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特此证明!





Diagnostic Significance of Combined Calcitoninogen, Platelet, and D-Dimer Assay in Severe Heatstroke: with Clinical Data Analysis of 70 Patients with Severe Heatstroke

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The significance of calcitoninogen detection among inpatients was discussed by analyzing the clinical characteristics of severe heatstroke (HS). HS patients who were admitted to the Second Hospital of Nantong University, Jiangsu Province, China, between July 1, 2015, and October 30, 2020, were reviewed. Patients' clinical characteristics and laboratory data were recorded, and they were divided into three groups, that is, a control group (heat cramps and heat exhaustion), an exertional HS (EHS) group, and a classical HS (CHS) group to compare the differences among them. Receiver operating characteristic (ROC) curves were plotted to evaluate patients' clinical utility. (1) The body temperatures in the EHS and CHS groups were significantly higher than in the control group (all $p < 0.05$). (2) The D-dimer (DD), procalcitonin (PCT), and Acute Physiology and Chronic Health Evaluation (APACHE) II score of the EHS group were significantly higher compared with the control and CHS groups (all $p < 0.05$); the platelets (PLT), C-reactive protein (CRP), blood sodium (Na), and intravenous glucose (GLU) of the EHS group were lower than in the control and CHS groups (all $p < 0.05$). (3) The ROC curve analysis showed the performance results for DD (area under the curve [AUC] 0.670, 95% confidence interval [CI] 0.547–0.777), PCT (AUC 0.705, 95% CI 0.584–0.808), and PLT (AUC 0.791, 95% CI 0.677–0.879). The sensitivity was 40.48%, 100%, and 73.81%, and the specificity was 96.43%, 32.14%, and 78.57%, respectively. Using three combined analyses, an elevated AUC of 0.838, 95% CI 0.731–0.916, with a sensitivity of 71.43% and a specificity of 85.71%, respectively, was revealed. Patients in the EHS group had higher DD, PCT, and APACHE II values, whereas PLT, CRP, Na, and GLU were reduced. The apparent decrease in the PLT, as well as the increase in PCT and DD values, could be considered as early sensitivity indicators of severe HS. A combined test of these three indicators presented significant diagnostic value for detecting severe cases of HS.

Keywords: severe heatstroke, exertional pyrexia, classic pyrexia, calcitoninogen, D-dimer, platelets

Introduction

HHEATSTROKE (HS) IS A clinical syndrome in which the body develops thermoregulatory dysfunction under the influence of exposure to heat and/or strenuous exercise, thus increasing the core temperature, which causes a potentially

fatal organismal disorder. Severe HS includes symptoms such as heat cramps, heat exhaustion, and pyrexia; the latter is a severe form of HS, during which the body's core temperature can rapidly rise above 40°C, accompanied by the central nervous system dysfunction that includes convulsions, delirium, and slipping into a coma (Tollefson, 2015; Zhang

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et al, 2020). Depending on the cause and the susceptibility of the population, exertional HS (EHS) and classical HS (CHS) types have been established. The clinical manifestations of these syndromes can vary widely among individuals (Epstein and Yanovich, 2019) and are often confused with the manifestation of an underlying disease, which may lead to a misdiagnosis. In addition, patients with severe HS often have a combination of cranial trauma and aspiration, which makes the clinical presentation and diagnosis more complicated.

With the normalization of the prevention and control of the new crown pneumonia epidemic, in June 2020, the General Office of China's National Health and Wellness Commission issued a notice on the prevention of HS in 2020, requiring all regions to pay full attention to the health hazards of HS and effectively avoid HS incidents. Therefore, biomarkers predicting the development pattern of severe HS will be helpful for the quick identification and treatment of this condition, which is important for establishing effective treatment aimed at brain protection.

Materials and Methods

General materials

A retrospective study was conducted to collect clinical data from 70 adult inpatients admitted to the Second Hospital of Nantong University, Jiangsu Province, China, between July 1, 2015, and October 30, 2020, who had been hospitalized to exclude definite systemic infections and were subsequently discharged with a diagnosis of severe HS. Patients who were diagnosed with HS, based on the *International Classification of Diseases* ([Ninth Revision], *Clinical Modification* [ICD-9-CM] codes, HS, ICD-9-CM 992.0), were included. The study complied with medical ethics standards and was approved by the Ethics Committee of the Second Affiliated Hospital of Nantong University. All participants took part in the study voluntarily and provided written informed consent before completing the study survey.

Data collection and grouping

For each participant, the time of onset, days of hospitalization, maximum body temperature (T max), white blood cells (WBC), neutrophils (N), hemoglobin (HB), platelets (PLT), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), blood lactate (LAC), C-reactive protein (CRP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) within 24 hours of admission were recorded. The blood urea nitrogen (BUN), serum creatinine (SCR), intravenous glucose (GLU), hemoglobin A1C (HbA1C), arterial blood gas analysis, saturation of pulse O₂ (SPO₂), actual bicarbonate (AB), blood potassium (K), blood sodium (Na), blood chloride (Cl), troponin I (TNI), myoglobin (MYO), creatine kinase isoenzyme (CKMB), B-type brain natriuretic peptide (BNP), D-dimer (DD), and Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated for all patients on admission.

According to the HS severity, and with reference to the Diagnostic Criteria for Occupational Heat Stroke (GBZ 41-2002), established by the Ministry of Health of the People's Republic of China, the participants were divided into a control group (heat cramps and heat exhaustion), an EHS group, and a CHS group.

The groups were as follows: The control group included: (1) heat cramps: the main manifestation of the muscle spasm is obvious, accompanied by contraction pain. It often occurs in the muscles of the extremities and abdominal muscles, especially in the gastrocnemius muscle, and is mostly symmetrical. (2) Heat exhaustion: rapid onset; the main clinical manifestations are thirst, sweating, headache, dizziness, nausea, vomiting, followed by wet and cold skin, decreased blood pressure, cardiac rhythm disturbance, dehydration, and body temperature can be slightly high or normal.

EHS is common in healthy young people with a history of working under high temperature, rapid rise in body temperature up to 40°C or more, and severe decrease in the level of consciousness and coma.

CHS is common in old, young, frail, and chronically ill patients, and usually has a gradual onset. It appears with confusion, delirium, coma, etc. The body temperature rises to 40°C–42°C, often accompanied by incontinence, heart failure, renal failure, and other manifestations. The index differences were subsequently compared among the three groups (Fig. 1).

Statistical analysis

The SPSS Statistics 21.0 software was used for data processing and analysis. The measurement data conforming to a normal distribution, for example, age, temperature, WBC, N, and Hb were expressed as the mean \pm standard deviation ($\bar{X} \pm S$); a *t*-test was conducted for making comparisons among the groups. For data conforming to a skewed distribution, for example, time to onset and DD, the results were expressed as a median and an interquartile range, and were compared by conducting a rank-sum test; the counted data were examined using a chi-square (χ^2) test. The significance of PLT, PCT, and DD for the early diagnosis of HS was analyzed by plotting the subject receiver operating characteristic (ROC) curve; $p < 0.05$ was considered a statistically significant difference result.

Results

General information

Of the 70 patients with severe HS, 46 (65.7%) were male and 24 (34.3%) were female; the participant ages ranged between 22 and 96 years (mean age 65.72 ± 16.64 years). The number of hospitalization days was 15.58 ± 14.49 days. The T max was $39.66^\circ\text{C} \pm 1.08^\circ\text{C}$. Nine cases died and 61 cases improved. Among them, 13 cases were admitted to the intensive care unit (ICU), 22 cases were mechanically ventilated, 1 case was treated with blood purification, and 20 cases were treated with vasoactive drugs; 35 patients had (in addition to HS) one or more underlying diseases, including 20 cases of hypertension, 12 cases of diabetes mellitus, 3 cases of coronary heart disease and atrial fibrillation, 3 cases of uremia, and 1 case of chronic obstructive pulmonary disease.

Comparing the clinical data of patients with pyrexia

Seventy patients were divided into 3 groups as follows: 28 patients in the control group (heat cramps and heat exhaustion), 24 patients in the EHS group, and 18 patients in the CHS group. The groups were not statistically different in

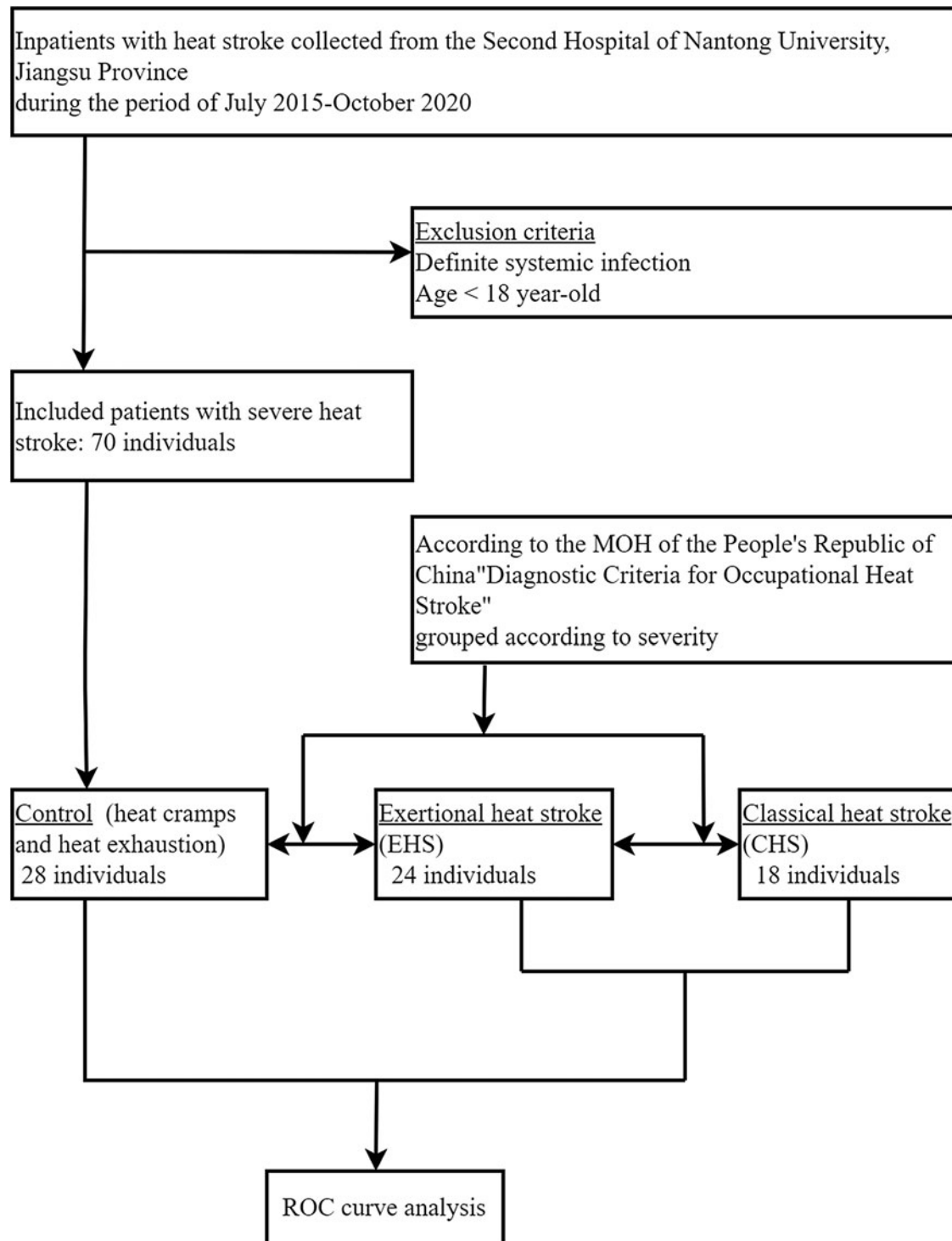


FIG. 1. Subgroup study of patients with heatstroke.

terms of age, gender, time of onset, or days of hospitalization (all $p < 0.05$) and were thus comparable. There was no statistical significance concerning PH, AB, BNP, ALT, AST, WBC, N, HB, ESR, LAC, SPO₂, K, Cl, TNI, MYO, CKMB, BNP, or BUN (all $p > 0.05$).

The body temperature results in the EHS and CHS groups were significantly higher than in the control group (all $p < 0.05$), but there was no statistical difference between the

EHS and CHS groups; DD, PCT, and APACHE II scores in the EHS group were significantly higher than in the control and CHS groups (all $p < 0.05$). While PLT, CRP, Na, and GLU in the EHS group were lower than those in the control and CHS groups (all $p < 0.05$), the decrease in PLT was more significant. The HbA1C in the CHS group was significantly higher than in the control and EHS groups (all $p < 0.05$) (Table 1 and Fig. 2).

TABLE 1. COMPARISON OF CLINICAL DATA OF THE THREE GROUPS OF PATIENTS

	Control	EHS	CHS	F/Z	p
Number	28	24	18	—	—
Age, years	66.89 ± 14.83	64.08 ± 21.46	66.11 ± 12.68	0.183	0.833
Male/Female	20/8	16/8	10/8	1.240	0.538
Time of onset, hours	22 (40)	24 (36)	23 (42)	0.796	0.672
Days of hospitalization, days	13.57 ± 9.41	15.46 ± 17.82	18.83 ± 16.62	0.707	0.497
T max, °C	38.73 ± 0.49	40.71 ± 0.58 ^a	40.64 ± 0.69 ^a	97.020	0.00
DD, µg/mL	1880.00 (3365.25)	10946.00 (11265.00) ^a	2110.00 (3497.50) ^b	10.160	0.006
WBC, × 10 ⁹ /L	11.66 ± 5.38	9.16 ± 3.46	10.80 ± 4.12	2.026	0.14
N, × 10 ⁹ /L	8.94 ± 3.23	7.34 ± 2.33	9.53 ± 3.81 ^b	2.897	0.62
HB, g/L	127.21 ± 24.77	123.83 ± 18.20	122.94 ± 14.16	0.299	0.743
PCT, ng/L	1.79 (9.81)	21.98 (57.97) ^a	2.88 (8.28) ^b	15.204	0.000
PLT, × 10 ⁹ /L	113 (74.75)	40 (16) ^a	100.5 (91.5) ^b	35.515	0.000
ESR, mm	13 (24.75)	23 (20)	18 (22.75)	2.834	0.242
CRP, mg/L	39.98 (130.6)	13 (13.56) ^a	38.84 (78.96) ^b	7.927	0.019
PH	7.41 ± 0.06	7.39 ± 0.09	7.40 ± 0.86	0.190	0.827
LAC, mmol/L	3.41 ± 1.45	2.88 ± 1.45	2.88 ± 0.99	1.319	0.274
SPO ₂ , %	93.74 ± 4.36	95.57 ± 3.98	93.78 ± 5.81	0.946	0.393
K, mmol/L	4.1 (0.93)	3.56 (1.4)	3.7 (0.74)	1.685	0.431
Na, mmol/L	139.31 ± 8.13	128.77 ± 28.33 ^a	140.97 ± 5.86 ^b	3.227	0.046
Cl, mmol/L	104.99 ± 8.52	97.86 ± 22.35	103.78 ± 6.65	1.674	0.195
AB, mmol/L	20.31 ± 4.08	22.78 ± 4.50	22.02 ± 3.91	2.376	0.101
GLU, mmol/L	7.166 (3.82)	5.95 (1.95) ^a	7.45 (5.68) ^b	6.3	0.043
HbA1C, %	5.85 ± 0.74	5.62 ± 0.67	7.09 ± 2.04 ^{a,b}	8.701	0.000
TNI, ng/mL	0.120 (0.9)	0.145 (1.3)	0.125 (0.6)	2.015	0.365
Myo, ng/mL	341 (653.75)	677 (860.88)	469 (715.93)	1.897	0.387
CKMB, ng/mL	25.5 (38.25)	48 (40)	29.5 (38.65)	2.435	0.296
BNP, ng/L	1055.2 (1252.55)	975.1 (3187)	453.5 (1275.58)	1.192	0.551
ALT, U/L	41.5 (41)	34 (49)	52.5 (94.25)	4.159	0.125
AST, U/L	50.5 (52)	69 (101)	76 (63.5)	2.449	0.294
SCR, mmol/L	86 (73.25)	81 (93)	80.5 (51.75)	0.783	0.676
BUN, mmol/L	8.11 (5.22)	6.53 (4.73)	7.85 (8.73)	0.512	0.774
APACHE II	16.25 ± 6.94	14.13 ± 5.55	21.83 ± 9.54 ^{a,b}	5.973	0.004

Age, days of hospitalization, temperature, WBC, N, Hb, PH, LAC, SPO₂, Na, Cl, AB, and HbA1C are expressed as mean ± standard deviation ($\bar{X} \pm S$); skewed distribution such as time of onset, DD, PCT, PLT, ESR, CRP, K, GLU, TNI, Myo, CKMB, BNP, ALT, AST, and SCR, and BUN were expressed as median (IQR).

^a $p < 0.05$ compared with the control group.

^b $p < 0.05$ compared with the EHS group.

AB, actual bicarbonate; ALT, alanine aminotransferase; APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CHS, classical heatstroke; CKMB, creatine kinase isoenzyme; Cl, chloride; CRP, C-reactive protein; DD, D-dimer; EHS, exertional heatstroke; ESR, erythrocyte sedimentation rate; GLU, glucose; HB, hemoglobin; HbA1C, hemoglobin A1C; IQR, interquartile range; K, potassium; LAC, lactate; N, neutrophils; Na, sodium; PCT, procalcitonin or calcitoninogen; PLT, platelets; SCR, serum creatinine; SPO₂, saturation of pulse O₂; T max, maximum body temperature; TNI, troponin I; WBC, white blood cells.

The predictive value of clinically relevant indicators for the early diagnosis and treatment of severe HS

Patients in the EHS and CHS groups were combined and assigned a value of 1, and the control population was assigned a value of 0. The indicators with statistically significant differences among the three groups were included in the predictive analysis, and the ROC curves were drawn and used to determine the diagnostic ability of the indicators for early pyrexia. The CRP and APACHE II scores at patient admission showed high sensitivity, that is, 95.24% and 85.71%, respectively, but low specificity, that is, 32.14% and 0%, respectively; the Na, GLU, and HbA1C% had high specificity, that is, 89.29%, 85.71%, and 82.14%, respectively, but low sensitivity.

The DD, PCT, and PLT of patients at the time of admission were diagnosed by a specific value for pyrexia, and the area under the curve (AUC) was 0.670, 0.705, and 0.791, respectively. The sensitivity was 40.48%, 100%, and 73.81%,

and the specificity was 96.43%, 32.14%, and 78.57%, respectively. In contrast, the specificity of the APACHE II score was 0, and the Jorden indexes for the CRP, Na, GLU, and HbA1C were low. Therefore, the tandem test results for DD, PCT, and PLT were used in the combined analysis with an AUC of 0.838, a sensitivity of 71.43%, and specificity of 85.71% (this method will improve the specificity but will reduce the sensitivity; as such, the index with a relatively high sensitivity needs to be selected first, which the authors will discuss later). The three tests further improved the Jorden indexes shown in Table 2 and Figure 3.

Discussion

Incomplete epidemiological surveys showed that the incidence of HS during summer heatwaves abroad ranged from 17.6 to 26.5 per 100,000 people, with hospital morbidity and mortality rates ranging from 14% to 65% and >60% among ICU patients (Liu et al, 2020). As the prevalence of hot

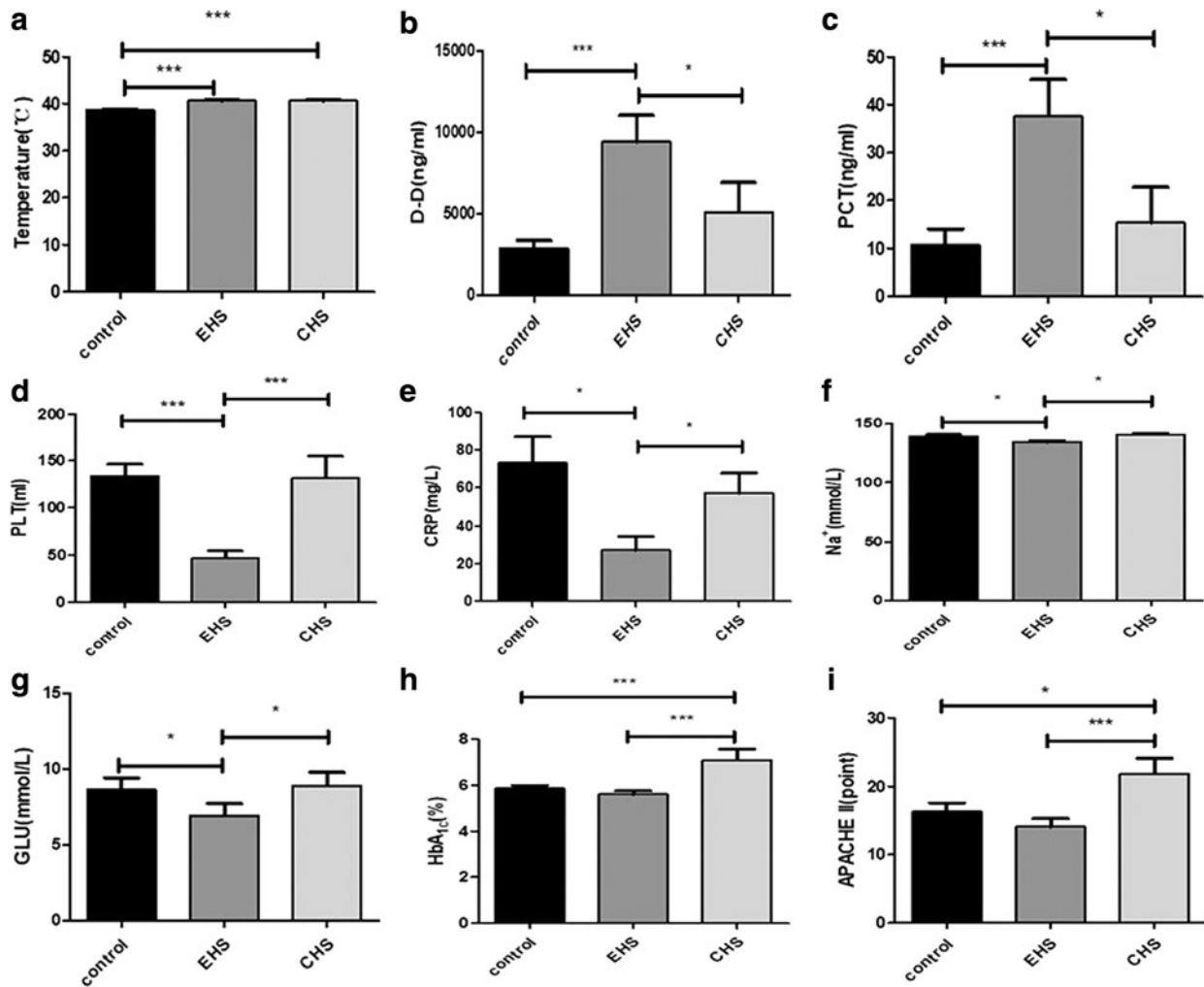


FIG. 2. Intergroup comparison of temperature, DD, PCT, PLT, CRP, Na, GLU, HbA_{1c}, and APACHE II (* $P < 0.05$, *** $P < 0.001$). (a) Temperature, (b) DD, (c) PCT, (d) PLT, (e) CRP, (f) Na, (g) GLU, (h) HbA_{1c}, (i) APACHE II. APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; DD, D-dimer; GLU, glucose; HbA_{1c}, hemoglobin A_{1c}; Na, sodium; PCT, procalcitonin; PLT, platelets.

climates increases, deaths due to heat injuries are expected to rise by 2.5-fold in the 2050s, from a current annual death of ~2000 in the United States (Robine et al, 2008). Local regional epidemiological data in China are as follows: 288 cases of HS were reported cumulatively in Changxing, Zhejiang, from 2016 to 2018 (Yan et al, 2020), with an

incidence of 15.15 per 100,000 people, including 23.61% severe cases and a morbidity and mortality rate of 0.35%; from 2013 to 2017 in Pudong, Shanghai, 1152 severe cases of HS were recorded; among these, 46.27% were HS (533/1152) and included 115 cases in the death group (Pan et al, 2019).

TABLE 2. PREDICTIVE VALUE OF CLINICALLY RELEVANT INDICATORS FOR EARLY DIAGNOSIS AND TREATMENT OF SEVERE HEATSTROKE

	Sensitivity	Specificity	Yoden index	AUC	95% CI
T max, °C	100	100	1	1	0.949–1.000
CRP, mg/L	95.24	32.14	0.2738	0.588	0.464–0.704
Na, mmol/L	26.19	89.29	0.1548	0.578	0.454–0.695
GLU, mmol/L	40.48	85.71	0.2619	0.597	0.472–0.712
HbA _{1c} , %	35.71	82.14	0.1786	0.541	0.418–0.661
APACHE II	85.71	0	0.1429	0.512	0.390–0.634
DD, μg/mL	40.48	96.43	0.3690	0.670	0.547–0.777
PCT, ng/L	100	32.14	0.3214	0.705	0.584–0.808
PLT, × 10 ⁹ /L	73.81	78.57	0.5238	0.791	0.677–0.879
DD+PCT+PLT	71.43	85.71	0.5714	0.838	0.731–0.916

AUC, area under the curve; CI, confidence interval.

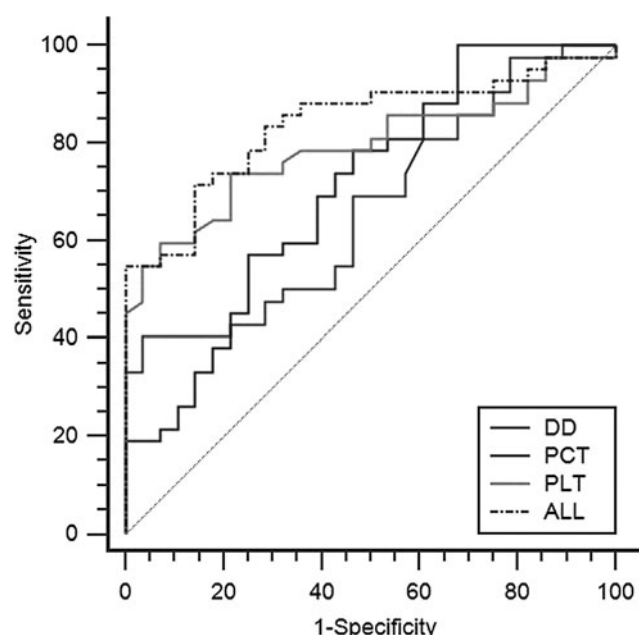


FIG. 3. ROC curve analysis of DD, calcitoninogen, and PLT on early severe heatstroke. ROC, receiver operating characteristic.

The exact pathogenesis of multiple organ dysfunction associated with severe HS is not fully understood (Hifumi et al, 2018; Peiris et al, 2017) and mainly includes the direct cytotoxic effects of a high core temperature and the activation of sepsis-like inflammatory cascades. The clinical manifestations of the impairment of multiple organ functions throughout the body in severe HS cases mainly include central nervous system damage (a loss of consciousness, mental disturbances, cerebral edema, and seizures), coagulation disorders (diffuse intravascular coagulation and prolonged blood clotting time), liver and kidney dysfunction, rhabdomyolysis, respiratory failure, and cardiovascular complications (arrhythmias and hypovolemic shock), causing changes in the corresponding systemic tests (Filep et al, 2020). The severity of organ tissue damage is directly proportional to the prognosis (Woods, 2021).

There is a lack of uniform criteria for diagnostic HS indicators and an absence of specific methods for the prognostic assessment of HS. Leon and Helwig (2010) concluded that individual systemic study indicators or scores did not provide a complete assessment of the interaction among multiple factors and were not completely reliable for assessing the prognosis of HS. We analyzed more than 2000 data samples collected from 70 critically ill hospitalized patients and compared them in separate groups according to ICU admission, mechanical ventilation, and vasoactive drugs. Furthermore, according to the HS severity, three groups, that is, a control (heat cramps and heat exhaustion), EHS, and CHS groups were established to compare the differences among the indicators of each group. An attempt was made to discover in-clinic test indicators that could determine the prognosis of severe HS in an effective, simple, and rapid manner.

Of the 70 patients with severe HS, 46 (65.7%) were male and 24 (34.3%) were female; their ages ranged from 22 to 96

years, with a mean age of 65.72 ± 16.64 years. Hyperthermia causes hyperventilation and increases the respiratory rate, and in foreign animal experiments, it was found that the respiratory rate was significantly faster than normal in pigs included in a model of severe HS, suggesting that respiratory rate may be an influential factor in the prognosis of severe HS (Voelckel et al, 2008). This study observed abnormal liver function in the majority of patients with severe HS in all three of these groups, but there was no difference when we compared them, and the liver was found to be the most vulnerable organ due to hypoxia and direct heat injury. Liver transaminases are a very sensitive marker of organ damage. In contrast, SCR and BUN did not show a corresponding increase with the degree of damage. Existing data suggest that the liver is the main site of heat injury and that most HS patients have liver tissue damage (Leon and Bouchama, 2015; Mozini et al, 2017). Wagner et al (2003) concluded that patients with abnormal liver function in cases of HS had a very poor prognosis.

Alzeer et al (1997) found that elevated serum ALT and AST in cases of HS could be used as an important reference indicator for determining the condition and the prognosis of HS. The additional analysis conducted in the present study concluded that patients with severe HS had liver function impairment, but there was no statistical difference among patients with severe HS, suggesting that liver function may be an influential factor in the development of HS and was not a risk factor for the assessment of a prognosis.

The APACHE II score is a commonly used clinical evaluation system for critical illness. It includes a summary of acute physiology, age, and chronic health status (Bylapudi et al, 2021). The theoretical maximum score is 71, and the higher the score, the more severe the condition. It was found that the APACHE II score was closely related to the severity of HS, and the higher the score, the more severe the disease (Ishikawa et al, 2021). In this study, the APACHE II score was increased in the CHS group compared with the control group, suggesting that this score had some significance for judging the prognosis of the CHS group; conversely, the score of the EHS group was lower compared with the control group, considering that the CHS group comprised primarily chronic patients with underlying diseases, some of whom were even bedridden, with a poor general condition at the time of admission and a higher APACHE II.

Furthermore, the specificity and sensitivity of the APACHE II score were found to be 0% and 85.71%, respectively, with low specificity, an AUC of 0.512, and a 95% confidence interval (CI) of 0.390–0.634. This suggested that the predictive value of the APACHE II score for assessing the prognosis of severe CHS was not high.

Serum PCT was a relatively specific marker for severe bacterial infections and sepsis in existing studies (Scheer et al, 2019). Yang et al (2012) found that the PCT level and the positive blood culture rate were higher in the EHS group compared with the sepsis group by comparing the serum PCT and the positive blood culture rate between patients with EHS and sepsis. The study concluded that, for patients with EHS and an elevated PCT, combined with blood culture and clinical analysis. In patients with significantly elevated serum PCT levels or positive blood cultures, aggressive anti-infective therapy should be used, even if no direct bacterial infection indication can be found.

In our study, PCT was collected from patients with severe HS and was higher in both the EHS and CHS groups compared with the control group, with the EHS group results being particularly significant. Additionally, 25 patients developed systemic infections in the middle and late stages of the disease, with lower respiratory tract infections dominating (EHS 12 vs. CHS 9).

Further analysis of the sensitivity of PCT at 100% considered this indicator to reflect the activity of the systemic inflammatory stress response, the production of which is influenced by a variety of factors and can be significantly abnormal, even in the absence of a bacterial infection or bacterial lesions. However, there is no unified standard for PCT diagnostic criteria and threshold values, and in our study, we found that the specificity was not high; in practice, PCT cannot be used on its own to diagnose or exclude infection in isolation from the clinical environment. Concurrently, because this study was conducted retrospectively, the sample size was small and may have given rise to shortcomings, which should be further studied by randomized controlled trials. Therefore, based on the results of this study, a significant increase in PCT can greatly reflect the severity and prognosis of HS, which can help to identify early pyrexia coinfection and guide the use of clinical antibiotics.

In the present study, the DD of the EHS group was significantly higher than in the control and CHS groups (all $p < 0.05$); the PLT of the EHS group was significantly lower compared with the control and CHS groups (all $p < 0.05$); the significant decrease of PLT in the early stage, in particular, suggested a poor HS prognosis. Coagulation dysfunction is also involved in the important pathological process of severe HS (Yin et al, 2018), and some studies suggest that abnormalities related to PLT and blood coagulation can reflect the severity of severe HS, and the application of anticoagulant therapy may help to improve the survival rate of patients (Zhong et al, 2021). The current abnormalities in coagulation mechanisms due to HS may be considered as related to the direct cytotoxic effects of heat stimulation and the cellular inflammatory response (induced by heat stimulation), leading to vascular endothelial damage and microthrombosis (Geng et al, 2015). In addition, thermal stimulation can cause PLT aggregation as well as a reduced number, depletion of coagulation factors, thus inhibiting bone marrow production and the release of PLT (Liu et al, 2019).

Current studies indicated the significance of PLT in the assessment of various diseases, such as cardiovascular diseases, diabetes mellitus, and cirrhosis (Jindal et al, 2011; Yilmaz et al, 2008), as well as the correlation between PLT reduction and the criticality and prognosis of patients with infectious shock (Guclu et al, 2013). The ROC curve analysis of DD in our study had a sensitivity of 40.48, a specificity of 96.43, and an AUC of 0.670, while PLT had a sensitivity of 73.81, a specificity of 78.57, and an AUC of 0.791; the larger the AUC, the higher the diagnostic efficacy of the index should be, and this can be used as a predictor of early diagnosis in patients with pyrexia.

The cascade of oxidative stress secondary to heat stimulation, the inflammatory response, the accumulation of metabolites, and the feedback interactions of the hypothalamic–pituitary–adrenal axis interact to influence, regulate, and constrain one another. In general, the level of CRP is low in human plasma and increases rapidly within a few

hours following an infection or stress; currently, CRP is recognized as a sensitive inflammatory indicator that can reflect the body's condition visually and truthfully (Cho et al, 2021a). In the present study, CRP differed among the three groups, while further analysis showed that CRP had a high sensitivity (95.24) but not a high specificity (32.14) in the early stage of pyrexia. While PCT is also a relevant indicator in response to systemic stress, when comparing AUC results overall, CRP was lower than PCT (0.588 vs. 0.705, respectively).

There are many etiologies related to disorders of the internal human environment in patients with severe HS, which can be caused by a single factor or by the interaction of multiple factors, resulting in disorders related to water, electrolytes, and blood GLU, including hyponatremia, hyperkalemia, hyponatremia, hypokalemia, hyperglycemia, and hypoglycemia. In our study, there was no significant difference among the three groups when comparing electrolytes K, CL, and AB, while differences were observed for Na, with hyponatremia predominating. Furthermore, the ROC analysis of Na had a specificity of 89.29, suggesting that patients with clinical pyrexia should pay particular attention to blood Na abnormalities. Hyponatremia can occur secondary to cerebral edema, and the faster its decline, the more severe the clinical condition. Hyponatremia is more dangerous if it occurs within 48 hours (Tudor and Thompson, 2019), and patients may suffer from convulsions and slip into a coma, thereby aggravating or leading to permanent neurological damage.

Our study found that GLU and HbA1C in the EHS group were lower than the remaining two groups ($p < 0.05$), considering that the stress response induced by severe HS may be dysregulated, resulting in higher or lower blood GLU. Second, hypoglycemia may be due to impaired liver function and insufficient liver glycogen storage, suggesting that the occurrence of possible hypoglycemic events should be alerted in the clinic, suggesting that GLU fluctuations above 5.95 mmol/L must be closely attended. It is recommended to pay close attention to the fluctuation of blood GLU in critically ill patients.

It was noted that sepsis could cause disturbances in GLU metabolism in the endocrine system and that severely elevated and decreased blood GLU were markers of disease severity (Keeley et al, 2017) and may also be important factors for a poor prognosis. Abnormal GLU metabolism can occur in patients with HS, accompanied by hyperglycemia or hypoglycemia. However, the precise threshold for pathological hyperglycemia in critically ill patients is unknown. In acute or severe disease cases, the stress response may be dysregulated (American Diabetes Association, 2020), resulting in higher or lower blood GLU, and hypoglycemia may be a result of insufficient sugar stores in the body. The difference in GLU that were found in the present study through the comparison of the three groups suggested the need for vigilance against possible hypoglycemic events in the clinical environment, and it is recommended that close attention be paid to GLU fluctuations above 5.95 mmol/L. Additionally, it is recommended that, for critically ill patients, attention should be paid to HbA1C to assess fluctuations in blood GLU.

Further analysis of the sensitivity and specificity of both was located at 35.71–40.48, as well as 82.14–85.71, with an overall assessment of AUC=0.541–0.597, as well as an

average ability to predict the early diagnosis of pyrexia. It is recommended that the design of future randomized controlled trials consider hyperglycemia, hypoglycemia, and glycemic variability.

In summary, the AUC of the ROC analysis of DD for predicting an early diagnosis in patients with pyrexia was 0.670 (95% CI 0.547–0.777) with a sensitivity of 40.48, and specificity of 96.43; the AUC of PCT for predicting early severe HS was 0.705 (95% CI 0.584–0.808). The AUC for PLT was 0.791 (95% CI 0.677–0.879) with a sensitivity of 73.81 and specificity of 78.57. An AUC=0.5–0.7 is generally effective for predicting early severe HS (Cho et al, 2021b). This study again combined the three (DD, PCT, PLT) as a predictor of early severe HS ROC, and the results showed that its AUC increased to 0.838 (95% CI 0.731–0.916) along with a sensitivity of 71.43, and a specificity of 85.71, which was overall higher than the results of the three above-noted single tests; this combined index achieved the best sensitivity and specificity for predicting the early diagnosis of patients with HS. This result suggests combining DD, PCT, and PLT in the future for a predictive assessment of early pyrexia to obtain higher accuracy.

Conclusion

The present research was a single-center retrospective study that investigated the early sensitive indicators of HS by focusing on the early case data of 70 patients, all of whom were admitted to the Second Hospital of Nantong University for HS; as such, the result may reflect selective bias. In the future, we aim to continue combining multicenter, large, randomized controlled studies and may add multiple time points to comprehensively observe the trends concerning PLT, PCT, and DD in patients with severe HS to further validate the significance of combining these three factors.

Authors' Contributions

L.W.: Conception and design of the research, analysis and interpretation of the data, obtaining financing, and writing of the article.

H.J.: Acquisition of data.

Y.S.: Analysis and interpretation of the data.

X.C.: Statistical analysis.

Z.C.: Acquisition of data.

Y.R.: Critical revision of the manuscript for intellectual content.

Y.Z.: Obtaining financing.

Ethics Approval and Consent to Participate

The study complied with medical ethics standards and was approved by the Ethics Committee of the Second Affiliated Hospital of Nantong University (2021KT007), and all tests and treatments were performed by signing an informed consent form. Meanwhile, the study was in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Author Disclosure Statement

No competing financial interests exist.

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References

- Alzeer AH, Hazmi MA, Warsy AS, et al. Serum enzymes in heat stroke: Prognostic implication. *Clin Chem* 1997;43(7): 1182–1187; doi: 10.1016/S0009-9120(97)00018-0.
- American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43(Suppl 1):S14–S31; doi: 10.2337/dc20-S002.
- Bylapudi SK, Nanjan S, Ramasamy S, et al. Role of Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II score in predicting outcomes of peritonitis due to hollow viscous perforation: A prospective observational study. *Cureus* 2021;13(12):e20155; doi: 10.7759/cureus.20155.
- Cho S, Kim YJ, Lee M, et al. Correction to: Cut-off points between pain intensities of the postoperative pain using receiver operating characteristic (ROC) curves. *BMC Anesthesiol* 2021a;21(1):191; doi: 10.1186/s12871-021-01410-w.
- Cho SH, Lim JE, Lee J, et al. Association between high-sensitivity C-reactive protein levels and depression: Moderation by age, sex, obesity, and aerobic physical activity. *J Affect Disord* 2021b;291:375–383; doi: 10.1016/j.jad.2021.05.040.
- Epstein Y, Yanovich R. Heatstroke. *N Engl J Med* 2019; 380(25):2449–2459; doi: 10.1056/NEJMr1810762.
- Filep EM, Murata Y, Endres BD, et al. Exertional heat stroke, modality cooling rate, and survival outcomes: A systematic review. *Medicina (Kaunas)* 2020;56(11):589; doi: 10.3390/medicina56110589.
- Geng Y, Peng N, Liu YN, et al. Physical effort affects heat-stroke thermoregulatory response and mortality in rats. *Shock* 2015;44(2):149–156; doi: 10.1097/SHK.0000000000000387.
- Guclu E, Durmaz Y, Karabay O. Effect of severe sepsis on platelet count and their indices. *Afr Health Sci* 2013;13(2): 333–338; doi: 10.4314/ahs.v13i2.19.
- Hifumi T, Kondo Y, Shimizu K, et al. Heat stroke. *J Intensive Care* 2018;6:30; doi: 10.1186/s40560-018-0298-4.
- Ishikawa D, Takehara Y, Takata A, et al. Combination of dirty mass volume and APACHE II score predicts mortality in patients with colorectal perforation. *World J Emerg Surg* 2021;16(1):17; doi: 10.1186/s13017-021-00359-y.
- Jindal S, Gupta S, Gupta R, et al. Platelet indices in diabetes mellitus: Indicators of diabetic microvascular complications. *Hematology* 2011;16(2):86–89; doi: 10.1179/102453311X12902908412110.
- Keeley A, Hine P, Nsutebu E. The recognition and management of sepsis and septic shock: A guide for non-intensivists. *Postgrad Med J* 2017;93(1104):626–634; doi: 10.1136/postgradmedj-2016-134519.
- Leon LR, Bouchama A. Heat stroke. *Compr Physiol* 2015;5(2): 611–647; doi: 10.1002/cphy.c140017.
- Leon LR, Helwig BG. Heat stroke: Role of the systemic inflammatory response. *J Appl Physiol* (1985) 2010;109(6): 1980–1988; doi: 10.1152/japplphysiol.00301.2010.
- Liu J, Wan M, Zhang Y, et al. Dysfunction of iron metabolism and iron-regulatory proteins in the rat hippocampus after heat stroke. *Shock* 2019;51(6):780–786; doi: 10.1097/SHK.0000000000001182.
- Liu SY, Wang Q, Lou YP, et al. Interpretations and comments for expert consensus on the diagnosis and treatment of heat stroke in China. *Mil Med Res* 2020;7(1):37; doi: 10.1186/s40779-020-00266-4.

- Mozzini C, Xotta G, Garbin U, et al. Non-exertional heatstroke: A case report and review of the literature. *Am J Case Rep* 2017;18:1058–1065; doi: 10.12659/ajcr.905701.
- Pan MZ, Xu HH, Dong CY, et al. Analysis on influencing factors of deaths from severe heat stroke in Shanghai, 2013–2017 [in Chinese]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2019;53(1):93–96; doi: 10.3760/cma.j.issn.0253-9624.2019.01.013.
- Peiris AN, Jaroudi S, Noor R. Heat stroke. *JAMA* 2017;318(24):2503; doi: 10.1001/jama.2017.18780. PMID: 29279936.
- Robine JM, Cheung SL, Le Roy S, et al. Death toll exceeded 70,000 in Europe during the summer of 2003. *C R Biol* 2008;331(2):171–178; doi: 10.1016/j.crv.2007.12.001.
- Scheer CS, Fuchs C, Gründling M, et al. Impact of antibiotic administration on blood culture positivity at the beginning of sepsis: A prospective clinical cohort study. *Clin Microbiol Infect* 2019;25(3):326–331; doi: 10.1016/j.cmi.2018.05.016.
- Tollefson J. Global-warming limit of 2°C hangs in the balance. *Nature* 2015;520(7545):14–15; doi: 10.1038/nature.2015.17202.
- Tudor RM, Thompson CJ. Posterior pituitary dysfunction following traumatic brain injury: Review. *Pituitary* 2019;22(3):296–304; doi: 10.1007/s11102-018-0917-z.
- Voelckel WG, Yannopoulos D, Zielinski T, et al. Inspiratory impedance threshold device effects on hypotension in heat-stroked swine. *Aviat Space Environ Med* 2008;79(8):743–748; doi: 10.3357/asm.2289.2008.
- Wagner M, Kaufmann P, Fickert P, et al. Successful conservative management of acute hepatic failure following exertional heatstroke. *Eur J Gastroenterol Hepatol* 2003;15(10):1135–1139; doi: 10.1097/00042737-200310000-00013.
- Woods SE. Immunosuppression is associated with epigenetic remodelling in a murine model of exertional heat stroke. *J Physiol* 2021;599(5):1373–1374; doi: 10.1113/JP280949.
- Yan F, Shi C, Shi CM, et al. Epidemiological characteristics of heatstroke in Changxing of Zhejiang, 2016–2018. *Chin J PHM* 2020;36(3):419–423; doi: 10.19568/j.cnki.23-1318.2020.03.034.
- Yang QY, Zuo XR, Cao Q. The value of procalcitonin in the differentiation of the cause of fever in patients with severe craniocerebral injury. *J Clin Med Pract* 2012;16(19):120–126; doi: 1672-2353(2012)19-0120-02.
- Yilmaz MB, Cihan G, Guray Y, et al. Role of mean platelet volume in triaging acute coronary syndromes. *J Thromb Thrombolysis* 2008;26(1):49–54; doi: 10.1007/s11239-007-0078-9.
- Yin HM, Lu Y, Shi XZ, et al. Study on dynamic changes of platelet count and function in severe heatstroke rats. *Med J Chin PLA* 2018;43(5):398–402; doi: 10.11855/j.issn.0577-7402.2018.05.07.
- Zhang W, Huo F, Yue Y, et al. Heat stroke in cell tissues related to sulfur dioxide level is precisely monitored by light-controlled fluorescent probes. *J Am Chem Soc* 2020;142(6):3262–3268; doi: 10.1021/jacs.9b13936.
- Zhong L, Wu M, Liu Z, et al. Risk factors for the 90-day prognosis of severe heat stroke: A case-control study. *Shock* 2021;55(1):61–66; doi: 10.1097/SHK.0000000000001589.

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