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Complement Activation in Patients With Heat-Related Illnesses: Soluble CD59 Is a Novel Biomarker Indicating Severity of Heat-Related Illnesses

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OBJECTIVES: Although multiple organ dysfunction syndrome (MODS) is the main cause of death in patients with heat-related illnesses, its underlying pathophysiological mechanism remains elusive. Complement activation is considered one of the main causes of MODS in patients with sepsis and trauma. Considering the pathophysiological similarity of heat related-illnesses with sepsis and trauma, the complement system might be activated in patients with heat-related illnesses as well. Our aim was to investigate whether excessive complement activation occurs in patients with heat-related illnesses.

DESIGN: Prospective observational study.

SETTING: Emergency department in the university hospital.

PATIENTS: Thirty-two patients with heat-related illnesses and 15 age-matched healthy controls were enrolled in this study.

INTERVENTIONS: Blood samples were collected from the study subjects for the measurement of complement factors.

MEASUREMENTS AND MAIN RESULTS: Complement component 3a (C3a), complement component 5a (C5a), C5b-9, complement factor B (Ba), Factor H, and soluble CD59 in plasma were measured. The levels of C3a, C5a, C5b-9, and Ba significantly increased in patients with heat-related illnesses on day 0 compared with those in the healthy controls. Soluble CD59 was significantly high in patients with heat-related illnesses on day 0 and showed a correlation with the severity of the condition (Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, and staging scores), Japanese Association for Acute Medicine disseminated intravascular coagulation scores, and the coagulation system (prothrombin time and fibrin degradation products).

CONCLUSIONS: The complement system was activated in patients with heat-related illnesses, suggesting that it is one of the causes of MODS. Soluble CD59 may be a potent biomarker for the severity of heat-related illnesses.

KEY WORDS: biomarker; complement system; heat-related illness; heatstroke; multiple organ dysfunction syndrome; soluble CD59

Heat-related illness has become a major social problem worldwide because of global warming; Hajat et al (1) reported that heat-related deaths are predicted to rise by approximately 257% from the current annual baseline of approximately 2,000 deaths by around 2,050. Heat-related illnesses (heat cramps, heat exhaustion, and heatstroke) occur after an individual is exposed to high environmental temperature with or without exertion (2, 3). The physical condition deteriorates dramatically postexposure owing to heat damage and vulnerability of the patients (4, 5). If not treated properly, such

illnesses can be fatal. The definition by Bouchama and Knochel (3) is most commonly used worldwide to define heatstrokes, that is, "an increasing core body temperature of 40 °C or more with hot, dry skin, and exhibition of central nervous system disorders." Although mortality tends to increase significantly as the maximum body temperature increases from 37°C to 40°C, several fatalities have been reported even in patients with a body temperature below 40°C (6). Hence, overt hyperthermia should not be considered an accurate biomarker for severity in patients with heat-related illnesses (6). Additionally, the deterioration of physical conditions may last even after the normalization of the body temperature (6).

Although the pathophysiology of heat-related illnesses remains to be elucidated, it has been reported that the cytokine-mediated systemic inflammation and excessive coagulation responses injure the vascular endothelium, resulting in microthromboses and multiple organ dysfunction syndrome (MODS) (3, 7, 8). Notably, excessive systemic inflammation and coagulopathy are also associated with sepsis and trauma, resulting in MODS (9, 10). Thus, similarities may exist among the pathophysiological mechanisms of sepsis, trauma, and heat-related illnesses.

Recently, the involvement of the complement system has been elucidated in sepsis and trauma (11, 12). Infections or traumas result in the rapid activation of the complement cascade (13, 14). In the case of sepsis and trauma, complement consumption and activation are repeated successively, leading to the formation of the C5b-9 complex, which binds to the surface of target cells and causes cytolysis or cell dysfunction. The products of complement activation generate inflammatory mediators that target and recruit other branches of the immune system, resulting in widespread cell and organ damage (11–13). Under normal conditions, complement activation is considered a beneficial reaction to the host; however, in a hyperactivated and consumed system, the complement and coagulation cascade can be harmful (14). Hence, complement activation should be tightly regulated.

Some membrane-bound complement regulators (e.g., CD59) that prevent excessive complement activation are present on cell surfaces (15). The behavior of CD59 in complement activation has received increased attention recently (16, 17). To the best of our knowledge, no study has investigated the pathogenic mechanisms in patients with heat-related illnesses from the perspective of complement activation. Here, we hypothesized that the complement system is activated in patients with heat-related illnesses, and its excessive activation is associated with the severity of the illness.

MATERIALS AND METHODS

Study Design and Patient Enrollment

A single-center prospective observational study involving patients with heat-related illnesses was performed. The study was approved by the ethics committee of Juntendo University, Urayasu Hospital (3–22). Patients with heat-related illnesses admitted to Juntendo University, Urayasu Hospital, a tertiary emergency medical center in Japan, from August 2019 to September 2021 were enrolled in this study after obtaining written informed consent from them or their legal representatives. Of 32 patients enrolled, 17 had exertional and 15 had nonexertional heat-related illnesses. All patients met the diagnostic criteria for heat-related illnesses, as determined by the Japanese Association of Acute Medicine (JAAM) Heat-Related Illness classification (2015) (18). Patients with malignant disease or on chronic steroid medication were excluded from the study. We examined the patient data for age, sex, and body temperature at admission. We determined the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (19), Sequential Organ Failure Assessment (SOFA) scores (20), and JAAM disseminated intravascular coagulation (DIC) scores (21) at three time points after admission (days 0, 3–4, and 5–6) to investigate the correlation with complement activation. In addition, we examined the platelet counts, fibrin degradation products, prothrombin time (PT) percentage activity, and activated partial thromboplastin time. Complement component 3 (C3) and complement component 4 (C4), 50% hemolytic complement activity (CH50), complement component 3a (C3a), complement component 5a (C5a), complement factor B (Ba), soluble C5b-9 (sC5b-9), soluble Factor H, and soluble CD59 (sCD59) were also assessed on days 0, 3–4, and 5–6. Control samples were obtained from the healthy volunteers. The healthy control (HC) group consisted of males ($n = 12$) and females ($n = 3$) aged 41 years (interquartile range [IQR], 33–47 yr). There was no significant difference in the age of patients and HCs.

Treatments

Rapid cooling and hydration were the fundamental treatments for heat-related illnesses. Cooling was conducted using conventional methods and an intravascular balloon catheter system. Regular management for organ dysfunction in the ICU, such as mechanical ventilation and continuous renal replacement therapy, was conducted, but we did not use specific treatments for coagulopathy.

Blood Sample Processing

Blood sample (10 mL) was collected via the peripheral vein of each healthy volunteer and via the arterial line or peripheral vein of patients with heat-related illnesses into tubes containing heparin. Blood collection from all patients with heat-related illnesses was performed at admission. The blood samples were centrifuged at $724 \times g$ for 5 min at 4°C, and the plasma was dispensed and stored at –80°C before analysis.

Measurement of Complement Components in Plasma

C3a, C5a, C5b-9, Ba, and Factor H levels in plasma were measured using the MicroVue C3a Plus EIA kit (A031), C5a EIA kit (A021), SC5b-9 Plus EIA kit (A020), Ba Fragment EIA kit (A033), and Factor H EIA kit (A039), respectively; all kits were sourced from Quidel, San Diego, CA. The plasma level of CD59 (sCD59) was measured using the RayBio Human CD59 Enzyme-Linked Immunosorbent Assay kit (ELH-CD59 RayBiotech, Norcross, GA). The assessments were performed according to the manufacturers' instructions.

Statistical Analysis

The data are expressed as median and IQRs for continuous variables, unless stated otherwise. Statistical analyses were performed using GraphPad Prism Version 6.03 for Windows (GraphPad Software, San Diego, CA). The data were analyzed for significant differences using an unpaired t test for comparisons between two groups. Kruskal-Wallis test was used for comparisons among four groups. For correlation analyses, Spearman rank analyses were performed. Differences were considered significant at $p < 0.05$.

RESULTS

Clinical Characteristics

Thirty-two patients with heat-related illnesses were enrolled and classified into three groups according to the JAAM Heat-Related Illness criteria. The patients comprised males ($n = 17$) and females ($n = 15$), of median age of 52 years (IQR, 29–75 yr), with a body temperature of 37.1 °C (36.6–39.0 °C), an APACHE II score of 7.5 (2.0–16.3), an SOFA score of 1.5 (0.0–5.0), and a JAAM DIC score of 0.0 (0.0–1.0). Two patients died during hospitalization (**Table 1**).

TABLE 1.
Characteristics of Patients With Heat-Related Illnesses

| Patient Characteristics	Stage I ($n = 4$)	Stage II ($n = 12$)	Stage III ($n = 16$)	Total ($n = 32$)
Age (yr), median (IQR)	32 (29–47)	30 (22–55)	66 (47–85)	52 (29–75)
Male, n (%)	1 (25)	5 (42)	11 (69)	17 (53)
Exertional heat-related illnesses, n (%)	2 (50)	7 (58)	8 (50)	17 (53)
Body temperature (°C), median (IQR)	37.1 (36.6–39.0)	36.9 (36.3–37.4)	38.6 (37.0–39.9)	37.1 (36.6–39.0)
Acute Physiology and Chronic Health Evaluation II, median (IQR)	1.0 (0.0–3.5)	3.5 (0.0–7.8)	14.0 (10.3–19.8)	7.5 (2.0–16.3)
Sequential Organ Failure Assessment score, median (IQR)	0.0 (0.0–0.0)	1.0 (0.0–1.8)	4.5 (2.0–5.0)	1.5 (0.0–5.0)
Japanese Association for Acute Medicine Disseminated Intravascular Coagulation score, median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	1.0 (0.0–1.0)	0.0 (0.0–1.0)
Mortality, n (%)	0 (0)	0(0)	2 (12.5)	2 (6.3)

IQR = interquartile range.

Complement System Is Activated in Patients With Heat-Related Illnesses

To check complement activation in patients with heat-related illnesses, representative complement activation products such as C3a, C5a, Ba, and sC5b-9 were measured. C3a and C5a levels significantly increased in patients with heat-related illnesses on day 0 compared with the HCs (C3a; $p = 0.0010$, C5a; $p < 0.0001$). Thus, the complement system was activated, and inflammation was increased during the initial phase of illness (**Fig. 1**, **A** and **B**). The level of sC5b-9, which is the final product in the complement cascade (11–13), significantly increased in patients with heat-related illnesses on day 0 ($p = 0.0001$) (**Fig. 1C**). Similarly, the level of Ba was also significantly increased ($p = 0.0003$) (**Fig. 1D**). These findings suggested that the alternative complement pathway was activated in patients with heat-related illnesses. Our results showed that the C3a, C5a, Ba, and sC5b-9 levels were significantly elevated in patients with heat-related illnesses compared with the HCs; the C3, C4, and CH50 levels were within the reference range (**Fig. S1**, http://links.lww.com/CCX/A970). Alterations in the soluble and membrane-bound regulators of complement activity occur after trauma, sepsis, and hemorrhagic shock (12–14). Hence, Factor H and sCD59, which are well-known representative complement regulators, were measured to investigate the dysregulated complement regulators. The sCD59 level was elevated on day 0 in patients with heat-related illnesses compared with the HCs ($p = 0.0014$) (**Fig. 1E**), whereas Factor H did not show a significant difference between patients with heat-related illnesses and the HCs (**Fig. 1F**).

Complement System Is Activated in Severe Heat-Related Illnesses

We classified the patients into three groups according to the JAAM Heat-Related Illness criteria to investigate the differences based on the condition's severity. Although the C3a, C5a, sC5b-9, and Ba levels were elevated in stage II and stage III patients with heat-related illnesses (C3a; $p = 0.0029$, C5a; $p < 0.0001$, sC5b-9; $p = 0.0006$, and Ba; $p = 0.0003$), no differences were noted between stage I patients with heat-related illnesses and the HCs (**Fig. 2A–D**). A significant increase in sCD59 was noted in stage III patients
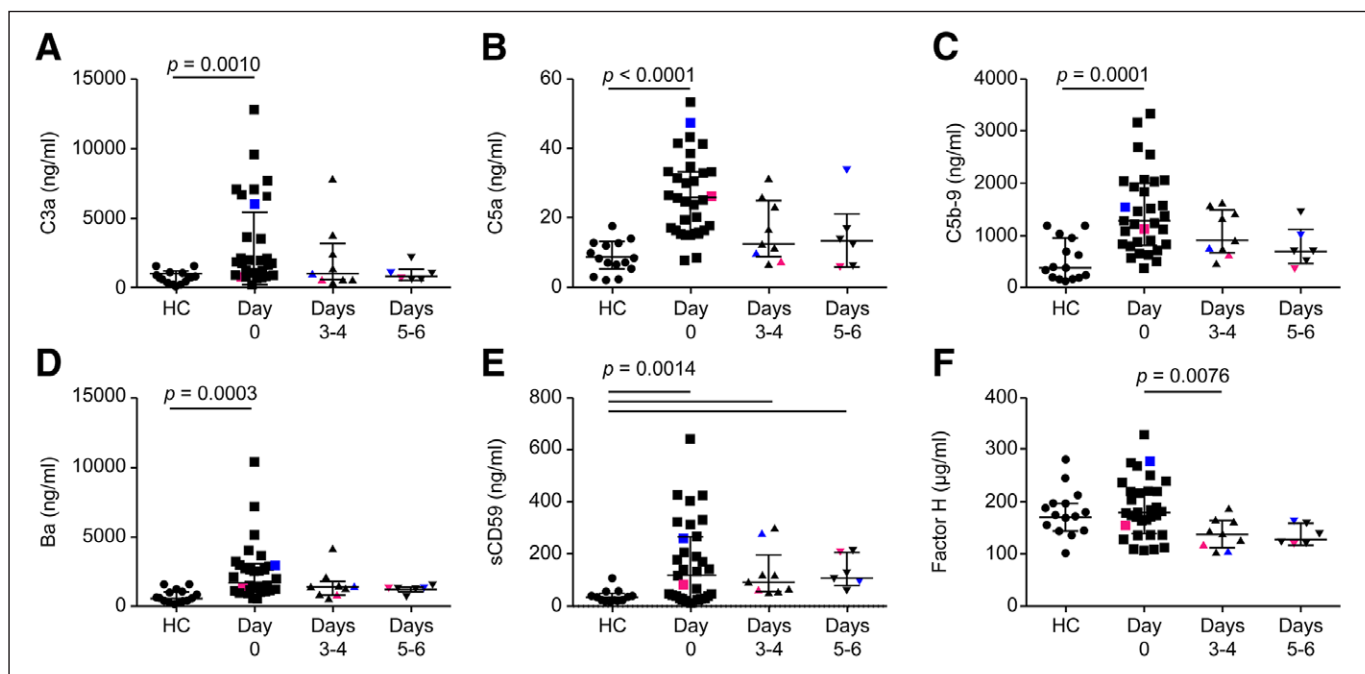
Figure 1. Serial changes in complement activation in patients with heat-related illnesses. **A–E**, Complement component 3a (C3a), complement component 5a (C5a), Ba fragment of complement factor B (Ba), soluble complement C5b-9, and soluble CD59 (sCD59) significantly increased in patients with heat-related illnesses on day 0 compared with those in the healthy controls (HCs). Data shown are median (interquartile range), and the groups were compared using Kruskal-Wallis test with Dunn post hoc test. **F**, Although difference in Factor H among the four groups, Dunn post hoc test did not show differences between the HCs and patients with heat-related illnesses on day 0. *Data in blue and red are from patients who died.*
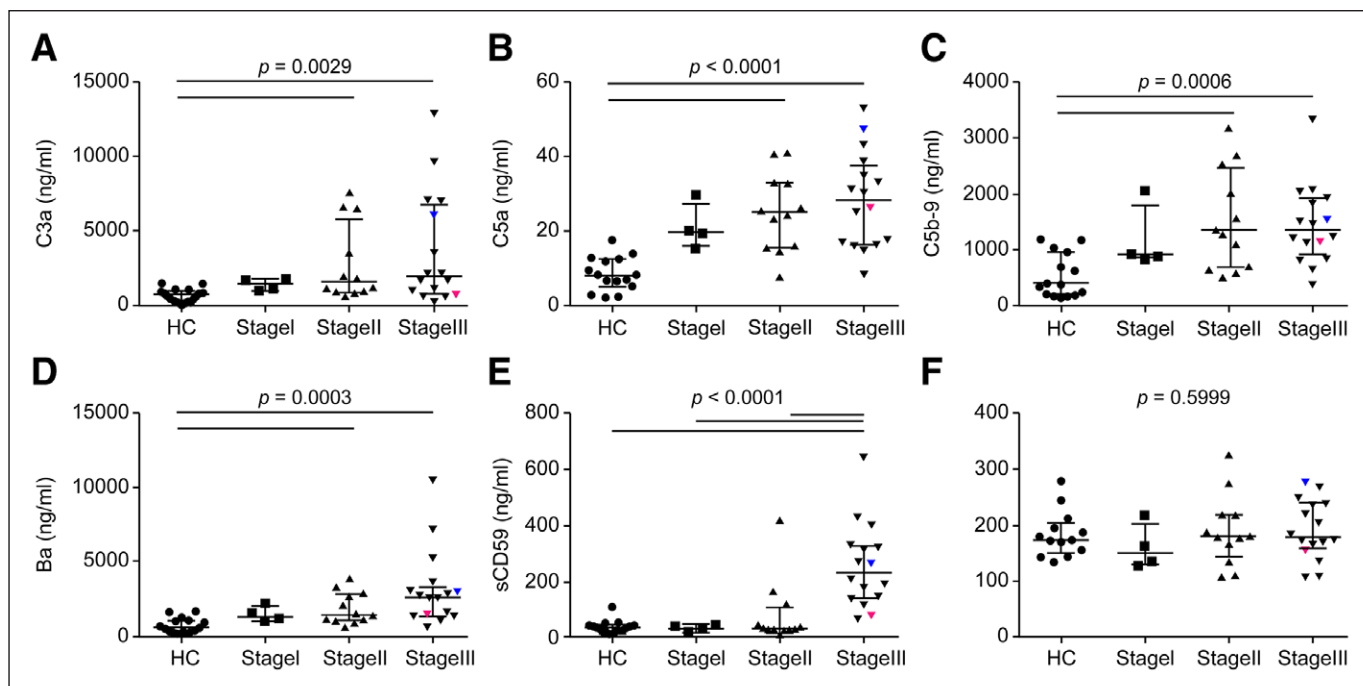
Figure 2. Complement system is activated in patients with severe heat-related illnesses. **A**−**D**, Complement component 3a (C3a), complement component 5a (C5a), Ba fragment of complement factor B (Ba), and soluble complement C5b-9 significantly increased in patients with stage II and stage III heat-related illnesses on day 0 compared with those in the healthy controls (HCs). Data shown are median (interquartile range), and the groups were compared using Kruskal-Wallis test with Dunn post hoc test. **E**, Stage III patients with heat-related illnesses showed a significant difference in the soluble CD59 (sCD59) level compared with the HCs, stage I patients, and stage II patients. **F**, Factor H did not demonstrate a significant difference between the HCs and patients with heat-related illnesses. *Data in blue and red* are from patients who died.

with heat-related illnesses compared with the HCs ($p < 0.0001$); however, no significant variations were observed in stage II and stage I patients compared with the HCs (**Fig. 2E**). Similarly, the level of Factor H was not significantly different between the HCs and patients with heat-related illnesses (**Fig. 2F**).

SCD59 Correlates With the APACHE II, SOFA, JAAM Staging System, and JAAM DIC Scores

To assess the relationship between sCD59 in circulation and clinical conditions (APACHE II, SOFA, JAAM staging system, and JAAM DIC scores), their correlation coefficients were investigated. The sCD59 level significantly positively correlated with the APACHE II scores ($p < 0.0001$, $r = 0.66$), SOFA scores ($p < 0.0001$, $r = 0.59$), stage ($p < 0.0001$, $r = 0.71$), and JAAM DIC scores ($p = 0.0065$, $r = 0.49$) (**Fig. 3**).

SCD59 Correlates With Fibrin Degradation Product

To clarify the association between sCD59 and coagulopathy in heat-related illnesses, their correlation

coefficients were investigated. The sCD59 level negatively correlated with fibrin-degradation product ($p = 0.0107$, $r = 0.40$), but not with PT, activated partial thromboplastin time, and platelet counts (**Fig. 4**).

DISCUSSION

Heat-related illnesses could result in MODS, which is speculated to be induced by cytokine-mediated systemic inflammation and excessive coagulation. However, the exact pathophysiology of MODS is unknown. Although extensive efforts have been made over the years to develop new treatment strategies for heatstroke, only the rapid control of body temperature has been accomplished (2, 3). To develop improved treatment strategies, an understanding of the pathophysiology of MODS in heatstrokes, which are induced by acute physiologic changes related to hyperthermia, tissue injury directly elicited by heat, inflammatory and anti-inflammatory cytokines, coagulation disorders, and endothelial-cell injury, is essential (3). Hence, microvascular injury, thrombosis, inflammation, and apoptosis may play an important role in the
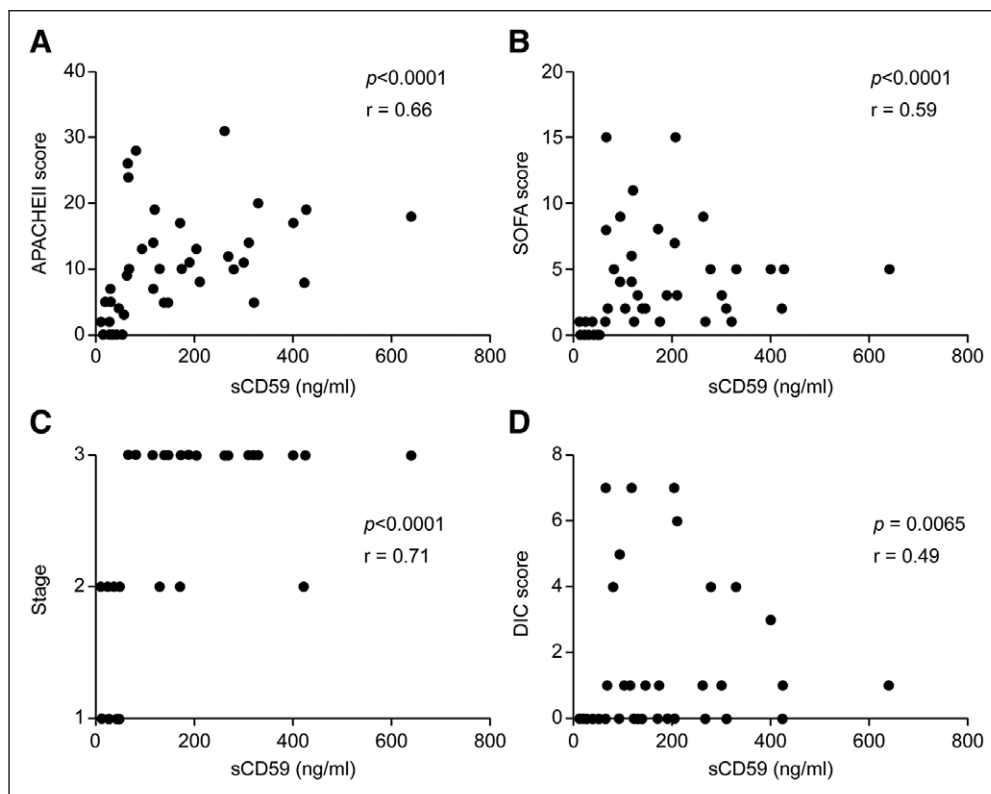
Figure 3. Correlation of soluble CD59 (sCD59) with Acute Physiology and Chronic Health Evaluation II (APACHE II) score (**A**), Sequential Organ Failure Assessment (SOFA) score (**B**), stage (**C**), and Japanese Association for Acute Medicine disseminated intravascular coagulation (DIC) score (**D**). **A**–**C**, Spearman rank correlation coefficient, $p < 0.0001$ ($n = 32$). The data points shown (**A**, 44; **B**, 47) are of samples from days 0, 3–4, and 5–6 following a diagnosis of heat-related illnesses, and the 32 data points (**C**) consist of samples from day 0. **D**, Spearman rank correlation coefficient, $p = 0.0065$ ($n = 32$). The 47 data points shown are of samples from days 0, 3–4, and 5–6 following a diagnosis of heat-related illnesses.
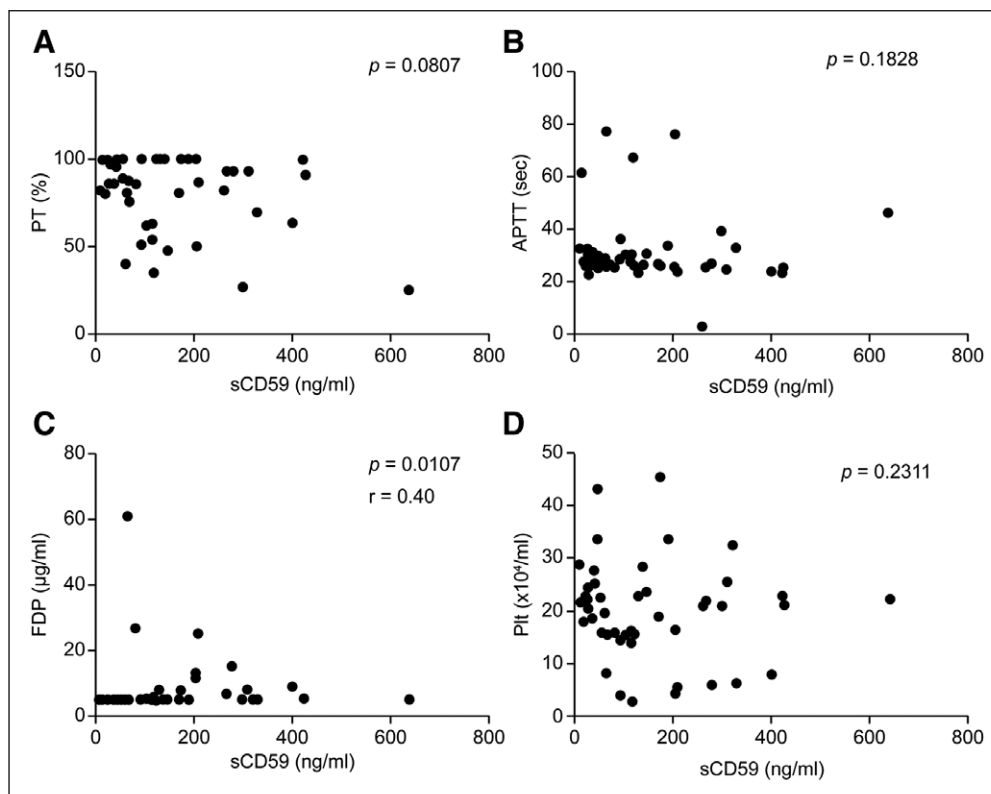
pathogenesis of heatstroke injury, which may be propagated by complement activation (22).

The heatstroke-related amplification of inflammation and coagulation is similar to the systemic inflammatory response syndrome (SIRS) in sepsis and trauma (7). Caserta et al (23) reported that SIRS is induced by circulating inflammation-related microRNAs, which trigger cytokine release, resulting in excessive activation of immune cells and endothelium. SIRS can cause a rapid exacerbation of clinical signs, resulting in DIC, multiple organ dysfunction, and death (9, 10). Hence, heatstroke is regarded as a form of hyperthermia associated with SIRS, leading to MODS and accompanying encephalopathy (24). Similarly, trauma causes the activation of complement and coagulation, which induces MODS (25). Considering the pathophysiological similarity between heatstroke and other SIRS-associated diseases, such as sepsis and trauma, studies on them may help elucidate the pathophysiology of heat-related illnesses. Numerous treatments targeting various biological pathways of inflammation and coagulation in sepsis have been tested, but none have shown a significant benefit on mortality (26). Human recombinant thrombomodulin, which was considered effective against sepsis-associated coagulopathy, did not significantly reduce 28-day all-cause mortality (26). Experimental and clinical studies have demonstrated that sepsis activates the coagulation and complement systems that may contribute to MODS and subsequent death (27). Complement-coagulation interaction contributes to the progression of sepsis, and blocking the negative effects of complement activation products may be a potential therapeutic strategy (27).

The complement system is essential for innate immune responses against invading pathogens. However, excessive activation of the complement system is harmful to the host (28, 29) and can be considered a "double-edged sword," especially with regard to MODS. Numerous studies have demonstrated that anticomplement therapy inhibits MODS in a sepsis model (30–33). In patients with trauma, complement activation is observed early and is correlated with the severity of injury, tissue hypoperfusion, and worse clinical outcomes (34). Given the similarity in the pathophysiology of sepsis, trauma, and heat-related illnesses, we hypothesized that complement activation is one of the causes of MODS in heat-related illnesses as well. To the best of our knowledge, our study is the first to demonstrate complement activation in patients with heat-related illnesses.

Figure 4. Correlation of soluble CD59 (sCD59) with fibrin-degradation product. **A** and **B**, Spearman rank correlation coefficient, not significant (*n* = 32). The 46 data points shown consist of samples from days 0, 3−4, and 5−6 following a diagnosis of heat-related illnesses. **C**, Spearman rank correlation coefficient, *p* = 0.0107 (*n* = 32). The 39 data points shown consist of samples from days 0, 3−4, and 5−6 following a diagnosis of heat-related illnesses. **D**, Spearman rank correlation coefficient, not significant (*n* = 32). The 47 data points shown are of samples from days 0, 3−4, and 5−6 following a diagnosis of heat-related illnesses. APTT = activated partial thromboplastin time, FDP = fibrin degradation product, Plt = platelet, PT = prothrombin time.

Previous studies have shown complement activation and a correlation between severity and complement factors (such as C3a and C5a) in patients with sepsis (35). Abe et al (36) suggested that sC5b-9 may reflect sepsis severity. Additionally, they demonstrated that conventional complement test results (C3, C4, and CH50) were similar, with most results being observed within the reference range among all patients with sepsis; this suggests that conventional complement tests may be insufficient for estimating the severity of sepsis (36). Our results showed that C3a, C5a, Ba, and sC5b-9 were significantly elevated in patients with heat-related illnesses compared with the HCs, whereas the C3, C4, and CH50 levels were within the reference range. Interestingly, this increase was observed on as early as day 0. In this study, the number of samples on days 3−4 and days 5−6 was not sufficient. This is because we did not collect blood samples after an improvement in the general conditions of patients. Therefore,

further investigation is needed to determine how long the elevation in complement factors would persist. Furthermore, these factors were elevated only in patients with severe heat-related illness (stages II and III), suggesting that these factors may reflect heat-related illness severity. Hence, activation of C3a, C5a, Ba, and sC5b-9 can be considered a biomarker for MODS in patients with heat-related illnesses rather than conventional complement tests.

C3a and C5a are anaphylatoxins that trigger an inflammatory cascade, smooth muscle contraction, vasodilation, histamine release from mast cells, and enhanced vascular permeability. Additionally, they mediate chemotaxis, inflammation, and generation of cytotoxic oxygen radicals (37). A number of studies have demonstrated that C3a and C5a are associated with MODS in trauma and sepsis. In patients with sepsis, the serum levels of C3a, C5a, and C5b-9 were significantly increased, and the complement component 5a receptor (C5aR) expression on neutrophils was decreased, which correlated with poor outcomes (38). Neutrophil dysfunction is considered a cause for immunosuppression, a well-known phenomenon in patients with sepsis (39). Xu et al (40) demonstrated that the reduced C5aR expression in neutrophils was associated with the functional impairment of neutrophils, MODS, and a poor prognosis in patients with sepsis. In patients with trauma, Hecke et al (41) showed that the C3a and C3a/C3 ratio can be considered in the well-known trauma scoring systems, such as Polytrauma Score, Injury Severity Score, and Trauma Injury Severity Score. Consequently, we found that

the levels of C3a and C5a were elevated in patients with heat-related illnesses; however, they were recognized only in severe cases (stages II and III). These findings were similar to those of previous studies in patients with sepsis and trauma (38, 40, 41). Considering that the levels of C3a and C5a were elevated in patients with heat-related illnesses, immunosuppression due to the down-regulation of the complement component 3a receptor (C3aR) and C5aR may occur during heat-related illnesses. However, in this study, the expression of C3aR and C5aR in neutrophils was not assessed. Furthermore, patients with heat-related illnesses may exhibit impaired innate immunity that may result in vulnerability to infections and increase their risk of nosocomial infections. Future studies must explore these aspects.

C5b-9 is the terminal membrane attack complex that directly lyses targeted (opsonized) pathogens or damaged host cells (36). Abe et al (36) measured the plasma levels of sC5b-9 as a marker of complement activation, showing that the degree of complement activation is related to DIC, severity, intensive interventions, and mortality. Although our results did not show a correlation between sC5b-9 and severity, coagulopathy, and DIC (**Fig. S2**, http://links.lww.com/CCX/A970), the level of sC5b-9 increased in patients with severe heat-related illness, revealing that the complement system was activated.

Three main pathways (classical, lectin, and alternative) can activate the complement system (42). Our study demonstrated an elevation in Ba, which is a representative factor in the alternative complement pathway (34); this suggested the activation of the alternative complement pathway in patients with heat-related illnesses.

The complement system has several regulators that inhibit excessive complement activation. CD59 is a membrane-anchored complement regulatory protein that is widely distributed on the membrane of human erythrocytes and leukocytes; it effectively inhibits C5b-9 formation, leading to the inhibition of cell lysis (43, 44). The detached form of CD59 present on the cell membrane, released into the circulation in a soluble form, is sCD59; it is detected in various body fluids, including urine, serum, and plasma (16, 17, 43–46), and functions as a biomarker for several diseases (16, 17). However, the role of sCD59 in these diseases remains elusive. In our study, the level of plasma sCD59 was elevated in patients with heat-related illnesses. Interestingly, it was elevated only in patients with stage III heat-related illnesses, whereas other complement factors were increased in stages II and III, suggesting that sCD59 may be more specific to severe cases. Furthermore, sCD59 showed a positive correlation with severity and coagulopathy. Hence, the increase in sCD59 does not exert a protective function against excessive complement activation. Although there are no established clinical tests that can adequately evaluate the severity of heatstroke, the platelet count, D-dimer, soluble thrombomodulin, and inflammation biomarkers such as interleukin-6 and histone H3 have been proposed as promising markers for the severity of heatstroke (47). This study raises the possibility of using sCD59 as a novel marker for the severity of heatstroke. In contrast, complement Factor H did not show significant differences between patients with heat-related illnesses and the HCs. Factor H is the major negative complement regulator of the alternative pathway. It is intriguing that not all complement regulators are altered in patients with heat-related illnesses. Further studies measuring other complement regulators in heat-related illnesses are required to elucidate this finding.

A limitation of our study is the small number of patients and the difference in sex distribution between the HC and patient groups. Our results show that the number of males with stage III disease is higher than the number of females, indicating the possibility of sex-based variation in susceptibility to heat-related illnesses. Additionally, the number of patients in each severity group was different, especially that of stage I patients was too small, which might affect the finding that complement activation occurs in severe cases of heat-related illnesses. Further studies with a higher number of patients with heat-related illnesses are required to ascertain the role of complement in MODS.

Considering that complement activation is one of the causes of MODS in heatstrokes, the complement system may be a promising target for the treatment of patients with heat-related illnesses. Several preclinical studies that target complement factors have been conducted in animal sepsis and hemorrhagic shock models (48–52). Although a few clinical trials targeting the complement system in sepsis and trauma have been conducted, their results have not been published yet (52). Similarly, further studies are required to establish valuable biomarkers and targets for the treatment of patients with heat-related illnesses.

CONCLUSIONS

Activation of the complement system was detected in patients with heat-related illnesses, and it can play an important role in the progression of MODS. Furthermore, sCD59 was associated with severity and coagulopathy, suggesting that it is a novel biomarker for the severity of heat-related illnesses.

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