THERAPEUTIC ADVANCES in
Hematology

Original Research

A nomogram based on lnLDH and lnNLR for predicting disseminated intravascular coagulation in patients with heat stroke

Ther Adv Hematol

2025, Vol. 16: 1–13

DOI: 10.1177/20406207241311386

Lulu Wan, Gan Lin, Jiale Yang, Anwei Liu, Xuezhi Shi, Jinhu Li, Lian Xie, Ronglin Chen and Huasheng Tong

Abstract

Background: Heat stroke (HS), a potentially fatal heat-related illness, is often accompanied by disseminated intravascular coagulation (DIC) early, resulting in a poorer prognosis. Unfortunately, diagnosis by current DIC scores is often too late to identify DIC. This study aims to investigate the predictors and predictive model of DIC in HS to identify DIC early.

Methods: This retrospective study analyzed clinical data of patients with HS in a tertiary hospital from January 1, 2008 to December 31, 2020. Univariate and multivariate logistic regression analyses were employed to identify the risk factors for DIC in HS. The predictive models based on these risk factors were constructed and externally validated, and their predictive efficacy was evaluated using receiver operating characteristic curves.

Results: A total of 219 HS patients, including 49 with DIC, were included. The independent risk factors for DIC were identified as follows: neutrophil percentage (Neu%), lymphocyte count, lymphocyte percentage (Lym%), creatine kinase-MB (CKMB), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), neutrophil–lymphocyte ratio (NLR), monocyte–lymphocyte ratio (MLR), and rhabdomyolysis (RM). After logarithmization, the final predictive model based on the logarithm of lactate dehydrogenase (lnLDH; odds ratio (OR) = 9.266, 95% confidence interval (95%CI; 4.379–19.607), $p < 0.0001$) and the logarithm of neutrophil–lymphocyte ratio (lnNLR; OR = 3.393, 95%CI (1.834–6.277), $p < 0.0001$) was constructed with the largest area under the curve (0.928). A nomogram incorporating lnLDH and lnNLR was developed and showed excellent discrimination and calibration capabilities.

Conclusion: Nine independent risk factors were identified for the occurrence of DIC in HS patients. The predictive model based on lnLDH and lnNLR can effectively predict the incidence of DIC. A nomogram based on lnLDH and lnNLR was developed to facilitate early identification and timely treatment of DIC in HS patients.

Keywords: disseminated intravascular coagulation, heat stroke, nomogram, risk factor

Received: 28 June 2024; revised manuscript accepted: 4 December 2024.

Correspondence to:
Ronglin Chen
Department of Intensive Care Unit, Longgang Central Hospital of Shenzhen, #6082 Longgang Avenue, Longgang District, Shenzhen 518116, Guangdong, China
ronglinch@outlook.com

Huasheng Tong
Department of Intensive Care Unit, General Hospital of Southern Theatre Command of PLA, #111 Liuhua Road, Guangzhou, 510010, Guangdong, China
fimmuths@163.com

Lulu Wan
Department of Intensive Care Unit, Longgang Central Hospital of Shenzhen, Shenzhen, China

Gan Lin
Jinhu Li
Department of Intensive Care Unit, General Hospital of Southern Theatre Command of PLA, Guangzhou, China

The First School of Clinical Medicine, Guangdong Pharmaceutical University, Guangzhou, China

Jiale Yang
Department of Intensive Care Unit, General Hospital of Southern Theatre Command of PLA, Guangzhou, China

Guangzhou University of Chinese Medicine, Guangzhou, China

Anwei Liu
Xuezhi Shi
Department of Intensive Care Unit, General Hospital of Southern Theatre Command of PLA, Guangzhou, China

Introduction

Heat stroke (HS), a fatal heat-related illness, is often characterized by a dramatic increase in core temperature and central nervous system abnormality, accompanied by multiple organ dysfunction.[1] Driven by global warming and extreme climate, the incidence of heat-related illness is increasing. The EMS HeatTracker website reported a statistically significant increase in call rates for heat-related emergency services from 10.5 to 14.9 per 100,000 people between 2018 and 2022.[2] It is concerning that heat-related deaths could increase by approximately 257% by the 2050s.[3]

Lian Xie
Department of Intensive Care Unit, General Hospital of Southern Theatre Command of PLA, Guangzhou, China
The First School of Clinical Medicine, Southern Medical University, Guangzhou, China

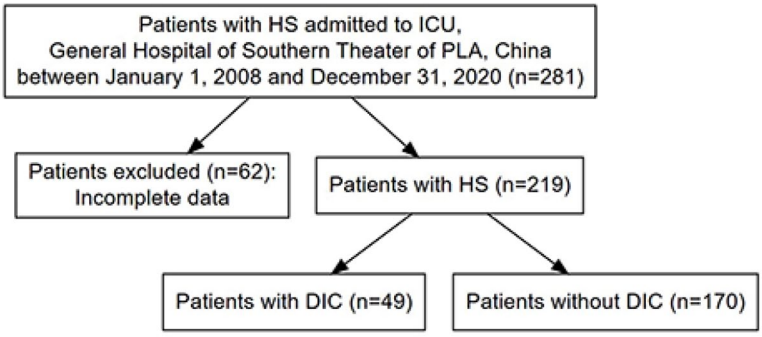

Figure 1. Flow diagram of included and excluded patients with HS.
DIC, disseminated intravascular coagulation; HS, heat stroke; ICU, intensive care unit; PLA, People's Liberation Army.

Several studies have shown that a significant proportion of patients with HS present with disseminated intravascular coagulation (DIC) early,[4] and DIC is also an independent risk factor for in-hospital mortality in HS.[5,6] Therefore, early recognition and treatment of DIC may reduce mortality in HS patients. Currently, the diagnosis of DIC is primarily based on DIC scores proposed by the International Society of Thrombosis and Hemostasis (ISTH) or the Japanese Association for Acute Medicine (JAAM). These scoring systems include platelet count, fibrinogen level, and prothrombin time (PT). However, DIC is not often diagnosed early according to the aforementioned DIC scores.[7] Independent predictive factors for the occurrence of DIC may be helpful in the early detection of DIC, but these factors remain to be elucidated. The current risk factors for DIC in patients with HS were still primarily based on Zeng et al.'s study,[8] which had a small sample size. To gain a more comprehensive understanding of DIC in patients with HS, this study aims to investigate its independent risk factors and establish a prediction model based on logarithm of lactate dehydrogenase (InLDH) and logarithm of neutrophil-lymphocyte ratio (InNLR) to predict the incidence of DIC.

Patients and methods

Patients

Two patient cohorts were examined in this study, a training cohort and a testing cohort. The training cohort used to develop the nomogram consisted of patients with HS diagnosed at the General Hospital of Southern Theatre Command between January 1, 2008 and December 31, 2020. The testing cohort patients for external validation of the nomogram were HS patients recruited at the same tertiary hospital between January 1, 2021 and October 30, 2023, based on the same recruitment criteria as the testing cohort. The clinical data of HS patients who entered into the study were collected, and a flow diagram is presented in Figure 1. The inclusion criteria for HS were as follows: (1) A history of high-intensity exercise or exposure to extreme heat and humid environment. (2) Meet one or more of the following criteria: (a) core temperature >40°C; (b) central nervous system dysfunction such as altered mental status, seizure, or coma; (3) multiple organ dysfunction (such as liver, kidney, rhabdomyolysis (RM), and gastrointestinal tract); and (4) severe coagulation dysfunction or DIC.[9] The exclusion criteria were as follows: (1) Age <18 years old. (2) Carcinoma, severe organ dysfunction, or hematologic system disease existing before the onset of HS. (3) Pregnancy or lactation. (4) Length of hospital stay <24 h. (5) Incomplete data (missing ISTH, Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), or Glasgow Coma Scale (GCS) score, or the loss of clinical data ⩾10%). The training cohort consisted of 219 patients, and the testing cohort consisted of 45 patients. The study's approach and research design were approved by the Medical Ethics Review Committee of the General Hospital of Southern Theater of PLA of China (No. NZLLKZ2022047). Informed consent was waived due to the retrospective design of this study.

Clinical characteristics and laboratory data

The data included general demographic information including age, sex, and underlying diseases, clinical parameters including vital signs, use of mechanical ventilation and vasoactive drugs, transfusion of blood products, serologic tests including blood routine, biochemistry, coagulation indicators, and other hematologic parameters within 24 h of admission. The outcome during the hospitalization in the intensive care unit (ICU) was defined as either survival or death. RM was defined as a creatine kinase (CK) level >1000 U/L. In addition, the patient's APACHE II score, GCS score, SOFA score, and DIC ISTH score were recorded within 24 h of admission. The diagnostic criterion for DIC was an ISTH score ⩾5. The ISTH score is defined as follows: First, Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC? Second, calculate a total score: (1) Platelet count (>100 = 0; <100 = 1; <50 = 2). (2) Elevated fibrin-related marker (e.g., D-dimmer; fibrin degradation products; no increase = 0; moderate increase = 2; strong increase = 3). (3) Prolonged PT (<3 s = 0; >3 but <6 s = 1; >6 s = 2). (4) Fibrinogen level (>1.0 g/L = 0; <1.0 g/L = 1).[10]

Statistical analysis

All data were analyzed using R software (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) and p-value <0.05 was considered statistically significant using a two-tailed test. Missing values that were less than 10% were filled using the Random Forest method from the "mice" package. Variables with missing values more than 10% were excluded. Normal variables were expressed as mean ± standard deviation, and t-tests were used for comparisons between groups. Non-normal variables were expressed as median with interquartile range, and Mann–Whitney U tests were used to compare between groups. Categorical variables were expressed as counts and percentages, and chi-square or Fisher's exact tests were used for between-group comparisons. Variables associated with the incidence of DIC in the univariate logistic regression analysis were included in the multivariate analysis to obtain independent risk factors for DIC. Results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). A predictive model was constructed based on the results of the multivariate logistic regression analysis. The accuracy of the predictive model was assessed using area under the curve (AUC), sensitivity, specificity, and Youden index. A nomogram was constructed to visualize the predictive model. Internal validation was performed by repeating the sampling 1000 times using the bootstrap method. Consistency was evaluated using the calibration curve plotted with the "rms" package. External validation was performed with additional data.

Results

Baseline characteristics of patients with HS

Of the 281 eligible patients, 219 patients were included in the final analysis, 49 of whom (22.4%) had DIC. The baseline demographic, clinical, and biochemical data are summarized in Table 1. The HS patients with DIC (13 (26.5%) cases) had a higher in-hospital mortality rate than the HS patients without DIC (10 (5.9%) cases, $p < 0.001$). Patients with DIC were more likely to develop coagulation disorders than those without DIC, showing longer PT (27.00 (21.40–34.10) vs 13.70 (11.90–15.38) s, $p < 0.001$) and activated partial thromboplastin time (APTT; 76.1 (46.00–120.90) vs 31.50 (26.20–38.27) s, $p < 0.001$), higher D-dimer (13.21 (7.64–20.00) vs 0.62 (0.28–2.28) μg/mL, $p < 0.001$), and lower fibrinogen (Fib; 2.10 (1.50–2.55) vs 2.60 (2.12–3.19) g/L, $p < 0.001$). Compared to the patients without DIC, the patients with DIC had lower hemoglobin (Hb) level (130.00 (114.00–141.00) vs145.00 (130.00–159.75) g/L, $p < 0.001$), lower hematocrit (HCT; (39.00 (34.00–42.00) vs 43.00 (38.70–46.00) %, $p < 0.001$), and lower platelet (45.00 (27.00–80.00) vs 205.50 (158.25–240.75) $\times 10^9$/L, $p < 0.001$). The incidence of transfusion of blood products (plasma 15 (30.6%) vs 8 (4.7%) cases, $p < 0.001$, platelets 11 (22.4%) vs 7 (4.1%) cases, $p < 0.001$, cryoprecipitate 13 (26.5%) vs 3 (1.8%) cases, $p < 0.001$)) in patients with DIC were significantly higher compared to those without DIC. Decreased Hb and HCT levels and increased plasma lactate dehydrogenase (LDH) levels (1148.00 (580.00–2243.00) vs 291.00 (230.50–401.75) U/L, $p < 0.001$) were found in patients with DIC, indicating massive destruction of red blood cells. Plasma aspartate aminotransferase (AST) levels (627.00 (167.00–2429.00) U/L) in the patients with DIC were

Table 1. Baseline characteristics in HS patients with DIC and without DIC.

Variables	Total (*N* = 219)	Without DIC (*N* = 170)	With DIC (*N* = 49)	*p*-Value
Death, *N* (%)	23 (10.5)	10 (5.9)	13 (26.5)	<0.001
Sex: female, *N* (%)	10 (4.6)	9 (5.3)	1 (2.0)	0.567
Underlying disease, *N* (%)	42 (19.2)	33 (19.4)	9 (18.4)	1
Vasoactive drugs, *N* (%)	24 (11.0)	14 (8.2)	10 (20.4)	0.032
Mechanical ventilation, *N* (%)	31 (14.2)	20 (11.8)	11 (22.4)	0.097
Transfusion of blood products				
Plasma, *N* (%)	23 (10.5)	8 (4.7)	15 (30.6)	<0.001
Platelet, *N* (%)	18 (8.2)	7 (4.1)	11 (22.4)	<0.001
Cryoprecipitate, *N* (%)	16 (7.3)	3 (1.8)	13 (26.5)	<0.001
DIC, *N* (%)	49 (22.4)	0 (0.0)	49 (100.0)	<0.001
RM, *N* (%)	77 (35.2)	40 (23.5)	37 (75.5)	<0.001
Length of ICU stay, days	4.00 (1.00–7.00)	3.00 (0.00–5.00)	8.00 (6.00–15.00)	<0.001
Length of hospital stay, days	7.00 (3.00–15.00)	5.00 (2.00–12.00)	17.00 (10.00–49.00)	<0.001
Age, years	30.00 (21.00–48.00)	31.00 (21.00–49.00)	26.00 (22.00–39.00)	0.199
APACHE II score	9.00 (5.00–17.00)	7.00 (4.00, 15.00)	13.00 (8.00–19.00)	0.003
SOFA score	3.00 (2.00–7.00)	3.00 (2.00–5.00)	7.00 (5.00–9.00)	<0.001
GCS score	15.00 (7.00–15.00)	15.00 (9.00–15.00)	8.00 (4.00–15.00)	<0.001
ISTH score	2.00 (0.00–4.00)	0.00 (0.00–2.00)	6.00 (5.00–7.00)	<0.001
Admission temperature, °C	37.00 (36.60–38.00)	37.00 (36.50–37.98)	37.30 (36.90–38.00)	0.151
MAP, mmHg	87.40 (15.52)	87.39 (15.82)	87.44 (14.58)	0.986
HR, beats/min	85.00 (74.50–110.50)	82.50 (73.25–102.75)	102.00 (85.00–124.00)	0.003
RR, breaths/min	20.00 (20.00–22.00)	20.00 (20.00–22.00)	20.00 (20.00–21.00)	0.66
WBC, $\times 10^9$/L	11.32 (8.14–14.84)	11.49 (7.83–15.35)	11.15 (8.47–13.73)	0.501
Neutrophil, $\times 10^9$/L	8.78 (5.84–12.48)	8.59 (5.44–12.49)	9.97 (7.23–12.12)	0.214
Neu%, %	82.90 (71.80–88.10)	78.55 (65.95–85.65)	89.50 (85.40–92.90)	<0.001
Monocyte, $\times 10^9$/L	0.54 (0.31–0.76)	0.56 (0.34–0.76)	0.42 (0.21–0.76)	0.054
Mono%, %	4.70 (3.30–6.30)	4.70 (3.70–6.30)	4.60 (2.20–6.50)	0.142
Lymphocyte, $\times 10^9$/L	1.32 (0.72–2.12)	1.58 (1.02–2.38)	0.54 (0.34–0.96)	<0.001
Lym%, %	11.10 (5.70–23.00)	14.05 (8.50–27.70)	4.90 (4.10–7.60)	<0.001

(Continued)

Table 1. (Continued)

Variables	Total (*N* = 219)	Without DIC (*N* = 170)	With DIC (*N* = 49)	*p*-Value
HCT, %	42.00 (37.30–45.30)	43.00 (38.70–46.00)	39.00 (34.00–42.00)	<0.001
Hb, g/L	141.00 (126.00–156.00)	145.00 (130.00–159.75)	130.00 (114.00–141.00)	<0.001
PLT, $\times 10^9$/L	178.00 (90.00–229.00)	205.50 (158.25–240.75)	45.00 (27.00–80.00)	<0.001
CK, U/L	582.00 (241.00–1864.50)	345.50 (205.50–907.25)	2342.00 (1064.00–4995.00)	<0.001
CKMB, ng/mL	19.60 (4.75–49.70)	15.00 (3.55–29.00)	74.00 (39.00–204.00)	<0.001
LDH, U/L	334.00 (245.50–587.50)	291.00 (230.50–401.75)	1148.00 (580.00–2243.00)	<0.001
AST, U/L	66.00 (28.00–205.50)	41.00 (26.00–93.00)	627.00 (167.00–2429.00)	<0.001
Cr, μmol/L	130.00 (93.50–186.00)	128.50 (91.25–180.75)	147.00 (108.00–201.00)	0.06
Glu, mmol/L	6.16 (5.30–8.05)	6.25 (5.32–8.49)	5.60 (4.80–7.20)	0.007
APTT, s	35.40 (27.80–43.30)	31.50 (26.20–38.27)	76.10 (46.00–120.90)	<0.001
PT, s	14.70 (12.50–18.85)	13.70 (11.90–15.38)	27.00 (21.40–34.10)	<0.001
Fib, g/L	2.50 (2.06–3.06)	2.60 (2.12–3.19)	2.10 (1.50–2.55)	<0.001
D-dimer, μg/mL	1.02 (0.36–5.70)	0.62 (0.28–2.28)	13.21 (7.64–20.00)	<0.001
INR	1.18 (1.04–1.58)	1.10 (1.01–1.26)	2.42 (1.86–3.44)	<0.001
NLR	7.51 (3.15–15.76)	5.69 (2.39–10.34)	17.34 (10.39–23.19)	<0.001
PLR	116.49 (72.83–182.82)	119.33 (83.28–187.89)	75.93 (36.36–160.00)	0.005
MLR	0.40 (0.20–0.77)	0.31 (0.17–0.62)	0.73 (0.40–1.45)	<0.001

APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK, creatine kinase; CKMB, creatine kinase-MB; Cr, creatinine; DIC, disseminated intravascular coagulation; Fib, fibrinogen; GCS, Glasgow Coma Scale; Glu, glucose; Hb, hemoglobin; HCT, hematocrit; HR, heart rate; HS, heat stroke; ICU, intensive care unit; INR, international normalized ratio; ISTH, International Society of Thrombosis and Hemostasis; LDH, lactate dehydrogenase; Lym%, lymphocyte percentage; MAP, mean arterial pressure; MLR, monocyte–lymphocyte ratio; Mono%, monocyte percentage; Neu%, neutrophil percentage; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; PLT, platelet; PT, prothrombin time; RM, rhabdomyolysis; RR, respiratory rate; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.

higher than in those without DIC (41.00 (26.00–93.00) U/L, $p < 0.001$). The patients with DIC also had higher incidence rates of RM (37 (75.5%) vs 40 (23.5%) cases, $p < 0.001$) and creatine kinase-MB (CKMB) levels (74.00 (39.00–204.00) vs 15.00 (3.55–29.00) ng/mL, $p < 0.001$). Although there were no significant differences in white blood cell (WBC) count, neutrophil, or monocyte counts between the two groups, the patients with DIC had significantly decreased lymphocyte counts, percentages, and platelet–lymphocyte ratio (PLR), while their neutrophil–lymphocyte ratio (NLR) and monocyte–lymphocyte ratio (MLR) were higher compared to those without DIC. These findings suggest that the patients with DIC suffer more severe inflammatory response. Compared to the patients without DIC, the patients with DIC had significantly higher APACHE II (13 (8–19) vs 7 (4–15), $p = 0.003$), ISTH (6 (5–7) vs 0 (0–2), $p < 0.001$), and SOFA (7 (5–9) vs 3 (2–5), $p < 0.001$) scores, as well as longer hospital stay (17 (10–49) vs 5 (2–12) days, $p < 0.001$) and length of ICU stay (8 (6–15) vs 3 (0–5) days, $p < 0.001$), while the GCS score (8 (4–15) vs 15 (9–15), $p < 0.001$) showed an opposite trend, indicating that the patients with DIC had more severe organ injury and central nervous system

injury, and higher mortality rates. Although there was no significant difference in mean arterial pressure between the two groups, patients with DIC required more vasoactive drugs (20.40% vs 8.20%, $p = 0.032$).

Independent predictors in HS patients with DIC

The results of the univariate logistic regression model are shown in Table 2. LDH was passively correlated with DIC in HS patients (OR = 1.003, 95%CI (1.002–1.004), $p < 0.0001$). The variables with $p < 0.05$ in the univariate logistic regression model were checked for multicollinearity using linear regression and then added into multivariate analysis. In the adjusted models, nine independent predictors were confirmed in multivariate analysis, including neutrophil percentage (Neu%), lymphocyte, lymphocyte percentage (Lym%), CKMB, LDH, AST, NLR, MLR, and RM, which were identified as the independent risk factors for onset of DIC (Table 3). LDH (OR = 1.004, 95%CI (1.001–8.006), $p < 0.01$), NLR (OR = 1.582, 95%CI (1.282–11.953), $p < 0.001$), MLR (OR = 11.581, 95%CI (3.011–12.543), $p < 0.01$), and RM (OR = 13.943, 95%CI (2.646–13.479), $p < 0.01$) were found to be independent risk factors of DIC in HS patients, indicating that HS patients with tissue damage, severe inflammatory response or RM are more likely to develop DIC.

Establishing and validating nomogram

In accordance with Harrell's guideline, which was applied due to the limited number of outcome events, two variables were selected to construct the model. LDH is a marker of cellular damage and an independent risk factor for DIC in HS patients. We wanted to investigate whether LDH could be involved in predicting DIC in HS patients. The predictive models were constructed by combining LDH and one of the above independent predictors. The model combining LDH and NLR achieved the highest AUC value, indicating that the model is the most reliable predictive tool for DIC in HS patients. LDH and NLR took a wide range of values, so their values were logarithmically transformed to facilitate analysis. Finally, a predictive model based on InLDH (OR = 9.266, 95%CI (4.379–19.607), $p < 0.0001$) and InNLR (OR = 3.393, 95%CI (1.834–6.277), $p < 0.0001$) was constructed, with an AUC of 0.928 (Tables 4 and 5). The incidence of DIC in patients with HS was assessed by summing the InLDH and InNLR scores calculated from the nomogram (Figure 2(a)). The nomogram, consisting of only two indicators, showed good predictive power with an AUC of 0.928 (Figure 2(b)). The predictive model was externally validated, yielding an AUC of 0.895 (Figure 2(c)). The calibration curve showed no deviation from the reference line, and there was good consistency between the predicted and observed values of the prediction model (Figure 2(d)). More information about this model was presented in the supplemental material.

Discussion

In this study, we found a high morbidity of DIC (22.4%) in patients with HS. The in-hospital mortality of HS patients with DIC (26.5%) was higher than that of patients without DIC (5.9%). After adjustment for the confounders, nine independent risk factors for DIC were identified, including Neu%, lymphocyte count, Lym%, CKMB, LDH, AST, NLR, MLR, and RM. The predictive model based on InLDH and InNLR with the largest AUC was established to predict the incidence of DIC, which was verified to have good consistency.

DIC is an early common complication in HS and occurs in approximately 11.2%–30% of patients with HS.[5,11,12] Our study found a similar result (22.4%) for the incidence of DIC. Zeng et al.[8] found that the mortality of patients with DIC was about 47.4%, which was significantly higher than that of patients without DIC.[13] Consistent with the previous studies, our study found a high mortality (26.5%) of DIC in patients with HS. Several studies have found that DIC was an independent risk factor for mortality in patients with HS.[6,14] DIC, an early event in HS, is characterized by extensive microthrombosis. On the one hand, early massive consumption of coagulation factors and platelets may lead to a hypocoagulable state and trigger bleeding, and secondary fibrinolytic antagonism may further exacerbate bleeding. On the other hand, extensive microthrombosis may impair tissue perfusion and promote the development of multiple organ dysfunction syndrome (MODS).[15,16]

DIC plays a significant role in the progression of HS, but the current diagnostic criteria are too late to diagnose DIC. Therefore, exploring predictive

Table 2. Univariate logistic analysis of factors associated with in-hospital incidence of DIC in HS patients.

Variables	OR	CI	*p*-Value
Transfusion of blood products			
Plasma, *N* (%)	8.934	3.51–22.742	<0.001
Platelet, *N* (%)	6.741	2.452–18.531	<0.001
Cryoprecipitate, *N* (%)	20.102	5.445–74.207	<0.001
Length of ICU stay, days	1.175	1.1–1.254	<0.001
Length of hospital stay, days	1.052	1.03–1.074	<0.001
SOFA score	1.381	1.238–1.541	<0.001
GCS score	0.860	0.802–0.921	<0.001
Neu%, %	1.167	1.1–1.237	<0.001
Lymphocyte, $\times 10^9$/L	0.186	0.098–0.352	<0.001
Lym%, %	0.847	0.791–0.907	<0.001
HCT, %	0.913	0.872–0.955	<0.001
Hb, g/L	0.972	0.959–0.985	<0.001
PLT, $\times 10^9$/L	0.959	0.947–0.971	<0.001
CKMB, ng/mL	1.008	1.004–1.011	<0.001
LDH, U/L	1.003	1.002–1.004	<0.001
AST, U/L	1.003	1.002–1.004	<0.001
APTT, s	1.042	1.026–1.059	<0.001
PT, s	1.690	1.433–1.993	<0.001
D-dimer, μg/mL	1.146	1.089–1.206	<0.001
INR	5.593	3.151–9.928	<0.001
NLR	1.093	1.054–1.133	<0.001
MLR	2.399	1.539–3.739	<0.001
RM, *N* (%)	10.021	4.775–21.031	<0.001
Glu, mmol/L	0.803	0.684–0.942	0.007
HR, beats/min	1.014	1.003–1.024	0.013
Vasoactive drugs, *N* (%)	2.857	1.18–6.917	0.02
APACHE II score	1.037	1.002–1.074	0.038

(Continued)

Table 2. (Continued)

Variables	OR	CI	*p*-Value
CK, U/L	1	1–1	0.136
Fib, g/L	1.040	0.974–1.109	0.242
PLR	0.998	0.995–1.002	0.341

APACHE, Acute Physiology and Chronic Health Evaluation; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CI, confidence interval; CK, creatine kinase; CKMB, creatine kinase-MB; DIC, disseminated intravascular coagulation; Fib, fibrinogen; GCS, Glasgow Coma Scale; Glu, glucose; Hb, hemoglobin; HCT, hematocrit; HR, heart rate; HS, heat stroke; ICU, intensive care unit; INR, international normalized ratio; LDH, lactate dehydrogenase; Lym%, lymphocyte percentage; MLR, monocyte–lymphocyte ratio; Neu%, neutrophil percentage; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; PLR, platelet–lymphocyte ratio; PLT, platelet; PT, prothrombin time; RM, rhabdomyolysis; SOFA, Sequential Organ Failure Assessment.

Table 3. Multivariate logistic analysis of factors associated with in-hospital incidence of DIC in HS patients.

Variables	DIC, OR (95%CI)			
	Univariate	Adjust I[a]	Adjust II[b]	Adjust III[c]
HR, beats/min	1.014 (1.003–1.024)*	1 (0.981–1.019)	1.019 (0.993–1.046)	1.042 (1.006–1.079)*
Neu%, %	1.167 (1.1–1.237)***	1.166 (1.082–1.257)***	1.235 (1.106–2.379)***	1.652 (1.224–2.229)**
Lymphocyte, $\times 10^9$/L	0.186 (0.098–0.352)***	0.257 (0.127–0.522)***	0.231 (0.091–3.585)**	0.061 (0.013–3.283)***
Lym%, %	0.847 (0.791–0.907)***	0.865 (0.802–0.933)***	0.825 (0.743–4.917)***	0.658 (0.517–4.838)**
HCT, %	0.913 (0.872–0.955)***	0.983 (0.924–1.045)	1.016 (0.939–5.099)	1.005 (0.915–5.105)
Hb, g/L	0.972 (0.959–0.985)***	0.991 (0.974–1.009)	0.997 (0.975–6.019)	0.99 (0.962–6.018)
CKMB, ng/mL	1.008 (1.004–1.011)***	1.005 (1.002–1.009)**	1.005 (1.001–7.008)**	1.007 (1.002–7.012)**
LDH, U/L	1.003 (1.002–1.004)***	1.003 (1.001–1.004)***	1.003 (1.001–8.004)**	1.004 (1.001–8.006)**
AST, U/L	1.003 (1.002–1.004)***	1.002 (1.001–1.003)***	1.002 (1.001–9.004)**	1.002 (1.001–9.004)**
Glu, mmol/L	0.803 (0.684–0.942)**	0.794 (0.653–0.965)*	0.755 (0.577–10.988)*	0.76 (0.572–10.011)
NLR	1.093 (1.054–1.133)***	1.096 (1.043–1.151)***	1.115 (1.041–11.194)**	1.582 (1.282–11.953)***
MLR	2.399 (1.539–3.739)***	2.083 (1.201–3.612)**	2.203 (1.077–12.506)*	11.581 (3.011–12.543)***
RM, *N* (%)	10.021 (4.775–21.031)***	6.769 (2.829–16.194)***	8.937 (2.597–13.748)**	13.943 (2.646–13.479)**

[a]Adjusted for APACHE II score, SOFA score, GCS score, underlying disease, sex, outcome, and age.
[b]Further adjusted for vasoactive drugs, mechanical ventilation, plasma, platelet, cryoprecipitate, LOI, and LOH.
[c]Further adjusted for admission temperature, CK, Cr, and PLR.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.
APACHE, Acute Physiology and Chronic Health Evaluation; AST, aspartate aminotransferase; CI, confidence interval; CK, creatine kinase; CKMB, creatine kinase-MB; Cr, creatinine; DIC, disseminated intravascular coagulation; GCS, Glasgow Coma Scale; Glu, glucose; Hb, hemoglobin; HCT, hematocrit; HR, heart rate; HS, heat stroke; ICU, intensive care unit; LDH, lactate dehydrogenase; LOH, length of hospital stay; LOI, length of ICU stay; Lym%, lymphocyte percentage; MLR, monocyte–lymphocyte ratio; Neu%, neutrophil percentage; NLR, neutrophil–lymphocyte ratio; OR, odds ratio; PLR, platelet–lymphocyte ratio; RM, rhabdomyolysis; SOFA, Sequential Organ Failure Assessment.

Table 4. Prediction model based on lnLDH and lnNLR.

Variable	β	OR	95%CI	*p*-Value
lnLDH	2.2264	9.266	4.379–19.607	<0.0001
lnNLR	1.2216	3.393	1.834–6.277	<0.0001
Constant	−18.0069			<0.0001

β, regression coefficient; CI, confidence interval; lnLDH, logarithm of lactate dehydrogenase; lnNLR, logarithm of neutrophil–lymphocyte ratio; OR, odds ratio.

Table 5. Comparison of ROCs between the prediction model, lnLDH and lnNLR.

Variable	AUC	95%CI	*p*-Value	SEN (%)	SPE (%)	YI
Prediction model	0.928	0.883–0.973	<0.001	87.8	85.3	0.731
lnLDH	0.904	0.85–0.958	<0.001	81.6	87.6	0.692
lnNLR	0.806	0.742–0.871	<0.001	79.6	73.5	0.531

AUC, area under the curve; CI, confidence interval; lnLDH, logarithm of lactate dehydrogenase; lnNLR, logarithm of neutrophil–lymphocyte ratio; ROC, receiver operating characteristic; SEN, sensitivity; SPE, specificity; YI, Youden Index.

markers and building predictive models for early detection and timely treatment of DIC may be hopeful. In the present study, we found that Neu%, lymphocyte count, Lym%, CKMB, LDH, AST, NLR, MLR, and RM were independently associated with the onset of DIC in HS, indicating that HS patients with DIC had more severe cell damage, hepatic impairment, and RM, impaired immune function, and higher disease severity and in-hospital mortality. As we know, heat stress and intense physical activity induce rhabdomyocyte destruction in HS, and high morbidity of RM (31%) in HS.[17] DIC is one of the complications of RM, and coagulation abnormalities have been reported in HS patients with RM syndrome in several cases.[18,19] Acute liver injury was frequently induced by HS, manifested by elevated alanine aminotransferase (ALT) and AST.[20] Acute liver injury was always accompanied by coagulation dysfunction, which may be partly related to coagulation factor deficiency.[21]

LDH is a biomarker of cell injury. Elevated LDH was frequently observed in HS patients, and LDH was significantly higher in non-survivors than in survivors,[22] which may be related to extensive vascular endothelial cell damage directly caused by hyperthermia. Initial LDH had been identified as an independent risk factor for COVID-19-associated coagulopathy.[23] In our study, LDH was found to be an independent risk factor for HS-associated DIC. Several studies have supported that endothelial injury was a core aspect of DIC in HS patients. Caspase-dependent endothelial cell injury and extensive microthrombosis were observed in animals with HS.[24] Several studies have described that elevated markers of endothelial injury were observed in vivo and in vitro, such as circulating angiotensin-converting enzyme, von Willebrand factor (vWF) antigen, and thrombomodulin.[25,26] The main factors involved in coagulation are endothelial cells, platelets, and coagulation factors. Endothelial cell injury can be induced by HS.[27] Injured endothelial cells express tissue factor (TF), which promotes the exogenous coagulation process involving coagulation factor VII.[28] Injured endothelial cells lose their intrinsic anticoagulant properties and are converted to a procoagulant state, promoting intravascular coagulation.[29] Injured endothelial cells also release vWF, which mediates platelet binding to subendothelial collagen, leading to platelet adhesion, aggregation, and thrombus formation.[30] Extensive vascular

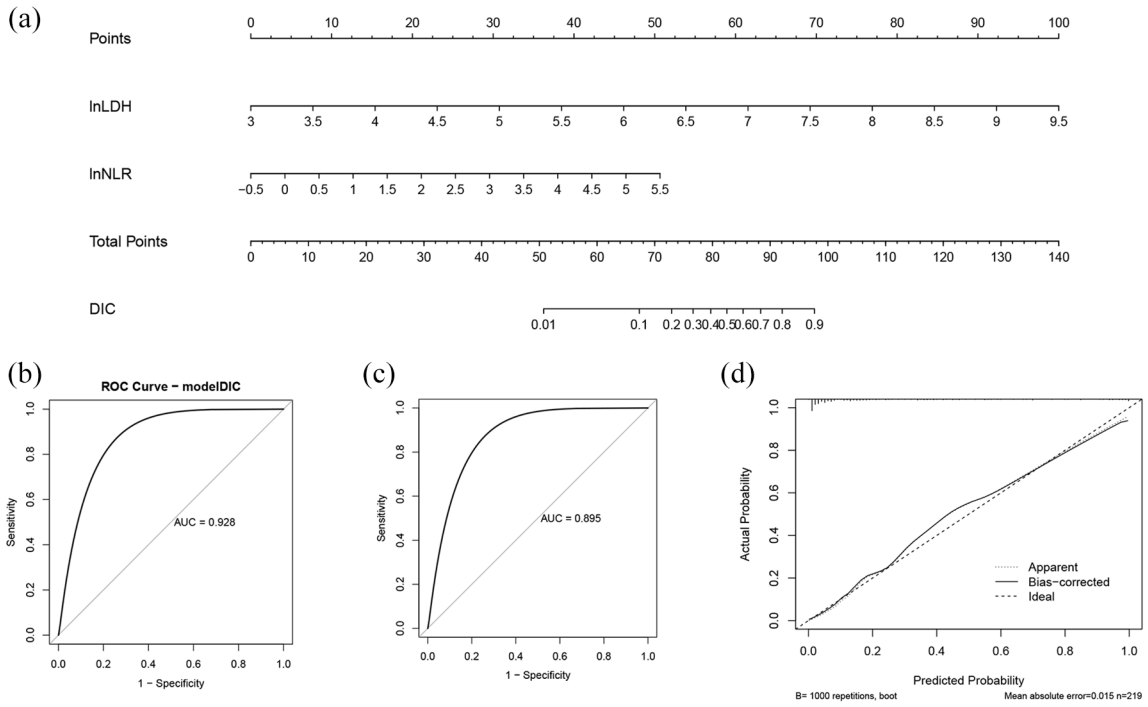

Figure 2. Assessment of a nomogram based on lnLDH and lnNLR of DIC in patients with HS. (a) Nomogram for predicting DIC in HS patients. (b) ROC curve assessing the ability of the nomogram to predict DIC. (c) ROC curve for the external validation of the model. (d) Calibration curves of the prediction model.
DIC, disseminated intravascular coagulation; HS, heat stroke; lnLDH, logarithm of lactate dehydrogenase; lnNLR, logarithm of neutrophil–lymphocyte ratio; ROC, receiver operating characteristic.

endothelial damage, massive platelet activation, and massive coagulation factor depletion may promote the formation of DIC.[24]

Hyperthermia-induced inflammatory and coagulation cascades based on vascular endothelial injury play a critical role in the pathogenesis of HS. Animal models of HS exhibited intense inflammatory responses, massive microthrombosis, extensive endothelial damage, and multiple organ injury.[24,31] NLR is an inflammatory marker at an early stage and has been identified as a prognostic biomarker in several inflammatory diseases, including sepsis and COVID-19.[32,33] In this study, we found that NLR was associated with the presence of DIC. There was no statistically significant difference in neutrophil count between the DIC and non-DIC patients. Increased NLR in HS patients with DIC may be associated with decreased lymphocyte counts. Lymphocytes play an important role in acquired immunity and influence the disease state. Jing et al. found that persistently decreased lymphocyte was associated with poor prognosis of HS patients.[34] Lymphocytes can be categorized as T cells, B cells, NK cells, etc., with T cells accounting for the largest proportion. It was found that T-cell-deficient animals had more severe organ dysfunction after heat stress, which may be related to the excessive inflammatory response caused by T-cell deficiency.[35] Severe inflammatory changes and excessive inflammatory cytokines had been observed during HS.[24,36] Inflammatory responses can promote platelet production and activation through several pathways. Activated leukocytes can release platelet-activating factors, which promote platelet activation and aggregation. The activity of blood coagulation factors is increased at the site of inflammation. Inflammation can mediate endothelial cell dysfunction, and inflammatory factors can induce the expression of TF in endothelial cells, while TF can initiate the coagulation cascade response to promote thrombosis.

Our research found several independent risk factors for the incidence of DIC in patients with HS. InLDH and InNLR were ultimately selected to construct the predictive model of DIC, which was also consistent with the pathophysiological mechanisms underlying HS. The predictive model, with high predictive efficiency, consisted of two factors that could be acquired early. Zeng et al.[8] included 87 patients and developed a nomogram consisting of maximum amplitude, ALT, total bilirubin, creatine, and albumin to predict the incidence of DIC in patients with HS (AUC:0.976, 95%CI:0.948–1.000). However, our current study still has some advantages. First, our sample size was larger, but it is still a small sample study, and the inclusion of too many variables for modeling may increase the risk of error. Second, more comprehensive inflammatory indicators were included in the analysis to account for the crosstalk between inflammation and coagulation. Our patients were younger, with higher GCS scores and lower APACHE II scores, exhibiting less severe organ dysfunction and more severe immune dysfunction.

This study has several limitations. First, it is a single-center, small-sample study, which only represents the clinical characteristics of patients with HS in the Southeast of China. Meanwhile, some variables were excluded due to partial missing data. Second, the patients with HS included in this study were mainly patients with exertional HS due to regional and hospital specificities, which may affect the extrapolation to the whole HS population. Finally, only static clinical and laboratory indicators within 24 h of admission were analyzed instead of dynamic data. More cases and data need to be included in the future.

Conclusion

In conclusion, the HS patients with DIC had a higher mortality than HS patients without DIC. The InLDH and InNLR were independent risk factors for the presence of DIC in HS patients. The prediction model based on InLDH and InNLR can effectively predict the incidence of DIC in HS patients.

Declarations

Ethics approval and consent to participate

The study's approach and research design were approved by the Medical Ethics Review Committee of the General Hospital of Southern Theater of PLA of China (No. NZLLKZ2022047). Informed consent was waived due to the retrospective design of this study.

Consent for publication

Not applicable.

Author contributions

Lulu Wan: Conceptualization; Investigation; Methodology; Writing – original draft.

Gan Lin: Formal analysis; Writing – original draft.

Jiale Yang: Formal analysis; Writing – original draft.

Anwei Liu: Formal analysis; Writing – original draft.

Xuezhi Shi: Investigation; Writing – original draft.

Jinhu Li: Investigation; Writing – original draft.

Lian Xie: Investigation; Writing – original draft.

Ronglin Chen: Funding acquisition; Investigation; Writing – review & editing.

Huasheng Tong: Funding acquisition; Investigation; Writing – review & editing.

Acknowledgement

None.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Natural Science Foundation of Guangdong Province (2022A1515010353, 2024A1515012909), the Science and Technology Program of Guangzhou City (2024A03J0643), and the Construction Fund of Key Medical Disciplines of Shenzhen Longgang District. The funding bodies had no specific role in the design of the study, collection, analysis and interpretation of data, and manuscript writing.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to

ethical restrictions but are available from the corresponding author on reasonable request.

ORCID iD
Lulu Wan https://orcid.org/0000-0001-9029-8581

Supplemental material
Supplemental material for this article is available online.

References

1. Bouchama A, Abuyassin B, Lehe C, et al. Classic and exertional heatstroke. *Nat Rev Dis Primers* 2022; 8: 8.
2. Harris E. New federal dashboard tracks heat-related illness in US. *JAMA* 2023; 330: 905.
3. Hajat S, Vardoulakis S, Heaviside C, et al. Climate change effects on human health: projections of temperature-related mortality for the UK during the 2020s, 2050s and 2080s. *J Epidemiol Community Health* 2014; 68: 641–648.
4. Sithinamsuwan P, Piyavechviratana K, Kitthaweesin T, et al. Exertional heatstroke: early recognition and outcome with aggressive combined cooling—a 12-year experience. *Mil Med* 2009; 174: 496–502.
5. Lin QW, Zhong LC, He LP, et al. A newly proposed heatstroke-induced coagulopathy score in patients with heat illness: a multicenter retrospective study in China. *Chin J Traumatol*: 2024; 27(2): 83–90.
6. Wu X, Qian J, He S, et al. Prediction of in-hospital mortality in patients with exertional heatstroke: a 13-year retrospective study. *Int J Environ Health Res*: 2024; 34(6): 2451–2462.
7. Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001; 86: 1327–1330.
8. Zeng Q, Zhong L, Zhang N, et al. Nomogram for predicting disseminated intravascular coagulation in heatstroke patients: a 10 years retrospective study. *Front Med (Lausanne)* 2023; 10: 1150623.
9. Liu SY, Song JC, Mao HD, et al. Expert consensus on the diagnosis and treatment of heat stroke in China. *Mil Med Res* 2020; 7: 1.
10. Toh CH and Hoots WK; SSC on Disseminated Intravascular Coagulation of the ISTH. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. *J Thromb Haemost* 2007; 5: 604–606.
11. Al-Mashhadani SA, Gader AG, Al Harthi SS, et al. The coagulopathy of heat stroke: alterations in coagulation and fibrinolysis in heat stroke patients during the pilgrimage (Haj) to Makkah. *Blood Coagul Fibrinolysis* 1994; 5: 731–736.
12. Yezli S, Yassin Y, Ghallab S, et al. Classic heat stroke in a desert climate: a systematic review of 2632 cases. *J Intern Med* 2023; 294: 7–20.
13. He L, Lin Q, Zhong L, et al. Thromboelastography maximum amplitude as an early predictor of disseminated intravascular coagulation in patients with heatstroke. *Int J Hyperthermia* 2022; 39: 605–610.
14. Hifumi T, Kondo Y, Shimazaki J, et al. Prognostic significance of disseminated intravascular coagulation in patients with heat stroke in a nationwide registry. *J Crit Care* 2018; 44: 306–311.
15. Bouchama A, Bridey F, Hammami MM, et al. Activation of coagulation and fibrinolysis in heatstroke. *Thromb Haemost* 1996; 76: 909–915.
16. Iba T, Helms J, Levi M, et al. The role of platelets in heat-related illness and heat-induced coagulopathy. *Thromb Res* 2023; 231: 152–158.
17. Thongprayoon C, Petnak T, Kanduri SR, et al. Impact of rhabdomyolysis on outcomes of hospitalizations for heat stroke in the United States. *Hosp Pract (1995)* 2020; 48: 276–281.
18. Masood U, Sharma A, Syed W, et al. Bowel ischemia from heat stroke: a rare presentation of an uncommon complication. *Case Rep Med* 2016; 2016: 5217690.
19. 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.
20. Tong H, Tang Y, Chen Y, et al. Hmgb1 activity inhibition alleviating liver injury in heatstroke. *J Trauma Acute Care Surg* 2013; 74: 801–807.
21. Ribeiro F, Bibi M, Pereira M, et al. Severe acute liver injury related to heat stroke. *Eur J Case Rep Intern Med* 2020; 7: 001382.
22. Liu S, Xing L, Wang J, et al. The relationship between 24-hour indicators and mortality in patients with exertional heat stroke. *Endocr Metab Immune Disord Drug Targets* 2022; 22: 241–246.

23. Tor YB, Ozbalak M, Kalayoglu-Besisik S, et al. Independent risk factors for Covid-19-associated coagulopathy. *Eur Rev Med Pharmacol Sci* 2023; 27: 7851–7860.
24. Roberts GT, Ghebeh H, Chishti MA, et al. Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. *Arterioscler Thromb Vasc Biol* 2008; 28: 1130–1136.
25. Shieh SD, Shiang JC, Lin YF, et al. Circulating angiotensin-converting enzyme, Von Willebrand factor antigen and thrombomodulin in exertional heat stroke. *Clin Sci (Lond)* 1995; 89: 261–265.
26. Bouchama A, Hammami MM, Haq A, et al. Evidence for endothelial cell activation/injury in heatstroke. *Crit Care Med* 1996; 24: 1173–1178.
27. Pei Y, Geng Y and Su L. Pyroptosis of huvecs can be induced by heat stroke. *Biochem Biophys Res Commun* 2018; 506: 626–631.
28. Bouchama A, Al-Mohanna F, Assad L, et al. Tissue factor/factor VIIa pathway mediates coagulation activation in induced-heat stroke in the baboon. *Crit Care Med* 2012; 40: 1229–1236.
29. Bombeli T, Karsan A, Tait JF, et al. Apoptotic vascular endothelial cells become procoagulant. *Blood* 1997; 89: 2429–2442.
30. Savage B, Almus-Jacobs F and Ruggeri ZM. Specific synergy of multiple substrate-receptor interactions in platelet thrombus formation under flow. *Cell* 1998; 94: 657–666.
31. Bouchama A, Roberts G, Al Mohanna F, et al. Inflammatory, hemostatic, and clinical changes in a baboon experimental model for heatstroke. *J Appl Physiol (1985)* 2005; 98: 697–705.
32. Huang Z, Fu Z, Huang W, et al. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. *Am J Emerg Med* 2020; 38: 641–647.
33. Liu Y, Du X, Chen J, et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with Covid-19. *J Infect* 2020; 81: e6–e12.
34. Ji J, Su P, Lin W, et al. Immune cells characteristics and their prognostic effects in exertional heatstroke patients: a retrospective cohort study. *Front Med (Lausanne)* 2022; 9: 867774.
35. Tan Y, Liu X, Yu X, et al. Lack of lymphocytes exacerbate heat stroke severity in male mice through enhanced inflammatory response. *Int Immunopharmacol* 2021; 101: 108206.
36. Lu KC, Wang JY, Lin SH, et al. Role of circulating cytokines and chemokines in exertional heatstroke. *Crit Care Med* 2004; 32: 399–403.