Outcome and risk factors associated with extent of central nervous system injury due to exertional heat stroke

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Abstract

To explore the relationship between the extent of central nervous system (CNS) injury and patient outcomes meanwhile research the potential risk factors associated with neurologic sequelae. In this retrospective cohort study, we analyzed data from 117 consecutive patients (86 survivors, 31 nonsurvivors) with exertional heat stroke (EHS) who had been admitted to intensive care unit (ICU) at 48 Chinese hospitals between April 2003 and July 2015. Extent of CNS injury was dichotomized according to Glasgow coma scale (GCS) score (severe 3–8, not severe 9–15). We then assessed differences in hospital mortality based on the extent of CNS injury by comparing 90-day survival time between the patient groups. Exploring the risk factors of neurologic sequelae. The primary outcomes was the 90-day survival rate which differed between the 2 groups (P = .023). The incidence of neurologic sequelae was 24.4%. For its risk factors, duration of recurrent hyperthermia (OR = 1.73, 95% CI: 1.20–2.49, P = .003), duration of CNS injury (OR = 1.39, 95% CI: 1.04–1.85, P = .025), and low GCS in the first 24 hours after admission (OR = 2.39, 95% CI: 1.11–5.15, P = .025) were selected by multivariable logistic regression. Cooling effect was eliminated as a factor (OR = 2.64, 95% CI: 0.40–1.73, 90-day survival rate was observed based on the extent of CNS injury in patients with EHS, and incidence was 24.4% for neurologic sequelae. Duration of recurrent hyperthermia, duration of CNS injury, and low GCS score in the first 24 hours following admission may be independent risk factors of neurologic sequelae. Cooling effect should be validated in the further studies.

Abbreviations: CNS = central nervous system, EHS = exertional heat stroke, GCS = Glasgow coma scale, ICU = intensive care unit.

Keywords: CNS injury, exertional heat stroke, neurologic sequelae, risk factors

1. Introduction

Heat stroke (HS) is a life-threatening illness characterized by core body temperatures above 40°C coupled with central nervous system (CNS) dysfunction, including delirium, convulsions, and/or coma.[1] HS mortality has increased dramatically in the past few decades, if the global warming continues to exist, the mortality will be growing in the following years.[2] The 1995 heat wave in Chicago resulted in over 600 deaths and more than 3300 hospitalizations, while the August 2003 heat wave in France resulted in approximately 14,800 fatalities.[3,4] With a hospital mortality rate up to 62.6%.[5] HS has become the most lethal critical illness associated with natural disasters.[5]

HS is a serious condition that occurs due to failure of thermoregulatory mechanisms when the body is exposed to excessive heat, triggering an exaggerated acute response followed by multiple organ dysfunction syndrome (MODS).[6] Two forms of HS have been recognized: classic heat stroke (CHS) typically occurs during extreme heat waves, affecting mainly very young or elderly populations, while exertional heat stroke (EHS) occurs more commonly in physically active individuals exercising in hot and humid climates.[6–7]

As the brain is extremely sensitive to hyperthermia, CNS impairment is one of the most serious complications of HS, occurring in 80.3% to 100% of affected patients admitted to intensive care units (ICUs) during the United States and European heat waves and 100% of soldiers.[2,8–10] Previous clinical studies have revealed that neurological disability negatively affects late...
ICU mortality in patients with heat-related conditions.\textsuperscript{11,12} Notably, approximately 20% to 30% of CHS survivors experience neurologic sequelae (eg, cerebellar ataxia, dysarthria, cognitive disorders, and anterograde amnesia) within a few days, weeks, or months of CHS onset despite rapid initiation of aggressive clinical treatments, including lowering of core body temperature and support of organ function.\textsuperscript{13-16} Bazille et al.\textsuperscript{17} performed neuropathologic studies in 3 patients who died from HS which identified Purkinje cells in cerebellum showed diffuse loss. We also noticed that the body core temperature of the 3 patients are over 42°C. In the study of Li et al.,\textsuperscript{18} hyperthermia for HS patients close to 40°C, abnormal signals in cerebellum were observed by magnetic resonance imaging. About 10 years ago, the American College of Sports Medicine (ACSM) had recognized that cooling rapidly could reduce neurological complications of EHS patients greatly, and body core temperature below 40.5°C in 60 minutes seldom result in lasting sequelae. But it still needs a lot of studies which with large sample size to verify this theory.\textsuperscript{19} Neurological and clinical studies of HS are relatively rare, and the criteria for diagnosing the condition remain outdated.\textsuperscript{20} Research regarding CNS injury due to HS has largely focused on animal experiments. Analyses of magnetic resonance images (MRIs) from a small number of clinical cases revealed that patients with HS who experience neurological sequelae exhibit abnormalities in the cerebral cortex, cerebellum, and/or hippocampus.\textsuperscript{17} However, previous studies have largely focused on CNS injury associated with CHS rather than EHS, which occurs sporadically, making it difficult to study large samples of patients.\textsuperscript{18} In the present study, we aim to investigate CNS injury in one of the largest documented samples of patients with EHS\textsuperscript{19} in order to elucidate the relationship between the extent of CNS injury and patient outcomes, to assess the incidence of neurologic sequelae, and to examine independent risk factors associated with this condition.

2. Material and methods

2.1. Setting

In the present retrospective cohort study, we collected and analyzed medical records of patients with EHS admitted to the ICUs of 48 hospitals in China. Since this study did not involve patient treatment, informed consent for this study was not required. But the written informed consent about using clinical data of each EHS patient for study was included in their clinical records. However, all patient information was protected throughout the process of data collection and analysis. This study was approved by the Institutional Review Board of Chinese People’s Liberation Army General Hospital, and all methods were in accordance with the Committee’s guidelines, meanwhile, we also obtained ethical approval from ethical committee of each participating hospital.

2.2. Patients and study design

All patients with EHS who had been admitted to the ICU at any of the study hospitals between April 2003 and October 2015 were enrolled in the present study. The patient sample consisted mainly of soldiers, athletes, laborers, and farmers. Upon admission to the ICU, patients were externally cooled with ice blankets, ice hats, and ice packs applied to the groin/axillary regions while simultaneous life-support therapies were implemented. Above cooling methods were used in each of the hospitals. No other cooling methods were applied in these hospitals. Inclusion criteria for the present study were as follows: age $\geq$18 years; a reliable history of performing strenuous exercise at the time of the EHS event in hot and humid climates, the information was obtained from medical records; recorded body surface temperature (axillary temperature) higher than 39°C (Note: Rectal temperature is usually substituted for core body temperature in clinical practice. Normal rectal temperature is usually 0.27–0.38°C higher than oral temperature, while axillary temperature is about 0.55°C less than the oral temperature)\textsuperscript{19}, and alteration of mental status (eg, coma, delirium, convulsions, and/or seizures). Patients with preexisting neurological conditions prior to EHS onset were excluded owing to possible interference when evaluating the degree of CNS impairment due to EHS alone. In addition, as the present study collected the worst clinical value from EHS patients in the first 24 hours after admitted to ICUs, patients with survival times under 24 hours were also excluded. Hospital mortality was not recorded until patients were discharged. The survival of EHS patients with neurological sequelae was evaluated by examining the 1-year telephone follow-up records obtained by the participated hospitals.

2.3. Definitions

The Glasgow coma scale (GCS) is the most widely used clinical scoring system for the assessment of consciousness, indicating the severity of CNS deterioration as follows: mild (GCS 13–15), moderate (GCS 9–12), or severe (GCS 3–8).\textsuperscript{20} In the present study, we classified patients with EHS into 2 groups according to the extent of CNS injury: severe (GCS 3–8) and not severe (GCS 9–15). Duration of CNS injury was calculated until the point at which the patient’s condition had improved such that he or she could open the eyes in response to speech, exhibit improved conversational ability, and attain a GCS score of at least 12. We defined neurologic sequelae as cerebellar ataxia, dysarthria, cognitive disorders, and/or anterograde amnesia that developed after patients had been discharged. Imaging tests or physical examination of nervous system were performed to assist doctors establish diagnosis. Animal experiments have revealed that increases in cerebral temperature of even 1°C above the normal 37°C for 60 minutes can cause neurologic deterioration and measurable histopathological lesions.\textsuperscript{19} Research has also confirmed that brain temperature is 0.5 to 2°C warmer than core temperature.\textsuperscript{21,22} Based on these facts, patients were considered to have hyperthermia on any day during which body surface temperature (axillary temperature) persisted at above 37°C for at least 1 hour, and the number of days that this occurred was defined as the duration of recurrent hyperthermia was recorded in days during the whole course of EHS but except for the temperature in the first 24 hours. The diagnosed time of neurological sequelae collapse was calculated from admitted to ICU to occur the neurological sequelae which were diagnosed by neurologist or ICU doctors. Cooling effects, play a vital roles in EHS patients’ outcome, were considered to have occurred when core body temperature dropped to 38.5°C within 2 hours after EHS onset.\textsuperscript{11}
2.5. Data collection

A case report form was designed in advance for the abstraction of patient data relevant to the aims of the study, including age and gender. The most severely abnormal values for the following clinical measures were extracted from patient records within 24 hours of ICU admission: GCS score, oxygen saturation, white blood cell count, neutrophilic granulocyte percentage, blood creatinine, blood urea nitrogen, pH, lactate, HCO3−, electrolytes (eg, potassium, sodium, calcium, and chloride), and blood glucose. In the first 24 hours, we also calculated and determined the worst patient scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA). As cooling, fluid resuscitation, oxygen therapy, and additional emergency treatments had begun prior to ICU admission, the most severely abnormal values for auxiliary temperature, respiratory rate, heart rate, and mean arterial pressure were collected from EHS onset up to 24 h following ICU admission. Finally, the duration of CNS injury, the duration of hyperthermia, the time of neurological sequelae collapse, exact neurological sequelae in each individual, and cooling effect were extracted from medical records.

2.6. Statistical analysis

In the present study, some clinical indices (eg, oxygen saturation, chloride, and blood glucose) had a fraction of missing values. The fraction of missing values was calculated for each variable and subsequently compared between the long-term neurologic sequelae group (21 EHS patients) and nonlong-term neurologic sequelae group (65 EHS patients) using the Pearson chi-square or Fisher exact test. For oxygen saturation, there are 5 and 25 missing values in the long-term neurologic sequelae group and nonlong-term neurologic sequelae group, respectively. Data in 3 cases without chloride in the former group and 13 cases without data of chloride in the later group. The values of blood glucose are missing only in 2 patients of nonlong-term neurologic sequelae group. We observed no statistical difference in the fraction of missing values for any of the afore-mentioned clinical indices (oxygen saturation $P = .221$, chloride $P = .751$, and blood glucose $P = 1$). In order to ensure the accuracy of results from this clinical study, we discarded the missing values. Continuous variables were expressed as mean ± SD when normally distributed or as median and interquartile ranges (IQR) when the data were skewed. Categorical data were expressed as number of cases or percentages.

Normally distributed continuous variables were compared using Student $t$ test, while variables exhibiting a skewed distribution were compared using the Mann–Whitney $U$ test. Categorical variables regarding both the extent of CNS injury and the occurrence of neurological sequelae were compared using Pearson chi-square or Fisher exact test. The Kaplan–Meier method and Pearson chi-square or Fisher exact test were utilized to analyze 90-day survival rates using the log-rank test. Variables from the univariate analysis that were associated with neurologic sequelae ($P$ value less than .1) were included in the multivariable logistic regression model using a backward conditional stepwise elimination. Odds ratios and 95% confidence intervals were calculated for all risk factors.

All data analysis was performed using SPSS Version 19 (SPSS, Chicago, IL). Differences were considered significant when the $P$ value associated with the 2-sided test was less than .05.

3. Results

Clinical data from a total of 119 patients were collected. Two patients were excluded, finally, a total of 117 patients were thus enrolled in the present study. The grouping method expressed as Fig. 1.

3.1. Demographic characteristics and baseline clinical data

Table 1 displays the demographic characteristics and basic clinical data of the 117 patients. Patients with EHS were predominantly male 110(94%). All patients in this study are healthy before EHS occur and none of the included patients complicated underlying disease or illness when EHS collapsed.

### Table 1. Demographics and baseline clinical characteristics of patients with EHS.

| Demographics and baseline clinical characteristics | Mean |
|---------------------------------------------------|------|
| Age $^*$                                        | 22 (19–37) |
| Sex (M/F)                                        | 110/7 |
| Axillary temperature, °C $^*$                    | 40.5 (39.6–41) |
| Respiratory rate, breath/min $^*$                | 26 (20–32) |
| Heart rate, beats/min $^*$                       | 124 (36) |
| Mean arterial pressure, mm Hg $^*$               | 73.7 (19.8) |
| APACHE-II                                        | 24 (8) |
| SOFA                                             | 12 (5) |
| GCS$^*$                                         | 5 (3–8) |
| Mortality (n, %)                                 | 31 (26.5) |

*APACHE-II=Acute Physiology and Chronic Health Evaluation II score, EHS=exertional heat stroke, GCS=Glasgow coma scale, SOFA=Sequential Organ Failure Assessment score.
For axillary temperature, 46 patients (39.3%), 44 (37.6%), 25 (21.3%), and 1 (0.8%) exhibited axillary temperatures between 39 and 40 °C; 40.1 and 41 °C; 41.1 and 42 °C; and greater than 42 °C, respectively. Forty-five (38.5%) patients exhibited signs of hypotension (mean arterial pressure < 65 mmHg).

### 3.2. Characteristics of CNS injury

All patients exhibited some degree of CNS injury. Ninety-three (79.5%) patients were classified as severe (GCS 3–8) CNS injury, while 24 (20.5%) patients were classified as not severe (GCS 9–15) CNS injury. Forty-four (37.6%) patients experienced deep coma (GCS = 3). The extent of CNS injury was significantly more severe in nonsurvivors (median GCS: 3; IQR 3–4.5) than in survivors (median GCS: 6; IQR 4–9) (P < .0001). Table 2 shows the exact neurological sequelae in each individual.

### 3.3. Study outcomes

The 90-day survival rate differed between the 2 groups (P = .0227) (Fig. 2). Besides, the comparison of 90-day survival rates were also made by Fisher exact test which take no account of the effect of time, the mortality was 31.2% (29/93) and 8.3% (2/24) in the severe CNS injury group and not severe CNS injury group, respectively, the difference was statistically significant (P = .035). Nineteen (61.3%) patients died within 7 days, 26 (83.9%) died within 14 days, and 30 (96.8%) died within 28 days of ICU admission. One patient (3.2%) died on the 63rd day. The median survival time was 5 days for the death (IQR 2–14). The incidence of neurologic sequelae in survivors was 24.4% (21/86 patients), none patients died within 1-year follow-up period after discharge from the hospital. Their neurologic sequelae were remain exist at this time.

### 3.4. Potential risk factors for neurologic sequelae

The analysis of potential risk factors associated with CNS injury due to EHS is presented in Table 3. Univariate analysis was conducted primarily to select the potential risk factors for neurologic sequelae. Compared to patients without neurologic sequelae, patients with neurologic sequelae exhibited higher axillary temperatures (P = .009) as well as significantly impaired cooling ability in the designated time span (P < .0001). The majority of patients with neurologic sequelae (76.2%; 16/21 patients) experienced hyperthermia over 40°C. Recurrent hyperthermia also persisted longer in these patients (P < .0001), even though cooling measures were initiated in both groups immediately after they were transferred to the ICUs, indicating a potential association between persistent fever and CNS injury in EHS.

Following the onset of EHS, all survivors expressed varying degrees of CNS dysfunction, and patients with neurologic sequelae exhibited more severe degrees of CNS injury during the first 24 hours following ICU admission than patients without such persistent neurological impairments (P = .005). Furthermore, patients with neurologic sequelae experienced longer durations of CNS injury than those without (P < .0001). In
Table 3
Univariate analysis of risk factors associated with long-term neurologic sequelae in patients with EHS.

| Variables | Total (n = 86) | Long-term neurologic sequelae (n = 21) | Nonlong-term neurologic sequelae (n = 65) | P |
|-----------|---------------|--------------------------------------|---------------------------------------|---|
| Age, (IQR) | 22 (19–23) | 41 (24–55) | 21 (19–24) | <.001 |
| Male, % | 80 (93%) | 19 (90%) | 61 (94%) | .63 |
| Axillary temperature, (IQR), °C | 40.4 (39.5–41) | 41 (40.1–41.5) | 40.1 (39.3–41) | .009 |
| Respiratory rate, (IQR), breath/min | 25 (20–30) | 25 (20–30) | 25 (20–30) | .54 |
| Heart rate, beats/min | 117 (57) | 120 (41) | 116 (36) | .70 |
| Mean arterial pressure, mm Hg | 74.4 (17.8) | 72.6 (20.7) | 75.0 (16.9) | .60 |
| pH, (IQR) | 7.4 (3.7–4) | 7.3 (3.7–7.5) | 7.4 (7.3–7.4) | .85 |
| Lactate, (IQR), mmol/L | 3.3 (1.4–5.8) | 4.1 (1.9–7) | 3.2 (1.5–5.4) | .186 |
| Electrolytes | | | | |
| Potassium, mmol/L | 3.3 (0.5) | 3.1 (0.6) | 3.4 (0.5) | .067 |
| Sodium, mmol/L | 138.7 (16.1) | 136.8 (6.3) | 139.3 (5.9) | .091 |
| Chloride, (IQR), mmol/L | 104.1 (5.4) | 102.3 (6.2) | 104.7 (5.7) | .102 |
| Calcium, (IQR), mmol/L | 1.9 (1.2–2) | 1.6 (1.1–1.9) | 1.9 (1.2–2.1) | .015 |
| Blood glucose, (IQR), (ng/mL) | 7.6 (5.1–9.3) | 7.4 (4.3–9.4) | 6.8 (5.9–9.3) | .85 |
| Cooling effect, n, % | 36 (42%) | 1 (3%) | 35 (4%) | <.001 |
| Duration of hyperthermia, (IQR), d | 3 (1–11.5) | 16 (12–27) | 2 (1–4) | <.001 |
| Duration of CNS dysfunction, (IQR), d | 2 (1–6) | 9 (5–13) | 1 (1–2.5) | <.001 |
| APACHE-II | 22 (7) | 27 (6) | 20 (7) | .001 |
| SOFA, (IQR) | 10 (7–13) | 13 (10–15) | 9 (7–13) | .002 |
| GCS, (IQR) | 6 (4–9) | 4 (3–7) | 7 (5–9) | .005 |

* n, the total number of EHS patients who have the data of oxygen saturation; r, the total number of EHS patients who have the data of chloride; and r, the total number of EHS patients who have the data of blood glucose. Cooling effect, core body temperature dropped to 38.5°C within 24 hours after EHS onset.

Table 4
Multivariate logistic regression analysis of independent risk factors for neurologic sequelae patients with EHS.

| Variables | OR | 95% CI | P |
|-----------|----|-------|---|
| Duration of recurrent hyperthermia | 1.73 | 1.20, 2.49 | .003 |
| Duration of CNS dysfunction | 1.39 | 1.04, 1.85 | .025 |
| GCS | 2.39 | 1.11, 5.15 | .025 |
| Cooling effect* | 2614.27 | 0.40, 1.73 x 10^7 | .079 |

* Cooling effect, core body temperature dropped to 38.5°C within 24 hours after EHS onset. Due to its very large OR value (P < .001), this clinical parameter may still be an independent risk factor of long-term neurologic sequelae in patients with EHS.

In general, the risk of developing neurologic sequelae was also significantly associated with higher APACHE-II (27±6 vs 20±7, P < .0001) and SOFA scores (13±10–13 vs 9±7–13, P = .002), respectively.

Previous studies have identified that inflammation, hypoxia, acid–base/electrolyte disturbances, hypoglycemia, and acute kidney injury could affect CNS injury. This result indicates that EHS patients are vulnerable to suffer from above complications.[27] However, univariate analysis revealed no significant difference for any of these factors between EHS patients with and without neurologic sequelae.

In order to avoid the exclusion of potentially meaningful variables, parameters with P values less than .1 were included in the multivariable analysis. The following 10 potential risk factors were identified and included in the multivariable logistic regression model in order to screen for independent risk factors for neurologic sequelae: axillary temperature, potassium, sodium, calcium, cooling effect, duration of persistent fever, duration of CNS injury, APACHE-II score, SOFA score, and GCS score.

3.5. Independent risk factors of neurologic sequelae

Multivariable analysis revealed the association of 3 independent risk factors in patients with neurologic sequelae: persistent fever, duration of CNS injury, and severity of CNS injury (GCS score) (Table 4). The highest relative risk for neurologic sequelae was observed in patients with the most severe degrees of CNS injury (lowest GCS scores) in the first 24-hours following ICU admission (OR = 2.393, 95% CI: 1.113–5.145, P = .025). The association of cooling effect was not statistically significant (OR = 2641.273, 95% CI: 0.403–1.731 x 10^7, P = .079).

4. Discussion

Research has documented that the brain is one of the organs most vulnerable to hyperthermia.[27] The results of the present study further support the notion that the CNS is particularly at risk in EHS. Our analysis revealed that CNS injury in patients with EHS is evident during the first 24-hours following ICU admission. Furthermore, we observed the following association: all 117 patients exhibited some degree of CNS injury; GCS was lower in nonsurvivors; and significant differences in 90-day survival time were observed between patients with and without neurologic sequelae. These results are consistent with findings from previous studies involving patients with CHS.[3,5] However, studies of...
CHS conducted by Pease et al.\(^\text{[11]}\) and Hausfater et al.\(^\text{[28]}\) have reported no differences in GCS between survivors and non-survivors. Therefore, the relationship between the extent of CNS injury within the first 24 hours of ICU admission and EHS mortality remains uncertain.

Cooling and other forms of supportive treatment allow some patients to gradually recover normal neurologic function following EHS, but a portion of patients left with neurologic sequelae. Several reports have described the characteristics of neurologic sequelae in patients with EHS.\(^\text{[13-15,20]}\) However, as compared to CHS, since the prevalence of EHS and its neurologic sequelae are relatively low, the sample sizes of these studies are rather small. To date, no study has yet reported the incidence of CNS sequelae in EHS survivors. In the present study, neurologic sequelae were observed in 24.4% of survivors. Although further investigation is required to confirm this finding, the strikingly unexpected higher percentage highlights the need for clinicians to closely monitor the development of neurologic sequelae in patients with EHS.

In early stages, CNS injury due to EHS is likely to be multifactorial.\(^\text{[10]}\) Hyperthermia itself has been known to induce heat cytotoxicity in the brain,\(^\text{[34]}\) while heat stress has been observed to increase cerebral metabolism, increase heat dissipation in the skin, and rapidly reduce blood flow to the brain. Hyperthermia directly suppresses cardiac tissue, following which decreases in cardiac output are observed. These factors contribute to ischemia and hypoxia in the brain. In addition, inflammation, hypotension, and dehydration are considered to be involved in the early stages of CNS injury due to HS, and researchers have speculated that these factors may also play a role in the development of brain damage in early stages of HS.\(^\text{[8,24,30]}\)

Interestingly, we observed that a lower GCS, which represents the degree of CNS injury, within the first 24 hours of ICU admission, is associated with greater risk for neurologic sequelae. During the early period of temperature elevation,\(^\text{[32]}\) Theoretically, if the patients experiencing HS and can be cooled from 40.5 °C to normal levels within 60 minutes, sequelae may be avoided.\(^\text{[9]}\) However, despite rapid cooling, approximately 30% of survivors experience neurologic sequelae, the cause of which remain unknown.\(^\text{[13]}\)

Leon and Bouchama\(^\text{[2]}\) have put forward an idea that recurrent hyperthermia may be associated with poor outcome of heat stroke patients. In the present clinical study, we observed an interesting phenomenon: although rapid cooling was initiated for patients with EHS experiencing neurologic sequelae, body temperatures in these patients did decrease but they experienced a long period of recurrent hyperthermia. Furthermore, patients with neurologic sequelae exhibited body temperatures higher than 37 °C for at least 1 hour per day on more days/for longer durations than patients without. Indeed, previous research indicated that hypothermic therapy was more effective in preserving CNS function in normothermic counterparts on CNS function following cerebral ischemia,\(^\text{[14]}\) when hyperthermia is superimposed on this condition, the extent of brain damage is aggravated.\(^\text{[13]}\) Although, the duration and magnitude of hyperthermia necessary to sustain neurological injury remain unknown, some animal experiments have identified that, under conditions of hypoxia-ischemia, significant alterations in both neurologic function and cerebral histopathology are observed when cerebral temperatures exceed 37 °C by 1 °C for 60 minutes,\(^\text{[22]}\) and that sustained increases of 1.5 °C may lead to cellular damage in the hippocampus.\(^\text{[16]}\) It is well known that HS-induced CNS injury is associated with hypoxic-ischemic cerebral injury in the acute phase.\(^\text{[37]}\) Hence, when hyperthermia persists for several days, one can expect more severe degrees of neurologic injury following EHS. The results of the present study indicate that even slight increases in body temperature due to EHS may result in irreversible damage to the CNS with prolonged duration.

Unexpectedly, statistical analysis revealed that cooling effect was not an independent risk factor for neurologic sequelae associated with EHS. However, the OR value for this parameter was very large, most likely due to the maldistribution of EHS patients with different cooling effects (only 1 patient reached the target of cooling in the neurologic sequelae group). Furthermore, the sample size of the neurologic sequelae group was small as well. If the sample size increases, more EHS patients with long-term neurologic sequelae may be included in this group, and the power of cooling effect in statistical analyses will increase subsequently. ACSM position statement had noticed that cooling immediately below 40.5 °C could tolerate sequelae rarely.\(^\text{[17]}\) Cooling could improve the symptom of CNS has been manifested by a report of 3 heat stroke patients using cooling device.\(^\text{[38]}\) By our clinical observations, the cooling effect had a significant relationship with neurologic sequelae. Therefore, further investigation is required to confirm cooling effect is associated with increased risk of CNS sequelae.

In the present study, we also observed that patients with EHS experiencing neurologic sequelae tend to exhibit longer periods of CNS injury. Previously, some researchers have suggested that extended coma may be a highly unfavorable prognostic indicator in patients with HS,\(^\text{[19]}\) though an adequate explanation for this finding has not been offered. In addition, Cheng et al.\(^\text{[40]}\) have recently reported a significant association between the duration of CNS injury and brain tissue damage based on brain imaging data.\(^\text{[10]}\) In light of these results, it is possible that longer durations of CNS injury in patients with EHS lead to damage of brain tissue, resulting in permanent CNS complications.

The present study possesses some limitations. First, this is a retrospective, multicenter cohort study, leading to inevitable bias during the process of data collection. But the prospective study of EHS is extremely difficult to undertake. The inclusion period spanned 12 years and involved in 48 hospitals, so the changes during the long period and the differences between the multiple hospitals in treatment might have biased the results. However, the clinical treatment for HS patients in the first 24 hours especially for the CNS finds no significant differences from their clinical records. Therefore, the effect of treatment for the long period and multicenter to bias in this study should be small. In addition, the most authoritative diagnostic criteria of EHS was chosen by us to minimize the bias.\(^\text{[1]}\) Second, the number of EHS patients in our study is still relative small, which may have decreased the power of the statistical analyses, leading to the exclusion of some independent risk factors, but this condition is limited by the characteristics of disease itself. However, we plan to collect data from more patients with EHS to continue the analysis of the present study.

5. Conclusions

In conclusion, in the present study, we observed a statistical difference in 90-day survival rate according to the extent of CNS
injury in patients with EHS, along with an incidence of 24.4% for neurologic sequelae. Duration of recurrent hyperthermia, duration of CNS injury, and low GCS within the first 24 hours of ICU admission may be independent risk factors for neurologic sequelae in patients with EHS. Although cooling effect was not identified as an independent risk factor in the present study, most likely due to the small sample size, further investigation utilizing a larger cohort is required to confirm cooling effect is associated with decreased risk of CNS sequelae.

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