

Early positivity for Japanese Association for Acute Medicine 2 criteria and subsequent overt disseminated intravascular coagulation in heat-related illness: a multicenter retrospective cohort study

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Abstract

Background

Heat-related illness can cause disseminated intravascular coagulation (DIC) and poor patient outcomes. The International Society on Thrombosis and Haemostasis (ISTH) overt DIC criteria mainly identify advanced coagulopathy, and earlier risk stratification is needed.

Objectives

To evaluate the frequency and clinical significance of progression to overt DIC and its association with early Japanese Association for Acute Medicine 2 (JAAM-2) DIC positivity.

Methods

We performed a multicenter retrospective cohort study using the OnelCU database in Japan. Patients aged ≥ 16 years with heat-related illness and sufficient data to calculate JAAM-2 DIC and ISTH overt DIC scores within 6 hours after hospital arrival and during the 6–72 hours thereafter were included. Progression was defined as meeting ISTH overt DIC criteria during 6–72 hours among patients without overt DIC within 6 hours.

Results

Among 309 patients, 40 (12.9%) had ISTH overt DIC within 6 hours and had higher ICU mortality than those without overt DIC (40.0% vs. 2.2%; $p < 0.001$). Among the 269 patients without overt DIC within 6 hours, 26 (9.7%) progressed to overt DIC within 72 hours and had higher ICU mortality than those without progression (19.2% vs. 0.4%; $p < 0.001$). In univariable analysis, JAAM-2 DIC positivity within 6 hours was associated with progression to overt DIC (odds ratio, 10.13; 95% confidence interval, 4.29–26.21; $p < 0.001$).

Conclusions

Early overt DIC and subsequent overt DIC progression were associated with increased ICU mortality in patients with heat-related illness. Early JAAM-2 DIC positivity may help identify patients who need repeated assessment of coagulation.

Background

Heat-related illness is a life-threatening condition characterized by hyperthermia-induced systemic inflammation, endothelial injury, coagulation activation, and progressive multiorgan dysfunction [1]. Coagulopathy with marked fibrinolytic activation is observed in patients with heat-related illness, and disseminated intravascular coagulation (DIC) has been associated with poor outcomes in this population [1, 2]. Previous multicenter studies from Japan have shown that DIC is independently associated with in-hospital mortality and that mortality increases according to DIC severity [2, 3]. However, the reported incidence and prognostic impact of DIC in heat-related illness have varied across studies, partly because of differences in patient populations and diagnostic criteria [4].

The International Society on Thrombosis and Haemostasis (ISTH) overt DIC criteria are widely used for the diagnosis of overt DIC [5, 6]. However, these criteria generally reflect a relatively advanced stage of coagulopathy accompanied by consumptive changes in platelet count and fibrinogen [7]. Therefore, some patients with heat-related illness may not meet the overt DIC criteria at initial assessment but may subsequently progress to overt DIC during the early hospital course [1, 8]. Early identification of patients at risk of such progression is therefore clinically important, yet the frequency, clinical significance, and early predictors of overt DIC progression remain unclear.

In sepsis-associated coagulopathy, the sepsis-induced coagulopathy score and the Japanese Association for Acute Medicine 2 DIC (JAAM-2 DIC) criteria have been proposed as tools for identifying early-phase coagulopathy preceding overt DIC [9–11]. However, no established approach is available for early risk stratification of subsequent overt DIC progression in heat-related illness. Therefore, we aimed to determine the frequency and prognostic significance of progression to overt DIC in critically ill adult patients with heat-related illness and to evaluate whether early JAAM-2 DIC positivity and other clinical factors may help identify patients at risk of such progression.

Methods

Design and setting

We conducted a multicenter retrospective cohort study using the OnelICU database (provided by MeDiCU, Inc., Osaka, Japan), an ongoing nationwide project in Japan that integrates minute-level physiologic data from intensive care units (ICUs) at tertiary care hospitals. The database contains continuously recorded vital signs and clinician-validated spot measurements linked to time-stamped medication administration records, laboratory data, procedures, and outcomes. Diagnoses are mapped to the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) through a natural language processing pipeline and are subsequently validated by intensivists. The database structure, data quality assurance workflow, and variable definitions have been described previously [12].

Under a master protocol approved by the Institutional Review Board (IRB) of Kansai Medical University (approval number: 2024015), 39 institutions had been approved for data contribution as of March 2026, and additional institutions were undergoing IRB procedures. In the present analysis, we included data

from 14 ICUs for which data extraction and quality assessment had been completed at the time of the study. Because the OneICU database is continuously updated, the present study used a fixed analytical dataset comprising hospital arrivals recorded between February 2013 and December 2025. This study was conducted in accordance with the Declaration of Helsinki and was approved by the IRB of Kansai Medical University (approval number: 2026008).

The board waived the requirement for informed consent because the dataset was fully anonymized and did not contain identifiable information on patients, hospitals, or treating physicians.

Participants

We identified patients aged 16 years or older who were admitted to an ICU and had heat-related illness defined by the ICD-10 codes T67.0–T67.9. Because the aim of this study was to evaluate early coagulopathy and subsequent progression to overt DIC, we excluded patients with out-of-hospital cardiac arrest, missing outcome data, or death within 6 hours after hospital arrival. Out-of-hospital cardiac arrest was identified using diagnosis codes and recorded resuscitation events immediately after hospital arrival. We also excluded patients with missing coagulation-related variables required to calculate the JAAM-2 DIC and ISTH overt DIC scores within 6 hours after hospital arrival, including platelet count, prothrombin time-international normalized ratio (PT-INR), fibrinogen, and fibrin-related markers. Fibrin/fibrinogen degradation products (FDP) and D-dimer were chosen as the fibrin-related markers. In addition, patients with missing variables required to assess JAAM-2 DIC and ISTH overt DIC scores during the 6–72 hours after hospital arrival were excluded because progression to overt DIC within 72 hours could not be evaluated.

Data collection

We collected data on demographic characteristics, comorbidities, physiologic variables, laboratory findings including coagulation markers, severity scores, organ support therapies, and outcomes. Variables of interest included age, sex, body mass index, Charlson Comorbidity Index, core body temperature, Glasgow Coma Scale score, heart rate, systolic blood pressure, arterial blood gas parameters including pH and lactate, creatinine, total bilirubin, creatine kinase, platelet count, PT-INR, fibrinogen, FDP, D-dimer, Sequential Organ Failure Assessment (SOFA) score, vasopressor use, and mechanical ventilation. Vasopressor use within 6 hours was defined as administration of norepinephrine, epinephrine, dopamine, vasopressin, or other vasopressor agents during the first 6 hours after hospital arrival.

For descriptive analyses of physiologic variables and laboratory data, the most abnormal value within each predefined time window was used. The initial 6-hour assessment was based on data obtained within 0–6 hours after hospital arrival, and the subsequent assessment was based on data obtained during 6–72 hours after hospital arrival.

DIC scores were calculated using the JAAM-2 DIC criteria and the ISTH overt DIC criteria [5, 6, 11, 13]. The components and thresholds of the JAAM-2 DIC criteria and the ISTH overt DIC score used in this study are summarized in Supplementary Table S1. The JAAM-2 DIC criteria are a revised version of the original JAAM DIC criteria in which the systemic inflammatory response syndrome component is omitted; DIC was defined as a JAAM-2 DIC score of ≥ 3 [11]. Overt DIC was defined as an ISTH DIC score of ≥ 5 [5, 6, 13].

The original ISTH overt DIC score assigns points for the PT component based on prolongation in seconds beyond the institutional reference value. In the present database, PT prolongation in seconds was not consistently available, whereas PT-INR was available. Therefore, the PT component was operationalized using PT-INR thresholds adopted in a previously published adapted ISTH DIC score: PT-INR ≤ 1.4 was assigned 0 points, PT-INR > 1.4 to ≤ 2.3 was assigned 1 point, and PT-INR > 2.3 was assigned 2 points [13]. For fibrin-related markers, thresholds for no increase, moderate increase, and strong increase were defined in accordance with previous studies as FDP values of < 10 , 10 to < 25 , and ≥ 25 $\mu\text{g/mL}$, respectively, or D-dimer values of < 5 , 5 to < 10 , and ≥ 10 $\mu\text{g/mL}$, respectively [14–16].

For DIC classification within the initial 6 hours after hospital arrival, JAAM-2 DIC and ISTH overt DIC scores were calculated from contemporaneous data, and the highest score observed during 0–6 hours was used. For the 6–72-hour period, both scores were evaluated in successive 24-hour intervals using available data within each interval. If multiple scores were available within an interval, the highest score for that interval was retained, and the representative score for 6–72 hours was defined as the highest of these interval-specific scores. Progression to overt DIC was defined as meeting the ISTH overt DIC criteria during 6–72 hours after hospital arrival among patients who did not meet the ISTH overt DIC criteria within the initial 6 hours.

Statistical analyses

Continuous variables are presented as median and interquartile range and were compared using the Wilcoxon-Mann-Whitney test. Categorical variables are presented as number and percentage and were compared using Fisher's exact test. To assess potential selection bias related to missing coagulation data, we compared baseline characteristics and outcomes between patients included in the final analysis and those excluded because of missing coagulation data after excluding patients with out-of-hospital cardiac arrest, death within 6 hours after hospital arrival, and missing outcome data. Among the patients who did not meet the ISTH overt DIC criteria within 6 hours after hospital arrival, univariable logistic regression analysis was performed to explore factors associated with progression to overt DIC within 72 hours. Candidate variables were selected a priori based on clinical relevance and early physiologic plausibility. Systolic blood pressure was modeled per 10-mmHg decrease for interpretability. Variables directly overlapping with the definition of overt DIC progression, such as platelet count, PT-INR, fibrinogen, fibrin-related markers, and the ISTH overt DIC score, were not modeled separately to reduce circularity. Mechanical ventilation and SOFA score were not included because they were considered treatment-related or composite severity markers that could be collinear with other early clinical

variables. Odds ratio (OR) and 95% confidence interval (CI) values were calculated. Because the number of progression events was limited, we did not perform multivariable logistic regression analysis. All tests were two-sided, with a p value < 0.05 considered to indicate statistical significance. All statistical analyses were performed using JMP Pro 17 (SAS Institute Inc., Cary, NC, USA).

Results

Patient selection and initial distribution of overt DIC

The patient flow is shown in Fig. 1. Of 526 patients with heat-related illness screened, 309 were included in the final analysis after exclusions. To assess potential selection bias related to missing coagulation data, we compared patients included in the final analysis with those excluded because of missing coagulation data after excluding those patients with out-of-hospital cardiac arrest, death within 6 hours after hospital arrival, and missing outcome data. Included patients had lower Glasgow Coma Scale scores, higher lactate and creatinine levels, more frequent use of vasopressors and mechanical ventilation, and higher SOFA scores, whereas ICU mortality did not differ significantly between the two groups (Supplementary Table S2). Among the 309 patients included in the final analysis, 40 patients (12.9%) met the ISTH overt DIC criteria within 6 hours of hospital arrival. Compared with the patients not meeting the overt DIC criteria within 6 hours, those with overt DIC had greater illness severity, more frequently circulatory failure and severe impaired consciousness, and markedly higher ICU mortality (40.0% vs. 2.2%, $p < 0.001$) (Table 1).

Table 1
Baseline characteristics and clinical outcomes according to overt DIC status at 6 hours

Characteristic/outcome	Overt DIC at 6 hours, n = 40	No overt DIC at 6 hours, n = 269	P value
Age, years	75 (67–82)	74 (62–82)	0.441
Male sex, n (%)	27 (67.5)	189 (70.3)	0.714
Body mass index, kg/m ²	22.7 (19–25.7)	22.1 (18.5–24.6)	0.578
Charlson Comorbidity Index	3.5 (3–4)	3 (2–4)	0.110
Core body temperature, °C	39.2 (38.2–40.5)	39.1 (38.0–40.2)	0.326
Glasgow Coma Scale score	3 (3–6)	11 (6–14)	< 0.001
Heart rate, beats/min	121 (95–135)	116 (96–134)	0.815
Systolic blood pressure, mmHg	101 (80–136)	130 (107–156)	< 0.001
pH	7.33 (7.23–7.45)	7.42 (7.37–7.47)	< 0.001
Lactate, mmol/L	5.5 (3.8–7.2)	3 (1.8–5.2)	< 0.001
Creatinine, mg/dL	1.8 (1.4–2.5)	1.5 (1.1–2.1)	0.013
Total bilirubin, mg/dL	1.1 (0.7–1.5)	0.9 (0.6–1.4)	0.084
Creatine kinase, U/L	1775 (307–5998)	277 (110–790)	< 0.001
PT-INR	1.7 (1.5–2.2)	1.1 (1.0–1.2)	< 0.001
FDP, µg/mL	140.4 (42.1–435.4)	5.7 (2.5–16.3)	< 0.001
D-dimer, µg/mL	78.7 (21.0–147.3)	3.1 (1.4–11.1)	< 0.001
Platelet count, ×10 ⁴ /µL	7.6 (4.5–9.7)	20.2 (15.9–27.5)	< 0.001
Fibrinogen, mg/dL	139 (61–215)	284 (218–370)	< 0.001
ISTH overt DIC score at 6 hours	6 (5–7)	0 (0–2)	< 0.001
Vasopressor use within 6 hours, n (%)	27 (67.5)	51 (19.0)	< 0.001
Mechanical ventilation within 6 hours, n (%)	30 (75.0)	97 (36.1)	< 0.001
SOFA score at 6 hours	12 (10–15)	5 (3–8)	< 0.001
ICU mortality, n (%)	16 (40.0)	6 (2.2)	< 0.001

Data are presented as median (interquartile range) or number (%)

DIC: disseminated intravascular coagulation; FDP: fibrin/fibrinogen degradation products; ICU: intensive care unit; IQR: interquartile range; ISTH: International Society on Thrombosis and

Characteristic/outcome	Overt DIC at 6 hours, n = 40	No overt DIC at 6 hours, n = 269	P value
Haemostasis; PT-INR: prothrombin time-international normalized ratio; SOFA: Sequential Organ Failure Assessment			

[Insert Table 1 here]

Progression to overt DIC within 72 hours and associated factors

Among the 269 patients not meeting the ISTH overt DIC criteria within 6 hours, 26 patients (9.7%) subsequently progressed to overt DIC within 72 hours. Patients with progression had markedly higher ICU mortality than those without progression (19.2% vs. 0.4%, $p < 0.001$). They also showed more severe impaired consciousness, circulatory failure, and coagulopathy at the 6-hour assessment. The JAAM-2 DIC score at 6 hours was significantly higher in the progression group, and JAAM-2 DIC positivity was more frequent in the progression group than in the non-progression group (69.2% vs. 18.1%, $p < 0.001$) (Table 2).

Table 2
Characteristics by subsequent overt DIC progression

Characteristic/outcome	Progression to overt DIC during 6–72 hours (n = 26)	No progression to overt DIC during 6–72 hours (n = 243)	P value
Age, years	80 (73–86)	73 (59–81)	0.006
Male sex, n (%)	16 (61.5)	173 (71.2)	0.366
Body mass index, kg/m ²	23.2 (21.1–24.6)	21.8 (18.4–24.6)	0.150
Charlson Comorbidity Index	4 (3–4)	3 (2–4)	0.026
Core body temperature, °C	40.1 (38.7–40.9)	39.0 (37.9–40.1)	0.009
Glasgow Coma Scale score	5 (3–10)	12 (7–14)	< 0.001
Heart rate, beats/min	123 (102–146)	116 (95–134)	0.139
Systolic blood pressure, mmHg	101 (78–121)	134 (112–157)	< 0.001
pH	7.39 (7.35–7.45)	7.42 (7.37–7.48)	0.061
Lactate, mmol/L	4.7 (3.0–6.6)	2.8 (1.7–4.7)	0.005
Creatinine, mg/dL	2.0 (1.6–2.9)	1.4 (1.0–2.0)	< 0.001
Total bilirubin, mg/dL	0.9 (0.6–1.7)	0.9 (0.6–1.4)	0.548
Creatine kinase, U/L	505 (233–1745)	267 (107–753)	0.009
PT-INR	1.2 (1.1–1.4)	1.1 (1.0–1.2)	0.002
FDP, µg/mL	49.5 (12.8–161.4)	5.1 (2.5–13.2)	< 0.001
D-dimer, µg/mL	15.4 (7.7–82.5)	2.7 (1.3–9.3)	< 0.001
Platelet count, ×10 ⁴ /µL	14.1 (12.2–20.0)	21.0 (16.4–28.7)	< 0.001
Fibrinogen, mg/dL	262 (229–348)	317 (251–411)	0.054
JAAM-2 DIC score at 6 hours	3 (2–4)	1 (0–2)	< 0.001
JAAM-2 DIC positivity at 6 hours, n (%)	18 (69.2)	44 (18.1)	< 0.001
ISTH overt DIC score at 6 hours	3 (2.8–4)	0 (0–2)	< 0.001
Vasopressor use within 6 hours, n (%)	15 (57.7)	36 (14.8)	< 0.001
Mechanical ventilation within 6 hours, n (%)	17 (65.4)	80 (32.9)	0.002

Characteristic/outcome	Progression to overt DIC during 6–72 hours (n = 26)	No progression to overt DIC during 6–72 hours (n = 243)	P value
SOFA score at 6 hours	10.5 (8–13)	4 (3–7)	< 0.001
ICU mortality, n (%)	5 (19.2)	1 (0.4)	< 0.001
ICU length of stay, days	11 (5–19)	4 (3–9)	< 0.001
Data are presented as median (interquartile range) or number (%)			
DIC: disseminated intravascular coagulation; FDP: fibrin/fibrinogen degradation products; ICU: intensive care unit; IQR: interquartile range; ISTH: International Society on Thrombosis and Haemostasis; PT-INR: prothrombin time–international normalized ratio; SOFA: Sequential Organ Failure Assessment			

[Insert Table 2 here]

In univariable logistic regression analysis, JAAM-2 DIC positivity within 6 hours was associated with progression to overt DIC within 72 hours (OR, 10.13; 95% CI, 4.29–26.21; $p < 0.001$). Vasopressor use within 6 hours was also significantly associated with overt DIC progression (OR, 7.77; 95% CI, 3.33–18.69; $p < 0.001$). Older age, higher core body temperature, lower Glasgow Coma Scale score, and lower systolic blood pressure, expressed as each 10-mmHg decrease, were associated with progression to overt DIC (Table 3).

Table 3
Factors associated with progression to overt DIC

Factor	Odds ratio	95% confidence interval	P value
Age, years	1.04	1.01–1.09	0.006
Core body temperature, °C	1.38	1.04–1.86	0.021
Glasgow Coma Scale score	0.81	0.73–0.90	< 0.001
Systolic blood pressure, per 10 mmHg decrease	1.25	1.12–1.41	< 0.001
Lactate, mmol/L	1.08	0.99–1.17	0.076
Creatinine, mg/dL	1.14	0.95–1.34	0.146
JAAM-2 DIC positivity at 6 hours	10.13	4.29–26.21	< 0.001
Vasopressor use within 6 hours	7.77	3.33–18.69	< 0.001
Odds ratios were estimated using univariable logistic regression models			
CI: confidence interval; DIC: disseminated intravascular coagulation; GCS: Glasgow Coma Scale; ISTH: International Society on Thrombosis and Haemostasis; JAAM-2: Japanese Association for Acute Medicine 2			

[Insert Table 3 here]

Discussion

In this multicenter retrospective cohort study of critically ill patients with heat-related illness, both overt DIC within 6 hours of hospital arrival and subsequent progression to overt DIC within 72 hours were associated with markedly increased ICU mortality. In addition, positivity for the JAAM-2 DIC criteria within 6 hours was associated with subsequent progression to overt DIC. These findings suggest that coagulopathy in heat-related illness is dynamic during the early ICU course and that early JAAM-2 DIC positivity may be useful for early risk stratification and for identifying patients who may warrant repeated assessment of coagulation.

Previous studies suggest that DIC in heatstroke is a clinically important determinant of prognosis. A recent systematic review and meta-analysis reported that the pooled raw mortality of heatstroke-associated DIC was 32%, while noting substantial heterogeneity according to the diagnostic criteria and study populations [4]. However, previous studies have generally not distinguished between patients who already had overt DIC at the initial assessment and those who subsequently progressed to overt DIC during the early ICU course. In this context, our findings suggest that the timing of overt DIC onset may provide additional prognostic information: patients who already met the ISTH overt DIC criteria within 6 hours of hospital arrival had markedly increased ICU mortality, and even among those without overt DIC initially, subsequent progression within 72 hours identified another high-risk subgroup.

Coagulation and fibrinolytic abnormalities in heat-related illness can develop early after onset and may continue even after initial cooling [17]. Accordingly, a single early coagulation assessment may be insufficient to capture the full extent of the coagulopathy. Previous studies have suggested that DIC-related abnormalities in heatstroke may become more apparent during the first 1 to 3 days after onset and that temporal changes in platelet counts and other coagulation markers may be more strongly associated with DIC development and outcomes than initial values alone [18]. In the present study, a subset of patients who did not meet the ISTH overt DIC criteria within 6 hours subsequently progressed to overt DIC within 72 hours. This finding underscores the importance of repeated assessment of coagulation during the early ICU course in patients with heat-related illness.

In sepsis-associated DIC, the ISTH overt DIC criteria generally reflect a relatively advanced stage of coagulopathy, whereas JAAM DIC criteria may identify earlier-phase coagulation abnormalities preceding overt DIC [7, 14, 19]. In our cohort, some patients who did not initially meet the ISTH overt DIC criteria later progressed to overt DIC, and early JAAM-2 DIC positivity was associated with that progression. These findings suggest that the early risk-stratification role of JAAM DIC criteria may also be applicable to heat-related illness. Importantly, our results do not imply that JAAM-2 DIC criteria can replace the ISTH overt DIC criteria. Rather, JAAM-2 DIC criteria may be useful for identifying patients at increased risk of subsequent overt DIC, thereby supporting closer monitoring and repeated assessment of coagulation after admission.

In univariable analysis, several early indicators of illness severity, including older age, higher core body temperature, lower Glasgow Coma Scale score, lower systolic blood pressure, and vasopressor use were associated with subsequent overt DIC. These findings suggest that patients who later progress to overt DIC already present with more severe systemic illness, including circulatory failure and neurologic dysfunction, at an early stage. Previous studies in heatstroke have likewise shown that early coagulopathy, circulatory failure, and central nervous system dysfunction are associated with worse outcomes [2, 3, 20, 21]. In this context, the associations of vasopressor use and lower Glasgow Coma Scale score in our study may be interpreted as markers of a high-risk clinical phenotype rather than competing alternatives to JAAM-2 DIC criteria.

Circulatory failure is an important complication of heat-related illness and has been associated with poor outcomes in prior studies [20, 21]. One possible mechanism linking circulatory failure to progression of coagulopathy is that shock-induced tissue hypoperfusion and hypoxia aggravate endothelial injury and amplify dysregulation of coagulation and fibrinolysis. In trauma, hypoperfusion has been linked to hyperfibrinolysis mediated by endothelial release of tissue plasminogen activator [22]. In heat-related illness, direct thermal endothelial injury, systemic inflammation, and shock-related hypoperfusion may act synergistically to promote coagulation activation and microvascular thrombosis [1]. Similarly, impaired consciousness reflected by a lower Glasgow Coma Scale score may indicate more severe systemic dysfunction and multiorgan involvement in patients who subsequently progress to overt DIC [3]. Our findings suggest that even among patients who do not initially meet the ISTH overt DIC criteria, a clinically important subgroup may progress to overt DIC during the early ICU course and experience markedly worse outcomes. Early identification of such patients is clinically important because it may prompt closer surveillance and repeated coagulation testing during the early ICU phase. Our findings also suggest that the JAAM-2 DIC criteria may help identify patients at increased risk of subsequent overt DIC.

This study has several limitations. First, because of its retrospective observational design, residual confounding by unmeasured variables cannot be excluded. Second, a substantial number of patients were excluded because of missing coagulation data required to calculate DIC scores. In the supplementary comparison excluding patients with out-of-hospital cardiac arrest, death within 6 hours after hospital arrival, and missing outcome data, patients included in the final analysis had greater early illness severity than those excluded because of missing coagulation data. This finding suggests possible severity-related selection, likely because coagulation testing was performed more frequently in the more severely ill patients. Therefore, the observed incidence of overt DIC and subsequent progression may not be generalizable to all patients with heat-related illness, particularly those with milder disease. Third, the number of progression events was limited. Therefore, we did not perform multivariable analysis, and the observed associations, including that of JAAM-2 DIC positivity, should be interpreted as exploratory rather than definitive independent effects. Fourth, JAAM-2 DIC and ISTH overt DIC criteria share several coagulation components, including platelet count, PT-related variables, and fibrin-related markers. Therefore, the observed association between early JAAM-2 DIC positivity and subsequent overt DIC progression may partly reflect structural overlap between the two scoring systems. Fifth, interfacility

differences in the timing of blood sampling and management strategies may have influenced coagulation parameters and the determination of overt DIC progression. Finally, identification of heat-related illness was based on diagnosis codes, and misclassification cannot be completely excluded.

Conclusion

In critically ill patients with heat-related illness, both overt DIC within 6 hours of hospital arrival and subsequent progression to overt DIC within 72 hours were associated with markedly increased ICU mortality. Early JAAM-2 DIC positivity was associated with subsequent overt DIC and may be useful for early risk stratification and for selecting patients who warrant repeated assessment of coagulation during the early ICU course.

Abbreviations

CI Confidence interval

DIC Disseminated intravascular coagulation

FDP Fibrin/fibrinogen degradation products

GCS Glasgow Coma Scale

ICD-10 International Classification of Diseases, Tenth Revision

ICU Intensive care unit

IQR Interquartile range

IRB Institutional Review Board

ISTH International Society on Thrombosis and Haemostasis

JAAM Japanese Association for Acute Medicine

JAAM-2 Japanese Association for Acute Medicine 2

OR Odds ratio

PT-INR Prothrombin time–international normalized ratio

SOFA Sequential Organ Failure Assessment

Declarations

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Authors' contributions

T.O. conceived and designed the study, contributed to the acquisition, analysis, and interpretation of the data, and drafted, edited, and submitted the manuscript. S.M. and J.Y. contributed to the study design and to the acquisition, analysis, and interpretation of the data, and revised the manuscript. T.Mu., J.S., D.M., K.K., T.T., T.Ma., K.S., H.K., and Y.N. contributed to data interpretation and critically reviewed the manuscript. All authors reviewed, discussed, and approved the final manuscript.

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Availability of data and materials

The data supporting the findings of this study are available from the corresponding author, on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Kansai Medical University (approval no. 2026008). The study was conducted following the Helsinki Declaration, and the need for additional written informed consent was waived because of the retrospective design.

Consent for publication

Not applicable.

Declarations of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) to improve the English of the article. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Competing interests

The authors declare that they have no competing interests.

References

1. Iba T, Connors JM, Levi M, Levy JH. Heatstroke-induced coagulopathy: Biomarkers, mechanistic insights, and patient management. *EClinicalMedicine*. 2022;44:101276. <https://doi.org/10.1016/j.eclinm.2022.101276>.
2. Hifumi T, Kondo Y, Shimazaki J, Oda Y, Shiraishi S, Wakasugi M, et al. Prognostic significance of disseminated intravascular coagulation in patients with heat stroke in a nationwide registry. *J Crit Care*. 2018;44:306–11. <https://doi.org/10.1016/j.jcrc.2017.12.003>.
3. Shimazaki J, Hifumi T, Shimizu K, Oda Y, Kanda J, Kondo Y, et al. Clinical characteristics, prognostic factors, and outcomes of heat-related illness (Heatstroke Study 2017–2018). *Acute Med Surg*. 2020;7:e516. <https://doi.org/10.1002/ams2.516>.
4. Umemura Y, Scarlatescu E, Nwagha TU, Levy JH, Othman M, Moore H, et al. Mortality, diagnosis, and etiology of disseminated intravascular coagulation-a systematic review and meta-analysis: communication from the ISTH SSC subcommittee on disseminated intravascular coagulation. *J Thromb Haemost*. 2025;23(8):2663–79. <https://doi.org/10.1016/j.jtha.2025.04.033>.
5. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M, Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86(5):1327–30.
6. Iba T, Levy JH, Maier CL, Helms J, Umemura Y, Moore H, et al. Updated definition and scoring of disseminated intravascular coagulation in 2025: communication from the ISTH SSC Subcommittee on Disseminated Intravascular Coagulation. *J Thromb Haemost*. 2025;23(7):2356–62. <https://doi.org/10.1016/j.jtha.2025.03.038>.
7. Iba T, Helms J, Connors JM, Levy JH. The pathophysiology, diagnosis, and management of sepsis-associated disseminated intravascular coagulation. *J Intensive Care*. 2023;11(1):24. <https://doi.org/10.1186/s40560-023-00672-5>.
8. Matsumoto H, Takeba J, Umakoshi K, Nakabayashi Y, Moriyama N, Annen S, et al. Successful treatment for disseminated intravascular coagulation (DIC) corresponding to phenotype changes in a heat stroke patient. *J Intensive Care*. 2019;7:2. <https://doi.org/10.1186/s40560-019-0359-3>.
9. Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. *BMJ Open*. 2017;7(9):e017046. <https://doi.org/10.1136/bmjopen-2017-017046>.
10. Iba T, Helms J, Levy JH. Sepsis-induced coagulopathy (SIC) in the management of sepsis. *Ann Intensive Care*. 2024;14:148. <https://doi.org/10.1186/s13613-024-01380-5>.
11. Yamakawa K, Umemura Y, Mochizuki K, Matsuoka T, Wada T, Hayakawa M, et al. Proposal and validation of a clinically relevant modification of the Japanese Association for Acute Medicine disseminated intravascular coagulation diagnostic criteria for sepsis. *Thromb Haemost*. 2024;124:1003–12. <https://doi.org/10.1055/s-0044-1786808>.
12. Kinoshita T, Umemura Y, Watanabe M, Uchida K, Nishimoto Y, Katayama S et al. Standardized multicenter critical care database integrating minute-level vital signs, laboratory tests, interventions,

- and outcomes: profile of the OnelCU database. medRxiv. 2025.
<https://doi.org/10.1101/2025.09.12.25335671>
13. Kienast J, Juers M, Wiedermann CJ, Hoffmann JN, Ostermann H, Strauss R, et al. KyberSept investigators. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. *J Thromb Haemost.* 2006;4(1):90–7. <https://doi.org/10.1111/j.1538-7836.2005.01697.x>.
 14. Gando S, Saitoh D, Ogura H, Fujishima S, Mayumi T, Araki T, Japanese Association for Acute Medicine Sepsis Registry Study Group, et al. A multicenter, prospective validation study of the Japanese Association for Acute Medicine disseminated intravascular coagulation scoring system in patients with severe sepsis. *Crit Care.* 2013;17(3):R111. <https://doi.org/10.1186/cc12783>.
 15. Umemura Y, Fujimoto M, Kinoshita T, Fujimi S, Yamakawa K, Oda J. Practical machine learning model for early and accurate prediction of disseminated intravascular coagulation before its progression to an OVERT stage. *Thromb Haemost.* 2026 Feb;18. <https://doi.org/10.1055/a-2806-3756>.
 16. Umemura Y, Okada N, Ogura H, Oda J, Fujimi S. A machine learning model for early and accurate prediction of overt disseminated intravascular coagulation before its progression to an overt stage. *Res Pract Thromb Haemost.* 2024;8(5):102519. <https://doi.org/10.1016/j.rpth.2024.102519>.
 17. Bouchama A, Bridey F, Hammami MM, Lacombe C, al-Shail E, al-Ohali Y, et al. Activation of coagulation and fibrinolysis in heatstroke. *Thromb Haemost.* 1996;76(6):909–15.
 18. Zhang L, Wang J, Gu T, Zhang H, Xiao H, Liu F. Effect of platelet dynamic changes on disseminated intravascular coagulation and prognosis in severe heatstroke patients. *Postgrad Med.* 2024;136(7):712–9. <https://doi.org/10.1080/00325481.2024.2394017>.
 19. Gando S, Saitoh D, Ogura H, Mayumi T, Koseki K, Ikeda T, Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group, et al. Disseminated intravascular coagulation (DIC) diagnosed based on the Japanese Association for Acute Medicine criteria is a dependent continuum to overt DIC in patients with sepsis. *Thromb Res.* 2009;123(5):715–8. <https://doi.org/10.1016/j.thromres.2008.07.006>.
 20. Bathini T, Thongprayoon C, Petnak T, Chewcharat A, Cheungpasitporn W, Boonpheng B, et al. Circulatory failure among hospitalizations for heatstroke in the United States. *Med (Basel).* 2020;7:32. <https://doi.org/10.3390/medicines7060032>.
 21. Misset B, De Jonghe B, Bastuji-Garin S, Gattolliat O, Boughrara E, Annane D, et al. Mortality of patients with heatstroke admitted to intensive care units during the 2003 heat wave in France: a national multiple-center risk-factor study. *Crit Care Med.* 2006;34:1087–92. <https://doi.org/10.1097/01.CCM.0000206469.33615.02>.
 22. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg.* 2007;245:812–8. <https://doi.org/10.1097/01.sla.0000256862.79374.31>.

Figures

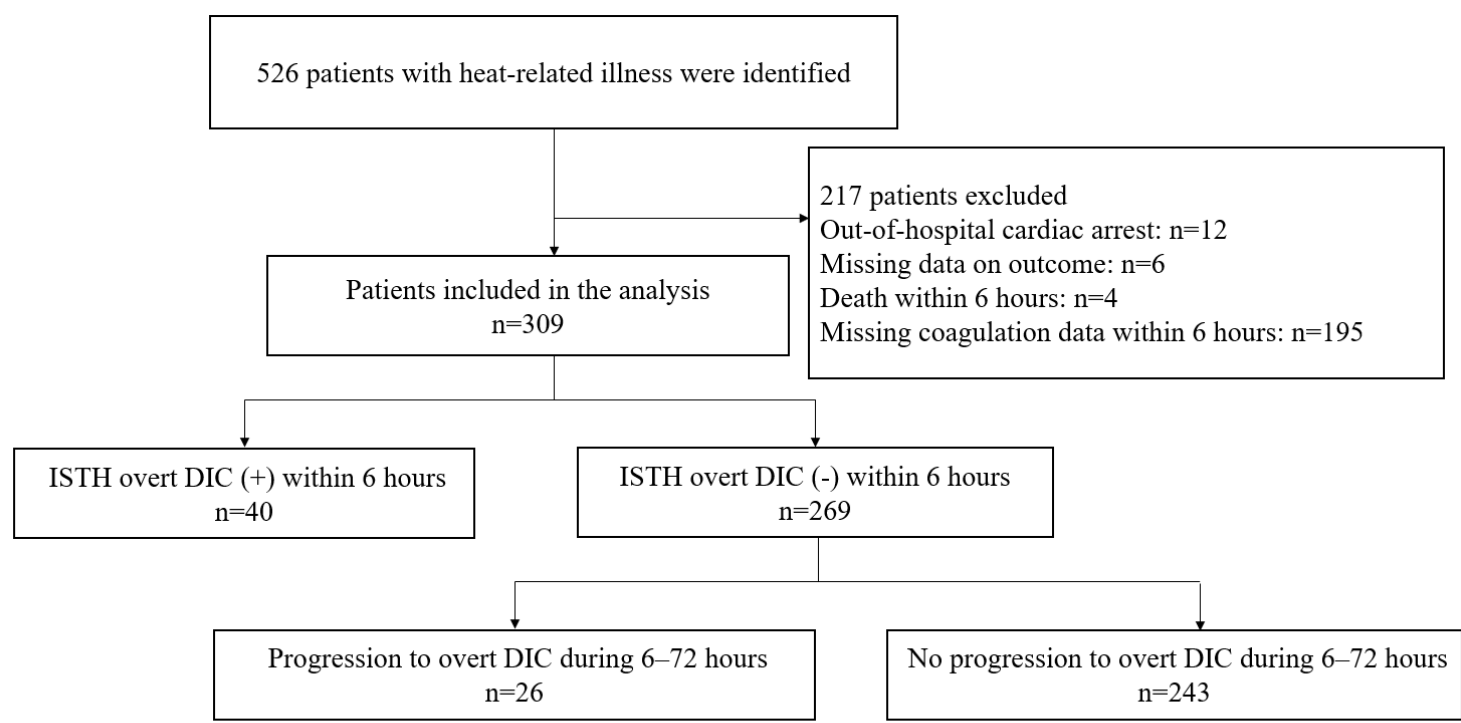


Figure 1

Patient flow chart. DIC, disseminated intravascular coagulation; ISTH, International Society on Thrombosis and Haemostasis

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