MILITARY MEDICINE, 185, S1:362, 2020

Low Incidence of Death and Renal Failure in United States Military Service Members Hospitalized with Exertional Heat Stroke: A Retrospective Cohort Study

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ABSTRACT Introduction: The goal of the current study was to characterize the rate and estimate associated mortality and morbidity of exertional heat stroke (EHS) in U.S. military service members. Materials and Methods: The current study was a retrospective cohort medical chart review study of all active-duty U.S. military service members, hospitalized with EHS at any MTF in the world between January1, 2007 and July 1, 2014. Enrolled patients were identified by altered mental status and elevated temperatures associated with physical exercise. Results: Out of 607 service members with an International Classification of Disease code indicating any type of heat injury, 48 service members met inclusion criteria for EHS. Core temperature was $M = 105.8$°F (41°C), standard deviation = 1.43, 90% were diagnosed with EHS prior to hospitalization, and 71% received prehospital cooling. Meantime to normothermia post-hospitalization was 56 minutes (standard deviation = 79.28). Acute kidney injury was diagnosed in 40% of patients although none developed hyperkalemia or required dialysis. Disseminated intravascular coagulation was rare (4%, $n = 2$) and overall observed mortality was very low (2%, $n = 1$). Conclusion: EHS is aggressively identified and treated in U.S. Military Treatment Facilities. Mortality and morbidity were strikingly low.

INTRODUCTION

Heatstroke is a life-threatening illness characterized by elevated core body temperature and alterations in mental status that, if left untreated, can lead to significant mortality and morbidity.[1] Two forms of heat stroke exist, classic heat stroke (CHS) and exertional heatstroke (EHS). CHS is caused by exposure to high environmental temperatures without significant physical activity and is typically seen in extremely young or old patients. Exertional heat stroke (EHS) is associated with exercise and is frequently seen in young healthy individuals. EHS is relatively rare in the civilian populations and typically occurs during sporting events such as long-distance running. The largest body of research on U.S. service members with exertional heat injuries comes from large epidemiologic databases such as the Defense Medical Surveillance System (DMSS) and the Total Army Injury and Health Outcomes (TAIHO) databases.[2,3] According to epidemiologic data from the DMSS, there were 2,536 cases of general exertional heat injury and 417 cases of Heat Stroke reported in active-duty U.S. military service members across all branches in 2015.[4]

Although nomothetic data from the DMSS and TAIHO are useful for general characterization of the disease process and epidemiologic surveillance, these data may have limited clinical utility for a number of reasons. For example, these databases do not include detailed clinical information such as patient temperatures, assessment of mental status, time to normothermia, and laboratory values. Database studies based on International Classification of Disease (ICD) codes, such as the DMSS and the TAIHO, often do not accurately reflect clinical diagnoses in the medical record.[5] Frequently the studies that do focus on patient-level data of U.S. Service members with EHS[2,6] often combined more benign conditions such as heat exhaustion and heat cramps with CHS and EHS into heterogeneous groups of heat-injury patients. These studies likely underestimated the risk from specific types of heat injury and limit the usefulness in guiding clinical care.

Morbidity and mortality rates from EHS and CHS have varied widely between civilian and military samples. Initial civilian studies that did focus exclusively on heatstroke did not differentiate between EHS and CHS.[1] Mortality rates from heat stroke have been reported as high as 50%, likely due to the inclusion of classic heatstroke patients who are typically older, civilian, and have more medical comorbidities.[1] Studies focused only on EHS have found mortality that ranged from 0% with aggressive use of ice water immersion during athletic events[7] to 26.5% in studies conducted at regional tertiary care referral hospitals.[8] The largest cohort study to date was a military sample, focusing on clinical data from EHS patients that enrolled 183 adult military men and women admitted to French Military Hospitals and found 31% of subjects developed renal failure.[9] However, these results

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Accepted for poster presentation 2018 Military Health System Research Symposium, August 2018, Kissimmee, FL; abstract #MHSRS-18-0122

The views expressed in this manuscript are those of the authors and do not necessarily reflect the position or policy of the Department of Defense, the Department of Veterans Affairs or the United States government

doi:10.1093/milmed/usz214

have limited external validity because the study used a lower temperature threshold (102.2 degrees Fahrenheit/39°C) than other studies on EHS, and patients who died from EHS were excluded.[7,8,10,11] Furthermore, the majority of EHS cohort studies have been conducted at large military and civilian regional referral centers where selection bias has the potential to have increased the observed rates of mortality and the frequency of complications seen.[8,11–13]

EHS is frequently seen in Military Treatment Facilities (MTFs)[4] and can have devastating consequences if not quickly and properly treated. Unfortunately, the limited valid research on the topic limits providers' abilities to use evidence-based medicine to guide clinical care. One previous study examined EHS treatment approaches in a military population: Indian Paratroopers who were diagnosed with EHS and who received aggressive cooling had a 100% survival rate despite almost universal acute kidney injury (AKI).[10] To the best of our knowledge, there are no cohort studies of EHS in US service members. Because of this apparent gap in the literature, the goal of the current study was to characterize the associated mortality and morbidity of EHS in U.S. military service members.

MATERIALS AND METHODS

Subjects/Setting

This study is a retrospective descriptive cohort study of all active-duty U.S. military service members including all branches, with EHS between January 1, 2007 and July 1, 2014 who were hospitalized at any MTF in the world. MTFs frequently provide initial care of injured or sick service members, but often lack subspecialist care. In those instances where patients require subspecialist care, such as nephrology/dialysis, patients are generally transferred to civilian hospitals or to a limited number of military regional referral centers. Using the Military Health System Management Analysis and Reporting Tool (M2), potential study subjects were identified. The M2 database contains all Department of Defense ambulatory and inpatient data records. Inclusion criteria were a documented core temperature elevation above 104°F (40°C) and evidence of altered mental status (AMS) associated with some form of exercise. Exclusion criteria were evidence of classic heatstroke defined as heat stroke with no evidence of physical activity. The Brooke Army Medical Center Institutional Review Board approved this study (study number C.2015.016d).

Procedures

The M2 database was searched for all individuals hospitalized at an MTF between January 1, 2007 and July 1, 2014 and diagnosed with ICD Code 9 codes of 992.0 (heatstroke and sunstroke), 992.1 (heat syncope), 992.2 (heat cramps), 992.3 (heat exhaustion anhidrotic), 992.4 (heat exhaustion due to salt depletion), 992.5 (heat exhaustion unspecified), 992.6 (heat fatigue transient), 992.7 (heat edema), 992.8 (other specified heat effects), and 992.9 (heat unspecified). Patients from the M2 database with heat injury-related ICD 9 diagnosis were then excluded if their medical records were missing/inaccessible/duplicate, or if they were not US service members. Two study authors, both physicians trained in Emergency Medicine (V.H. and S.O), were blinded to study purpose, were trained in data abstraction, and identified M2 cases for inclusion. Patients who met inclusion criteria were enrolled in the study and their clinical data (study variables) abstracted from the Armed Forces Health Longitudinal Technology Application (AHLTA) medical record.

Study Variables

EHS was operationalized as core temperature elevation equal to or greater than 104°F (40°C) with evidence of AMS associated with some form of physical activity such as running or hiking/rucking. AMS was defined as a Glasgow Coma Scale of less than 15 documented in the medical record. Two temperatures readings were operationalized as clinical variables: (1) temperature reading at arrival to an MTF emergency department and (2) highest temperature recorded in the medical record including a report from prehospital providers. Three temperature reduction methods were identified and coded: ice-water immersion, conductive cooling, or combination therapy. Diagnosis location was defined as either prehospital (Emergency Medical Services/medic) or MTF. Time to normothermia was operationalized as time in minutes after arrival in the Emergency Department until the patient had a documented temperature below 99°F (37.2°C). The shock was operationalized as mean arterial blood pressure of less than 65 mm Hg, or systolic blood pressure of less than 90 mm Hg. Disseminated intravascular coagulation (DIC) was coded present when there was significant evidence of coagulopathy and/or fibrinolysis and medical record included a diagnosis of DIC during the indexed hospitalization. AKI was operationalized as an abrupt increase in serum creatinine > 0.3 mg/dL within 48 hours of hospitalization, or serum creatinine increasing >1.5 times the patient's known baseline. Hyperkalemia was operationalized as serum potassium > 5.1 mmol/L. The need for dialysis was coded if the medical record identified that the patient either received dialysis or was transferred to another facility to receive dialysis. Mortality was operationalized as any evidence of death within 30 days of indexed hospitalization for EHS.

Data Collection and Validation

The current study was conducted using published guidelines for conducting medical record review studies.[14] Study authors responsible for data abstraction were trained in the data abstraction process, understood their work would be checked for accuracy, and they were blinded to study purpose. *A priori* definitions of study variables and inclusion/exclusion criteria were made. The reliability of abstracted data was evaluated and primary investigator (B.D.) adjudicated any disagreement between data abstractors.

TABLE I. Descriptive Statistics of Study Variables

Variable	Mean	SD	Median	Quartiles (1st, 2nd, 3rd, 4th)
Age	26.1	6.48	–	20, 24.5, 31, 41
Temperature on arrival	100	14.23	–	99.6, 102.6, 105, 107
Highest temperature	105.8	1.43	–	104.4, 106, 107, 108.8
Initial creatine	1.58	0.48	1.5	1.3, 1.5, 1.83, 2.79
Max creatine	1.603	0.57	1.5	1.3, 1.5, 1.85, 4
Initial potassium	4.21	0.47	4.2	3.9, 4.2, 4.6, 5.6
Max potassium	4.37	0.46	4.3	4.05, 4.3, 4.65, 5.6
Initial CPK	3114.48	7617.31	428.5	251, 428.5, 1843.75, 33600
Max CPK	4222.65	8308.43	1123.5	382, 1123.5, 4057.75, 39156
Initial AST	146.50	216.56	57	30, 57, 101.25, 1005
Max AST	185.13	242.90	70	39, 70, 202, 1005
Initial ALT	181.20	550.49	54	29, 54, 118, 3705
Max ALT	213.44	557.72	57	35, 57, 141, 3705

Data Analysis Plan

Because this is a descriptive study, no formal hypotheses were tested. The effective sample was summarized and described using the mean and standard deviation (SD) or median and interquartile ranges for nonnormally distributed variables (Table 1). Six variables were not normally distributed (i.e., skewness and kurtosis > 1): maximum creatine, maximum creatine phosphokinase (CPK), initial potassium, maximum potassium, initial aspartate aminotransferase (AST), maximum AST, initial alanine aminotransferase, and maximum alanine aminotransferase. The concordance of agreement between data abstractors was calculated using interclass coefficient,[10] as each rater had assessed each subject, and the reliability was calculated from a single variable (i.e., patient's maximum recorded temperature). Inter-rater reliability of data abstractors was evaluated using the interclass correlation coefficient and was found to be 0.99, (95% = .985–.996).

RESULTS

There were 2.5 million service members ($n = 2{,}605{,}4000$) in the M2 database during the study timeframe, approximately 600 ($n = 607$) were diagnosed with an ICD code indicating any kind of heat injury. Those subjects with inaccessible/duplicate medical records or who were not U.S. service members were excluded ($n = 286$). Of the remaining eligible sample ($n = 321$) less than 15% ($n = 48$) met criteria for EHS and were enrolled in the current study (Fig. 1). The most common reason for eligible subjects not meeting criteria for EHS was lack of documented temperature equal to or greater than 104°F (40°C) and accounted for 46% of all exclusions. The current sample was mostly male (87.5%, $n = 42$) and young ($M = 26.10$, SD) = 6.48; range = 18–41). The average highest core temperature documented during prehospital/hospital care was on average 105.8°F (41°C), SD = 1.43; range = 102.6–108.8. The average core temperature upon arrival to an MTF was 100°F (37.8°C), SD = 14.23; range = 96.9–107.

Most participants were diagnosed with EHS by prehospital staff (90%, $n = 43$). Additionally, most participants (71%, $n = 34$) received prehospital cooling. Of the 43 participants who were diagnosed with EHS prior to arrival at an MTF, only 11% ($n = 5$) did not receive prehospital cooling measures. Most participants were recorded as receiving combination temperature reduction therapy (42%, $n = 20$). The average time from Emergency Department arrival to normothermia was 56.1 minutes, SD = 79.28; range 0–194 minutes.

Although 40% ($n = 19$) of patients showed evidence of AKI, none developed hyperkalemia or required dialysis. Most participants (83%, $n = 40$) did not meet criteria for shock but two participants (4%) had a diagnosis of DIC based on medical record documentation during the index hospitalization. The study sample had an extremely low rate of mortality (2%, $n = 1$).

DISCUSSION

The current study represents the first clinical cohort study focusing on EHS in U.S. service members. Overall, we found that U.S. service members with EHS had low rates of mortality (2%) and morbidity. For example, major complications such as shock and DIC only developed in 18% and 4% of subjects, respectively. The low rate of serious medical events was somewhat surprising given that the average initial temperature of the cohort was 105.8°F (41°C) and five patients were recorded with core temperatures above 108°F (42.2°C). Although 40% of the enrolled subjects had evidence of AKI, no patients developed clinically significant sequelae such as hyperkalemia or required dialysis.

Our observed mortality rate of 2% was significantly lower than previously published clinical cohort studies that reported mortality rates of 7–26%[8,15] but was similar to reported mortality from general heat injury in epidemiology data on U.S. service members.[2,3] Wallace et al.[2] and Carter et al.[3] looked at mortality in hospitalized patients with all forms of exertional heat injury, including EHS as well as more benign forms of exertional heat injury, and found mortality rates of 2.8% and 0.7%, respectively. It has been postulated that time to cooling/duration of hyperthermia is the single most

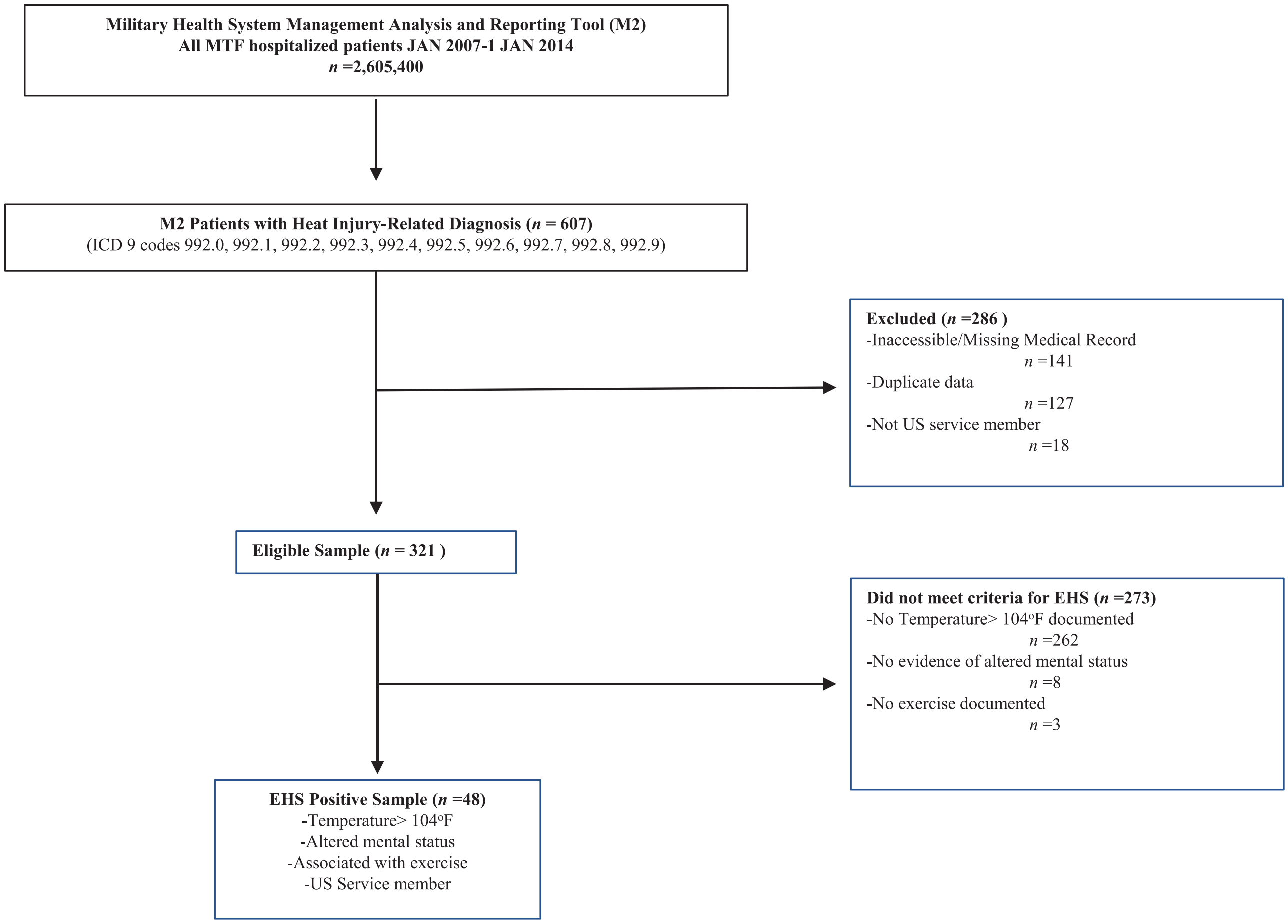

FIGURE 1. Study enrollment flowchart.

important variable to reduce mortality.[16–19] In our cohort, 90% of patients were diagnosed with EHS by prehospital providers and the majority (70%) received prehospital cooling. Furthermore, the average time to normothermia after arrival in the Emergency Department was less than an hour. This evidence of early identification and aggressive treatment of EHS is consistent with the US military emphasis on the prevention and treatment of heat injuries[3,20] and may account for the low rates of mortality and morbidity that were observed.

Our results differ significantly from previous findings reported in Yang et al.[15] and Sithinamsuwan et al.,[8] which reported mortality rates of 26.5% and 7.1%, respectively. Differences in patient selection and duration of hyperthermia may account for the observed differences. Both studies were conducted at large military and civilian regional tertiary care referral centers, which tend to treat more critically ill patients compared to MTFs, treat a broader spectrum of EHS severity. Both previous studies also reported prolonged periods of hyperthermia, ranging from 2 to 3.5 hours to achieve temperatures below 100.4–101.3° (38–38.5°C).[8,15] This is in contrast to our study, which had an average time from Emergency Department arrival to a temperature of less than 99°F (37.2°C) of 56.1 minutes. Our findings are more similar to the study by Deshwal et al.,[10] who found that with aggressive cooling and despite almost universal AKI, no patients with EHS required dialysis and their mortality rate was 0%. Overall, these results suggest that the population and treatment setting plays a large factor in observed rates of mortality and morbidity from EHS.

The major clinical implication suggests that patients with EHS who are aggressively treated rarely progress to renal failure requiring dialysis, nor do they frequently develop other significant complications such as DIC, even in the presence of AKI. Although EHS can cause a delayed elevation (24–72 hours) in creatinine, potassium, liver function tests, and CPK, no patients in the current sample developed biomarker elevations that warranted additional interventions or changes in clinical management. Demartini et al.[7] reported that in their 18-year experience performing on-site medical coverage for the Falmouth road race, they were successful in discharging 93% of their patients with EHS (average initial core temperature of 106.5°F/41.4°C) to home after aggressive cooling thus avoiding Emergency Department evaluation or inpatient admission. Also, the observed mortality in our study of 2% is consistent with the mortality risk of other conditions that are managed as an outpatient.[21] Thus, the authors conclude that outpatient management of EHS after effective cooling is a potentially reasonable strategy as long as the patient has a normal neurologic exam can tolerate oral fluids and has close follow-up with the ability to recheck laboratory studies available.

Results should be interpreted within potential study limitations. The current cohort of EHS patients may not be exhaustive of all patients with EHS as there may be some individuals in the M2 database that had EHS within the study timeframe and were missed. Because of resource constraints, the initial medical chart review was limited to only those patients that were hospitalized at an MTF for heat-related illness and thus the current sample may over select for severely heat-injured patients, in which case the low morbidity and mortality rates are even more striking. Some EHS patients may have initially presented to outpatient clinics, although we believe this is unlikely. Military service members are frequently seen at battalion aid stations (BAS) for initial evaluation. Those patients who are low acuity and/or successfully treated at a BAS would likely not be hospitalized and would be seen in an outpatient clinic for follow-up. The M2 database that this research was based on does not include BAS encounters or outpatient visits. Some U.S. service members may have been treated for EHS at civilian hospitals outside the military health system. Finally, our dataset only included patients that were hospitalized at an MTF so any prehospital deaths would not have been included in our cohort.

Overall, the study suffered from low enrollment primarily due to duplicate/inaccessible medical records or missing data. Many of the study subject's medical records were stored locally at the treating MTF and were not accessible to the authors via AHLTA. The second most common reason for potential subjects to be excluded was the lack of documented temperature equal to or greater than 104°F (40°C). Although some of these excluded patients likely did have EHS and just lacked temperature documentation, the authors chose to use this strict definition of EHS in order to ensure they were collecting data that accurately reflected the disease process in question. Although the use of this exclusion criteria likely decreased our cohort size, and Army regulations and technical documents do not include a specific temperature level in their definition of EHS,[20] the authors feel that an objective assessment of temperature elevation is important for research purposes to quantify the disease process and limit confounding variables. Furthermore, our use of a temperature definition in the study's inclusion criteria mirrors other cohort studies on EHS[7–11,15,16] and allows a more accurate comparison between studies.

Given the nature of military medicine, it is likely that our current sample may not be representative of civilian populations. The military patient population tends to be young, healthy, and physically fit at baseline, which may mitigate the morbidity and mortality of EHS and could diminish the external validity of these results to non-military populations.

CONCLUSION

Current data suggest that EHS in US service members is identified early and aggressively treated. Likely because of these procedures, the observed mortality and morbidity were much lower than in other patient populations with mortality of less than 2% and no instances of patients developing AKI that required dialysis. These findings suggest that outpatient management of exertional heatstroke after effective cooling is a potentially reasonable strategy as long as the patient has a normal neurologic exam, can tolerate oral fluids, and has close follow-up with the ability to recheck laboratory studies available.

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