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Diagnostic Biomarkers for Heat Stroke and Heat Exhaustion: A Scoping Review

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Review Article

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Abstract

Objectives: As the global incidence of heat-related illnesses escalates in the wake of climate change-induced heat waves, the critical necessity for reliable diagnostic tools becomes apparent. This scoping review aimed to summarize the existing body of published evidence on biomarkers that could potentially be utilized for the diagnosis of heat-related illness in the clinical setting.

Methods: We conducted a thorough search of 3 databases, including Embase, MEDLINE, on Ovid, and The Cochrane Library (Wiley) databases from October 11, 2022 up until January 15, 2024. We also manually included studies by searching the reference lists of the included articles. Studies that performed statistical validation were summarized in detail.

Results: 2877 citations were identified and screened, with 228 studies reviewed as full text. 56% of these studies were conducted within China or North America. The studies identified 113 biomarkers. Most common biomarkers studied were troponin I, IL-6, platelets, and ALT. The studies exhibited considerable variation, reflecting the diverse range of investigated biomarkers and the absence of standardized statistical validation for the biomarkers.

Conclusions: Numerous biomarkers have been evaluated in the literature, but none have been studied to impact clinical practice. There is significant variation in the methodology and statistical validation. There is a need for further research to identify clinically relevant biomarkers for heat related illnesses.

Climate change, characterized by rising global temperatures, presents a significant threat to public health.[1–4] This escalation has led to a surge in the frequency, duration, and severity of heat waves, with predictions indicating a continuation of this trend.[5] Over the last 2 decades, there has been a notable 54% rise in heat-related mortality and morbidity among individuals aged 65 and above.[6] Additionally, climate change has been identified as the cause of more than one third of all heat-related deaths during the warm seasons worldwide.[7]

Despite the increasing awareness of possible heat stress and its detrimental impact on the population, especially those vulnerable to its effects, the diagnosis of heat illness (HI) often relies on a "diagnosis of exclusion."[8,9] Heat injuries encompass a range of conditions, spanning from milder forms like heat syncope and heat exhaustion to severe and life-threatening conditions such as heat stroke.[10] Early diagnosis is crucial for severe heat related illness (HRI), as effective and feasible treatment with rapid cooling, commonly referred to as the "golden hour," yields optimal clinical outcomes.[11,12]

In recent years, the significance of biomarkers in clinical medicine has increased. According to the Food and Drug Administration (FDA), biomarkers are a measurable indicator with extensive potential applications, including research, therapy development, diagnosis, prognosis, disease progression monitoring, and treatment response assessment.[13] The identification of ideal biomarkers holds the possibility for early diagnosis and treatment that overall enhance clinical outcomes. The use of biomarkers in oncology trials[14] has been linked to increased success rates, particularly in breast, melanoma, and lung cancer trials.[15–17] Parker et al.'s study on 4 cancer indications revealed that employing biomarkers, such as HER2 in breast cancer, led to a remarkable 5-fold reduction in the risk of clinical trial failure.[18] However, for the ideal utilization of biomarkers, they must be both disease-specific and universal for a condition for reliable and accurate measurement across a range of patients.[19]

The role of biomarkers in the diagnosis and management of severe HRI is poorly understood. Our primary objective is to conduct a comprehensive review of existing literature on HRI biomarkers applicable in acute care settings.

Methods

Search Strategy

The review was conducted using a scoping review framework outlined by Arksey and O'Malley[20] and adhering to the guidance provided by the Joanna Briggs Institute.[21] The PRISMA-ScR checklist[22] was used to ensure standardization of reporting. Furthermore, the protocol has been registered in Open Science for review.[23]

A systematic search was conducted on MEDLINE, Embase, and The Cochrane Library (Wiley) databases on October 11, 2022, and a final search was repeated on January 15, 2024. The search period was from 1946 to January 2024 and utilized a combination of subject headings and keywords related to heat disorders and biomarkers. The complete list of search terms can be found in the Supplemental Table 1 (Appendix). The search was conducted by a specialist librarian at the Weill Cornell Library.

The search results, consisting of the identified citations, were imported into Covidence, a tool utilized for systematic or scoping reviews to facilitate screening and data extraction. All included papers underwent a review and selection process conducted by at least 2 independent reviewers (JP, WF, and MBM). The reviewers carried out the screening process, evaluating titles, abstracts, and full texts of the selected citations according to the predefined inclusion criteria. Exclusion reasons for sources of evidence during the full-text screening were documented. Any discrepancies between the reviewers were resolved through discussion and reaching a consensus. The search results and the study inclusion process are visually depicted in a PRISMA-ScR flow diagram Figure 1.

Study Selection

We included experimental studies, case studies, case-control studies, prospective, and retrospective cohort studies reporting candidate biomarkers for diagnosis or prognosis identified during exposure to heat. We excluded studies that primarily aimed to understand the pathogenesis of heat stress and did not investigate chemical markers with the potential for use in the clinical setting. Both human and animal studies with all types of HRI were included. Pre-prints, non-English studies, book chapters, conference proceedings, editorials/letters, and reviews were excluded.

Data Extraction and Synthesis of Results

Two independent reviewers utilized an extraction chart they developed to extract data from the studies included. The extracted data were added to Covidence. The following information was extracted: authors, study country, publication date, study design, whether the

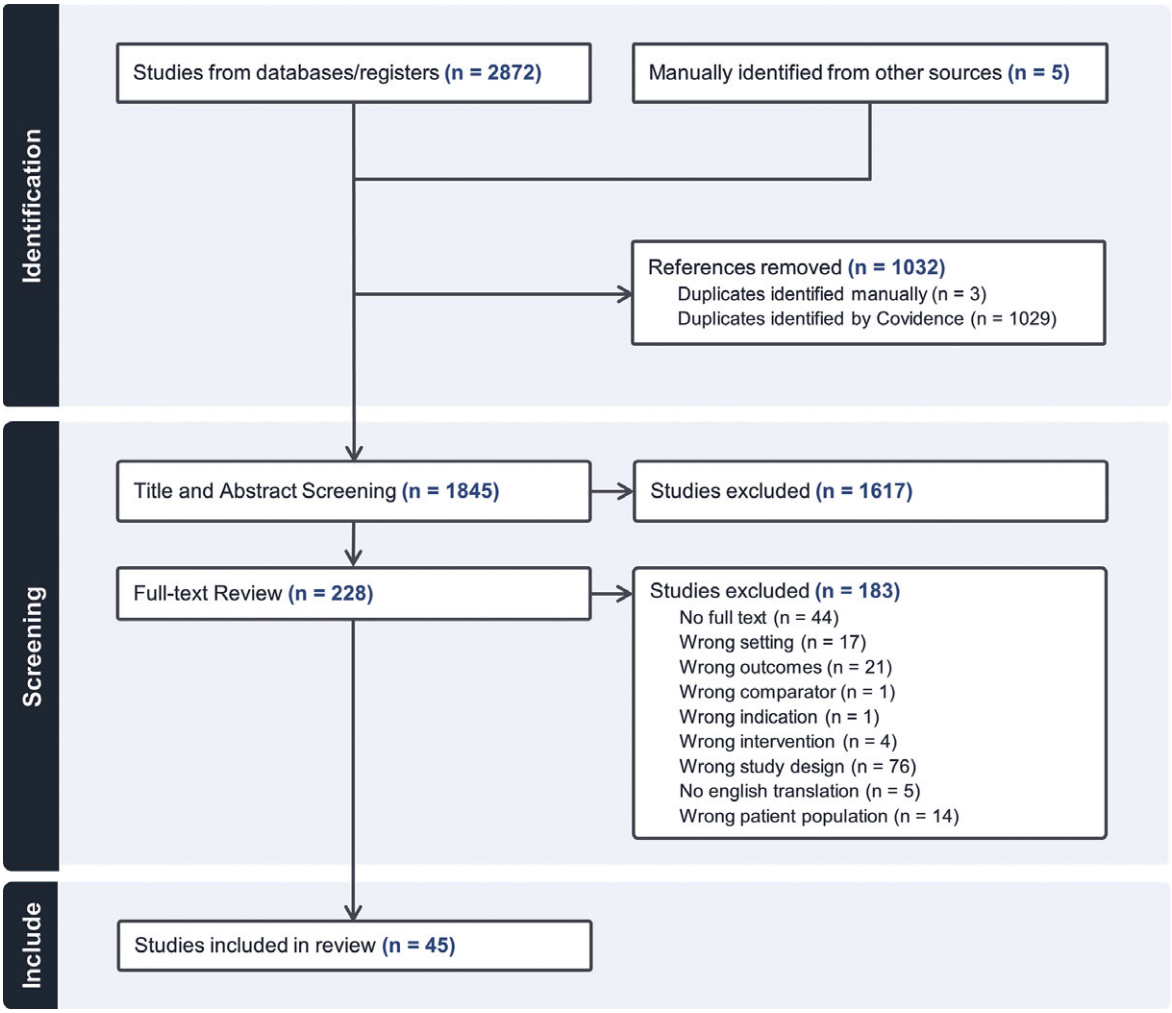

Figure 1. PRISMA.

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study involved animals or humans, number of subjects included, biomarker investigated, findings, and if the primary the marker could function as diagnostic and prognostic biomarker for HRI.

The extracted data was exported from Covidence to an Excel spreadsheet for further analysis.

Participations/Population

The study includes both human and animals subjects. Human participants consisted of patients across diverse age groups, genders, and racial/ethnic backgrounds diagnosed with heat-related disorders, including but not limited to heat stroke (HS), sunstroke, and heat exhaustion (HE). Nevertheless, individuals who experienced hyperthermia attributable to infectious causes (such as extreme fever resulting from viral or bacterial infections), medication-induced heat stroke (inclusive of pharmaceuticals and psychotropic substances), or extreme environmental conditions (e.g., confined spaces, saunas, cars, Bikram Yoga sessions, or electric blankets) were intentionally excluded from the scope of consideration in this review.

Selection of Biomarkers

Considering the broad spectrum of biomarkers highlighted in different studies, we selected the most pertinent markers when multiple options were available. Our decision-making was guided by the markers' relevance to the investigation and their central emphasis in the paper.

Ethics Statement

Ethical approval was not required.

Results

Summary of Extracted Studies

Initially, we identified 2877 articles. Following deduplication, 1845 unique articles underwent screening based on title and abstract. Subsequently, 228 progressed to full-text evaluation. Of these, 183 were excluded for various reasons outlined in Figure 1, including lack of relevance to heat biomarkers and focus on non-medical aspects such as animal or environmental research. Ultimately, 45 articles met the eligibility criteria (Figure 1, Prisma).

Study characteristics

Of the 45 studies, 14 were published from China followed by 9 from the US. Study designs predominantly included experimental research (n = 21),[24–44] followed by prospective cohort studies (n = 16),[45–60] retrospective cohort studies (n = 6),[61–66] 1 case report,[67] and 1 case control[68] (*Figure 2*). Of the experimental studies, 15 studies involved animal models,[24,25,27–37,40,41] while 4 studies focused on human participants,[26,38,43,44] 1 on human autopsies,[42] and 1 study on human cells.[69] The predominant use of rodent models, particularly rats and mice, is observed in most animal studies. Out of the remaining 30 human studies, 21 concentrated on normal population samples,[26,43,45–49,51–54,57–59,61–64,67,70,71] with the rest involving military recruits (n = 5),[38,50,55,60,66] athletes (n = 2),[44,65] human autopsy cases (n = 1)[42] and human cells (n = 1).[39] The scope of studies involving human participants exhibited significant variability, ranging from 1-2216 individuals (Figure 3). Most studies examined blood-based biomarkers in either plasma, serum, or whole blood. Other fluid types included urine (n = 3)[43,46,60] and CSF (n = 1).[42] Finally, 12 studies investigated biomarkers in tissue (cardiac, intestinal, liver).[25,27–32,34,40–42,69]

Diagnostic Perspectives

Only 5 studies focused on identifying diagnostic biomarkers,[25,39,44,65,67] while 27 studies focused on prognostic biomarkers and 13 on biomarkers that could potentially assist with both diagnosis and prognosis.[29,31,34,35,38,43,45,47,50–53,57,59] Those biomarkers with diagnostic value were the following: IL-6, TNF-a, 15-keto-13,14-dihydro-PGF2α, 8-iso-PGF2α, MDA; CRP; lncRNA, miRNA; troponin I; NMET, MET, serum osmolarity, copeptin, KIM1, and NGAL. A detailed overview of these biomarkers can be found in Table 1.

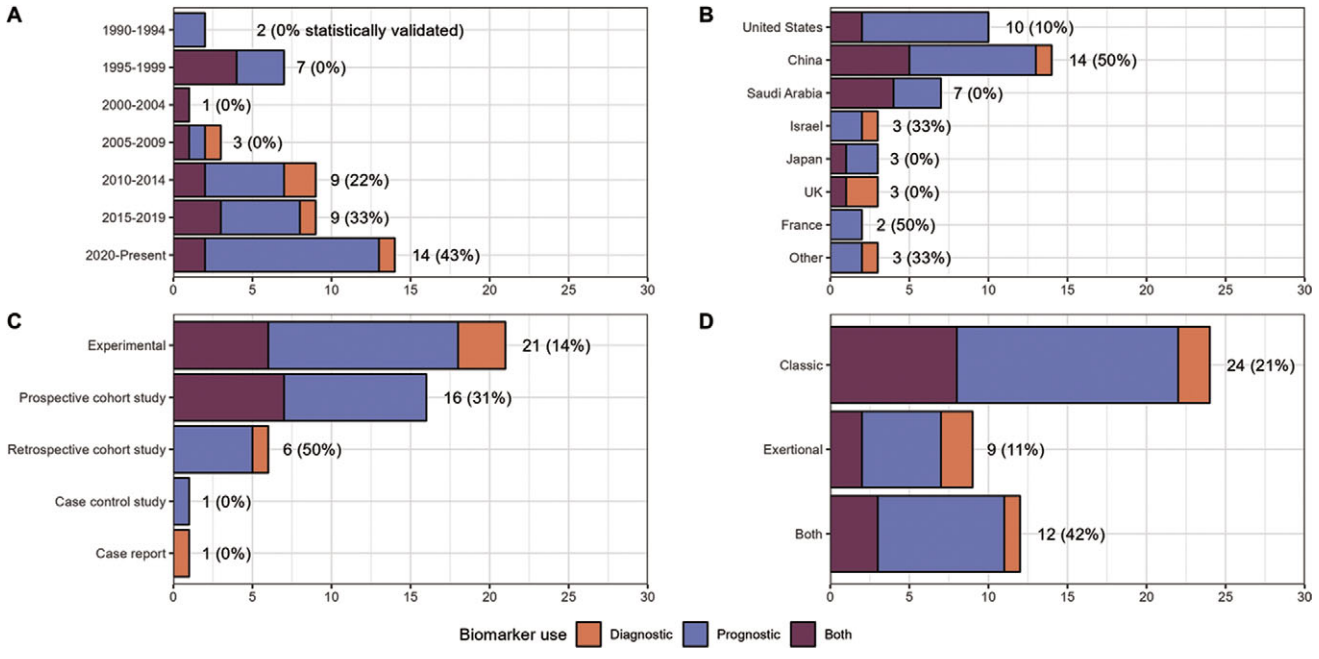

Figure 2. Study details.

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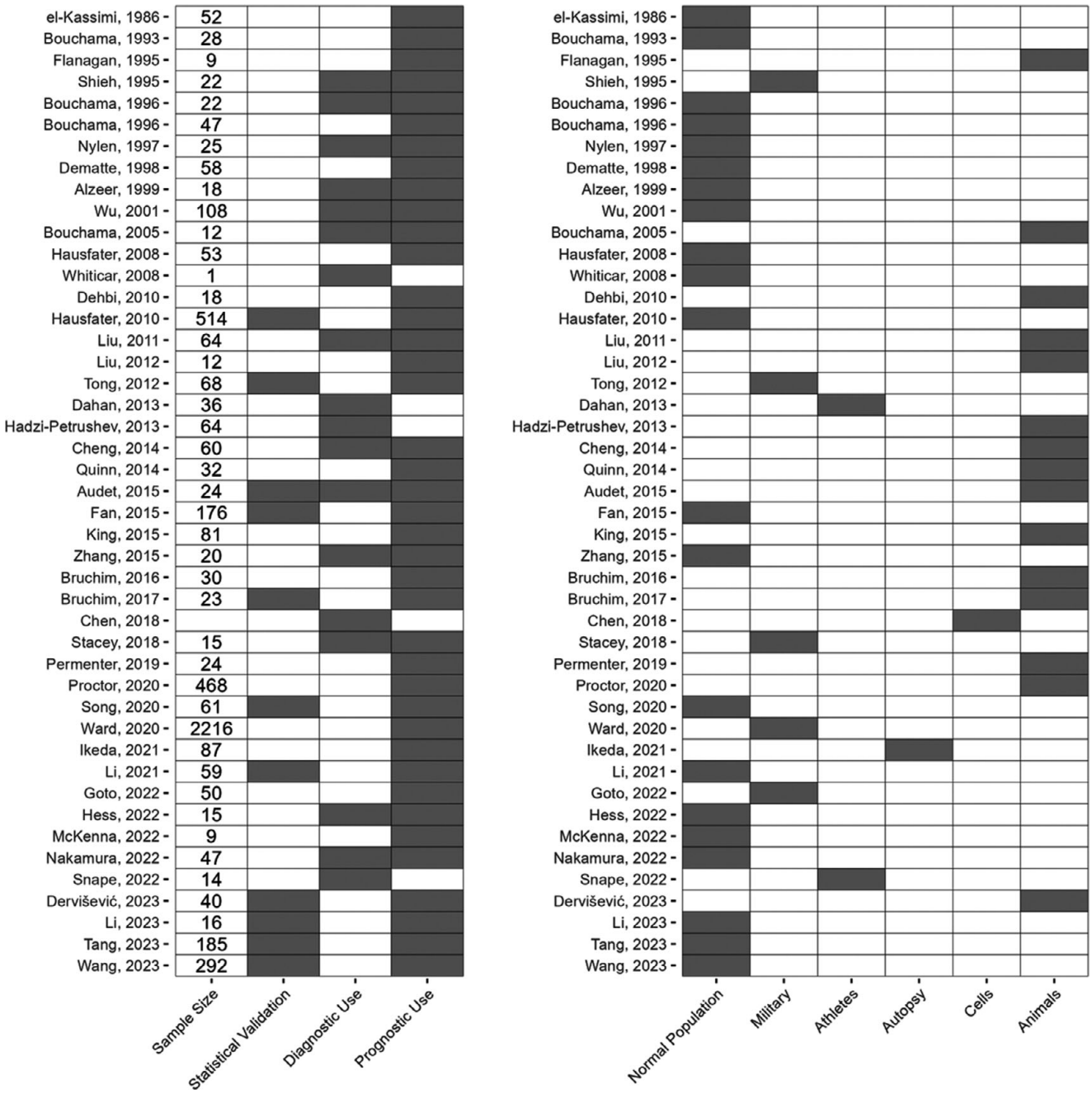

Figure 3. Biomarker details.

Validation

The statistical analysis in most of the studies predominantly focused on variations in biomarker levels and their correlation with elevated temperatures, lacking comprehensive validation. Thirty-five studies evaluated only the differences in mean and a *P* value, without analytic validation (determine by sensitivity, specificity, accuracy, precision, or AUC values). Of the 107 biomarkers, only 15 biomarkers and 2 scores (MODS, APACHE 2)[61,63] used statistical validation to determine their accuracy and reliability for diagnosis or prognosis for HRI (Table 2). These validated biomarkers include troponin I,[35,54] histones,[37,58] procalcitonin,[55,63] HSP 70,[24] WBC count,[61,71] NEU,[61] LYM,[61] AST,[58,72] ALT,[58] Creatinine,[72] platelets,[71] vWF,[47] S100A8,[47] and SAA-1.[47] Furthermore, none of the studies with proper statistical validation demonstrated potential for diagnosing HRI; instead, they were primarily utilized to evaluate severity or assess the likelihood of mortality after heat stress. However, it is important to note that in recent years there has been a modest increase in the number of such validated studies.

Biomarkers

Cytokines and inflammatory biomarkers

Cytokine IL-6 was one of the most frequently investigated HRI biomarkers and demonstrated diagnostic[25,29,31,57] and prognostic[29,31,42,49,57] utility. Bouchama's investigations in 1993 and over a decade later highlight the association between IL-6 alterations and HI severity, suggesting its potential to predict HS mortality.[29,49]

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Table 1. List of all included studies with biomarkers investigated, summary of findings, and biomarker use (diagnostic/prognostic utility)

Author	Biomarker investigated	Comments	Biomarker use
Hadzi-Petrushev[25]	lL–6 | TNF-a | 15-keto–13,14-dihydro-PGF2a | 8-iso-PGF2a |malondialdehyde	Acute heat exposure resulted in an increase in plasma levels of IL–6, TNF-α, 8-iso-PGF2α, and malondialdehyde. An increase was only observed for MDA in older rats.	Diagnostic
McKenna[26]	I-FABP | CLDN–3 | LBP	Both exertional heating protocols induced mild thermal and physiological stress, leading to similar levels of enterocyte damage (measured by I-FABP). However, intermittent exercise at higher intensity resulted in higher bacterial endotoxin translocation (measured by LBP), potentially increasing the risk of local and systemic inflammation. However, CLDN–3 did not increase.	Prognostic
El-Kassimi[48]	PT | aPTT | platelets | FDP	Among heat stroke patients, 23% developed ARDS and were also diagnosed with DIC (characterized by elevations in PT, aPTT, and low platelets or raised FDP). This suggests that DIC may play a role in mediating ARDS in heat stroke. Screening for coagulation markers in heat stroke patients could serve as a predictor for the development of ARDS.	Prognostic
Bouchama[49]	IL–6 | IL–1b | IFN-gamma	Elevated levels of IL–6, IFN-gamma, and IL–1b were observed in the acute phase response, indicating the involvement of a complex cytokine network. Although plasma IL–6 levels correlated with heatstroke severity (SAP score), predicting clinical outcomes based on individual cytokine levels remains uncertain. Additionally, there was no significant correlation between IFN-gamma levels and clinical outcomes in heatstroke patients.	Prognostic
King[27]	I-FABP–2 | BUN | CK | ALT | glucose	All tested markers except glucose showed a marked rise in levels across all time points in the experimental groups compared to controls. Glucose levels fell significantly in EHS but were raised in EXC compared to naive controls. However, this drop was followed by a sustained rise (4 days) in glucose levels in the EHS group. Therefore, hypoglycemia can be a diagnostic marker of EHS at ED arrival. Significantly higher levels of FABP–2 were observed across all recovery time points between the following groups: (1) EXC/EHS vs NC = Both exercise and heat individually are associated with a rise in I-FABP2. (2) EHS vs EXC (at 0.5 h): Similar to exercise alone, heat also has a significant additional effect on I-FABP2 levels.	Prognostic
Shieh[50]	ACE | vwfa | thrombomodulin | PRA	The study found higher levels of circulating TM, PRA, and vWf:Ag, along with lower ACE values in ExHS patients upon admission. These changes suggest possible endothelial cell injuries, indicating a potential for hemostatic failure and/or DIC. Measuring these markers could help assess endothelial cell injury in ExHS patients, which could support the prognosis of ExHS patients.	Prognostic and Diagnostic
Flanagan[28]	HSP72	HSP72 levels increased in the liver, kidney, and small intestine, particularly in the liver of animals exposed to high heating rates. However, no significant increase was observed in the brain or kidney, suggesting tissue-specific differences in heat shock protein responses. It is speculated that HSP increases in certain tissues may indicate susceptibility to early thermal damage. Moreover, greater increases in the high heating rate group imply that the rate of heating, rather than the duration of heating, is an important predictor of tissue damage or injury in heat stroke. This marker could function as a potential biomarker for the prognosis of organ dysfunction during heatstroke.	Prognostic
Bouchama[51]	Plasma endothelin | ICAM–1 | vWFa	In the examined patient cohort, increased serum levels of endothelin, ICAM–1, and vWF:a were found in 100%, 80%, and 77% of heat stroke patients, respectively, suggesting endothelial cell activation or injury. There was a significant correlation between circulating ICAM–1 and endothelin concentrations. Plasma endothelin concentration correlated negatively with temperature.	Prognostic and Diagnostic
Bouchama[70]	TAT | PAP | soluble fibrin | anti-thrombin III | protein C | plasminogen | D-Dimer	Heatstroke patients showed elevated PT and D-dimer levels, decreased platelet counts, and a non-significant decrease in fibrinogen. On admission, increased PAP and TAT levels indicated activated fibrinolysis and coagulation. Cooling	Prognosis

(*Continued*)

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Table 1. (*Continued*)

Author	Biomarker investigated	Comments	Biomarker use
		sustained coagulation activation but markedly attenuated fibrinolysis. Patients without severe symptoms had milder activation. This highlights the link between heat stress and activated coagulation and fibrinolysis. Cooling interventions, although effective in attenuating the fibrinolytic system, appeared to sustain activation within the coagulation system.	
Nylen[52]	Procalcitonin	Classic heatstroke is associated with a 20-fold increase in mean serum procalcitonin upon admission compared with controls (p<.011). The procalcitonin concentration subsequently increases to a plateau by 6 h and remains elevated at 24 h compared with the admission level (p<.0001). Procalcitonin levels > 0.5 ng/mL at 6 h post-exposure are significantly associated with survival.	Prognostic and Diagnostic
Wu[53]	Hsp60 | Hsp71 | Hsp90a | Hsp90b	Increased levels of antibodies to Hsp–71 and Hsp–90a were observed in the exertional heat stroke group compared to controls. Additionally, titers of anti-Hsp–71 were significantly higher in both severe and mild exertional heat stroke groups compared to controls.	Prognostic and Diagnostic
Bouchama[29]	lL6 | thrombomodulin | PT | aPTT | D-dimer | fibrinogen | Platelets | creatinine | ALT | LDH | CK | urea | glucose	The experiment showed an increase in IL–6, markers of endothelial injury, markers of coagulation, urea, and glucose between the groups, with a greater increase in the severe group. The peak IL–6 and thrombomodulin levels also correlated with the severity of clinical manifestations, tissue injury, and death. All subjects with peak elevations in IL–6 and thrombomodulin belonged to the severe group and died, representing the prognostic ability of IL–6 and thrombomodulin in predicting mortality from heat stroke.	Prognostic and Diagnostic
Hausfater[64]	Serum procalcitonin (PCT) levels	Heatstroke was associated with increased PCT levels irrespective of the presence of concurrent bacterial infection. Patients who experienced heatstroke with elevated PCT levels exhibited a more severe illness, although no correlation between PCT levels and mortality was established.	Prognostic
Whiticar[67]	Troponin I | ALT | AST |CK	Serum troponin I was elevated after 24 h (1.09 ng/mL) of EHS admission and peaked on day 2, along with markers of tissue injury and coagulopathy such as creatine kinase level (4496 U/L), grossly deranged liver function (ALT 3883 U/l, AST 2431 U/L), and a fall in platelet count to 87000/dL.	Diagnostic
Dehbi[30]	Hsp–72a | Hsp–60 | Hsc–70	Hsp–72 was significantly elevated in severe but not moderate heatstroke, with the highest levels observed in baboons with more severe MODS and death (plasma Hsp–72 levels correlated significantly with markers of cell injury/organ dysfunction). In contrast, no significant difference in tissue expression or release into circulation of Hsp–60 was detected. These findings add further evidence that upregulation of heat shock proteins may be an important component of the host response to heatstroke, and circulating levels of Hsp–72 may serve as a marker of heatstroke severity and outcome.	Prognostic
Hausfater[54]	Troponin I	Survival rates were notably lower in patients exhibiting a higher elevation of cTnI. Among the criteria evaluated as part of the risk score for predicting death in heat stroke patients, only a severe elevation in cTnI was independently associated with increased mortality in the high-risk group of patients.	Prognostic
Liu[31]	GM-CSF | lL–4 | MCP–1 | MIP–1a | lL–1b | lL–2 | lL–6 | lL–10 | lL–12p40 | TNF-a	Testing the inflammatory pathogenesis of intestinal injury in heat stroke found no significant changes in GM-CSF, IL–4, MCP–1, and MIP–1α. However, IL–1B and IL–10 increased during heat stress and cooling, while IL–2 and IL–12p40 decreased during heat stroke but increased during cooling. IL–6 and TNF-α showed no change during heat exposure but increased significantly during cooling. Changes in cytokines at 6 h were more pronounced in the group reaching 41 degrees compared to 40 and 42 degrees, suggesting 40 degrees may not be severe enough and 42 degrees may induce irreversible damage. IL–1β, IL–10, and IL–12p40 correlated significantly (positively or inversely) with intestinal injury scores (r=0.338, p=0.006; r=0.324, p=0.009; r=−0.421, p=0.01, respectively).	Prognostic

(*Continued*)

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Table 1. (*Continued*)

Author	Biomarker investigated	Comments	Biomarker use
Liu[32]	Intestinal fructose 1,6-bisphosphatase (FBP) | proteomics	14 proteins that were differentially regulated in the small intestine of mice subjected to heat stress. Among these proteins, 7 were downregulated and the other 7 were up-regulated. The study further confirmed that the down-regulated expression of intestinal fructose 1,6-bisphosphatase (FBP) correlated with the severity of small intestine lesions during heat stress and cooling treatment, suggesting that I-FBP could be a potential biomarker for the prognosis of gut dysfunction during heatstroke. However, the study does not provide statistical significance to the use of I-FABP as a clinical prognostic biomarker.	Prognostic
Tong[55]	Procalcitonin (PCT)	Elevated PCT levels upon admission were significantly associated with higher mortality rates and independently predicted poor outcomes in patients. The positive correlation with APACHE 2 scores and higher PCT levels in the MODS group underscored the predictive value of admission PCT for a severe disease course. The statistically significant ROC-AUC further emphasized the close relationship between PCT levels and prognosis in exertional heatstroke patients.	Prognostic
Dahan[65]	CRP	This study showed that individuals arriving at the hospital with hyperpyrexia and neurological deficits, coupled with normal-to-low CRP levels upon admission, are highly likely to be experiencing HS.	Diagnostic
Quinn[33]	HR | SBP | troponin I | glucose | BUN | albumin | ALT	HR and SBP responses observed during heat exposure were found to be more sensitive biomarkers of HS severity than core temperature or thermal strain. In the study, mild heat stroke (MILD) did not change cTnI, BUN, glucose, or ALT levels at 24 hours. Albumin was lower in MILD than in controls. Moderate heat stroke (MODERATE) increased cTnI and ALT, and decreased glucose and albumin compared to controls. Severe heat stroke (SEVERE) elevated cTnI, BUN, and ALT, and reduced glucose and albumin compared to controls. cTnI was higher in SEVERE than in MODERATE. BUN and glucose showed similar trends but did not reach statistical significance.	Prognostic
Cheng[34]	Hsp–60 | Hsp–60 mRNA	Hsp 60 expression demonstrated an increase in both in vivo and in vitro conditions; however, the rise in in vivo conditions was delayed. This alteration corresponded with histopathological damage to myocardial cells, suggesting that variations in Hsp–60 expression may serve as predictors for organ damage in heat stress.	Prognostic and Diagnostic
Fan[71]	Platelets | WBC	Both platelet and WBC levels are good predictors of HS-induced AKI. Nadir platelet levels were an independent predictor of exertional heatstroke-induced AKI with a ROC-AUC of 0.73, offering a sensitivity of 90% and specificity of 81%. Meanwhile, admission WBC counts outperformed peak WBC counts in predicting AKI, demonstrating an ROC-AUC of 0.66 with a sensitivity of 63% and specificity of 79%.	Prognostic
Zhang[57]	I-FABP | DAO | IL–1a | IL–6 | TNF-a | CRP | procalcitonin | WBC	Both FABP and DAO were increased across all time points compared to controls and were positively correlated with blood endotoxin levels; therefore, these can be used to indicate HS severity as well as predict blood endotoxemia and hence prognosis. IL–1a, IL–6 (cytokines), as well as markers of inflammation such as CRP and PCT, were significantly higher in the HS group compared to controls, therefore providing strength to their use as diagnostic biomarkers of heat stroke. TNF-a and WBC, however, showed no significant difference.	Prognostic and Diagnostic
Audet[35]	Troponin I	cTnI levels at maximum core temperature (Tc max) were significantly elevated in all heat-exposed groups compared with controls. They were also positively correlated with heat stroke (HS) severity. Therefore, cTnI can be a potential biomarker for both the diagnosis and prognosis of HS.	Prognostic and Diagnostic
Bruchim[36]	eHsp–72	Median eHSP72 levels did not show significant differences between outcome groups at any time point. However, a positive correlation with aPTT and lactate in the surviving group at 12 hours indicates that serum levels of Hsp–72 at the 12-hour time point post-hospitalization appear to be crucial in predicting survival.	Prognostic

(*Continued*)

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Table 1. (*Continued*)

Author	Biomarker investigated	Comments	Biomarker use
Bruchim[37]	Serum histones (sHs)	sHs levels were notably elevated in exHS, especially in non-survivors. The concentration of sHs at presentation correlated significantly with biomarkers such as serum urea, total CO2 concentrations, CK activity, and PT at 12 hours post-presentation. The ROC curve for sHs as a survival marker had an area under the curve of 0.72, with a cutoff point of 13.7 ng/mL, indicating a sensitivity of 60% and specificity of 88%. Notably, gender, body weight, and age did not significantly impact sHs concentrations.	Prognostic
Stacey[38]	Copeptin	The variation in copeptin levels mirrored the core temperature (Tc) response, in line with the occupational and physiological threshold of Tc=38 °C. This suggests that copeptin could be a valuable future tool for evaluating health risks linked to working in thermally stressful environments.	Prognostic
Chen[39]	lnc-RNA | mi-RNA	This study validates the feasibility of high-throughput sequencing analysis of exosome RNA, demonstrating that RNA sequencing is a reliable method to screen and identify novel lncRNAs that could serve as biomarkers for HS. The research reveals significant differences in expression levels of lncRNAs and miRNAs, suggesting their potential diagnostic utility for HS.	Diagnostic
Permenter[40]	mi-RNA	This study successfully identified miRNAs that exhibit altered expression patterns in response to heat stress. These findings have unveiled potential pathways influenced by these differentially expressed miRNAs, suggesting their potential utility as biomarkers for detecting organ injuries resulting from heat stress.	Prognostic
Proctor[41]	D-dimer | thrombin-antithrombin 3 complex (TAT) | anti-thrombin (ATIII) | soluble thrombomodulin (TM) | tissue factor | platelets	This study has demonstrated the potential to predict heatstroke severity immediately after heat stress exposure using markers of coagulation and CBC differentials. Furthermore, the findings have revealed that the presence of coagulopathy with diagnostic features resembling those seen in DIC predicts the severity of illness and organ damage even before histopathological changes are observed.	Prognostic
Ikeda[42]	lL–6 | lL–8 | NSE | MBP	The study found that the survival period was positively correlated with IL–6 and IL–8 in CSF but not in blood. No correlations were found between NSE and MBP and survival period. Moreover, it showed that CNS disorders caused by heat stroke are pathologically different from those caused by CNS stimulants such as amphetamines. Particularly, in cases involving CNS stimulants, pathological differences based on IL–6 can be observed.	Prognostic
Li[58]	H3	The 28-day mortality rate in heatstroke patients was 18.2%. Non-survivors had significantly higher levels of plasma exosomal histone H3 compared to survivors and healthy controls, and these levels showed a positive correlation with disease severity and organ dysfunction. Plasma exosomal histone H3 levels had a high predictive value for mortality risk, with a sensitivity of 95% and specificity of 91.67% at a cutoff value of 307 pg/100 μg.	Prognostic
Hess[43]	L-FABP | TBARS | TRX–1 | IL–17a | IGFBP–7 | TIMP–2 | NGAL | KIM–1	This study tested the changes in AKI urinary and blood biomarkers with heat stress. The primary outcome was the product of IGFBP7 and TIMP–2 (IGFBP7·TIMP–2), which provided an index of kidney injury risk. The levels of these urinary markers changed significantly upon heat exposure, and this change was influenced by the intensity and duration of heat exposure.	Prognostic and Diagnostic
Nakamura[59]	C3a | C5a | C5b–9 | Ba | Factor H | CD–59	sCD–59, C3a, C5a, Ba, and sC5b–9 were higher in heat-stressed patients, especially those with severe illness. sCD–59 levels were positively correlated with prognostic scores such as APACHE 2, SOFA, JAAM DIC score, and JAAM stage. sCD59 was associated with severity and coagulopathy, and the alternative complement pathway was activated in patients with heat-related illnesses. The magnitude of this activation can be used to predict disease severity and prognosis.	Prognostic and Diagnostic

(*Continued*)

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Table 1. (*Continued*)

Author	Biomarker investigated	Comments	Biomarker use
Goto[60]	KIM–1 | NGAL | L-FABP | NAG | Î²2 microglobulin	The levels of NGAL, L-FABP, and NAG were higher in patients with a >2 severity score (JAAM-HS-WG criteria) compared to those with a 0 score. Moreover, only L-FABP was significantly higher when levels of biomarkers were compared between the AKI and non-AKI groups. Therefore, L-FABP is useful for detecting severe heatstroke and heatstroke-induced AKI. Additionally, although urinary KIM–1 levels were not elevated in patients with severe heat-related illness or heatstroke-induced AKI, there was a significant positive correlation between sCysC and urinary KIM–1 levels, suggesting that urinary KIM–1 may detect heatstroke-induced AKI	Prognostic
Snape[44]	NMET | MET | copeptin | KIM–1 | NGAL | sOsmo	The biomarkers NMET, copeptin, sOsmo, and NGAL showed good reliability and sensitive responses to an acute bout of heat stress. However, KIM–1 and MET displayed poor reliability and reproducibility. Therefore, the increase in levels of MET post-exertional heat stroke (EHS) cannot be used to establish its place as a reliable diagnostic marker.	Diagnostic
Wang[72]	ALB | PLT | WBC | NEUT | TC | LYM | ALP | BUN | Cr | AST| ALT | TIBL| DIBL | Lac | PT	The research identified three primary risk factors (creatinine, AST, and SBP) associated with in-hospital mortality, showing predictive ability with ROC curves of 0.763 in the training cohort and 0.739 in the validation cohort. This multicenter study pinpoints essential risk factors for in-hospital mortality in ICU patients with heat stroke, offering clinicians a personalized tool for assessment and management.	Prognostic
Dervisevic[24]	Troponin I | HS 70 kDa	Elevated water temperature, surpassing rat body temperature, triggered changes in cTnI and Hsp70 levels, suggesting potential hyperthermic myocardial damage. Notably, cTnI indicates cardiomyocyte damage, while Hsp70 provides insights into the mechanism of death.	Prognostic
Ward[66]	RBC | HB | Hct| PLT | PT (prothrombin time)|PTT | WBC | NEUT | BUN |Ca | Cl | Cr | AST| ALT | CK| ALP |LDH |Myo| ALB |TIBL|	Overall, disturbances in clinical laboratory analytes peak within 0–4 days post-injury, persisting beyond reference ranges for up to 16 days. These disturbances range from immediate and slightly depressed (RBCs; Day 1) to delayed and significantly elevated (CK; Day 3). Most disruptions last only a day (Cr, Ca, Cl, Myo, WBC, and Neu). Persistent disturbances in PTT, AST, ALT, and CK define the prolonged biochemical recovery period, emphasizing the protracted nature of these alterations.	Prognostic
Alzeer[45]	NO	NO production is enhanced in patients with heat stroke, and this increase is proportional to the severity of illness as demonstrated by a strong correlation with APACHE 2 scores.	Prognostic and Diagnostic
Dematte[46]	yGT | PLT | PT | PTT | D-dimer | LYM | urea | myoglobin| creatinine kinase | AST| ALT | PHOSPH| TIBL| Lac|	53% experienced moderate to severe renal insufficiency (elevated creatinine and ALP), 45% had DIC (decreased platelets), and 10% developed ARDS, with only mildly elevated ASP, TIBL, and LDH. 57% showed evidence of infection at admission, and the in-hospital mortality rate was 21%. While most survivors regained near-normal function, 33% had moderate to severe impairment at discharge. One year later, no improvement was noted, and an additional 28% had succumbed to the complications.	Prognostic
Song[63]	Procalcitonin	The findings showed that PCT and its dynamic trend are poor predictors of prognosis for patients with HS, while APACHE II and MODS scores had good predictive value. Additionally, there was no difference in PCT in patients with bacterial infections. However, PCT differed among those with CHS and EHS.	Prognostic
Li[47]	SAA–1 |H3| S100A8| vWF	Exosomal vWF, SAA, and S100A8 levels, enriched in severe HS patients, correlate with disease severity and organ dysfunction. These markers are useful for differentiating between mild and severe HS and aiding in prognosis assessment.	Prognostic
Tang[61]	WBC | NEU | LYM | NLR | APACHE 2 | HR | SBP | BUN | Creatinine | AST | ALT | ALB | troponin I | BNP | LDH | CK | CKMB	NLR was higher in patient who died from severe HS compare to survivors. NLR is a low-cost, rapid, and an easily accessible clinical indicator that is particularly suitable for use in the emergency room to help clinicians quickly determine prognosis of severe heatstroke patients. Combination of NLR with APACHEII is more effective in predicting severe heatstroke prognosis.	Prognostic

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Table 2. List of studies with statistically validated biomarkers

Authors	Type of heat	Biomarkers investigated	Outcome	ROC-AUC	Threshold	Sensitivity/ specificity	Utility
Hausfater[54]	Classic Heat	Serum cTnI	Mortality	0.68	0.30 ng/mL	0.66 / 0.66	Prognostic
Tong[55]	Exertional heat	Serum PCT (admission)	Mortality	0.705 (p = 0.019)	–	–	Prognostic
Fan[71]	Not distinguished	PLT (admission)	HS induced AKI	0.67 (p < 0.01)	< 63 × 109/L	0.79 / 0.83	Prognostic
		PLT (nadir count)		0.73 (p < 0.01)	< 30 × 109/L	0.9 / 0.81	
		WBC (admission)		0.66 (p < 0.01)	> 15 × 109/L	0.63 / 0.79	
		WBC (peak)		0.58 (p < 0.01)	> 20 × 109/L	0.57 / 0.72	
Audet[35]	Classic heat	cTnI (at Tc Max)	Presence of HS	–	–	1.0 / 0.92	Diagnostic and Prognostic
Bruchim[37]	Both	Serum Histones	Survival	0.72	< 13.7 ng/mL	0.6 / 0.88	Prognostic
Song[63]	Both	Serum PCT	Survival	0.599 (95% CI: 0.353,0.846; p = 0.370)	–	–	Prognostic
		APACHE 2		0.932 (95% CI: 0.861,1.000; p < 0.001)	–	–	
		MODS		0.857 (95% CI: 0.744,0.970; p < 0.001)	–	–	
Li[58]	Both	Histone H3	Mortality	0.9668	> 307 pg/100 µg	0.95 / 0.92	Prognostic
		ALT		0.9028	–	–	
		AST		0.7882	–	–	
Wang[72]	Both	Creatinine	Mortality	0.760 (95% Cl: 0.697,0.815)	–	0.84 / 0.62	Prognostic
		AST		0.660 (95% Cl: 0.594,0.723)	–	0.77 / 0.51	
		SBP		0.660 (95% Cl: 0.594,0.723)	–	0.38 / 0.92	
Tang[61]	Both	WBC	Mortality	0.5936 (95% CI: 0.4906,0.6965)	11.3 × 10^9/L	0.60 / 0.59	Prognostic
		NEU		0.6141 (95% CI: 0.5163,0.7119)	7 × 10^9/L	0.76 / 0.43	
		LYM		0.337 (95% CI: 0.2367,0.4374)	0.6 × 10^9/L	0.67 / 0.64	
		NLR		0.772 (95% CI: 0.6953,0.8488)	7.27	0.83 / 0.63	
		APACHE 2		0.75 (95% CI: 0.6762,0.8426)	18	0.81 / 0.64	
Dervišević[24]	Classic	HSP70	HS induced cardiomyocyte damage	–	> 31.36ng/mL	0.86 / 0.83	Prognostic
Li[47]	Classic	Plasma exosomal vWF	Mortality	0.7232 (95% CI: 0.5182,0.9282; P = 0.047)	655 pg/100 µg	0.88 / 0.76	Prognostic
		Plasma exosomal SAA–1		0.7649 (95% CI: 0.6070,0.9227; P = 0.019)	1,184 pg/100 µg	0.75 / 0.79	
		Plasma exosomal S100A8		0.7202 (95% CI: 0.5110,0.9295; P = 0.050)	1,063 pg/100 µg	0.75 / 0.79	

WBC: white blood cell, Tc: core temperature, APACHE 2: Acute Physiology and Chronic Health Evaluation 2, MODS: Multi-organ Dysfunction Score, ALT: alanine transaminase, AST: aspartate aminotransferase, NEU: neutrophil count, LYM: lymphocyte count, NLR: neutrophil-lymphocyte ratio, HSP: heat shock protein, vWF: von Willebrand factor, SAA-1: serum amyloid A-1, PCT: procalcitonin, SBP: systolic blood pressure, PLT: platelets, cTnI: cardiac troponin I.

Zhang et al. identified elevated IL-6 levels in HS patients, supporting its role in intensive care settings.[57] Similarly, Hadzi-Petrushev et al. observed increased plasma IL-6 levels following acute heat exposure in mice, further reinforcing its diagnostic relevance.[25]

Another proinflammatory cytokine with potential diagnostic value was TNF-α;[31,57] however, only 1 study was diagnostic and found an increase in TNF-a in response to heat.[25]

Apart from cytokine-mediated inflammation, systemic inflammatory markers such as CRP[57,65] and procalcitonin (PCT)[52,55,57,63,64] were examined in multiple studies. Dahan et al. revealed that the presence of a normal-to-low CRP in patients admitted to the hospital with hyperpyrexia and neurological deficits strongly indicates HS.[65] This contrasts with the observation made by Zhang et al., who reported significantly higher levels of both CRP and PCT in

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individuals with HS compared with their controls.[57] The majority of studies included in this review, reported an increase in PCT levels, suggesting its potential usefulness in predicting a less favorable prognosis in patients with heat exposure. However, an exception was noted in the recent study by Song et al., as their analysis indicates no significant correlation between PCT levels and the prognosis of HS.[63]

White blood cell (WBC) count and lymphocyte ratios were also explored as prognostic markers. One study found that WBC count predicted HS-induced acute kidney injury (AKI) (ROC-AUC: 0.66, sensitivity: 63%, specificity: 79%).[71] Additionally, the neutrophil-to-lymphocyte ratio (NLR) exhibited high sensitivity (83%) and specificity (63%) for predicting severe HS cases in emergency settings.[61]

Coagulation and endothelial injury biomarkers

Apart from cytokine-mediated systemic inflammation, severe HRI also frequently promotes excessive coagulation response and endothelial cell injury. It is not surprising that platelets were the frequently included biomarkers amongst this category, followed by other markers related to coagulation and endothelial injury. Two studies investigated markers linked to the raised incidence of disseminated intravascular coagulation (DIC) due to heat stress,[41,46] while others concentrated on endothelial injury, changes in platelet counts, and incidence of acute kidney injury (AKI).[71]

Cardiac biomarkers

Another focus of investigations centered on specific organ systems and markers clinically utilized to identify pathological changes within these organs. Interestingly, troponin I emerged as the most frequently evaluated cardiac biomarker, with 6 articles assessing its alterations in response to heat exposure.[24,33,35,54,61,67] In all studies, elevated troponin levels were noted in response to heat exposure, suggesting its diagnostic potential for organ damage, as well as potentially predicting severe cases of HRI.[35,54] Dervišević's recent animal study demonstrated a positive correlation between hyperthermic myocardial damage and the values of troponin I and HSP70, with a PPV 96% and NPV 55%.[24] Similar to the prospective study by Hausfater at el. where survival rates were notably lower in patients with elevated troponin with a sensitivity and specificity of 66%.[54] These findings further highlight the potential of troponin as a prognostic biomarker for HRI.

Further studies assessed point-of-care cardiac troponin testing for HRI diagnosis, including an animal model study by Audet et al.[35] and a clinical study by Whiticar,[67] which observed increased troponin levels 24 hours post-admission in HS patients. These findings suggest that troponin may serve as a valuable biomarker for both diagnosis and severity assessment of HRI.

Renal, hepatic, and interstitial biomarkers

Renal biomarkers were extensively examined, with 18 studies investigating kidney injury markers in the context of HRI.[26,28,43,44,60,71,72] These markers ranged from common ones such as creatinine (Cr) and BUN to less common biomarkers for acute and tubular kidney injury, including L-FABP (Liver-type Fatty Acid-Binding Protein), NAG (N-Acetyl-beta-D-Glucosaminidase), NGAL (Neutrophil Gelatinase-Associated Lipocalin), and KIM-1 (Kidney Injury Molecule-1).[60] Furthermore, markers of oxidative stress in the kidneys, such as TBARS (Thiobarbituric Acid Reactive Substances), TIMP-2 (Tissue Regeneration Inhibitor of Metalloproteinases-2), and TRAX (Urinary Truncated AlphaX-I),[43] were also subjects of investigation. However, only NMET, MET, copeptin, KIM-1, NGAL, and osmolarity demonstrated alterations consistent with prior heat stress exposure, though statistical validation of their accuracy for HRI diagnosis remains lacking.[44] Wang et al. assessed the hospital mortality in patients with HS admitted to intensive care units (ICUs) and found a significant association with three risk factors: Cr, aspartate aminotransferase (AST), and systolic blood pressure (SBP).[72] Additionally, AST predicted liver failure with a sensitivity of 77% and specificity of 51%, while SBP acted as an independent risk factor for overall prognosis in heat-exposed patients (sensitivity 38% and specificity 92%).

Other liver markers assessed for the diagnosis of heat exposure were 15-keto-13,14-dihydro-PGF2α, 8-iso-PGF2α, and malondialdehyde; however, their reliability as indicators of heat exposure was not established.[25]

Interstitial damage was evaluated through 7 markers, including I-FABP, LBP, CLDN-3, FGF-21, FFA, FBP, and DAO, though none demonstrated strong diagnostic or prognostic potential. Additionally, only 1 study assessed biomarkers in the CNS namely Neuron-Specific Enolase (NSE) and Myelin Basic Protein (MBP) for the prognosis after heat stress.[42] Interestingly, While IL-6 and IL-8 in cerebrospinal fluid (CSF) were linked to survival rates, NSE and MBP did not correlate with outcomes.

Proteins and molecular biomarkers

Circulating heat-inducible heat-shock proteins (HSPs) have also emerged as a promising point in studies investigating responses to heat stress, frequently examined as potential prognostic or dual prognostic and diagnostic biomarkers indicative of susceptibility to HRI. Six studies explored the potential of HSP as biomarkers of heat exposure, specifically HSP-60, HSP-70, HSP-71, HSP-72a, and HSP-90.[24,28,30,34,36,53] However, none demonstrated their utility in diagnosing heat-related conditions and only 1 study included human participants. Wu et al. assessed the increase in HSP antibodies in young males during training.[53] Overall, elevation in HSP expression was predominantly associated with tissue damage.[30] Increased levels of HSPs were identified in various organs, including the liver, kidney, small intestines,[28] and myocardial tissue.[34] These findings provided evidence that the upregulation of HSPs may be an important marker for HS prognosis. However, as noted earlier, only the study by Dervišević et al. assessed the accuracy of HSP70 for HRI.[24]

Additionally, epigenetic molecules such as histones and RNA[37,39,40,47,58] were assessed as potential diagnostic or prognostic biomarkers for heat exposure. lnc-RNA and miRNA both showed diagnostic value as a marker for HS,[39] and miRNA exhibited additional potential of detecting organ injury after heat exposure.[40] Permenter et al. propose miRNA not only as a potential biomarker for organ injuries but also as pharmacological target for preventing heat injury resulting from heat stress.[40] In contrast, both Bruchim et al. and Li et al. revealed that elevated histone 3 (H3) levels correlated with increased mortality in HS.[37,58] Li showed that at a cut-off value of 307 pg/100 μg, H3 was found to be sensitive (95%) and specific (91.67%) in predicting mortality in HS patients.[58]

Moreover, proteomics has also been used to identify potential proteins for HRI, as investigated in the study by Liu et al. and Li et al.[32,47] Liu et al. showed differential expressions of 14 different proteins due to HS, while down-regulation of intestinal FBP emerged as a potential prognostic marker for gut dysfunction during heat stroke.[32] Li et al. employed a proteomic investigation and revealed an enrichment of exosomal vWF, SAA, and S100A8 in patients with HS, particularly in severe cases. The concentration of these proteins exhibited a positive correlation with disease severity and organ dysfunction. This discovery supports the differentiation

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between mild and severe HS and contributes to determining the prognosis of individual cases. vWF exhibited a sensitivity of 88% and specificity of 76%. For SAA-1, the sensitivity and specificity were 75% and 79%, respectively, and for S100AB, the values were 75% and 79%.[47]

Discussion

With an increase in excessive heat exposure on humans, a conclusive diagnostic test that could adequately diagnose HRI at initial presentation is urgently needed. Implementing the use of heat biomarkers as a simple diagnostic test could help quickly identify patients exposed to threateningly high temperatures. This could ultimately help provide adequate management that is not only simple but also highly efficient, thereby decreasing morbidity and mortality in these often already vulnerable populations.

We identified 45 articles with a total of 113 markers that were differentially expressed in subjects exposed to heat stress. Although 30 of these were human studies, the diverse study designs with an overall small sample size, inappropriate clinical and statistical validation, different types of heat exposure, and a variety of biomarkers prevent direct comparisons. Furthermore, the lack of universal gold standards and cutoff values hinders conclusive statements, resulting in inconsistencies when interpreting test results and raising uncertainties about their clinical significance.

Only 5 studies focused on biomarkers primarily for diagnosing HRI, and none of these studies conducted analytic validation. Snape et al. investigated the reliability of the biomarkers involved using Bland-Altman plots to evaluate dependability in post-Exercise Heat Stress Test (EHST) concentration. However, this method proved inadequate for assessing new biomarkers as it lacked comprehensive clinical validation. While the results suggested good reliability for NMET, copeptin, and NGAL, the analysis was constrained to a single time point and included only patients after EHST. This limitation is a significant weakness when it comes to biomarker research, particularly for new markers, as it does not provide a comprehensive evaluation over multiple time points or a diverse patient population.

Troponin has been one of the most investigated biomarkers, but only 1 study specifically assessed its diagnostic value, while the remaining used troponin for HRI prognosis. Whiticar's case report, included only a single participant, and observed elevated troponin levels, with a peak 2 days after admission following EHS. However, most reviewed studies assessed troponin to identify myocardial injury due to heat, using troponin as a prognostic marker which appears more intuitive. Audet et al. suggested using troponin for both diagnosis and prognosis of HS. Their study reported elevated levels in all groups exposed to heat compared to controls. Conversely, Dervišević's study emphasized that troponin lacks specificity for heat and recommended considering an additional marker, such as HSP 70 in HS assessment. Moreover, a correlation suggests that patients with known cardiac disease are often more susceptible to HRI, adding complexity to the biomarker's applicability.

Despite the lack of analytic validation, microRNA markers show the high potential among biomarkers for diagnosis and prognosis of HRI. This is attributed to the stability of microRNAs in various bodily fluids, including blood, and their crucial roles in gene expression regulation. Their stability in extreme conditions and specific expression patterns in response to heat stress make them promising candidates for reliable HS biomarkers.[73] The experimental study by Chen et al. examined the expression of lncRNA and miRNA in human cells, proving that sequencing is a powerful method for identifying novel RNAs with potential as diagnostic biomarkers for HS.

A total of 27 reviewed articles identified potential biomarkers for prognostic assessment in patients with HRI. Among the examined biomarkers, platelets, troponin, IL-6, ALT, CRP, and procalcitonin were frequently investigated, showing primary prognostic significance. However, these markers are widely employed for various other conditions, leading to potential variability in their specificity and sensitivity as heat biomarkers in clinical settings. Therefore, the interpretation of these markers in the context of HRI requires careful consideration of their limitations and potential confounding factors. IL-6 cytokines, one of the most studied biomarkers,[25,29,31,42,49,57] remains non-specific for HRI. Similarly, lack of specificity was noticed for markers for coagulation and endothelial injury. Previous literature observed that HS was associated with DIC, resulting in progressive decline in PLT and fibrinogen (Fib), elevated D-dimer, and prolonged PT and APTT.[74,75] However, DIC has been recognized as a prognostic indicator in other conditions, including sepsis[76] and trauma,[77] which raises questions about its reliability as a biomarker for heat exposure. Additionally, while platelets have been explored in numerous studies as a potential biomarker for heat exposure, their widespread clinical use introduces a significant challenge as a definitive marker unique to HRI.[78]

Several studies have targeted specific organs and organ systems known for their sensitivity to heat stress, investigating biomarkers such as ALT and or CK to identify these effects.[79,80] However, the validation for heat specificity and accuracy is still in progress, and the use of these markers as diagnostic tools for HRI remains questionable. It is important to recognize that these measurements need to be viewed with caution, as elevations may indicate other pathologies not necessarily a direct consequence of heat related organ injury itself. This is particularly important given that many HRI patients belong to a vulnerable population with comorbidities affecting these organ systems.[81] We also found a significant focus on kidney function in HS, aligning with prior research highlighting the effect of heat exposure on kidney functions.[82] Frequently observed among critically ill HS patients are potential complications such as AKI, ALI, and shock. Wang et al. focused on a single-factor analysis identifying Cr, AST, and SBP as practical indicators for severe heat stroke, introducing a tool for clinical evaluation.[72] There is also a known correlation between inflammation and heat stress.[83] PCT showed potential relevance in exertional HS prognosis, while CRP lacked statistical validation and showed conflicting results. However, Dahan et al.'s study showed promising findings, suggesting potential support for early diagnosis, which can be challenging to differentiate from infections.[65] Finally, PCT was examined across 4 distinct investigations for predicting HRI severity, but only 2 studies statistically validated their findings and the more recent study by Song et al. concluded that PCT was not a reliable biomarker for HS prognosis.[63]

Markers like HSP and epigenetic biomarkers, while promising, often require expensive assessments[28,30,34,39,40] and use impractical tissue samples, making them less than ideal for clinical settings, particularly in the ER.[84] H3 demonstrated promising sensitivity and specificity in predicting mortality risk, suggesting its potential as a clinical biomarker for HRI. This observation aligns with the recent review by Iba et al., which emphasized the use of H3, along with other inflammatory markers, as a promising indicator for the severity of HS[75] establishing histones as prognostic markers. Ultimately, the heat shock response triggers an increase in protein synthesis and regulation, highlighting the diverse roles of HSPs in the body.[85]

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Identifying reliable biomarkers for heat stroke is crucial for enhancing clinical decision-making.[86] An ideal biomarker would be easily accessible, cost-effective, and rapidly measurable, allowing for real-time decision-making in emergency settings. It should be detectable in readily available biological fluids such as blood, urine, or saliva, eliminating the need for invasive sampling. Additionally, it must exhibit high sensitivity and specificity to differentiate heat stroke from other hyperthermic conditions and predict severity with accuracy.[87] A clinically useful biomarker should provide actionable information, guiding interventions like fluid resuscitation, antibiotic administration, or critical care admission decisions.[88] Current candidates, including IL-6, troponin, and procalcitonin, show promise but lack specificity for heat related conditions. These and other potential biomarkers need to be validated using clear diagnostic and prognostic thresholds, through large-scale, multicenter clinical trials in emergency settings.

Limitations

The primary limitation of this scoping review is the heterogeneity of the research including variable study designs, participant characteristics, and data analyses. The variation extended to the inclusion of both human patients and animal studies, rendering direct comparisons challenging. Moreover, limited analytic and clinical validation procedures conducted across the selected papers, affecting the comprehensive assessment of marker accuracy and reliability. Finally, scoping reviews generally lack quality assessment of the papers while potentially introducing bias and affecting the overall reliability of the review's findings.

Conclusion

In summary, our findings underscore the limitation of the current body of knowledge on the available biomarkers for the diagnosis and prognosis of HRI. The current literature lacks robust study designs, including limited number of large experimental investigations, trials, or prospective cohort studies, required for comprehensive biomarker evaluation.

Data availability. The author declares that data supporting the findings of this study are available within the article.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/dmp.2025.10069.

Author contribution. **JR** designed the research, critically reviewed, and revised the manuscript for important intellectual content. **JP** conducted screening, data collection, and data analysis. She drafted the initial manuscript and edited it. **MBM** also conducted screening, data collection, and data analysis, and drafted the manuscript. **WF** critically reviewed and revised the manuscript and participated in the screening process. **BR** created the tables and figures and provided support for the analysis. Finally, **CJ** conducted the literature search strategies.

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References

1. **Marchetti E**, **Capone P**, **Freda D.** Climate change impact on microclimate of work environment related to occupational health and productivity. *Annali dell'Istituto superiore di sanita.* 2016;**52**(3):338–342.
2. **Malik SM**, **Awan H**, **Khan N.** Mapping vulnerability to climate change and its repercussions on human health in Pakistan. *Glob Health.* 2012;**8**(1):31.
3. **Brennan M**, **O'Shea PM**, **Mulkerrin EC**. Preventative strategies and interventions to improve outcomes during heatwaves. *Age Ageing.* 2020;**49**(5):729–732.
4. "**WHO**". Heatwaves. Published 2018. Accessed January 22, 2024. https://www.who.int/health-topics/heatwaves#tab=tab_1.
5. **Gosling SN**, **McGregor GR**, **Páldy A.** Climate change and heat-related mortality in six cities part 1: model construction and validation. *Int J Biometeorol.* 2007;**51**(6):525–540.
6. **Liu J**, **Varghese BM**, **Hansen A**, et al. Heat exposure and cardiovascular health outcomes: a systematic review and meta-analysis. *Lancet Planet Health.* 2022;**6**(6):e484–e495.
7. **Sorensen C**, **Hess J.** Treatment and prevention of heat-related illness. *New England J Med.* 2022;**387**(15):1404–1413.
8. **Schlader ZJ**, **Davis MS**, **Bouchama A.** Biomarkers of heatstroke-induced organ injury and repair. *Exp Physiol.* 2022;**107**(10):1159–1171.
9. **Saenz S**, **Prine B**, **Smith K**, **Smith M.** Exertional heat illness: a clinical overview. *Consultant360.* 2019.
10. **Leiva DF**, **Church B.** Heat Illness. In: *StatPearls*. Treasure Island (FL) ineligible companies. Disclosure: Ben Church declares no relevant financial relationships with ineligible companies.: StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.
11. **Heled Y**, **Rav-Acha M**, **Shani Y**, et al. The "golden hour" for heatstroke treatment. *Mil Med.* 2004;**169**(3):184–186.
12. **Wang H**, **Chen W**, **Li S**, et al. Advances in pre-hospital recognition and cooling treatment of exertional heat stroke. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* 2018;**30**(10):1006–1010.
13. **Goodsaid F**, **Frueh F.** Biomarker qualification pilot process at the US Food and Drug Administration. *AAPS J.* 2007;**9**(1):E105–108.
14. **Hayashi K**, **Masuda S**, **Kimura H.** Impact of biomarker usage on oncology drug development. *J Clin Pharm Ther.* 2013;**38**(1):62–67.
15. **Parker JL**, **Lushina N**, **Bal PS**, et al. Impact of biomarkers on clinical trial risk in breast cancer. *Breast Cancer Res Treat.* 2012;**136**(1):179–185.
16. **Falconi A**, **Lopes G**, **Parker JL**. Biomarkers and receptor targeted therapies reduce clinical trial risk in non-small-cell lung cancer. *J Thorac Oncol.* 2014;**9**(2):163–169.
17. **Rubinger DA**, **Hollmann SS**, **Serdetchnaia V**, et al. Biomarker use is associated with reduced clinical trial failure risk in metastatic melanoma. *Biomark Med.* 2015;**9**(1):13–23.
18. **Parker JL**, **Kuzulugil SS**, **Pereverzev K**, et al. Does biomarker use in oncology improve clinical trial failure risk? A large-scale analysis. *Cancer Med.* 2021;**10**(6):1955–1963.
19. **Byrnes SA**, **Weigl BH**. Selecting analytical biomarkers for diagnostic applications: a first principles approach. *Expert Rev Mol Diagn.* 2018;**18**(1):19–26.
20. **Arksey H**, **O'Malley L.** Scoping studies: towards a methodological framework. *Int J Socl Res Methodol.* 2005;**8**(1):19–32.
21. **Peters MD**, **Godfrey C**, **McInerney P**, et al. Scoping reviews. *Joanna Briggs Institute Reviewer's Manual.* 2017;**2015**:1–24.
22. **Tricco AC**, **Lillie E**, **Zarin W**, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med.* 2018;**169**(7):467–473.
23. **Jedlicka C.** Biomarkers of heat stroke and heat exhaustion: a scoping review. *osfio/zf7q6. Published October* **20**, 2022.
24. **Dervišević E**, **Hasić S**, **Katica M**, et al. Heat-related biomarkers: focus on the correlation of troponin I and 70 kDa heat shock protein. *Heliyon.* 2023;**9**(4):e14565.
25. **Hadzi-Petrushev N**, **Mladenov K**, **Sopi R**, et al. Enhanced lipid peroxidation and inflammation during heat exposure in rats of different ages: role of alpha-tocopherol. *J Therm Biol.* 2013;**38**(8):474–479.
26. **McKenna Z**, **Houck J**, **Ducharme J**, et al. The effect of prolonged interval and continuous exercise in the heat on circulatory markers of intestinal barrier integrity. *Eur J App Physiol.* 2022.
27. **King MA**, **Leon LR**, **Mustico DL**, et al. Biomarkers of multiorgan injury in a preclinical model of exertional heat stroke. *J Appl Physiol (*1985*).* 2015;**118**(10):1207–1220.
28. **Flanagan SW**, **Ryan AJ**, **Gisolfi CV**, et al. Tissue-specific HSP70 response in animals undergoing heat stress. *Am J Physiol.* 1995;**268**(1 Pt 2):R28–32.

29. **Bouchama A**, **Roberts G**, **Al Mohanna F**, et al. Inflammatory, hemostatic, and clinical changes in a baboon experimental model for heatstroke. *J App Physiol (Bethesda, Md: 1985).* 2005;**98**(2):697–705.
30. **Dehbi M**, **Baturcam E**, **Eldali A**, et al. Hsp-72, a candidate prognostic indicator of heatstroke. *Cell Stress Chaperones.* 2010;**15**(5):593–603.
31. **Liu Z**, **Sun X**, **Tang J**, et al. Intestinal inflammation and tissue injury in response to heat stress and cooling treatment in mice. *Mol Med Rep.* 2011; **4**(3):437–443.
32. **Liu Z**, **Liu JH**, **Liu Y**, et al. Proteomic analysis and identification of intestinal FBP as a predictor of gut dysfunction during heatstroke in mice. *J Surg Res.* 2012;**173**(2):332–340.
33. **Quinn CM**, **Duran RM**, **Audet GN**, et al. Cardiovascular and thermoregulatory biomarkers of heat stroke severity in a conscious rat model. *J App Physiol (Bethesda, Md: 1985).* 2014;**117**(9):971–978.
34. **Cheng YF**, **Sun JR**, **Chen HB**, et al. Association of Hsp60 expression with damage to rat myocardial cells exposed to heat stress in vivo and in vitro. *Genet Mol Res.* 2014;**13**(4):9371–9381.
35. **Audet GN**, **Quinn CM**, **Leon LR**. Point-of-care cardiac troponin test accurately predicts heat stroke severity in rats. *Am J Physiol Regul Integr Comp Physiol.* 2015;**309**(10):R1264–1272.
36. **Bruchim Y**, **Segev G**, **Kelmer E**, et al. Hospitalized dogs recovery from naturally occurring heatstroke; does serum heat shock protein 72 can provide prognostic biomarker? *Cell Stress Chaperones.* 2016;**21**(1):123–130.
37. **Bruchim Y**, **Ginsburg I**, **Segev G**, et al. Serum histones as biomarkers of the severity of heatstroke in dogs. *Cell Stress Chaperones.* 2017;**22**(6): 903–910.
38. **Stacey MJ**, **Delves SK**, **Britland SE**, et al. Copeptin reflects physiological strain during thermal stress. *Eur J Appl Physiol.* 2018;**118**(1):75–84.
39. **Chen H-S**, **Tong H-S**, **Zhao Y**, et al. Differential expression pattern of exosome long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) in vascular endothelial cells under heat stroke. *Med Sci Monit.* 2018;**24**(dxw, 9609063):7965–7974.
40. **Permenter MG**, **McDyre BC**, **Ippolito DL**, **Stallings JD**. Alterations in tissue microRNA after heat stress in the conscious rat: potential biomarkers of organ-specific injury. *BMC Genom.* 2019;**20**(1):141.
41. **Proctor EA**, **Dineen SM**, **Van Nostrand SC**, et al. Coagulopathy signature precedes and predicts severity of end-organ heat stroke pathology in a mouse model. *J Thromb Haemost.* 2020;**18**(8):1900–1910.
42. **Ikeda T**, **Tani N**, **Watanabe M**, et al. Evaluation of cytokines and structural proteins to analyze the pathology of febrile central nervous system disease. *Legal Med.* 2021;**51**(100889186):101864.
43. **Hess HW**, **Stooks JJ**, **Baker TB**, et al. Kidney injury risk during prolonged exposure to current and projected wet bulb temperatures occurring during extreme heat events in healthy young men. *J App Physiol (Bethesda, Md: 1985).* 2022;**133**(1):27–40.
44. **Snape D**, **Wainwright B**, **Woods DR**, et al. Reliability of biomarkers of physiological stress at rest and post-exertional heat stress. *Int J Sports Med.* **2022**(8008349, grk).
45. **Alzeer AH**, **Al-Arifi A**, **Warsy AS**, et al. Nitric oxide production is enhanced in patients with heat stroke. *Intens Care Med.* 1999;**25**(1):58–62.
46. **Dematte JE**, **O'Mara K**, **Buescher J**, et al. Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med.* 1998;**129**(3):173–181.
47. **Li Y**, **Li H**, **Ma W**, et al. Proteomic profiling of serum exosomes reveals acute phase response and promotion of inflammatory and platelet activation pathways in patients with heat stroke. *PeerJ.* 2023;**11**:e16590.
48. **el-Kassimi FA**, **Al-Mashhadani S**, **Abdullah AK**, et al. Adult respiratory distress syndrome and disseminated intravascular coagulation complicating heat stroke. *Chest.* 1986;**90**(4):571–574.
49. **Bouchama A**, **al-Sedairy S**, **Siddiqui S**, et al. Elevated pyrogenic cytokines in heatstroke. *Chest.* 1993;**104**(5):1498–1502.
50. **Shieh SD**, **Shiang JC**, **Lin YF**, et al. Circulating angiotensin-converting enzyme, von Willebrand factor antigen and thrombomodulin in exertional heat stroke. *Clin Sci (London, England: 1979).* 1995;**89**(3):261–265.
51. **Bouchama A**, **Hammami MM**, **Haq A**, et al. Evidence for endothelial cell activation/injury in heatstroke. *Crit Care Med.* 1996;**24**(7):1173–1178.
52. **Nylen ES**, **Al Arifi A**, **Becker KL**, et al. Effect of classic heatstroke on serum procalcitonin. *Crit Care Med.* 1997;**25**(8):1362–1365.
53. **Wu T**, **Chen S**, **Xiao C**, et al. Presence of antibody against the inducible Hsp71 in patients with acute heat-induced illness. *Cell Stress Chaperones.* 2001;**6**(2):113–120.
54. **Hausfater P**, **Doumenc B**, **Chopin S**, et al. Elevation of cardiac troponin I during non-exertional heat-related illnesses in the context of a heatwave. *(London, England).Crit Care* 2010;**14**(3):R99.
55. **Tong H-S**, **Liu Y-S**, **Wen Q**, et al. Serum procalcitonin predicting mortality in exertional heatstroke. *Emerg Med J.* 2012;**29**(2):113–117.
56. **Fan H**, **Zhao Y**, **Zhu J-H**, et al. Thrombocytopenia as a predictor of severe acute kidney injury in patients with heat stroke. *Renal Failure.* 2015;**37**(5): 877–881.
57. **Zhang L**, **Fan X**, **Zhong Z**, et al. Association of plasma diamine oxidase and intestinal fatty acid-binding protein with severity of disease in patient with heat stroke. *Am J Emerg Med.* 2015;**33**(7):867–871.
58. **Li Y**, **Liu Z**, **Shi X**, et al. Prognostic value of plasma exosomal levels of histone H3 protein in patients with heat stroke. *Exp Ther Med.* 2021;**22**(3): 922.
59. **Nakamura Y**, **Sueyoshi K**, **Miyoshi Y**, et al. Complement activation in patients with heat-related illnesses: soluble CD59 is a novel biomarker indicating severity of heat-related illnesses. *Crit Care Explor.* 2022;**4**(4): e0678.
60. **Goto H**, **Shoda S**, **Nakashima H**, et al. Early biomarkers for kidney injury in heat-related illness patients: a prospective observational study at Japanese Self-Defense Force Fuji Hospital. *Nephrol Dial Transplant.* 2022(n7j, 8706402).
61. **Tang Y**, **Gu T**, **Wei D**, et al. Clinical relevance of neutrophil/lymphocyte ratio combined with APACHEII for prognosis of severe heatstroke. *Heliyon.* 2023;**9**(10):e20346.
62. **Wang L**, **Fu X**, **He M**, et al. Risk factor analysis and nomogram for predicting in-hospital mortality in ICU patients with heat stroke: a national multicenter study. *J Multidiscip Healthc.* 2023;**16**:3189–3201.
63. **Song X**, **Liu X**, **Wang H**, et al. Diagnostic value of procalcitonin in patients with heat stroke. *Arch Microbiol Immunology.* 2020;**04**(01).
64. **Hausfater P**, **Hurtado M**, **Pease S**, et al. Is procalcitonin a marker of critical illness in heatstroke? *Intens Care Med.* 2008;**34**(8):1377–1383.
65. **Dahan E**, **Dichtwald S**, **Amar E**, et a. Low plasma C-reactive protein level as an early diagnostic tool for heatstroke vs central nervous system-associated infection in the ED. *Am J Emerg Med.* 2013;**31**(8):1176–1180.
66. **Ward MD**, **King MA**, **Gabrial C**, et al. Biochemical recovery from exertional heat stroke follows a 16-day time course. *PLoS One.* 2020;**15**(3): e0229616.
67. **Whiticar R**, **Laba D**, **Smith S.** Exertional heat stroke in a young man with a documented rise in troponin I. *Emerg Med J.* 2008;**25**(5):283–284.
68. **Bouchama A**, **Bridey F**, **Hammami MM**, et al. Activation of coagulation and fibrinolysis in heatstroke. *Thromb Haemost.* 1996;**76**(6):909–915.
69. **Chen H-S**, **Tong H-S**, **Zhao Y**, et al. Differential expression pattern of exosome long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) in vascular endothelial cells under heat stroke. *Med Sci Monit.* 2018;**24**: 7965–7974.
70. **Bouchama A**, **Bridey F**, **Hammami MM**, et al. Activation of coagulation and fibrinolysis in heatstroke. *Thromb Haemost.* 1996;**76**(6):909–915.
71. **Fan H**, **Zhao Y**, **Zhu J-H**, et al. Thrombocytopenia as a predictor of severe acute kidney injury in patients with heat stroke. *Renal Fail.* 2015;**37**(5): 877–881.
72. **Wang L**, **Fu X**, **He M**, et al. Risk factor analysis and nomogram for predicting in-hospital mortality in ICU patients with heat stroke: a national multicenter study. *J Multidiscip Healthc.* 2023;**16**:3189–3201.
73. **Mitchell PS**, **Parkin RK**, **Kroh EM**, et al. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci USA.* 2008; **105**(30):10513–10518.
74. **Hemmelgarn C**, **Gannon K.** Heatstroke: thermoregulation, pathophysiology, and predisposing factors. *Compend Contin Educ Vet.* 2013;**35**(7):E4.
75. **Iba T**, **Connors JM**, **Levi M**, et al. Heatstroke-induced coagulopathy: biomarkers, mechanistic insights, and patient management. *EClinicalMedicine.* 2022;**44**:101276.
76. **Gando S**, **Saitoh D**, **Ogura H**, et al. A multicenter, prospective validation study of the Japanese Association for Acute Medicine disseminated

https://doi.org/10.1017/dmp.2025.10069 Published online by Cambridge University Press

intravascular coagulation scoring system in patients with severe sepsis. *Crit Care.* 2013;**17**(3):R111.
77. **Sawamura A**, **Hayakawa M**, **Gando S**, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. *Thromb Res.* 2009;**124**(5):608–613.
78. **Chen Y**, **Zhong H**, **Zhao Y**, et al. Role of platelet biomarkers in inflammatory response. *Biomark Res.* 2020;**8**:28.
79. **Thongprayoon C**, **Qureshi F**, **Petnak T**, et al. Impact of acute kidney injury on outcomes of hospitalizations for heat stroke in the united states. *Diseases.* 2020;**8**(3).
80. **Roberts GT**, **Ghebeh H**, **Chishti MA**, et al. Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. *Arterioscler Thromb Vasc Biol.* 2008;**28**(6):1130–1136.
81. **Kenny GP**, **Yardley J**, **Brown C**, et al. Heat stress in older individuals and patients with common chronic diseases. *Cmaj.* 2010;**182**(10):1053–1060.
82. **Chapman CL**, **Johnson BD**, **Parker MD**, et al. Kidney physiology and pathophysiology during heat stress and the modification by exercise, dehydration, heat acclimation and aging. *Temperature (Austin).* 2021;**8**(2):108–159.
83. **Leon LR**, **Helwig BG**. Heat stroke: role of the systemic inflammatory response. *J App Physiol.* 2010;**109**(6):1980–1988.
84. **Mayeux R.** Biomarkers: potential uses and limitations. *NeuroRx.* 2004;**1**(2):182–188.
85. **Hu C**, **Yang J**, **Qi Z**, et al. Heat shock proteins: biological functions, pathological roles, and therapeutic opportunities. *MedComm.* 2022;**3**(3):e161.
86. **Schlader ZJ**, **Davis MS**, **Bouchama A.** Biomarkers of heatstroke-induced organ injury and repair. *Exp Physiol.* 2022;**107**(10):1159–1171.
87. **Parikh NI**, **Vasan RS**. Assessing the clinical utility of biomarkers in medicine. *Biomark Med.* 2007;**1**(3):419–436.
88. **Strimbu K**, **Tavel JA**. What are biomarkers? *Curr Opin HIV AIDS.* 2010;**5**(6):463–466.

https://doi.org/10.1017/dmp.2025.10069 Published online by Cambridge University Press