Original Article

Clinical characteristics, prognostic factors, and outcomes of heat-related illness (Heatstroke Study 2017–2018)

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Aim: Heat-related illness is common, but its epidemiology and pathological mechanism remain unclear. The aim of this study was to report current clinical characteristics, prognostic factors, and outcomes of heat-related illness in Japan.

Methods: We undertook a prospective multicenter observational study in Japan. Only hospitalized patients with heat-related illness were enrolled from 1 July to 30 September 2017 and 1 July to 30 September 2018.

Results: A total of 763 patients were enrolled in the study. Median age was 68 years (interquartile range, 49–82 years) and median body temperature on admission was 38.2°C (interquartile range, 36.8–39.8°C). Non-exertional cause was 56.9% and exertional cause was 40.0%. The hospital mortality was 4.6%. The median Japanese Association for Acute Medicine disseminated intravascular coagulation (JAAM DIC), Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores on admission were 1 (0–2), 4 (2–6), and 13 (8–22), respectively. To predict hospital mortality, areas under the receiver operating characteristic curves were 0.776 (JAAM DIC score), 0.825 (SOFA), and 0.878 (APACHE II). There were 632 cases defined as heatstroke by JAAM heat-related illness criteria, 73 cases diagnosed as having DIC. A total of 16.6% patients had poor neurological outcome (modified Rankin Scale ≥ 4) at hospital discharge. In the multivariate analysis, Glasgow Coma Scale and platelets were independent predictors of mortality. Type of heatstroke, Glasgow Coma Scale, and platelets were independent predictors of poor neurological outcome. Body temperature was not associated with mortality or poor neurological outcome.

Conclusions: In this study, hospital mortality of heat-related illness was <5%, one-sixth of the patients had poor neurological outcome. The APACHE II, SOFA, and JAAM DIC scores predicted hospital mortality. Body temperature was not associated with mortality or poor neurological outcome.

Key words: Disseminated intravascular coagulation, heat-related illness, heatstroke, modified Rankin Scale, multiple organ failure

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Received 30 Jan, 2020; accepted 22 Apr, 2020

Funding Information

Heatstroke Study 2017–2018 was supported by Health and Labour Sciences Research Grants.

INTRODUCTION

HEAT-RELATED ILLNESS IS common, but its epidemiology and pathological mechanism remain unclear. In Japan, the number of patients with heat-related illness in summer has recently increased because of global warming and the urban heat island phenomenon; therefore, social attention to heat-related illness has been increasing every year.[1]

To clarify the epidemiology of heat-related illness, the Japanese Association for Acute Medicine (JAAM) undertook nationwide research into heat-related illness through the "Heatstroke STUDY" in 2006, 2008, 2010, 2012 and 2014.[2,3] However, these studies have several limitations. First, the severity of heat-related illness as assessed by measures such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) score or Sequential Organ Failure Assessment (SOFA) score was not available, and no data on neurological prognosis were provided. Thus, the prognostic factors adjusted for severity of heat-related illness or neurological outcome have not been examined. To solve these problems of the previous studies, we undertook a new multicenter study of patients with heat-related illness (Heatstroke Study 2017–2018). The aim of this study was to report current clinical characteristics, prognostic factors, and outcomes of heat-related illness in Japan.

METHODS

Study setting and design

WE UNDERTOOK A prospective multicenter observational study. In total, 115 hospitals participated in the present study after Institutional Review Board approval was received from each hospital listed in Appendix S1. The study periods ran from 1 July to 30 September 2017 and from 1 July to 30 September 2018. Diagnosis of heat-related illness was confirmed by physicians, and only patients admitted to the hospital during the study periods were enrolled.

Inclusion criteria

We included consecutive patients who were hospitalized with a confirmed diagnosis of heat-related illness.

Definitions

Diagnosis of disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) was defined according to the JAAM DIC diagnostic criteria, with a total score ≥4 establishing a diagnosis of DIC. The score considers systemic inflammatory response syndrome, platelets, prothrombin time, and fibrin degradation product or D-dimer levels.[4]

Japanese Association for Acute Medicine heat-related illness classification

Japanese Association for Acute Medicine established criteria for heat-related illness.[5,6] Heatstroke is defined when patients meet more than one of the following criteria: (i) Glasgow Coma Scale (GCS) score ≤ 14, (ii) serum creatinine or total bilirubin level ≥ 1.2 mg/dL, (iii) JAAM DIC score ≥ 4.

Data collection

Patients' demographics, prehospital information collected by emergency medical services (EMS), situation causing heat exposure, admission physiology, cooling method and time, laboratory data, SOFA score, APACHE II score, JAAM DIC score, survival at hospital discharge and at 28 days after admission, and modified Rankin Scale (mRS) scores before arrival, at hospital discharge, and at 28 days after admission were collected.

Statistical analysis

Variables are expressed as median (interquartile range) or number (frequency). Differences between the groups were tested with the Mann–Whitney *U*-test. Baseline values were compared using the χ^2-test. Mortality and neurological prognosis were analyzed using multivariable logistic regression analyses. The predictivity of hospital mortality was evaluated by receiver operating characteristic (ROC) analysis, with the areas under the ROC curves (AUC) showing the highest sensitivity. Statistical analysis was carried out using SPSS version 20 software (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics

THE PRESENT STUDY enrolled 763 patients, 244 in 2017 and 519 in 2018. Among them, 537 (70.4%) were men, and the median patient age was 68 (49–82) years. Patient presentation to hospital was by EMS in 599 (78.5%) patients, 88 (11.5%) patients walked in, 40 (5.2%) patients were transported from another hospital, and unknown for 36 (4.7%) patients. Heat illness occurred indoors in 332 patients (43.5%), outdoors in 401 (52.5%) patients, and location was unknown in 30 (3.9%) patients. Causes of heat-related illness were daily activity in 429 (56.2%), office work in 5 (0.7%), physical work in 240 (31.5%), sports activity in 65 (8.5%), and unknown in 24 (3.1%) patients. Among the patients, 434 (56.9%) were admitted for non-exertional causes (daily activity and office work), and 305 (40.0%) were admitted for exertional causes (physical work and sports activity). Figure 1 shows the age groups of patients for every 10-year period and the type of heat-related illness. The hospital mortality rate was 4.6% (35/763), and 319 patients (41.8%) were admitted to the intensive care unit. The median length of hospital stay was 4 (2–10) days. Patient characteristics are shown in Table 1.

The median prehospital body temperature (BT) was 38.7°C (37.0–40.1°C), and the median BT on admission was 38.2°C (36.8–39.8°C). The median JAAM DIC, SOFA, and APACHE II scores on admission were 1 (0–2), 4 (2–6), and 13 (8–22), respectively. To predict hospital mortality, ROC curves were created, and AUCs were 0.776 (JAAM DIC score), 0.825 (SOFA), and 0.878 (APACHE II) (Fig. 2).

Treatment

Overall, 395/763 (51.8%) patients underwent active cooling therapy. In patients with BT over 39°C on admission, 230 of 267 (86.0%) underwent active cooling, whereas in patients with BT over 40°C on admission, 148 of 161 (91.9%) underwent active cooling. Cooling methods are shown in Table 2. The overall median time from arrival to the start of active cooling was 9 (3–20) min. In patients whose BT was over 40°C on admission, the median time from arrival to reaching a BT of 38°C was 105.5 (73–212.5) min, and the median time from the start of active cooling to reaching a BT of 38°C was 83.5 (48.5–148.75) min. In the univariate analysis, time from arrival to start of cooling, time from arrival to reaching 38°C, and time from start of cooling to reaching 38°C did not predict mortality.

Neurological outcome

Figure 3 shows the proportions of mRS scores at hospital discharge. The number of patients with poor neurological outcome (mRS ≥ 4) at hospital discharge was 127 (16.6%). Among the survivors (646/763), the mRS score had elevated by over 2 points in 78 (12.0%) patients at hospital discharge. Only 15 of these 78 patients could be followed up at 28 days; only four patients showed an improved mRS and 11 patients had no change.

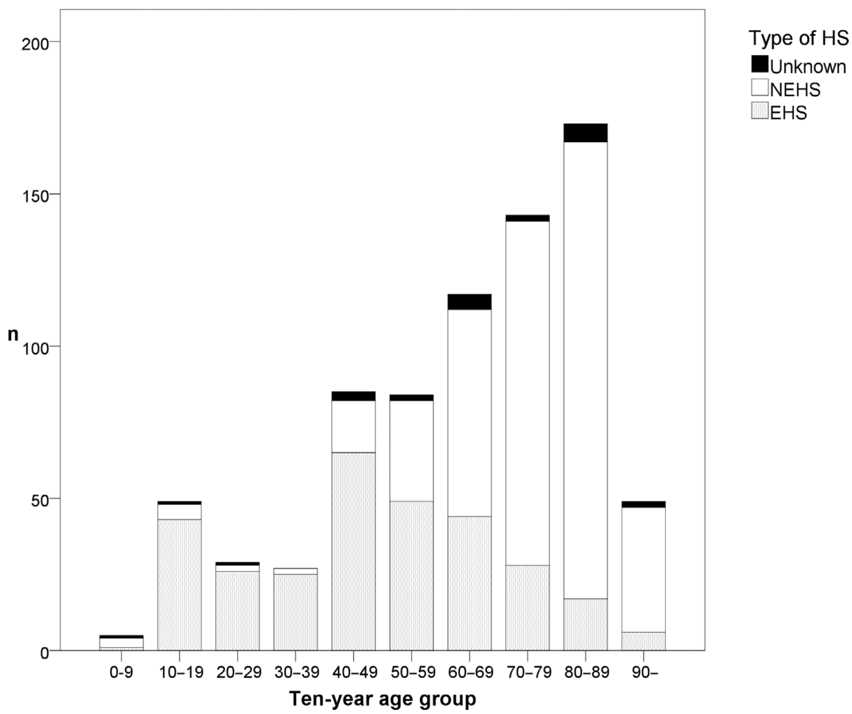


Fig. 1. Number of Japanese patients hospitalized with heat-related illness, 1 July to 30 September 2017 and 1 July to 30 September 2018, grouped by 10-year age groups and the type of heat-related illness. EHS, exertional heatstroke; HS, heatstroke; NEHS, non-exertional heatstroke.

Table 1. Characteristics of Japanese patients hospitalized with heat-related illness

Variable	Overall (n = 763)	Survivors (n = 646)	Non-survivors (n = 35)	P-value
Age (years)	68 (49–82)	68 (49–81)	77 (65–90)	<0.01
Sex (male)	537 (70.4)	451 (69.8)	25 (71.4)	0.84
Type of HS (EHS)	305 (40.0)	269 (41.6)	9 (25.7)	0.05
GCS on admission	14 (10–15)	14 (11–15)	3 (3–10)	<0.01
sBP on admission (mmHg)	126 (108–146)	125 (109–146)	99 (78–147)	0.04
HR on admission (b.p.m.)	102 (84–123)	101 (84–121)	122 (79–143)	0.09
RR on admission (r.p.m.)	24 (18–30)	23 (18–30)	25 (19–32)	0.32
BT on admission (°C)	38.2 (36.8–39.8)	38.1 (36.7–39.7)	39.8 (37.9–41.2)	<0.01
Serum total bilirubin (mg/dL)	0.9 (0.7–1.4)	0.9 (0.7–1.3)	0.9 (0.7–1.4)	0.61
Serum creatinine kinase (U/L)	248 (118–600)	238 (117–541)	806 (386–1130)	<0.01
Serum creatinine (mg/dL)	1.4 (0.9–2.2)	1.4 (0.9–2.2)	1.8 (1.4–2.3)	0.02
Serum lactate (mmol/dL)	2.6 (1.7–4.7)	2.6 (1.7–4.4)	6.4 (2.2–10.9)	<0.01
Platelet ($*10^4/mm^3$)	21 (16–26)	22 (17–27)	13.5 (10–17)	<0.01
JAAM DIC score	1 (0–2)	1 (0–1)	3 (1–4)	<0.01
SOFA	4 (2–6)	3 (2–5)	10 (8–12)	<0.01
APACHE II	13 (8–22)	12 (8–20)	32 (24–37)	<0.01

APACHE, Acute Physiology and Chronic Health Evaluation; BT, body temperature; DIC, disseminated intravascular coagulation; EHS, exertional heatstroke; GCS, Glasgow Coma Scale; HR, heart rate; HS, heatstroke; JAAM, Japanese Association for Acute Medicine; r.p.m., respirations per minute; RR, respiratory rate; sBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment.

Association between JAAM heat-related illness criteria and mortality

According to the JAAM heat-related illness criteria, 632/763 (82.8%) patients were defined as having heatstroke (Table 3). Among the patients with heatstroke, the mortality of those who met only one criterion was 1.1%, whereas it was 25.0% in those who met all criteria (odds ratio 3.04).

The number of patients defined as having DIC (JAAM DIC score ≥ 4) was 73 (9.6%), and 32 patients underwent anti-DIC therapy with a protease inhibitor (n = 2), antithrombin (n = 10), recombinant thrombomodulin (n = 15), heparin (n = 4), plasma transfusion (n = 11), or platelet transfusion (n = 2). There was no significant difference in mortality between the patients treated or not treated with anti-DIC therapy.

Prognostic factors of mortality and neurological outcome

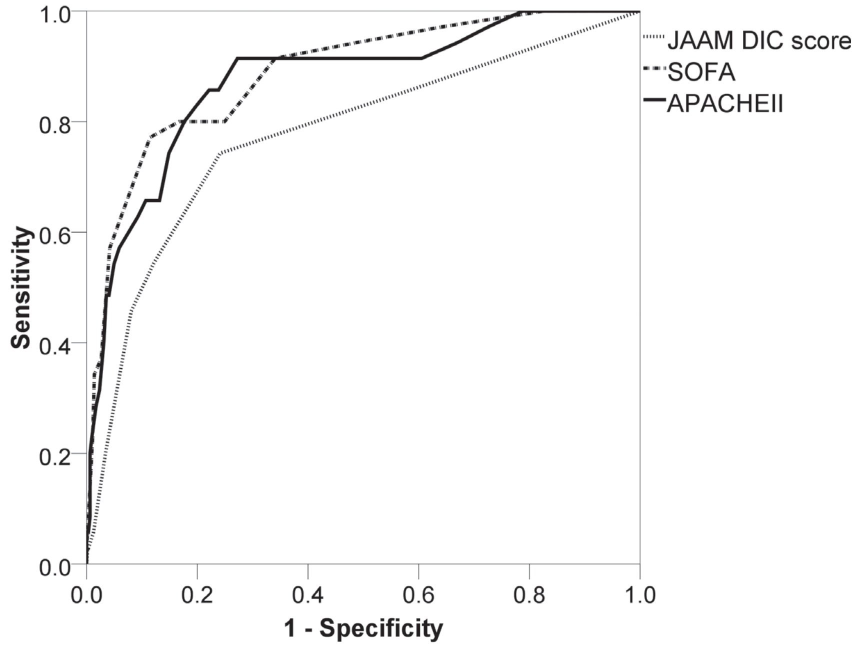
Table 1 shows the results of the univariate analysis of mortality. In the multivariate analysis, GCS and platelets were independent predictors of mortality, whereas age and BT on admission were not (Table 4). Good neurological status (mRS ≤ 3) was present in 683 patients before admission. Among these 683 patients at hospital discharge, 92 (13.5%) had a poor neurological outcome (mRS ≥ 4). In multivariate analysis, type of heatstroke, GCS, and platelets were independent predictors of poor neurological outcome, whereas BT, systolic blood pressure, serum creatinine, and total bilirubin were not (Table 5).

DISCUSSION

JAPANESE ASSOCIATION FOR Acute Medicine undertook nationwide research through the "Heatstroke STUDY" every 2 years from 2006 to 2014 to clarify the present situation of heat-related illness.[2,3] This registry targeted both outpatients and hospitalized patients. It was important to survey outpatients because many of them suffered heat-related illness. However, assessment of SOFA and APACHE II scores, which are standard severity scores used in emergency and intensive care medicine, was not mentioned.

This study aimed to clarify the current situation of severe heat-related illness in Japan. The numbers of patients with heat-related illness transported to hospital increases in the summer in Japan, so the study periods were limited to July through September. In 2018, Japan was scorched by an intense heat and because there were so many patients with heat-related illness.[7,8] The number of enrolled patient in 2018 was twice as many as in 2017.

Almost all patients who suffered heat-related illness due to exertional activities were young, whereas non-exertional heat illness was dominant among older patients. Of patients aged in their 60s, half suffered exertional and half non-exertional heat-related illness. Our results indicated that patients



	AUC	*P*-value	95% CI
DIC score	0.776	<0.01	0.69–0.87
SOFA	0.851	<0.01	0.81–0.89
APACHE II	0.859	<0.01	0.82–0.90

Fig. 2. Receiver operating characteristic (ROC) curves of the Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Japanese Association for Acute Medicine disseminated intravascular coagulation (JAAM DIC) scores in predicting hospital mortality among Japanese patients hospitalized with heat-related illness, 1 July to 30 September 2017 and 1 July to 30 September 2018. AUC, area under the ROC curve; CI, confidence interval.

suffering non-exertional heatstroke were at higher risk for poor neurological outcome; thus, how to prevent and treat non-exertional heatstroke is an important problem for the aging society of Japan.

In the present study, we determined the mRS score three times: before admission, at hospital discharge, and 28 days following discharge. To our knowledge, this is the first study to assess neurological outcomes of heat-related illness. Overall mortality was 4.6%, but in survivors, because so many patients had neurological disability (mRS $\geq$ 4), the morbidity rate was 16.6%. Some studies have shown the mechanism of neurological dysfunction after heat-related illness, but it was not reported whether neurological dysfunction was reversible.[9,10,11,12] Additional study will be needed in the future to clarify the effect of heatstroke on long-term neurological function.

Only half of all patients underwent active cooling, but more than 90% of the patients with high BT (over 40°C) underwent active cooling. Dominant methods were evaporative or fan cooling and infusion of cold fluid. Although gel pads and intravascular devices have been developed for hyperthermia therapy, reports on their effectiveness for heat-related illness are limited.[13,14] Ice water immersion is widely used in the USA and Europe.[15,16] When we planned our research, ice water immersion was not recognized in Japan. This method was only used for exertional heatstroke, but non-exertional heatstroke was dominant in Japan. Therefore, we did not investigate this method. But ahead of the 2020 Olympic Games in Japan, the ice water immersion technique is slowly spreading.

There is no doubt that cooling is the most important therapy for heatstroke, but in the present study, there was no evidence that rapid cooling will result in a good outcome.[17] It was difficult to discern any difference because over 90% of the patients with high BT quickly underwent active cooling.

The JAAM heat-related illness classification was well followed in Japan.[5,6] Heatstroke in a patient was defined as the presence of at least one organ failure (central nervous system disorder, hepatic/renal dysfunction, or coagulation disorder). There was no objective definition of each organ failure in the original classification, so we defined central nervous system disorder as a GCS score ≤14, hepatic/renal dysfunction as serum creatinine/total bilirubin ≥1.2 mg/dL, and coagulation disorder as a JAAM DIC score ≥4. More than 80% of the patients in the present study were defined as having heatstroke, and positive values of the criteria predict mortality.

Table 2. Cooling methods used for patients hospitalized with heat-related illness

Cooling method	*n* (%)
(1) External cooling	126 (16.5)
(2) Internal cooling	15 (2.0)
(3) (1) + (2)	58 (7.6)
(4) Only infusion of cold	196 (25.7)
(5) No cooling	292 (38.3)
(6) Unknown	76 (10.0)
Internal cooling method	*n* = 73
Gastric lavage	35
Bladder lavage	2
Intravascular cooling	28
External cooling method	*n* = 184
Evaporative	84
Fan	78
Gel pad	28
Blanket	20

Table 3. Japanese Association for Acute Medicine (JAAM) heat-related illness classification and mortality

	n (%)	
GCS ≤ 14	407 (64.4)	
Tbil ≥ 1.2	241 (38.1)	
Cre ≥ 1.2	428 (67.7)	
JAAM DIC score ≥ 4	73 (11.5)	
Positive value of criteria	*n*	Mortality (%)
1	262	1.1
2	243	5.3
3	107	13.1
4	20	25.0

Odds ratio 3.04; $P < 0.01$; 95% confidence interval, 2.08–4.44.
Heatstroke ($n = 632$) is defined according to the JAAM heat-related illness classification.
Cre, creatinine; DIC, disseminated intravascular coagulation; GCS, Glasgow Coma Scale; Tbil, total bilirubin.

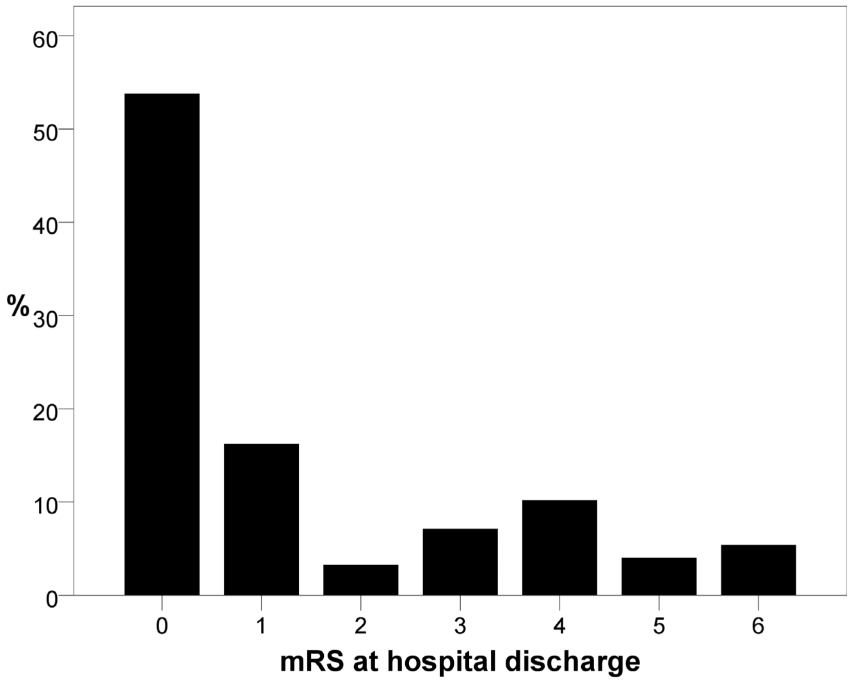


Fig. 3. Proportions of modified Rankin Scale (mRS) scores at hospital discharge of Japanese patients hospitalized with heat-related illness

Table 4. Predictors for mortality in Japanese patients hospitalized with heat-related illness

Variable	OR	95% CI	*P*-value
Age	1.01	0.98–1.04	0.43
GCS on admission	0.74	0.66–0.82	<0.01
BT on admission	0.89	0.70–1.14	0.36
Platelets	0.89	0.83–0.95	<0.01

BT, body temperature; CI, confidence interval; GCS, Glasgow Coma Scale; OR, odds ratio.

Table 5. Predictors for poor neurological outcome in Japanese patients hospitalized with heat-related illness

Variable	OR	95% CI	*P*-value
Age	1.01	0.99–1.03	0.43
Sex (male)	0.78	0.39–1.34	0.31
Type of HS (EHS)	0.20	0.08–0.05	<0.01
BT on admission	0.94	0.77–1.15	0.55
sBP on admission	1.00	0.99–1.01	0.47
GCS on admission	0.79	0.72–0.85	<0.01
Serum creatinine	1.15	1.00–1.32	0.05
Serum total bilirubin	1.04	0.80–1.35	0.76
Platelets	0.95	0.90–0.99	0.02

BT, body temperature; CI, confidence interval; EHS, exertional heatstroke; GCS, Glasgow Coma Scale; HS, heatstroke; OR, odds ratio; sBP, systolic blood pressure.

In multivariate analysis, GCS and platelets were independent predictors of mortality. Because the number of deaths was limited in the present study, we selected factors from basic demographic physiological data and factors related to JAAM heat-related illness classification (GCS, serum total bilirubin and creatinine, and platelets). Glasgow Coma Scale score and platelets were also independent predictors of neurological outcome. Bouchama and Knochel classified heat-related illness by temperature, and this classification is widely accepted throughout the world, but the JAAM classification did not include BT.[18] A previous study reported that BT was an independent predictor of mortality.[19] In the present study, BT at admission was not an independent prognostic factor of mortality or neurological outcome. In Japan, EMS personnel cannot measure core BT, so it is usually measured after the patient is transported to hospital. Thus, BT at admission might not be the actual maximum BT. Rather than knowing the maximum BT, it might be more important to know how long the high temperature has continued. Furthermore, a prolonged high BT could be reflected in the SOFA or APACHE II score, which has a high AUC for predicting mortality.[20]

The presence of DIC has been reported to be a prognostic factor of sepsis, trauma, and heatstroke,[21,22,23] and the present study also showed this to be an independent prognostic factor of heatstroke. Disseminated intravascular coagulation in heat-related illness differs from that in sepsis because, in heat-related illness, fibrinolysis has occurred in the acute phase.[24,25] The JAAM DIC diagnostic criteria were mainly designed for sepsis, but they are also useful for evaluating the severity of heat-related illness. Whether DIC in heat-related illness is a therapeutic target is not known. Only 32 patients in the present study underwent anti-DIC therapy. Although anti-DIC therapy, such as antithrombin or recombinant thrombomodulin, is widely used in septic DIC, the effectiveness of anti-DIC therapy in heatstroke remains unknown.[26,27]

LIMITATIONS

ALTHOUGH MORE THAN 100 hospitals participated in this study, only 763 patients were enrolled over the 2 years. The number of patients with heat-related illness depends on the climate, and we did not satisfy the expected number of enrollees. Furthermore, the mortality rate for heat-related illness was not high, as only 35 enrollees did not survive. Therefore, we limited the multivariate analysis for mortality to only four values. More enrolled patients are needed for an accurate analysis.

The most important limitation of this study pertained to the diagnosis of heat-related illness itself. There was no specific definition for the diagnosis of heat-related illness, so we enrolled patients in whom the physician diagnosed heat-related illness. Sepsis, stroke, and other diseases are important differential diagnoses, but sometimes these diseases are complicated and difficult to diagnose. Moreover, although BT is an important factor in heat-related illness, high BT is not the only cause. In the JAAM heat-related illness classification, there is no definition of BT. Therefore, we did not set a limit on BT for enrollment in the present study. In the multivariate analysis, BT was not an independent predictor of mortality. Establishing an accurate diagnosis of heat-related illness is an important problem that will require further study in the future.

CONCLUSIONS

WE UNDERTOOK NATIONWIDE research into heat-related illness in Japan. Over 80% of the patients were diagnosed with heatstroke as defined by JAAM heat-related illness criteria. Hospital mortality was <5%, and one-sixth of the patients had poor neurological outcome. The

APACHE II, SOFA, and JAAM DIC scores predicted hospital mortality. Body temperature was not associated with mortality or poor neurological outcome.

ACKNOWLEDGEMENT

HEATSTROKE STUDY 2017 –2018 was supported by Health and Labour Sciences Research Grants.

DISCLOSURE

APPROVAL OF THE Research Protocol: Present study was approved by Institutional Review Board of Teikyo University Hospital (No: 17-021-3) and that of each participated hospital.

Informed Consent: Informed consent was obtained in the form of opt-out method.

Registry and the Registration No. of the study/Trial: N/A.

Animal Studies: N/A.

Conflict of Interest: All authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. List of hospitals participating in the present study.