Studying the Biochemical Profile of Patients after Exertional Heat Stroke: A Case Series

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ABSTRACT **Background:** Exertional heat stroke (EHS) is common among individuals engaged in high-intensity physical activity. It can lead to long-term organ damage and be a life-threatening condition when diagnosed and treated incorrectly.

Objectives: To track the changes in biomarkers among EHS patients, to suggest a standardized protocol of clinically relevant biomarkers to be followed during hospitalization

Methods: We conducted a retrospective analysis on biomarker changes in seven EHS patients (aged 18–25 years) who were hospitalized for a minimum of 84 hours. Diagnosis of heat stroke was based on extreme body temperature and neurological deficits. Biomarkers indicative of kidney function, liver function, coagulation, muscle breakdown, and systemic inflammation during their hospitalization were analyzed.

Results: The initial average rectal temperature (T_{re}) was 41.1°C. Patients were cooled to approximately 38.5°C before being transferred to the emergency department (ED). Within the first 24–36 hours of hospitalization, biomarker levels reach peak levels depending on EHS severity. Renal biomarkers rose to 1.5–3 times normal values, while transaminases increased 7–15 times. Creatine phosphokinase, indicating muscle injury, reached an average of 100 times its reference range. Within 24–72 hours. all biomarker levels were normalized.

Conclusions: There is often a gap between the initial temperature of an EHS patient and the temperature recorded at ED admission after cooling. Accurate assessment is context-specific and requires precise biomarker follow-up. Clinical evaluation should continue for at least 48 hours to track organ damage and guide prognosis.

IMAJ 2026; 28: 357–362

KEY WORDS: biomarkers, body core temperature, clinical evaluation, exertional heat stroke, multi-organ damage

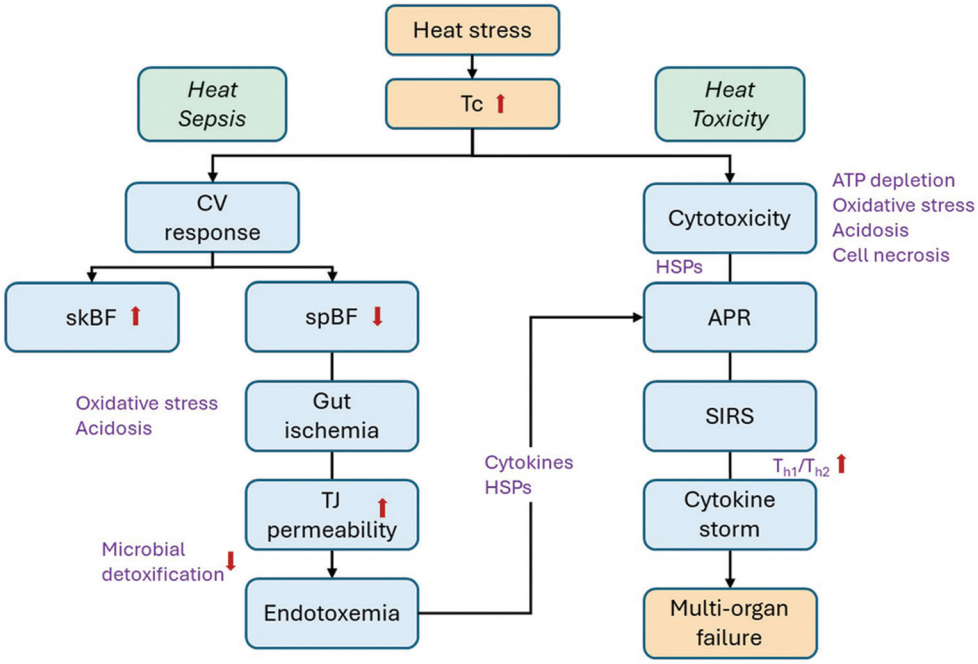
Exertional heat stroke (EHS) represents the most severe manifestation within the spectrum of exertional heat illnesses [1]. Various intrinsic and extrinsic factors can increase susceptibility to EHS; however, it primarily results from excessive metabolic heat generated during intense physical activity, which exceeds the body's capacity for heat dissipation [2,3]. The resulting rise in core body temperature initiates a complex pathophysiological cascade involving both direct heat toxicity and sepsis-like response (heat sepsis), which ultimately leads to widespread cellular and organ injury [4,5] [Figure 1].

The clinical course of EHS progresses through distinct stages: an initial hyperthermic neurologic phase, followed by hematological and enzymatic phases [2]. These stages may deteriorate to severe disturbances in renal and hepatic functions, progressive coagulopathy, and systemic inflammatory response syndrome (SIRS), and may potentially be fatal. Therefore, a delay in recognition and prompt application of effective treatment (cooling) can significantly worsen outcomes [6-8]. However, recognition of heat stroke during exercise remains low [9], and individuals who collapse from suspected EHS may not promptly be transported to an emergency department (ED) or evacuated as a heat stroke case.

In clinical settings, biochemical markers in blood provide crucial insights into a patient's condition, guiding treatment decisions. Despite their importance, there is no standardized protocol for monitoring these markers in EHS patients. A recent study involving over 2500 cases of EHS among U.S. active duty service members revealed that only 60% had at least one clinical laboratory value recorded in the ED on the day of the injury, which then decreased with less than 10% having laboratory results by the fourth day post-injury [10]. In part, this situation stems from a limited understanding of symptoms dynamics and the timing of multiorgan failure, compounded by cases

Figure 1. The dual pathway model of heat stroke

APR = acute phase response, CV = cardiovascular, HSP = heat shock protein, SIRS = systemic inflammatory response syndrome, skBF = skin blood flow, spBF = splanchnic blood flow, Tc = body-core temperature, TJ = tight junction, T_{h1} = Type 1 T helper cells, T_{h2} = Type 2 T helper cells



where patients arrive at the ED with body temperatures lower than expected for heat stroke. This evaluation can lead to premature discharge without a comprehensive assessment of the patient's condition. For example, the U.S. Army reported that of approximately 475 diagnosed cases of EHS in 2024, about 60% were not hospitalized [11].

EHS involves progressive multiorgan dysfunction, which is reflected by specific biomarkers. In this study, we aimed to describe changes in the biochemical profiles of EHS patients during hospitalization.

PATIENTS AND METHODS

We conducted a retrospective case series analyzed the biochemical profiles of seven young male soldiers (aged 18–25 years) who collapsed during intense physical exercises between 2018 and 2023 and were hospitalized for at least 4 days with the diagnosis of EHS [Table 1]. Data were sourced from the Israel defense Forces (IDF) heatstroke database, encompassing laboratory results obtained during hospitalization and information investigated by the ad-hoc investigatory board that investigated each case. None of the soldiers had pre-existing or concurrent illnesses in the days preceding the events, and there were no identified genetic factors known to predispose them to such events. The study was approved by the institutional review board of the IDF Medical Corps (1198-2012-IDF).

All the patients were treated in the field prior to evacuation, mostly by cooling with large volumes of tap water (cooling rate ~0.1–0.15°C/min), and they arrived at the ED within 1–2 hours after they collapsed. Blood samples for laboratory analysis were collected at 12-hour intervals from the time of admission (TOA) and continued for at least 84 hours post-collapse. The mean values were calculated for each time point and a polynomial trendline was used to illustrate the trend of change. Based on their clinical evaluation, all patients were discharged after 4–6 days of observation and treatment.

RESULTS

BODY CORE TEMPERATURE

The average rectal temperature (T_{re}) at the time of collapse was 41.1°C, accompanied by signs such as confusion, imbalance, excitation, fatigue, and loss of consciousness. On arrival at the hospital (1–2 hours post-collapse), the average T_{re} was 37.8°C [Table 1].

Table 1. Basic characteristics of the patients (n=7)

	Mean ± SD	Range
Age (year)	20.4 ± 2.2	18–25
Height (cm)	177.5 ± 6.6	166–189
Weight (kg)	81.5 ± 12.9	67–110
BMI (kg/m^2)	26.2 ± 3.5	22.4–32.8
Pre-cooling T_{re} (°C)	41.1 ± 0.9	39.9–42.3
T_{re} at ED (°C)	37.8 ± 1.1	36.7–40

BMI = body mass index, ED = emergency department, SD = standard deviation, T_{re} = rectal temperature

RENAL FUNCTION

Calculated creatinine clearance levels were significantly low (> 110 ml/min) during the first 24 hours before stabilizing within the reference range after 36 hours [Figure 2A]. This level is indicative of an acute kidney injury (AKI) during the initial phase, which gradually resolved. However, AKI persisted in some cases even after 72 hours.

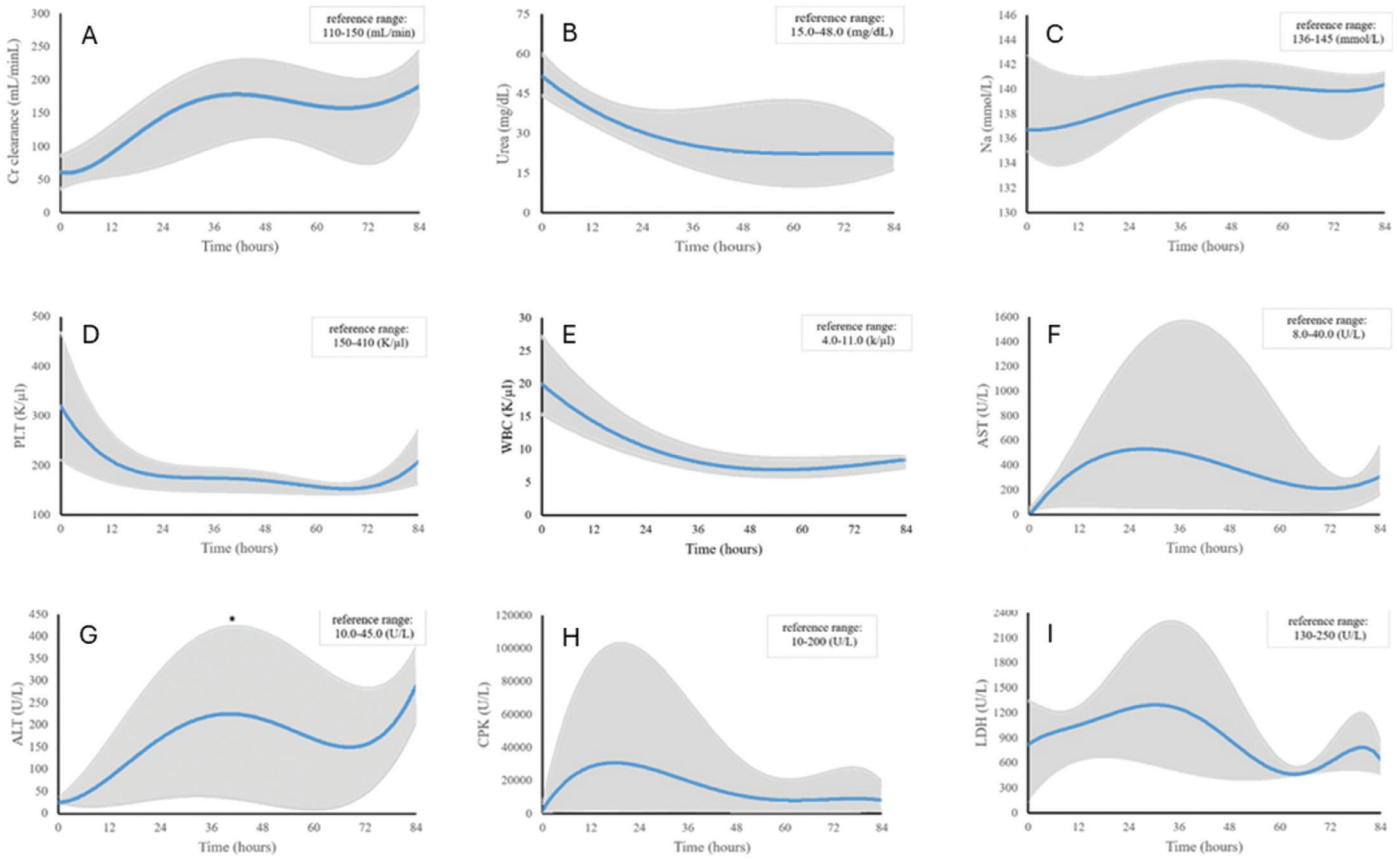
Out-of-range urea levels were observed in three of the six soldiers at TOA (results missing for one) [Figure 2B]. Urea levels peaked initially and normalized within 24 hours. Throughout most of the follow-up period, the urea-to-creatinine ratio remained elevated at 22.4 (normal range < 20), indicative of pre-renal AKI.

SERUM SODIUM CONCENTRATIONS

A wide range in sodium serum levels was observed at TOA, with a mean value of 136 mmol/L [Figure 2C]. Severe hyponatremia ([Na^+] 129 mmol/L) was evident in one of the seven patients. Average sodium levels remained within the normal range throughout the follow-up period, while showing a slight increase after 24 hours.

Figure 2. Biomarker pattern of change in EHS patients over 84 hours of hospitalization

Polynomial trend line (blue), max-min range (gray)
*Outlier = max value of 1600 U/L, this patient was not included in the calculation of the average value of ALT (Figure 2G)



PLATELETS

The average platelet count during the initial hospitalization stage was at the upper normal range (~300 k/μL) [Figure 2D]. Thrombocytosis (platelet count > 450 k/μL) was observed in one patient, likely associated with inflammation. Platelet counts decreased within 24 hours and stabilized at the lower end of the normal range.

WHITE BLOOD CELLS

In all seven patients, white blood cell (WBC) counts were elevated at TOA, with a mean count of 20.4k/μL [Figure 2E], indicating an inflammatory condition that was resolved within 24 hours.

TRANSAMINASES

Alanine transaminase (ALT) and aspartate transaminase (AST) exhibited similar patterns of change, although with varying degrees of severity. AST levels showed a sharper increase and peaked earlier compared to ALT [Figure 2F]. Despite this finding, AST displayed a tendency to recover, although remaining slightly elevated 84 hours post-collapse, whereas ALT remained significantly elevated and showed signs of a secondary increase during the same period [Figure 2G]. The AST/ALT ratio was initially greater than 1 during the first 48 hours. In patients where it dropped below 1 within approximately 48 hours, it indicates the potential progression to a more severe liver injury.

MUSCLE INTEGRITY

Creatine phosphokinase (CPK) levels were extremely high [Figure 2H], peaking between 12–24 hours and indicative of clinical rhabdomyolysis, although myoglobin levels were not measured to fully conclude this diagnosis. Generally, CPK levels remained elevated throughout the follow-up period suggesting prolonged muscle damage.

In this cohort, lactate dehydrogenase (LDH) levels peaked at 24 hours [Figure 2I], reaching levels 4 to 6 times higher than normal. Such high levels suggest rhabdomyolysis, but they can also indicate damage or dysfunction in other tissues (e.g., liver, kidney). The dynamics of LDH follow a pattern like that of CPK, although they are generally less pronounced.

DISCUSSION

In this study, we examined the dynamics of changes in biochemical markers in EHS patients during the first 84 hours of hospitalization. On admission to the ED, biomarker levels in these patients were comparable to those seen in moderate to severe heat stroke [12]. Our case series cannot reliably differentiate between moderate and severe cases; however, in general, severe EHS is characterized by greater magnitude and longer duration of organ-system biomarker abnormalities. In addition, coagulopathy and SIRS may indicate a more severe clinical condition.

In the case of EHS, exercise itself contributes to alterations in blood biomarkers level; thus, during the initial stage of hospitalization it is often difficult to distinguish between the acute effects of exercise (e.g., rhabdomyolysis, hyponatremia) and the multi-organ dysfunction due to a heat stroke [13]. This fact, combined with the initial relatively low T_{re} measured at the ED due to the effective cooling at the pre-hospital treatment phase, may obscure the true clinical condition of an EHS patient. A recent report on a large EHS cohort noted that fewer than 40% had consecutive tests within 24 hours [10]. Consequently, patients arriving at the ED with T_{re} lower than expected for heat stroke, coupled with nonspecific biomarkers values, may mask the correct diagnosis, leading to premature discharge from hospitalization.

Current understanding of EHS pathophysiology suggests that excessive elevation in core temperature facilitates pathways leading to systemic inflammatory dysfunction resulting in a multi-organ dysfunction [Figure 1] [6]. The high WBC count on admission to the ED reflects an inflammatory state. Initially, platelet counts were within the normal range, but dynamic changes show relative thrombocytosis. This situation, along with the elevated WBC count, indicates transient immune activity due to intense physical exercise or combined with the heat injury response, although C-reactive protein (CRP) levels as a direct inflammatory marker were unavailable in this cohort. Yet, platelets are acute-phase reactants, and although thrombocytosis is usually benign, the underlying etiology (i.e., intense exercise and EHS) may increase the risk of adverse clinical outcomes. Thus, most critical for primary care practitioners is the early stage of the syndrome because prompt recognition and treatment can be lifesaving. While SIRS was not observed in our patients, prolonged SIRS has been reported in other cases of EHS [12,14]. We think that by the immediate and effective prehospital cooling protocol, which sharply reduced core body temperature, the cascade of events leading to SIRS was interrupted.

Coagulation disturbances are common in heatstroke, ranging from mild activation of coagulation and fibrinolysis to severe disseminated intravascular coagulation [15]. While it is not a standard protocol to continuously

monitor markers such as prothrombin time (PT) or partial thromboplastin time (PTT) in cases of EHS, some researchers showed mildly elevated PTT levels initially, with peak values occurring after 72–84 hours. [10]. Substantively, international normalized ratio (INR) values, as a marker of coagulation, were monitored in the ED. However, only three patients had repeated measurements and two had markedly prolonged INR (data not shown). Besides its value in reflecting coagulopathy, prolonged INR is a sign of hepatic injury and thus should be more closely monitored.

Elevated urea and decreased creatinine clearance indicate AKI. Subsequently, estimated glomerular filtration rate was impaired during the first 24 hours (< 90 ml/min: data not shown). In our patients, AKI resolved within 24–36 hours, consistent with other reports [4,10]. The high urea-to-creatinine ratio suggests pre-renal AKI, possibly due to the decreased kidney blood flow associated with heat stroke.

Dehydration is a risk factor underlying EHS and is common during prolonged intensive exercise [4]. There were not enough indicators in our cohort to fully ascertain fluid balance. However, average [Na^+] levels remained within normal range for the entire follow-up duration and in some cases even low levels of [Na^+] were observed. This situation is due to overhydration and possibly also to large volumes of fluids infused before evacuation to cover suspected dehydration. It is, therefore, recommended that in cases suspected of EHS fluids should be administered cautiously, if at all, during initial treatment until evaluation at the ED.

Hepatic injury is also typical in EHS due to the cytotoxic effects of heat [15]. In most cases of EHS, liver injury is asymptomatic, with only mild and reversible elevation in ALT and AST levels that typically resolve spontaneously. Prolonged high transaminase levels (AST and ALT) are associated with fulminant hepatic injury, potentially necessitating liver transplantation [16]. Nevertheless, establishing whether elevated transaminase levels indicate liver or muscle injury is not straightforward. In our cohort, three patients presented an AST/ALT ratio lower than 1, at 36 to 72 hours from admission to the hospital. In parallel, CPK/ALT and CPK/AST ratios in these patients were below the cutoff value of 15, indicating liver injury rather than rhabdomyolysis [17]. To further determine whether the elevated transaminases levels in these patients were due to hepatic injury or muscle damage, we examined their INR levels. Two of the three patients had markedly prolonged INR values (peak 2.57 and 2.86), while in the third patient it was only mildly elevated (1.3). This situation was observed concurrently with a decrease in the ratios of AST/ALT, CPK/ALT, and CPK/AST. Subsequently, the two patients presented with a significant acute liver injury. In the third patient the liver injury was milder, which is also indicated by the lower transaminase levels. It follows that AST/ALT, CPK/ALT, and CPK/AST ratios could be used to better differentiate patients with transaminases levels elevation due to hepatic injury or muscle damage that might be evident only after about 48 hours from the event.

Rhabdomyolysis is common in EHS, with elevated CPK levels characteristic of the syndrome, although not pathognomonic. CPK levels usually peak at 12–36 hours of hospitalization, but some researchers noted a peak 2–3 days post-incident [10]. In our patients, CPK levels remained elevated throughout the follow-up period of 84 hours, aligning with other observations where CPK levels return to normal after 7 days [10]. CPK levels in the hundreds of U/L range may be associated with physical exercise, while levels in the thousands are more likely to indicate true rhabdomyolysis. This extensive elevation may be the consequence of the cytotoxic effects of heat on tissues and cells [15]. Unfortunately, levels of myoglobin in blood or urine are not readily followed and were not monitored in our patients.

LDH is released during tissue damage and serves as a marker for various injuries and diseases (e.g., rhabdomyolysis, liver and kidney dysfunction) [18]. The levels of LDH isoenzymes, which are not typically assessed, could have provided more insights into the origin of the elevated LDH. In this context, studying the LDH/CPK ratio may be valuable as it could help differentiate muscle damage from damage to other tissues, particularly in cases of central nervous system dysfunction.

LIMITATIONS

In this study, we focused on recent EHS cases requiring hospitalization for at least 72 hours, with laboratory tests monitored every 12 hours. This narrow focus may limit the generalizability of our findings to less severe EHS cases. In addition, the limited database and potentially the fast-response protocol for EHS cases in the IDF may have influenced the observed recovery timelines for certain biomarkers. Nonetheless, our findings are largely consistent with broader studies reporting diverse results, suggesting that while our study emphasized more severe cases, it still contributes to a broader understanding of EHS recovery patterns.

CONCLUSIONS

Monitoring changes in biochemical profiles of EHS patients provides valuable insights into clinical conditions and recovery timelines. Hospitalization is context specific; however, by integrating the current data with the relevant literature, we recommend hospitalizing suspected EHS patients for at least 48 hours to monitor trends in biomarker changes that reflect illness severity (including CRP and troponin), particularly as peak levels may manifest later in the course of the disease. Last, in the context of EHS, the literature largely focuses on male soldiers, with limited data on female soldiers. Future studies should address this growing part of the military population.

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Capsule

Colorectal cancer screening: an update to the American Cancer Society guideline, 2026

Wolf and colleagues updated the American Cancer Society (ACS) colorectal cancer (CRC) screening guideline to incorporate newly approved molecular screening tests, including multitarget stool RNA (mt-sRNA), next-generation multitarget stool DNA (mt-sDNA), and blood-based cell-free DNA assays. The ACS reaffirms that average-risk adults should begin CRC screening at age 45 and continue through age 75 if life expectancy exceeds 10 years. The new mt-sRNA and next-generation mt-sDNA tests demonstrated high sensitivity for CRC detection and are recommended as preferred stool-based screening options. In contrast, blood-based screening tests showed lower sensitivity for advanced precancerous lesions and early-stage cancers and are recommended only for individuals who decline or do not complete preferred screening tests. The guideline emphasizes that offering multiple screening options improves participation and that any positive non-colonoscopy test should be followed by colonoscopy, ideally within six months. No need for screening after the age of 85.

CA Cancer J Clin 2026; 76 (3): e70083
Eitan Israeli