocardial damage and heat stroke (20). The multivariate regression analysis of this study has shown that CPK has certain value in judging the condition and prognosis, consistent with the results of Ye *et al* (21).

Table III. Predictors of mortality in heat stroke patients, univariate Cox regression analysis.

Variables	β	SE	Wald	df	OR	95% CI	P-value
Age	0.008	0.014	0.335	1	1.008	0.981-1.035	0.563
Sex	0.126	0.449	0.078	1	1.134	0.470-2.736	0.780
BMI	0.026	0.059	0.196	1	1.027	0.914-1.153	0.658
SBP	0.013	0.010	1.689	1	1.013	0.993-1.033	0.194
Heart rate	0.023	0.008	8.555	1	1.024	1.008-1.040	0.003
Respiratory rate	0.027	0.030	0.793	1	1.027	0.968-1.090	0.373
Hypertension	-0.016	0.483	0.001	1	0.984	0.382-2.536	0.973
Diabetes mellitus	0.240	0.744	0.104	1	1.271	0.296-5.459	0.747
COPD	3.084	4.285	0.518	1	21.854	0.005-96958.873	0.472
Stroke	0.563	1.025	0.302	1	1.757	0.236-13.091	0.582
Tumor	3.067	4.774	0.413	1	21.478	0.002-248485.152	0.521
NA	0.025	0.020	1.648	1	1.026	0.987-1.066	0.199
K	-0.396	0.328	1.462	1	0.673	0.354-1.279	0.227
WBC	0.074	0.035	4.332	1	1.076	1.004-1.153	0.037
Hemoglobin per 10 g/l	0.064	0.131	0.244	1	1.067	0.826-1.378	0.621
PLT	0.017	0.005	12.599	1	1.017	1.008-1.027	<0.001
ALT per 100 U/l	0.091	0.062	2.163	1	1.095	0.97-1.236	0.141
AST per 100 U/l	0.050	0.038	1.674	1	1.051	0.975-1.133	0.196
TBIL	0.026	0.008	9.684	1	1.026	1.010-1.043	0.002
ALB	0.095	0.044	4.636	1	1.100	1.009-1.200	0.031
TCH	-0.412	0.272	2.288	1	0.662	0.389-1.129	0.130
LDH per 100 U/l	0.129	0.043	8.920	1	1.138	1.045-1.239	0.003
CPK per 1,000 U/l	0.184	0.043	18.525	1	1.202	1.105-1.306	<0.001
TNI	0.023	0.054	0.178	1	1.023	0.920-1.139	0.673
BNP per 1,000 pg/ml	0.033	0.024	1.837	1	1.033	0.986-1.083	0.175
Creatinine per 10 umol/l	0.039	0.013	9.132	1	1.039	1.014-1.066	0.003
PCT	0.021	0.006	11.877	1	1.022	1.009-1.034	0.001
CRP per 10 mg/l	0.038	0.067	0.332	1	1.039	0.911-1.186	0.564
PA	0.189	0.041	21.536	1	1.208	1.115-1.308	<0.001
PT	0.141	0.022	39.364	1	1.151	1.102-1.203	<0.001
APTT	0.046	0.013	11.952	1	1.047	1.020-1.075	0.001
FBG	-0.467	0.306	2.327	1	0.627	0.344-1.142	0.127
D-dimer	0.057	0.020	8.117	1	1.059	1.018-1.102	0.004
Type	-0.067	0.463	0.021	1	0.936	0.378-2.318	0.886
Infection	2.705	1.025	6.966	1	14.960	2.007-111.533	0.008
Shock	1.838	0.484	14.401	1	6.285	2.432-16.242	<0.001
IPPV	2.855	0.626	20.823	1	17.369	5.097-59.196	<0.001

BMI, body mass index; SBP, systolic blood pressure; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; TCH, total cholesterol; LDH, lactic dehydrogenase; CPK, creatine phosphate kinase; TNI, troponin; BNP, brain natriuretic peptide; PCT, procalcitonin; CRP, C-reactive protein; PA, prealbumin; PT, prothrombin time; APTT, activated partial thromboplastin time; FBG, fibrinogen; IPPV, invasive positive pressure ventilation.

Coagulation dysfunction can occur in the early stage of heatstroke patients, resulting in DIC whose characteristic pathological injury is extensive thrombosis. On the one hand, continuous consumption causes thrombocytopenia and clotting factor deficiency leading to bleeding. On the other hand, extensive thrombosis causes tissue perfusion disorder that is one of the important mechanisms of the occurrence of severe heat stroke MODS (22,23). The multivariate regression analysis of Zhao et al (24) found that DIC is an main risk factor affecting the prognosis of exertional heatstroke patients, with the mortality of patients coexisting of 70.83%. Therefore, coagulation dysfunction is the most severe complication

Table IV. Predictors of mortality in heat stroke patients, multivariate Cox regression analysis.

Variables	β	SE	Wald	df	OR	95.0% CI	P-value
IPPV	1.962	0.653	9.022	1	7.111	1.977-25.574	0.003
PLT	0.010	0.004	5.646	1	1.010	1.002-1.019	0.017
ALB	0.148	0.065	5.221	1	1.159	1.021-1.316	0.022
CPK	0.142	0.046	9.319	1	1.152	1.052-1.262	0.002
per 1,000 U/l							
PA	0.186	0.061	9.271	1	1.204	1.068-1.357	0.002
PT	0.091	0.031	8.811	1	1.096	1.032-1.164	0.003

IPPV, invasive positive pressure ventilation; PLT, platelet; ALB, albumin; CPK, creatine phosphate kinase; PA, prealbumin; PT, prothrombin time.

Table V. Comparison of AUC among various parameters for survival in heat stroke patients.

Variables	AUC	SE	P-value	95% CI	Sensitivity	Specificity	Cut-off
IPPV	0.842	0.051	<0.001	0.743-0.941	0.857	0.827	
CPK	0.694	0.069	0.006	0.558-0.829	0.571	0.778	1676.200
PT	0.862	0.046	<0.001	0.771-0.953	0.810	0.778	17.650
PLT	0.780	0.057	<0.001	0.668-0.892	0.905	0.568	125.500
ALB	0.652	0.064	0.032	0.527-0.777	0.619	0.691	32.450
PA	0.845	0.044	<0.001	0.760-0.931	0.857	0.778	17.950

AUC, area under the receiver operating characteristic curve; IPPV, invasive positive pressure ventilation; CPK, creatine phosphate kinase; PT, prothrombin time; PLT, platelet; ALB, albumin; PA, prealbumin.
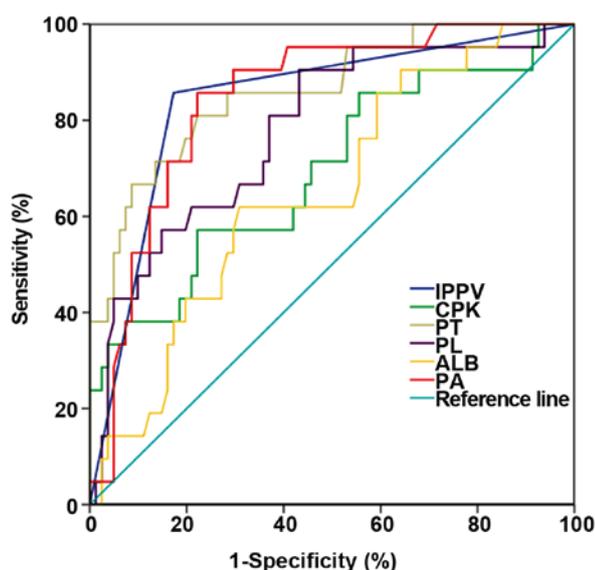

Figure 2. Comparison of AUC values among various parameters for survival in heat stroke patients. AUC, area under the receiver operating characteristic curve; IPPV, invasive positive pressure ventilation; CPK, creatine phosphate kinase; PT, prothrombin time; PLT, platelet; ALB, albumin; PA, prealbumin.

of heatstroke (24). In the blood specimen monitoring of patients with severe heat stroke within 24 h of admission, Pan *et al* (25) found that PT and APTT significantly prolong, but PLT significantly decreases in death group compared with survival group. The analysis of receiver operating characteristic

(ROC) curve has shown that PLT has a predictive value for patients with severe heat stroke (25). Li *et al* (26) found that prothrombin time on admission, international normalized ratio and fibrinogen can effectively predict the clinical prognosis of heatstroke patients (26). In this study, a multivariate regression analysis was performed on the clinical data of 102 heatstroke patients. The results showed that PT and PLT are independent risk factors affecting the prognosis of patients among all the main clinical parameters collected at admission.

In this study, patients with low serum prealbumin level are found to be correlated with invasive positive pressure ventilation, with invasive mechanical ventilation being an independent risk factor for death in heatstroke patients. Nutritional supplementation in patients with low prealbumin level may shorten extubation time.

Increasing evidence shows that not caused by simple thermal exposure resulting in direct injury, the pathophysiological response of severe heat stroke MODS is a systemic inflammatory response syndrome secondary to thermal injury, which in turn manifests as 'sepsis', further triggering MODS (27,28). After heatstroke, the pro-inflammatory and anti-inflammatory factors in the body are out of balance, and then tissue damage caused by pro-inflammatory response and immunosuppression caused by excessive anti-inflammatory response may occur in patients (29). Experimental studies have shown that when the inflammatory response in heatstroke rats is reduced with different methods, the degree of organ damage is reduced, with improved survival rate (30). At present, there are few studies

on the changing trends of PCT and CRP, generally considered to be acute phase biomarkers of inflammatory response, in heatstroke patients. Serum PCT monitoring was performed on 68 exertional heatstroke patients within 2 h of admission. Tong et al (31) found that the PCT of non-survivors is higher than that of survivors. After confounding factors adjusted, PCT concentration is also an independent risk factor for mortality, but may not be a good indicator predicting heat stroke accompanied by infection (31). The studies of Hausfater et al show that serum PCT can be induced to release even in the absence of bacterial infection in exertional heatstroke patients (14). Surprisingly, although the CRP level is moderately elevated [4.45 (1.38-14) mg/l], there is no statistically significant difference between survival group and non-survival group [4.2 (1.4, 12.9) vs. 8.7 (1.4, 24.7), P=0.360]. CRP, also an acute phase reaction protein, is positively correlated with the degree of inflammation and tissue damage (32), but often taking time to respond and increase serum concentration after infection or inflammation (33). Studies have also shown that the kinetics of CRP is slower in sepsis and systemic inflammatory response than that in inflammatory mediator (including PCT, leptin, IL-6 and TNF-α) (34,35). Therefore, the decline in CRP sensitivity in the early stage of heatstroke can be explained by these facts. Used as a differential diagnosis in patients with non-infectious high fever at the early stage of admission, CRP saves patients' valuable time and avoids unnecessary diagnostic checks.

In the univariate analysis used to determine main risk factors affecting the prognosis in this group of studies, the results obtained are similar to those worldwide, indicating that these parameters are representative. Multivariate Cox regression analysis is used to remove confounding factors and screen out independent risk factors affecting the prognosis of heatstroke, so as to analyze and evaluate the sensitivity and specificity of each risk factor. Besides, it evaluates the effect of prealbumin on prognosis for the first time, being the highlight of this group of studies, with accurate and reliable results.

There are also some shortcomings in this study. First, study design is observation, so the causal relationship between prealbumin and other markers needs further confirmation. Secondly, the number of cases included in the study, which is relatively small, is derived from a single hospital, with limited representativeness that may cause statistical bias. In addition, most of the cases are mainly typical heat stroke, cannot fully representing other types of heat stroke. Therefore, further long-term multi-center clinical studies with large samples are necessary for confirming factors affecting the prognosis of heatstroke.

In summary, the measurement of prealbumin is a useful tool evaluating the nutritional and inflammatory status of heatstroke patients. Moreover, the lower level of serum prealbumin is independently associated with the increase of death risk.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

QY and WL collected and interpreted the general information of patients. JY and JJ acquired and analyzed the observation indicators. TX and YZ contributed to statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University (Changzhou, China). Patients who participated in this research had complete clinical data. The signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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