

# Indicators of Acute Kidney Injury as Biomarkers to Differentiate Heatstroke from Coronavirus Disease 2019: A Retrospective Multicenter Analysis

Hirofumi Obinata<sup>1,2</sup>, Shoji Yokobori<sup>1,3</sup>, Kei Ogawa<sup>4</sup>, Yasuhiro Takayama<sup>5</sup>,  
Shuichi Kawano<sup>2</sup>, Toshimitsu Ito<sup>2</sup>, Toru Takiguchi<sup>1</sup>, Yutaka Igarashi<sup>1</sup>,  
Ryuta Nakae<sup>1</sup>, Tomohiko Masuno<sup>1</sup> and Hayato Ohwada<sup>4</sup>

<sup>1</sup>Department of Emergency and Critical Care Medicine, Nippon Medical School, Tokyo, Japan

<sup>2</sup>Self-Defense Forces Central Hospital, Tokyo, Japan

<sup>3</sup>Japan Association of Acute Medicine Heatstroke and Hypothermia Surveillance Committee, Tokyo, Japan

<sup>4</sup>Department of Industrial Administration, Tokyo University of Science, Tokyo, Japan

<sup>5</sup>Department of Emergency Medicine, Flowers & Forest Tokyo Hospital, Tokyo, Japan

**Background:** Coronavirus disease 2019 (COVID-19) and heat-related illness are systemic febrile diseases. These illnesses must be differentiated during a COVID-19 pandemic in summer. However, no studies have compared and distinguished heat-related illness and COVID-19. We compared data from patients with early heat-related illness and those with COVID-19.

**Methods:** This retrospective observational study included 90 patients with early heat-related illness selected from the Heatstroke STUDY 2017-2019 (nationwide registries of heat-related illness in Japan) and 86 patients with laboratory-confirmed COVID-19 who had fever or fatigue and were admitted to one of two hospitals in Tokyo, Japan.

**Results:** Among vital signs, systolic blood pressure (119 vs. 125 mm Hg,  $p = 0.02$ ), oxygen saturation (98% vs. 97%,  $p < 0.001$ ), and body temperature (36.6°C vs. 37.6°C,  $p < 0.001$ ) showed significant between-group differences in the heatstroke and COVID-19 groups, respectively. The numerous inter-group differences in laboratory findings included disparities in white blood cell count ( $10.8 \times 10^3/\mu\text{L}$  vs.  $5.2 \times 10^3/\mu\text{L}$ ,  $p < 0.001$ ), creatinine (2.2 vs. 0.85 mg/dL,  $p < 0.001$ ), and C-reactive protein (0.2 vs. 2.8 mg/dL,  $p < 0.001$ ), although a logistic regression model achieved an area under the curve (AUC) of 0.966 using these three factors. A Random Forest machine learning model achieved an accuracy, precision, recall, and AUC of 0.908, 0.976, 0.842, and 0.978, respectively. Creatinine was the most important feature of this model.

**Conclusions:** Acute kidney injury was associated with heat-related illness, which could be essential in distinguishing or evaluating patients with fever in the summer during a COVID-19 pandemic.

(J Nippon Med Sch 2021; 88: 80–86)

**Key words:** heat-related illness, coronavirus disease, COVID-19, heatstroke, machine learning

## Introduction

The novel coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in December 2019 in Wuhan, China. It has since spread worldwide and is now a global threat. The number of confirmed COVID-19

cases has exceeded 10.5 million, and the number of deaths has exceeded 516,000<sup>1</sup>. Infection by human coronaviruses peaks in winter, but there is still some infection risk in summer<sup>2,3</sup>. In the southern hemisphere, the COVID-19 pandemic began during summer.

In summer, heat-related illness is one of the most im-

Correspondence to Hirofumi Obinata, Department of Emergency and Critical Care Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan

E-mail: h-obinata@nms.ac.jp

[https://doi.org/10.1272/jnms.JNMS.2021\\_88-107](https://doi.org/10.1272/jnms.JNMS.2021_88-107)

Journal Website (<https://www.nms.ac.jp/sh/jnms/>)

portant public health issues. Recently, owing to global warming and urbanization-associated inner-city heat islands, the risks of heat-related illness have been increasing<sup>4</sup>. The severity of heat-related illness ranges from mild heat exhaustion to the most severe presentation, heatstroke. Elderly adults with chronic medical conditions are particularly vulnerable, and the heatstroke-related mortality rate in these patients exceeds 50%<sup>4</sup>. Prevention and early intervention are crucial, and reducing heat stress is one of the most important preventive measures. However, during the current pandemic, masks function both as a vapor barrier and a heat source<sup>5</sup>, although they are recommended to prevent disease transmission<sup>6</sup>, and would therefore be an additional risk for heat-related illness in summer. Therefore, in the summer early recognition and intervention play more important roles than usual, even among younger populations.

Early heat-related illness and COVID-19 have similar clinical symptoms, including fever and fatigue, which are nonspecific symptoms of systemic diseases. Clinicians sometimes have difficulty in making a differential diagnosis when patients present with such complaints. However, surveillance and discrimination are important in clinical practice, as is infection control by means of appropriate personnel protective equipment or isolation, especially for emergency services and emergency departments<sup>7</sup>. There are no studies comparing patient populations with heat-related illness and COVID-19. Thus, this study compared data from patients with early heat-related illness and those with COVID-19 presenting with general fatigue and fever.

### Materials and Methods

This retrospective observational study was approved by the Institutional Review Board of Nippon Medical School (approval no. B-2020-134) and was conducted in accordance with the ethical standards evinced in the 1964 Declaration of Helsinki and its later amendments. The requirement for individual informed consent was waived due to the retrospective observational study design.

#### Patients with Heat-Related Illness

We examined data from all patients registered in three prospective, nationwide, observational multicenter registries of heat-related illness in Japan, ie, the Heatstroke study of 2017, 2018<sup>8</sup>, and 2019. These registries are maintained by the Japanese Association for Acute Medicine Committee. In total, 115 hospitals participated in the studies, which were conducted from July 01, 2017 to September 30, 2017; from July 01, 2018 to September 30,

2018; and from July 01, 2019 to September 30, 2019. Heat-related illness was diagnosed by physicians, and these studies included mild cases to critically ill cases, eg, heatstroke and death. We intended to analyze early heat-related illness; thus, the exclusion criteria were disturbance of consciousness, need for emergency transportation, age <18 years, and pregnancy. The studies were approved by each hospital's institutional review board and were conducted in accordance with the ethical standards evinced in the 1964 Declaration of Helsinki and its later amendments.

#### Patients with COVID-19

We examined data from all patients with COVID-19 infection, as confirmed by reverse transcription polymerase chain reaction (RT-PCR), who were admitted to one of two hospitals in Tokyo, Japan—namely, the Japan Self-Defense Forces Central Hospital and Flowers & Forest Tokyo Hospital—between February 01, 2020 and May 01, 2020 with complaints of fever or fatigue. In accordance with local public health regulations, both these hospitals accepted patients with relatively mild symptoms. The exclusion criteria were absence of fever or fatigue on admission, need for emergency transportation, age <18 years, and pregnancy. The studies were approved by the Institutional Review Boards of the Self-Defense Forces Central Hospital (approval no. 02-014) and Nippon Medical School (approval no. B-2020-134), which is a proxy institutional review board of the Flowers & Forest Tokyo Hospital, and were conducted in accordance with the ethical standards evinced in the 1964 Declaration of Helsinki and its later amendments.

#### Data Collection

Data were collected for the following variables in each sample: age, sex, past medical history (hypertension, cardiovascular disease, cerebrovascular disease, and diabetes mellitus), vital signs on arrival (heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate, body temperature, and saturation of percutaneous oxygen (SpO<sub>2</sub>)), and laboratory findings on arrival (white blood cell count (WBC), hemoglobin, platelet count, blood urea nitrogen (BUN), creatinine, total bilirubin, aspartate transaminase, alanine transaminase, creatine kinase (CK), C-reactive protein (CRP), prothrombin time-international normalized ratio, D-dimer, sodium, potassium, chlorine and glucose). Moreover, data on other systemic symptoms (headache, nasal discharge, sore throat, cough, myalgia or arthralgia, abdominal pain, nausea, diarrhea, and dyspnea) and contact history were collected.

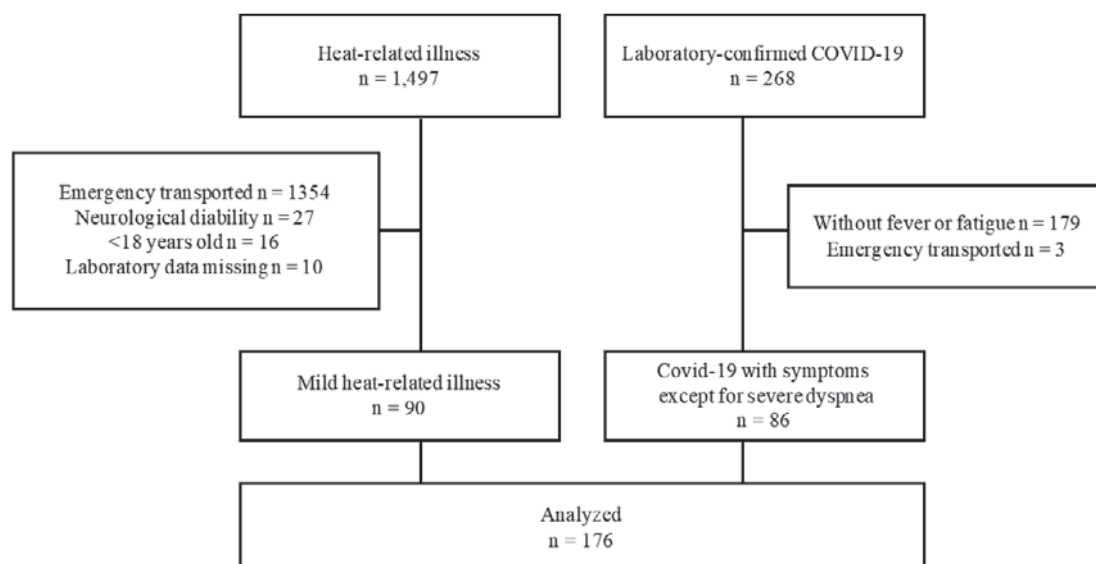


Fig. 1 Study flowchart. Heat-related illness sample: Among 1,497 patients included in Heatstroke Study 2017-2019, data from 90 were analyzed. COVID-19 sample: Among 268 patients admitted to two hospitals, data from 86 were analyzed. Ultimately, a total of 176 patients were analyzed. COVID-19: coronavirus disease 2019

### Statistical Analysis

Patient data are expressed as medians and interquartile ranges. For nonparametric data, the Mann-Whitney U test was used for continuous variables, and the  $X^2$  test was used for categorical variables. Multiple stepwise logistic regression analysis was used to develop a classification model for differentiating COVID-19 from heat-related illness, based on the significance of risk factors in univariate analysis. Receiver operating characteristic curves were plotted and area under the curve (AUC) was calculated. All statistical analyses were performed by using StatFlex v7.0 (Artech, Osaka, Japan), and differences were considered statistically significant at  $p < 0.05$ .

Random Forest, a type of supervised classification machine learning model, was used to develop a model to distinguish heat-related illness from COVID-19. We performed 5-fold cross-validation for the Random Forest model to optimize evaluation metrics. Classification performance was evaluated by accuracy, precision, sensitivity, specificity, recall, F1 score, and AUC. The Python language was used to code the algorithm.

### Results

#### Patient Enrollment and Baseline Characteristics

Among the 1,497 patients with heat-related illness who were included in the Heatstroke Study 2017-2019, 1,407 patients were excluded because of need for emergency transportation ( $n=1,354$ ), age  $<18$  years ( $n=16$ ), disturbance of consciousness ( $n=27$ ), and missing data ( $n=10$ ).

The COVID-19 group comprised 268 patients with laboratory-confirmed COVID-19, and 182 patients were excluded for absence of fever or fatigue ( $n=179$ ) and need for emergency transportation ( $n=3$ ). Ultimately, this study included 176 patients (heat-related illness,  $n=90$ ; COVID-19,  $n=86$ ) in the analysis (Fig. 1).

The patients' baseline characteristics are shown in Table 1. Age did not significantly differ between those with heat-related illness and those with COVID-19. There were significant differences in systolic blood pressure (119 vs. 125 mm Hg, respectively,  $p=0.02$ ), SpO<sub>2</sub> (98% vs. 97%, respectively,  $p<0.001$ ), and body temperature (36.6°C vs. 37.6°C,  $p<0.001$ ) between those with heat-related illness and COVID-19. There were numerous differences in laboratory findings between the groups, including WBC ( $10.8 \times 10^3/\mu\text{L}$  vs.  $5.2 \times 10^3/\mu\text{L}$ , respectively,  $p<0.001$ ), hemoglobin (16.6 vs. 15.0 g/dL, respectively,  $p<0.001$ ), platelet count ( $26 \times 10^4/\mu\text{L}$  vs.  $19 \times 10^4/\mu\text{L}$ , respectively,  $p<0.001$ ), BUN (26.1 vs. 14 mg/dL, respectively,  $p<0.001$ ), creatinine (2.2 vs. 0.85 mg/dL, respectively,  $p<0.001$ ), total bilirubin (1.0 vs. 0.6 mg/dL, respectively,  $p<0.001$ ), CK (259 vs. 79 U/L, respectively,  $p<0.001$ ), CRP (0.2 vs. 2.8 mg/dL, respectively,  $p<0.001$ ), D-dimer (0.5 vs. 0.6  $\mu\text{g}/\text{mL}$ , respectively,  $p=0.04$ ), potassium (4.3 vs. 4.1 mEq/L, respectively,  $p<0.01$ ), chlorine (99 vs. 102 mEq/L, respectively,  $p<0.001$ ), and glucose (122 vs. 104 mg/dL, respectively,  $p<0.001$ ). The clinical symptoms of patients with COVID-19 included cough (49%), exertional dyspnea (23%), headache (20%), myalgia or arthralgia (15%), rhi-

Table 1 Baseline characteristics of patients

	Heat-related illness (n = 90)	COVID-19 (n = 86)	p-value
Age, years	48 [35-62]	53 [41-67]	0.09
Male, % (n)	81 (90.0)	58 (67.4)	0.001<
Body mass index	24.0 [21.3-26.2]	23.3 [20.1-26.4]	0.50
Past medical history			
Cardiovascular	3	5	0.42
Respiratory	2	10	0.01
Renal	0	1	0.30
Hepatitis	0	0	N/A
Diabetes mellitus	0	3	0.07
Vital signs			
Systolic blood pressure, mm Hg	119 [108-134]	125 [114-139]	0.02
Diastolic blood pressure, mm Hg	78 [69-91]	80 [72-90]	0.58
Heart rate, bpm	90 [82-103]	88 [78-100]	0.20
Respiratory rate, bpm	19 [16-21]	19 [16-22]	0.54
Oxygen saturation, %	98 [96-99]	97 [95-98]	0.001<
Body temperature, °C	36.6 [36.1-37.0]	37.6 [36.8-38.3]	0.001<
Laboratory findings			
White blood cell count, 10 <sup>3</sup> /μL	10.8 [7.2-15.1]	5.2 [4.2-6.6]	0.001<
Hemoglobin, g/dL	16.6 [14.9-17.8]	15.0 [14.1-15.8]	0.001<
Platelet count, 10 <sup>4</sup> /μL	26.0 [21.5-29.6]	19.0 [15.9-23.7]	0.001<
Blood urea nitrogen, mg/dL	26.1 [19.7-36.8]	14.0 [10.0-17.0]	0.001<
Creatinine, mg/dL	2.2 [1.35-2.9]	0.85 [0.70-1.03]	0.01<
Total bilirubin, mg/dL	1.0 [0.7-1.3]	0.6 [0.4-0.7]	0.001<
Aspartate transaminase, U/L	34 [24-46]	33 [23-57]	0.89
Alanine transaminase, U/L	37 [23-55]	34 [17-51]	0.35
Creatine kinase, mg/dL	259 [170-432]	79 [55-135]	0.001<
C-reactive protein, mg/dL	0.2 [0.1-0.5]	2.8 [0.3-6.3]	0.001<
Prothrombin time (international normalized ratio)	1.00 [0.90-1.10]	1.00 [1.00-1.10]	0.05
D-dimer, μg/mL	0.5 [0.5-0.7]	0.6 [0.5-1.0]	0.04
Sodium, mEq/L	137 [136-140]	139 [136-141]	0.05
Potassium, mEq/L	4.3 [3.9-4.6]	4.1 [3.8-4.3]	0.01<
Chlorine, mEq/L	99 [94-108]	102 [98-104]	0.001<
Glucose, mg/dL	122 [107-153]	104 [93-116]	0.001<

COVID-19: coronavirus disease 2019

norrrhea (10%), sore throat (9%), diarrhea (9.3%), and abdominal pain (6%). These data were unavailable from the Heatstroke Study. In the COVID-19 group, 37% of the patients had a history of close contact with a COVID-19 patient.

#### Distinguishing between Heat-Related Illness and COVID-19

A classification model of COVID-19 and heat-related illness was established by three-factor multiple logistic regression, as follows:  $LP_{\text{COVID-19}} = 4.192 - 0.2010 \times \text{WBC} - 3.494 \times \text{Creatinine} + 1.230 \times \text{CRP}$  (Table 2). This model yielded an AUC of 0.966 (Fig. 2). The Random Forest model yielded an accuracy of 0.908, precision of 0.976, sensitivity of 0.842, specificity of 0.977, recall of 0.842, F1

score of 0.902, and AUC of 0.978 (Fig. 2). Feature importance analysis is shown in Figure 3. Creatinine was the most important feature of this model. Other important features were WBC, BUN, CRP, and CK.

#### Discussion

This is the first study to compare heat-related illness and COVID-19, both of which are systemic febrile illnesses. Creatinine level was the most important factor in distinguishing heat-related illness from COVID-19. The data indicated that nearly half of the COVID-19 patients had fever or fatigue but no cough and that approximately one third of the COVID-19 patients had close contact with persons known to be infected with COVID-19. Al-

Table 2 Parameters of logistic regression model

Variable	Partial regression coefficient	Standard error	p-value
Intercept	4.192	0.971	
WBC, 10 <sup>3</sup> / $\mu$ L	-0.2010	0.0837	<0.01
Creatinine, mg/dL	-3.494	0.814	<0.001
CRP, mg/dL	1.230	0.393	<0.01

WBC: white blood cell count; CRP: C-reactive protein

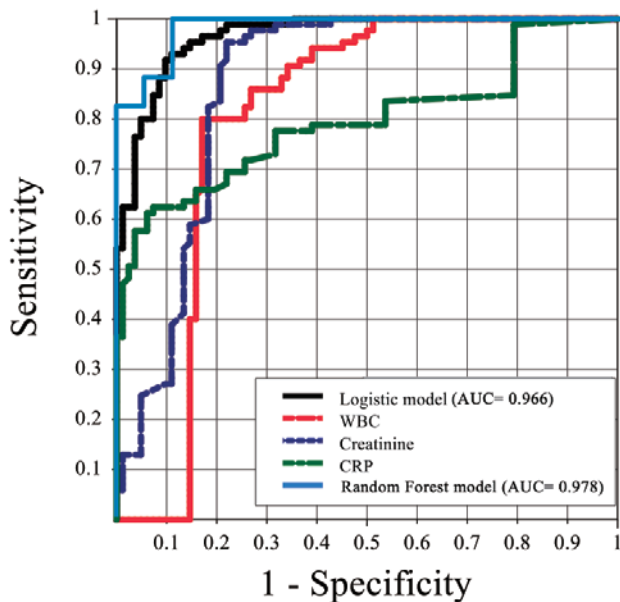


Fig. 2 Receiver operating characteristic curve analysis for classification of heat-related illness and COVID-19 with a multiple logistic regression model and Random Forest model.

COVID-19: coronavirus disease 2019; WBC: white blood cell count; CRP: C-reactive protein

though COVID-19 is a viral disease with major symptoms centered on the respiratory system, some patients with COVID-19 do not have respiratory symptoms early in the course of the infection or even after developing more severe disease<sup>9,10</sup>. Contact with known sick individuals—a key factor in the diagnosis of any infectious disease—might be insufficient during the present pandemic. Therefore, differentiation based on presenting symptoms and history might be difficult.

The logistic regression model and Random Forest model based on laboratory findings and other clinical information were highly accurate. The two models revealed that creatinine, WBC, and CRP were important factors in differential diagnosis. Leukopenia, especially lymphopenia, and CRP elevation are characteristic of COVID-19 and other viral infections<sup>11</sup>. Serum creatinine levels were significantly elevated in patients with heat-

related illness. Although acute kidney injury (AKI) is reported to be common in severe COVID-19 patients<sup>12</sup>, AKI prevalence was not high in the present COVID-19 group, perhaps because our COVID-19 patient dataset excluded patients requiring emergency transport, which indicates presence of severe disease before arrival, or because the COVID-19 patients became ill during the winter and spring, when they are less likely to be dehydrated. Despite the many mechanisms of AKI development in COVID-19 patients, such as the effects of SARS-CoV-2 on kidney endothelial cells, the prior trigger for AKI in COVID-19 would be volume depletion caused by lack of volume resuscitation in hospital<sup>13</sup>. In this context, heat-related illness by itself, or when undiagnosed, might exacerbate COVID-19.

There are no reports of complications of heat-related illness and COVID-19. However, heat-related illness would affect the outcome of COVID-19. It would be more important to recognize heat-related illness coincident with COVID-19 than to simply distinguish heat-related illness from COVID-19. The standard method for diagnosing COVID-19 is detection of SARS-CoV-2 RNA by RT-PCR. However, this complex test requires a high level of expertise and takes several hours to generate test results. Recently, rapid antigen detection tests for SARS-CoV-2 have been developed<sup>14,15</sup>. Although the sensitivity and the specificity of these tests is unclear, they could become important tools for COVID-19 diagnosis. However, these tools cannot detect “hidden” heat-related illness. Our data suggest that heat-related illness, even during the early stage, impairs renal function. Blood sampling tests would be useful, but simpler tests would be preferred during a pandemic, to prevent medical exhaustion and provide early intervention from an emergency department or even pre-hospital. Urine liver fatty acid-binding protein (L-FABP) measured by a rapid assay kit is reported to predict AKI within 15 minutes, even in the emergency department<sup>16</sup>. In conjunction with rapid testing for COVID-19, a rapid L-FABP test for AKI could help reduce overlooked hidden heat-related illness or se-

### Difference between Heatstroke and COVID-19

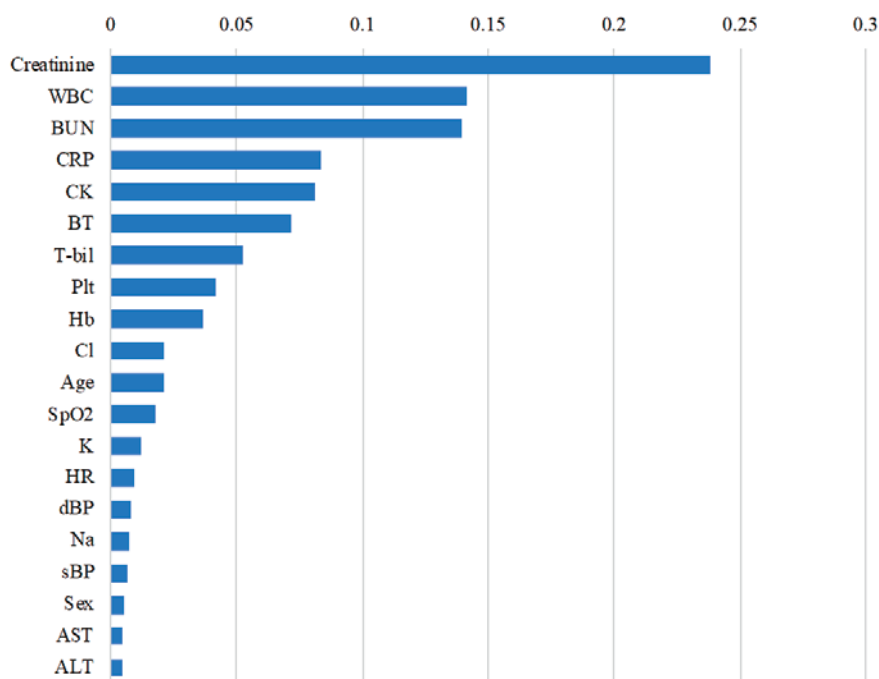


Fig. 3 Ranking of feature importance in the Random Forest model.

Cre: creatinine; WBC: white blood cell count; BUN: blood urea nitrogen; CRP: C-reactive protein; CK: creatine kinase; BT: body temperature; T-bil: total bilirubin; Plt: platelet count; Hb: hemoglobin; Cl: chlorine; HR: heart rate; dBP: diastolic blood pressure; sBP: systolic blood pressure; AST: aspartate transaminase; ALT: alanine transaminase

vere COVID-19.

This study has some limitations. First, there was selection bias. We only compared patients with relatively mild symptoms who could present for treatment unassisted, which excluded over 90% of patients in the Heatstroke Study and most patients with severe COVID-19. Moreover, we did not determine the cause of heat-related illness, including classic and exertional. This situation might be confined to limited clinical practice. However, we believe that because this is the first study of this topic, our comparisons of mild cases of COVID-19 and heat-related illness for differential diagnosis are notable. Second, our study did not include patients with complications of COVID-19 and heat-related illness; collecting data on such cases will be indispensable during the summer of a pandemic. Third, sample sizes were small, which can result in overfitting issues in machine learning models. Although we used 5-fold cross-validation to verify the model and achieved high performance, larger studies should confirm the findings of the machine learning model. Our models did not include laboratory findings of lactate dehydrogenase (LDH) or clinical symptoms. Although LDH is an important COVID-19 biomarker, it was not included in the Heatstroke Study dataset. Clinical symptoms, especially respiratory symp-

oms, are vital information but were also not included in the Heatstroke Study dataset. However, even without information on LDH or clinical symptoms, our model achieved high accuracy. The model would be more accurate if LDH values and data on clinical symptoms were added. Finally, our model cannot make a definitive diagnosis. A diagnosis of COVID-19 should be made by using RT-PCR, and careful observation remains indispensable.

In summary, although nearly half of patients with COVID-19 presented with cough, there was no clinically significant difference in any vital sign except body temperature between the groups. However, there were numerous differences in laboratory findings between groups. Laboratory examination could distinguish between these diseases. Early recognition of AKI could be important during a summer COVID-19 pandemic. However, further studies are required in order to identify how heat-related illness affects COVID-19.

**Acknowledgement:** We thank all the medical staff who participated in the Heatstroke STUDY and the medical staff of the Japan Self-Defense Forces Central Hospital and Flowers & Forest Tokyo Hospital who were involved in the management and treatment of patients with COVID-19.

**Funding:** The Heatstroke STUDY 2017-2019 was supported by Health and Labor Sciences Research Grants.

**Conflict of Interest:** None declared

### References

- World Health Organization. Coronavirus disease (COVID-19) [Internet]. 2020 [cited 2020 Jul 1]. Available from: <http://www.who.int/emergencies/diseases/novel-coronavirus-2019>
- Aldridge RW, Lewer D, Beale S, et al. Seasonality and immunity to laboratory-confirmed seasonal coronaviruses (HCoV-NL63, HCoV-OC43, and HCoV-229E): results from the Flu Watch cohort study. *Wellcome Open Res* [Internet]. 2020 [cited 2020 Jul 1]. Available from: <https://doi.org/10.12688/wellcomeopenres.15812.1>
- Baker RE, Yang W, Vecchi GA, Metcalf CJE, Grenfell TB. Susceptible supply limits the role of climate in the early SARS-CoV-2 pandemic. *Science*. 2020 May 18;eabc2535.
- Epstein Y, Yanovich R. Heatstroke. *New Engl J Med*. 2019; 380:2449–59.
- Morabito M, Messeri A, Crisci A, Pratali L, Bonafede M, Marinaccio A, WORKLIMATE Collaborative Group. Heat warning and public and workers' health at the time of COVID-19 pandemic. *Sci Total Environ*. 2020;738:140347.
- World Health Organization. Coronavirus disease (COVID-19) advice for the public: When and how to use masks [Internet]. 2020 [cited 2020 Jul 1]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/when-and-how-to-use-masks>
- Vaidyanathan A, Malilay J, Schramm P, Saha S. Heat-related deaths - United States, 2004-2018. *MMWR Morb Mortal Wkly Rep*. 2020;69:729–34.
- Shimazaki J, Hifumi T, Shimizu K, et al. Clinical characteristics, prognostic factors, and outcomes of heat-related illness (Heatstroke Study 2017-2018). *Acute Med Surg*. 2020;7:e516.
- Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. *Am J Resp Crit Med*. 2020.
- Couzin-Frankel J. The mystery of the pandemic's 'Happy Hypoxia'. *Science*. 2020;368:455–6.
- Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - a systematic review. *Life Sci*. 2020;254:117788.
- Yan X, Jin Y, Li R, Zhang Z, Sun R, Chen D. Prevalence and impact of acute renal impairment on COVID-19: a systematic review and meta-analysis. *Crit Care*. 2020;24:356.
- Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. *Lancet Resp Med*. 2020;8:738–42.
- Schoy A, Anantharajah A, Bodéus M, Kabamba-Mukadi B, Verroken A, Rodriguez-Villalobos H. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. *J Clin Virol*. 2020;129:104455.
- Porte L, Legarraga P, Vollrath V, et al. Evaluation of novel antigen-based rapid detection test for the diagnosis of SARS-CoV-2 in respiratory samples. *Int J Infect Dis*. 2020; 99:328–33.
- Suzuki G, Ichibayashi R, Yamamoto S, Nakamichi Y, Watanabe M, Honda M. Clinical significance of urinary L-FABP in the emergency department. *Int J Emerg Med*. 2019;12:24.

(Received, July 6, 2020)

(Accepted, July 31, 2020)

(J-STAGE Advance Publication, August 31, 2020)

Journal of Nippon Medical School has adopted the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>) for this article. The Medical Association of Nippon Medical School remains the copyright holder of all articles. Anyone may download, reuse, copy, reprint, or distribute articles for non-profit purposes under this license, on condition that the authors of the articles are properly credited.