# Ferroptosis in heatstroke: Mechanisms and therapeutic perspectives (Review)

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Received December 19, 2025; Accepted August 10, 2026

DOI: 10.3892/ijmm.2026.5984

**Abstract.** Heatstroke is a life-threatening condition characterized by hyperthermia and systemic inflammatory response, often leading to multi-organ dysfunction and high mortality. Despite advances in understanding its pathophysiology, effective targeted therapies remain limited. Recent studies have highlighted ferroptosis, an iron-dependent, lipid peroxidation-driven form of regulated cell death, as a critical mechanism in heatstroke-induced organ injury. This review synthesizes current evidence on the role of ferroptosis in heatstroke, including key signaling pathways such as Hippo-Yes-associated protein-acyl-CoA synthetase long-chain family member 4, dysregulated heat shock response, and antioxidant defense failure. The present study also explored potential ferroptosis-related biomarkers and therapeutic strategies targeting this cell death pathway. Understanding ferroptosis in heatstroke not only unveils novel pathophysiological insights but also opens avenues for early diagnosis and targeted intervention.

**Contents**



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*Key words:* ferroptosis, heatstroke, mechanism, therapeutic perspectives

## 1. Introduction

Heatstroke stands as one of the most severe medical emergencies within the spectrum of heat-related illnesses, characterized by a core body temperature >40˚C and concomitant central nervous system dysfunction (1-3). Its epidemiological burden is substantial and escalating, fueled notably by the increasing frequency and intensity of heatwaves due to global climate change. Populations at heightened risk include outdoor laborers, athletes, military personnel, the elderly and individuals with chronic comorbidities (4-6). Despite advances in public health awareness and critical care, heatstroke continues to portend high morbidity and mortality rates, primarily due to the progression to multiple organ dysfunction syndrome (MODS). The socio-economic impact, including healthcare costs and loss of productivity, underscores the urgent necessity for continued and deepened research into its pathophysiology (7,8).

The cornerstone of current clinical management for heatstroke remains rapid body cooling, complemented by organ-supportive therapies (9). While prompt cooling is undeniably life-saving, it often proves insufficient to halt the insidious cascade of systemic inflammatory response, coagulopathy and subsequent organ failure that can unfold hours after the initial hyperthermic insult (1,10). This clinical dilemma highlights a critical gap in our therapeutic strategies: The lack of targeted, mechanism-based interventions designed to disrupt the specific molecular pathways driving tissue injury once the hyperthermic trigger has been initiated (11,12). The limitations of supportive care alone emphasize the imperative to move beyond symptomatic management and toward precision medicine strategies.

The pathophysiological understanding of heatstroke has evolved from a simplistic view of direct heat cytotoxicity to a recognition of a complex network involving a systemic inflammatory 'cytokine storm', disseminated intravascular coagulation (DIC), endothelial injury, and programmed cell death (13-15). Historically, apoptosis and necrosis were considered the principal modes of cell demise (16). However, these classical pathways cannot fully explain the fulminant and widespread nature of organ damage, particularly in exertional heatstroke (17-20). This conceptual gap has prompted

the exploration of alternative regulated cell death modalities. Among these, ferroptosis, an iron-dependent form of cell death driven by uncontrolled lipid peroxidation, has recently surged to the forefront (21). Distinct from apoptosis, necrosis and pyroptosis in its morphological and biochemical hallmarks (22), ferroptosis is characterized by glutathione (GSH) depletion, inactivation of the lipid repair enzyme GSH peroxidase 4 (GPX4), and the iron-catalyzed peroxidation of polyunsaturated fatty acids in cellular membranes (23,24).

It is within this context that the present review was situated. The present review aimed to systematically synthesize and critically evaluate the burgeoning evidence implicating ferroptosis in the pathogenesis and progression of heatstroke and delve into the key molecular regulators and signaling networks, such as the Hippo-Yes-associated protein (YAP)-acyl-CoA synthetase long-chain family member 4 (ACSL4) axis and the dysregulated heat shock response, that link heat stress to ferroptosis execution. The present review meticulously detailed the evidence for ferroptosis-driven injury across major organ systems, including skeletal muscle, heart, brain, liver and kidneys and explored the translational potential of this knowledge by discussing emerging ferroptosis-related biomarkers and evaluating the promise of ferroptosis inhibitors as novel therapeutic agents. By providing a comprehensive overview of this rapidly advancing field, the present review sought to not only consolidate our current understanding but also to illuminate a path forward for future research and clinical innovation, ultimately aiming to improve outcomes for patients afflicted by this devastating condition. Compared with other regulated cell death modalities, such as apoptosis, pyroptosis, necroptosis, and PANoptosis, ferroptosis is uniquely positioned to explain the clinical features of heatstroke for four reasons: i) Iron dependence: The massive rhabdomyolysis and hemolysis in exertional heatstroke release torrents of free iron and heme, providing the obligatory substrate for ferroptosis but not for apoptosis or pyroptosis; ii) lipid peroxidation as executioner: The severe oxidative stress burst in heatstroke directly generates polyunsaturated fatty acid (PUFA)-phospholipid peroxidation, the hallmark of ferroptosis, whereas pyroptosis relies on gasdermin pore formation and necroptosis on mixed lineage kinase domain-like protein (MLKL)-mediated membrane rupture; iii) Mitochondrial morphology: Ferroptosis displays shrunken mitochondria with increased membrane density, which aligns with the mitochondrial dysfunction observed in heatstroke, whereas apoptosis features mitochondrial fragmentation and cristae expansion; and iv) Therapeutic reversibility: Ferroptosis can be rescued by iron chelator deferoxamine (DFO) and lipophilic antioxidants, whereas PANoptosis and necroptosis inhibitors have shown limited efficacy in heatstroke models. These features collectively justify ferroptosis as the central focus of the present study.

## 2. Pathophysiological mechanisms of heatstroke

The pathogenesis of heatstroke is a complex network process involving multiple components and pathways (25). Its core feature is an uncontrolled rise in core body temperature (typically >40˚C), which triggers two primary pathological processes: Direct heat toxicity and an indirect systemic inflammatory response syndrome (SIRS) (14,26,27). With ongoing research, the pathophysiology of heatstroke has been further delineated into several interconnected components, including direct heat toxicity injury, systemic inflammatory response, coagulation dysfunction, endothelial dysfunction and multiple organ failure (14,28-30).

*Direct cytotoxic effects of hyperthermia*. When the body is exposed to extreme heat, thermal stress can directly cause irreversible damage to cells and tissues (31). Hyperthermia directly disrupts delicate cellular structures, leading to denaturation of critical proteins, inactivation of enzyme systems, altered fluidity and impaired integrity of cell membranes and mitochondrial dysfunction (32,33). This direct thermal injury effect is non-specific and can affect all cells in the body; however, vascular endothelial cells are considered an early and critical target of heat stress injury (34). Damage and dysfunction of endothelial cells compromise vascular barrier integrity, resulting in vascular leakage, tissue edema and triggering subsequent coagulation abnormalities and an inflammatory cascade (35,36).

At the molecular level, heat stress-induced mitochondrial dysfunction leads to excessive production of reactive oxygen species (ROS), which further oxidatively modify proteins, lipids and nucleic acids, exacerbating cellular damage (37,38). Concurrently, although the upregulation of heat shock protein (HSP) expression offers some protective effects, under sustained hyperthermia, these protective mechanisms are overwhelmed, failing to prevent cell death (39-41).

*Systemic inflammatory response and cell death*. Building upon direct heat injury, the body initiates a potent immune and inflammatory response (42). Damaged cells and tissues release large quantities of damage-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1) (43). These DAMPs initiate innate immune responses by activating pattern recognition receptors such as Toll-like receptor 4 (TLR4). Activated immune cells (such as monocytes/macrophages and neutrophils) produce and release a tsunami of pro-inflammatory cytokines (such as TNF-α, IL-1β and IL-6), creating a 'cytokine storm' that further exacerbates tissue damage and organ failure (44).

The cytokine storm not only amplifies local inflammation but also affects distant organs via the circulatory system, leading to SIRS, characterized by fever, tachycardia, tachypnea and significant changes in white blood cell count. Simultaneously, heat stress activates multiple programmed cell death pathways, including apoptosis, necrosis, pyroptosis and the recently proposed PANoptosis (an inflammatory cell death program involving pyroptosis, apoptosis and necrosis concurrently) (20,45-49). These modes of cell death further release DAMPs, forming a positive feedback loop that continuously drives the inflammatory response and organ injury (50).

*Coagulation system activation and endothelial dysfunction*. Heatstroke is often accompanied by a severe imbalance in the coagulation-anticoagulation systems. Endothelial damage exposes subendothelial collagen and tissue factor, activating the extrinsic coagulation pathway (10). Concurrently, inflammatory cytokines (such as TNF-α and IL-6) induce the

expression of tissue factor on monocytes and endothelial cells, further initiating the coagulation cascade (51). Clinical and experimental studies both indicate that heatstroke patients exhibit thrombocytopenia, prolonged coagulation times, and elevated D-dimer levels, consistent with the features of DIC (52,53).

Endothelial dysfunction plays a central role in this process. Direct heat stress injury to endothelial cells leads to abnormal vasodilation, microthrombus formation and inadequate tissue perfusion, consequently causing ischemic and hypoxic injury (54-56). Disruption in nitric oxide (NO) metabolism, characterized by insufficient NO production leading to excessive vasoconstriction in the early stage, and overactivation of inducible nitric oxide synthase (iNOS) leading to persistent vasodilation and hypotension in the later stage, further exacerbates circulatory failure (57-60).

Notably, endothelial cells are uniquely vulnerable to ferroptosis. Their plasma membranes are enriched in PUFA due to high fluidity requirements and they are directly exposed to circulating free iron and heme released during rhabdomyolysis and hemolysis (19,61,62). Heat stress disrupts endothelial GPX4 expression and System Xc-activity, leading to uncontrolled lipid peroxidation. Ferroptotic endothelial cells lose barrier integrity, triggering microthrombus formation and DIC, thereby creating a vicious cycle in which endothelial ferroptosis amplifies the systemic inflammatory response (63-65). This mechanistic bridge positions endothelial ferroptosis as a central driver of multi-organ dysfunction in heatstroke.

*Integrated mechanisms of multiple organ dysfunction*. The aforementioned pathological processes interact collectively, ultimately leading to MODS. The liver is one of the organs vulnerable in heatstroke; hyperthermia and ischemia-reperfusion (I/R) injury lead to hepatocyte necrosis, sharply elevated transaminases and synthetic failure (66). The kidneys suffer acute kidney injury due to reduced renal blood flow, direct heat toxicity and hemoglobinuria (secondary to rhabdomyolysis) (67). The central nervous system manifests cerebral edema, blood-brain barrier disruption and neuroinflammation, often resulting in consciousness impairment, seizures, or even coma (28). Impaired intestinal barrier function allows for gut microbiota translocation; endotoxin [lipopolysaccharide (LPS)] entering the circulation further stimulates systemic inflammation and coagulation responses, constituting a 'second hit' (68).

In summary, the pathophysiological mechanism of heatstroke is a vicious cycle initiated by direct heat toxicity, formed through the interplay of an inflammatory storm, coagulation activation, endothelial injury and various cell death pathways. Understanding this complex network is crucial for developing targeted early interventions to block disease progression. In this process, cell death plays a pivotal role. Historically, apoptosis and necrosis have been considered the primary forms of cell death in heatstroke. Studies have shown that moderate heat stress (such as 43-45˚C) can activate intrinsic or extrinsic apoptotic pathways, such as the $Ca^{2+}$-mediated mitochondrial apoptosis pathway or p53-dependent pathways, leading to orderly, programmed cell death. By contrast, extreme hyperthermia (such as >49˚C) can rapidly induce cell membrane rupture and release of intracellular contents, resulting in typical necrosis and triggering a more intense inflammatory response. However, apoptosis and necrosis alone cannot fully explain the fulminant and progressive nature of organ damage observed in heatstroke. This gap in understanding has prompted researchers to explore the roles of other forms of programmed cell death, bringing ferroptosis into focus under such investigative context. A schematic diagram of the simple mechanism is shown in Fig. 1 and these pathological mechanisms are summarized in Table I.

## 3. Ferroptosis in the pathogenesis and progression of heatstroke

Ferroptosis, formally named in 2012, is an iron-dependent form of regulated cell death characterized by lipid peroxidation, which is distinct from traditional cell death modalities such as apoptosis, necrosis, autophagy and pyroptosis in its morphological, biochemical, and genetic features (21). Its core biochemical event involves the depletion of intracellular GSH or the inactivation of GPX4, leading to the massive accumulation of iron-catalyzed PUFA lipid peroxides that ultimately disrupt cell membrane integrity and induce cell death (69,70). In recent years, multiple cutting-edge studies have confirmed that ferroptosis is not only a core pathological mechanism underlying heatstroke, particularly exertional heatstroke (EHS)-induced MODS, but its regulatory network also involves multi-level molecular events ranging from transcription factors to metabolic enzymes, providing a new theoretical basis for the screening of clinical diagnostic biomarkers and the development of targeted interventions (19,71-73).

To classify cell death as ferroptosis in the context of heatstroke research, four minimum evidentiary features should be met: i) Iron dependence: The death must be attenuated by iron chelators (DFO) or exacerbated by iron overload; ii) PUFA-phospholipid peroxidation: Evidence of MDA/4-HNE accumulation or involvement of ACSL4/LPCAT3 in lipid remodeling; iii) Disruption of the GPX4/System Xc-axis: Measurable depletion of GSH, loss of GPX4 activity, or failure of solute carrier family 7 member 11 (SLC7A11) expression; and iv) Reversibility with canonical inhibitors: rescue by Ferrostatin-1 (Fer-1), Liproxstatin-1 (Lip-1), or DFO, but not by caspase inhibitors (Z-VAD-FMK) or necroptosis inhibitors (Nec-1). Studies that do not meet these criteria should be described as 'ferroptosis-associated' rather than definitive evidence of ferroptosis.

*Regulators and signaling networks of ferroptosis in heatstroke*. The microenvironment for ferroptosis initiation in heat stress is constituted by a 'triple-hit' combination of oxidative stress burst, dysregulated iron metabolism and uncontrolled inflammatory response (74). Recent systematic explorations based on EHS animal models have revealed key molecular axes connecting heat stress signals to ferroptosis execution pathways (19,75,76). These mechanisms not only deepen the understanding of heatstroke pathophysiology but also indicate directions for developing precise therapeutic strategies.

*Hippo-YAP-ACSL4 signaling axis: A core executory pathway for heat stress-driven ferroptosis*. Research into the molecular mechanisms of EHS-induced rhabdomyolysis has achieved a

Table I. Pathophysiological mechanisms of heatstroke.

| Mechanism | Key processes and features | (Refs.) |
|---|---|---|
| Direct cytotoxicity | Protein denaturation, enzyme inactivation, membrane damage, mitochondrial dysfunction, excessive ROS production | (31-38) |
| Systemic inflammatory response | DAMP release (such as HMGB1), TLR4 activation, cytokine storm (TNF-α, IL-1β, IL-6), SIRS development | (42-50) |
| Coagulation activation and endothelial dysfunction | Endothelial damage, tissue factor exposure, DIC features (thrombocytopenia, elevated D-dimer), dysregulated NO metabolism | (10,51-60) |
| Multiple organ dysfunction | Hepatic injury, acute kidney injury, cerebral edema and BBB disruption, intestinal barrier failure and endotoxin translocation | (28,61-63) |

DAMP, damage-associated molecular patterns; HMGB1, high mobility group box 1; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; IL-6, interleukin-6; SIRS, systemic inflammatory response syndrome; DIC, disseminated intravascular coagulation; NO, nitric oxide; BBB, blood-brain barrier; ROS, reactive oxygen species.

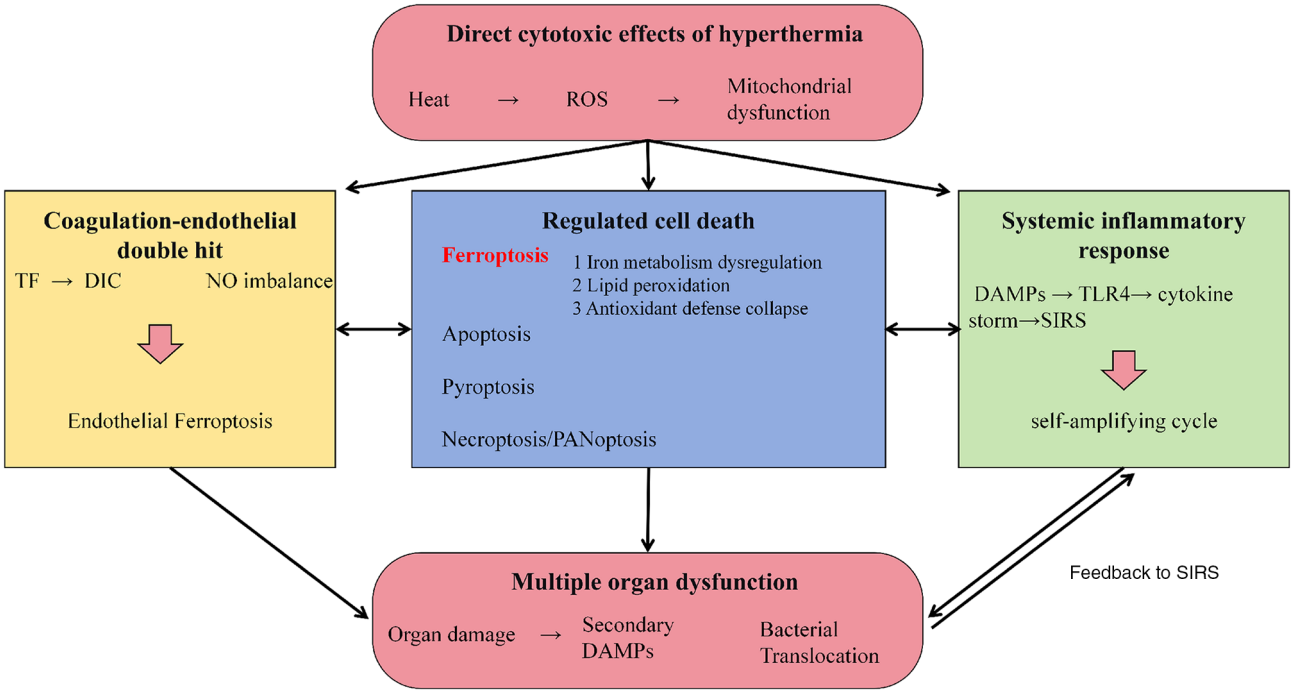


Figure 1. Schematic diagram illustrating the key pathophysiological mechanisms of heatstroke. Pathophysiological mechanisms of heatstroke. Severe heat stress (>40˚C) triggers four interconnected core processes: i) Direct cytotoxicity (protein denaturation, mitochondrial ROS burst); ii) systemic inflammatory response (DAMPs→TLR4→cytokine storm); ii) coagulation-endothelial dysfunction (tissue factor exposure, DIC, microthrombosis); and iv) regulated cell death, with ferroptosis as a principal execution mechanism driven by iron overload, ACSL4-mediated lipid peroxidation, and antioxidant defense collapse (System $Xc^-$/GSH/GPX4). Bidirectional crosstalk links ferroptosis to inflammation (oxidized phospholipid DAMPs, NLRP3 priming) and endothelial injury (endothelial ferroptosis→barrier disruption). These processes interact collectively in a vicious cycle culminating in MODS. ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; TLR4, Toll-like receptor 4; DIC, disseminated intravascular coagulation; ACSL4, acyl-CoA synthetase long-chain family member 4; GSH, glutathione; GPX4, GSH peroxidase 4; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; MODS, multiple organ dysfunction syndrome; NO, nitric oxide; SIRS, systemic inflammatory response syndrome; TF, tissue factor.

breakthrough (77). A study, utilizing single-cell sequencing and transcriptomic analysis, first demonstrated in an EHS mouse model that heat stress specifically activates YAP, a key effector of the Hippo signaling pathway (78). Activated YAP translocates to the nucleus and forms a transcriptional complex with transcription factors TEAD1/TEAD4, collectively upregulating the expression of ACSL4 (77,79). ACSL4 is a key executor of ferroptosis; it catalyzes the conversion of long-chain polyunsaturated fatty acids (PUFAs, especially arachidonic acid and adrenic acid) into their corresponding acyl-CoA esters, which are subsequently incorporated into membrane phospholipids, becoming preferred substrates for lipid peroxidation (80-82). The study further confirmed through gene knockout and pharmacological inhibition experiments that ACSL4 deficiency markedly alleviated ferroptosis in the skeletal muscle of EHS mice, reduced

plasma myoglobin levels, and improved renal injury, thereby delineating a complete signaling chain at the molecular level: 'Heat stress → Hippo-YAP activation → ACSL4 upregulation → lipid remodeling → ferroptosis outburst' (77,83). Notably, this signaling axis does not exist in isolation; subsequent research revealed that YAP transcriptional activity is also directly regulated by heat shock factor 1 (HSF1), forming complex feedback loops (84).

*Dual regulatory role of the heat shock response system: The transition from protection to failure at the 'tipping point'.* The heat shock response (HSR) is a core endogenous protective mechanism for cells coping with environmental stresses such as high temperature (85). Its key regulator, HSF1, exerts chaperone functions by inducing the expression of the HSP family to maintain proteostasis (85-87). However, a complex 'bidirectional dialogue' and 'time-dependent switch' relationship exists between the HSR system and ferroptosis. On one hand, specific HSP members have been identified as negative regulators of ferroptosis (88). For instance, the phosphorylated form of heat shock protein B1 (HSPB1, also known as HSP27) can directly antagonize ferroptosis by stabilizing the actin cytoskeleton and inhibiting iron influx. HSP90 is considered a common regulatory node connecting ferroptosis and necroptosis and its inhibitors can promote ferroptosis execution (89). On the other hand, when the intensity or duration of heat stress exceeds the compensatory capacity of the HSR, HSF1 may trans-activate pro-ferroptotic genes, forming a 'protection-to-damage' switch (90). A study revealed the paradoxical role of HSP70 in EHS: Early upregulation of HSP70 inhibits lipid peroxidation by enhancing GPX4 stability, but sustained heat stress leads to HSP70 overexpression, which interacts with iron-responsive element-binding protein 2, however, promoting the expression of the iron uptake protein transferrin receptor 1 (TFR1), exacerbating iron overload and ferroptosis (91-93). This 'HSR paradox' phenomenon suggests that the timing and intensity of intervention are crucial determinants of therapeutic success (94).

The transition from HSP70-mediated protection to HSF1-driven pro-ferroptotic signaling is not a binary switch but a dose-dependent and time-dependent continuum. At moderate thermal stress (≤42˚C) and early time points (<6 h), HSP70 functions as a chaperone stabilizing GPX4 and HSF1, thereby protecting against ferroptosis. At severe thermal stress (>43˚C) or prolonged exposure (>12 h), the HSR system becomes overwhelmed, HSF1 translocates to the nucleus and upregulates TFR1 expression via direct promoter binding and HSP70 dissociates from GPX4. The severity of the thermal dose determines the relative balance between HSP70-GPX4 binding (protective) and HSF1-TFR1 activation (pro-ferroptotic). Under intermediate stress conditions, HSP70 can simultaneously exert both roles in different cellular compartments, reflecting the complexity of the heat shock response (95-98).

*Systemic collapse of core antioxidant pathways: Multi-Layered defense failure from nuclear factor erythroid 2-related factor 2 (Nrf2) to ferroptosis suppressor protein 1 (FSP1).* Nrf2 is the most critical transcription factor for intracellular antioxidant stress responses (99). Under basal conditions, Nrf2 is anchored in the cytoplasm by Keap1 and subjected to continuous degradation (100). Under the severe oxidative stress caused by heatstroke, activation of the Nrf2 pathway should initiate the transcription of a series of protective genes, including GPX4, SLC7A11 (a subunit of the cystine/glutamate antiporter xCT), and heme oxygenase-1 (HO-1) (73,101-103). However, there is a dual dysfunction of 'suppression-exhaustion' in the Nrf2 pathway in EHS patients and animal models (104). In the acute phase, overactivated p53 inhibits SLC7A11 expression, severing the cystine uptake-GSH synthesis pathway, leading to GPX4 inactivation due to cofactor depletion (21,77,105,106). Concurrently, high concentrations of TNF-α in the inflammatory microenvironment can activate the NF-κB pathway, inducing the expression of the Nrf2 inhibitory protein Keap1, forming a cascading inhibitory effect (107-113). More critically, a series of studies revealed a parallel defense axis, GPX4-independent ferroptosis defense axis; the FSP1-CoQ10-NAD(P)H system (77,104,114-116). FSP1 utilizes its NAD(P)H-dependent reductase activity to reduce CoQ10 to the antioxidant form ubiquinol (CoQ10H2), which directly scavenges lipid peroxyl radicals (75,115). In EHS models, FSP1 expression in skeletal muscle and liver tissues shows a dynamic 'rise-then-fall' pattern: Early upregulation represents a cellular compensatory response, but sustained heat stress leads to increased methylation in the FSP1 promoter region, suppressing its transcription and ultimately causing the failure of both the GPX4 and FSP1 systems, resulting in an irreversible outburst of ferroptosis (22,117,118). Additionally, dihydroorotate dehydrogenase, localized to mitochondria, has also been confirmed as an endogenous inhibitor of ferroptosis. By competitively utilizing CoQ10, it forms a mitochondrial-cytosolic collaborative defense network with FSP1 (119).

Based on current evidence, System Xc-failure (SLC7A11/GSH depletion) is considered the primary driver of ferroptosis in heatstroke, while FSP1/CoQ10 failure acts as a secondary, compensatory pathway that becomes critical when GPX4 is already compromised. System Xc-is the dominant antioxidant defense because heat stress directly inhibits cystine uptake and glutamate efflux, leading to rapid GSH depletion. FSP1/CoQ10 provides a parallel pathway that can partially compensate for GPX4 loss, but it is insufficient alone to prevent ferroptosis when System Xc-is severely impaired. Lethal injury typically requires failure of both pathways, but System Xc-failure is the earlier and more decisive event. This hierarchical model of defense collapse is supported by the observation that DFO and Fer-1 (which target the iron-peroxidation axis) are more effective than Nrf2 activators alone in heatstroke models (11,115,120).

*Vicious cycle of iron metabolism dysregulation and ferroptosis amplification.* Systemic iron metabolism dysregulation induced by heatstroke is a key driver for the continuous amplification of ferroptosis. A study found that serum ferritin levels in EHS patients are markedly positively associated with disease severity (APACHE II score) and the number of organ failures (121). This elevation is not merely an acute phase response but rather a consequence of increased iron release caused by ferroptosis-associated ROS activating ferritinophagy (22). Ferritin heavy chain 1 is selectively degraded via autophagy mediated by NCOA4 under heat stress, releasing large amounts of free $Fe^{2+}$ (122,123). This

$Fe^{2+}$ catalyzes the generation of ·OH via the Fenton reaction, further exacerbating lipid peroxidation (124). Simultaneously, imbalance in the hepcidin-ferroportin (FPN) axis leads to iron retention within parenchymal cells (hepatocytes, renal tubular epithelial cells), creating an 'iron trap' microenvironment (125,126). A preclinical study using FPN conditional knockout mice confirmed that deletion of FPN in intestinal epithelial cells worsened EHS-related intestinal barrier injury and increased bacterial translocation, whereas intervention with DFO reversed this process and markedly reduced the incidence of multiple organ failure (77,126,127). This reveals the central role of the 'iron overload-ferroptosis-organ injury-systemic inflammation' vicious cycle in heatstroke progression.

*Interplay between ferroptosis and other regulated cell death programs in heatstroke*. Heatstroke pathology is multi-modal and ferroptosis does not operate in isolation. Multiple cell death modalities may coexist in the same tissue, with ferroptosis dominating in iron-rich tissues (kidney and liver) and pyroptosis or necroptosis more prominent in immune cells (19,73). The present study highlighted four cross-talk nodes, distinguished by evidence strength:

i) Ferroptosis-pyroptosis axis (best supported): Ferroptotic cells release lipid peroxidation products (such as oxidized phospholipids) that act as DAMPs, activating the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome and triggering pyroptosis in neighboring macrophages (128,129). Conversely, IL-1β and IL-18 released during pyroptosis can further deplete GSH and exacerbate ferroptosis, creating a bidirectional amplification loop (130,131). This cross-talk is supported by evidence in heatstroke models (such as cGAS-STING-NLRP3 pathway activation) (132).

ii) Ferroptosis-endothelial injury axis (emerging evidence): Endothelial cells are uniquely vulnerable to ferroptosis due to their PUFA-rich plasma membranes and direct exposure to circulating free iron (19). Ferroptotic endothelial injury exposes subendothelial tissue factor, disrupts tight junctions, and promotes barrier dysfunction (19), thereby fueling the coagulation cascade. Conversely, endothelial damage-driven ischemia and ROS generation create a microenvironment that further sensitizes endothelial cells to ferroptosis.

iii) Ferroptosis-coagulation axis (plausible but under-investigated): DIC and microthrombosis generate regional ischemia-hypoxia, which exacerbates ferroptosis through ROS accumulation and iron-mediated Fenton chemistry. In turn, ferroptosis-derived oxidized phospholipids can activate platelets and propagate coagulation cascade signaling (133), forming a vicious cycle. Direct experimental validation in heatstroke models remains limited.

iv) Ferroptosis-necroptosis axis (largely theoretical): Potential interactions via RIPK3-ROS signaling or MLKL pore-mediated ion influx have been proposed in other disease contexts (134), but specific evidence in heatstroke is currently lacking.

This multi-modal interplay underscores that heatstroke is not a single-mechanism disease and that therapeutic strategies must address multiple injury pathways simultaneously. These pathological mechanisms are summarized in Table II.

*Ferroptosis-driven multiple organ injury in heatstroke*. Ferroptosis is an iron-dependent, lipid peroxidation-driven form of regulated cell death. It is not confined to a single organ during the course of heatstroke but is extensively involved in the pathological process of multiple organ injury. The mechanisms and evidence of ferroptosis in major organ damage induced by heatstroke are systematically elaborated below and shown in Fig. 2.

*Muscle injury*. Exertional heatstroke is frequently accompanied by rhabdomyolysis (RM), which is a typical manifestation of ferroptosis. Evidence primarily derives from EHS models, given that rhabdomyolysis is a hallmark of EHS. Generalization to classical heat stroke (CHS) should be made with caution. Studies have confirmed that ACSL4 expression is upregulated in skeletal muscle following EHS. By promoting the incorporation of polyunsaturated fatty acids into membrane phospholipids and driving lipid peroxidation, ACSL4 directly leads to ferroptosis in muscle cells. ACSL4-mediated ferroptosis causes rupture of the myocyte membrane, releasing large amounts of myoglobin, potassium ions, and creatine kinase (CK). This not only results in local muscle tissue necrosis, disordered fiber arrangement, and edema, but these released substances entering the circulation can also induce secondary damage such as acute kidney injury (AKI) (77,135-138). In animal models, using ACSL4 inhibitors (such as Rosiglitazone) or the ferroptosis inhibitor Fer-1 markedly alleviated EHS-induced rhabdomyolysis, reduced serum CK and myoglobin levels, and improved muscle function (19). The dominant trigger is ACSL4 upregulation driven by Hippo-YAP activation, which promotes PUFA-phospholipid peroxidation and leads to rhabdomyolysis. Secondary mechanisms, including HSP70 chaperone failure and Nrf2 antioxidant collapse, further amplify ferroptotic damage but are summarized here as contributory rather than primary drivers.

*Cardiac injury*. As a high-metabolic-rate organ, the heart is highly sensitive to heat stress and oxidative stress. Evidence mixed from generic heat-stress models and EHS models and direct CHS-specific cardiac data are limited. Experiments indicate that heat stress can directly induce ferroptosis in cardiomyocytes, characterized by the accumulation of intracellular lipid peroxides (such as MDA) and decreased activity of GPX4 (135,139,140). The molecular mechanism involves activation of the TLR4/nuclear factor kappa B (NF-κB)/p53 signaling pathway: Heat stress upregulates NF-κB and p53 via TLR4, which subsequently suppresses the expression of the cystine/glutamate antiporter (System $Xc^-$) subunit SLC7A11. This leads to impaired GSH synthesis, GPX4 inactivation, and ultimately, accumulation of lipid peroxides and ferroptosis in cardiomyocytes. This pathway may be a crucial mechanism for cardiac dysfunction, arrhythmias, and even heart failure resulting from heatstroke. Inhibition of TLR4 (such as with TAK-242) or application of ferroptosis inhibitors can markedly mitigate heat stress-induced myocardial

Table II. Key signaling pathways and mechanisms of ferroptosis in heatstroke.

| Mechanism | Key molecules/pathways | Role and effect | (Refs.) |
|---|---|---|---|
| Hippo-YAP-ACSL4 Axis | YAP activation → ACSL4 upregulation → Lipid remodeling → Ferroptosis | Core pathway driving ferroptosis in skeletal muscle and kidney, mediating rhabdomyolysis | (72-78) |
| Heat shock response system | HSF1/HSPs (e.g., HSP70, HSPB1) | Dual role: Protective initially, but promotes ferroptosis under sustained stress via iron metabolism dysregulation | (79-89) |
| Antioxidant defense systems | Nrf2/GPX4, FSP1/CoQ10, DHODH | Collapse leads to lipid peroxide accumulation and ferroptosis execution | (90-110) |
| Iron metabolism dysregulation | Ferritinophagy (NCOA4-mediated), hepcidin-ferroportin axis imbalance | Increases intracellular free iron, fueling Fenton reaction and amplifying ferroptosis | (111-117) |

YAP, yes-associated protein; ACSL4, acyl-coA synthetase long-chain family member 4; HSF1, heat shock factor 1; HSPs, heat shock proteins; HSP70, heat shock protein 70; HSPB1, heat shock protein B1; Nrf2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; CoQ10, coenzyme Q10; DHODH, dihydroorotate dehydrogenase; NCOA4, nuclear receptor coactivator 4.

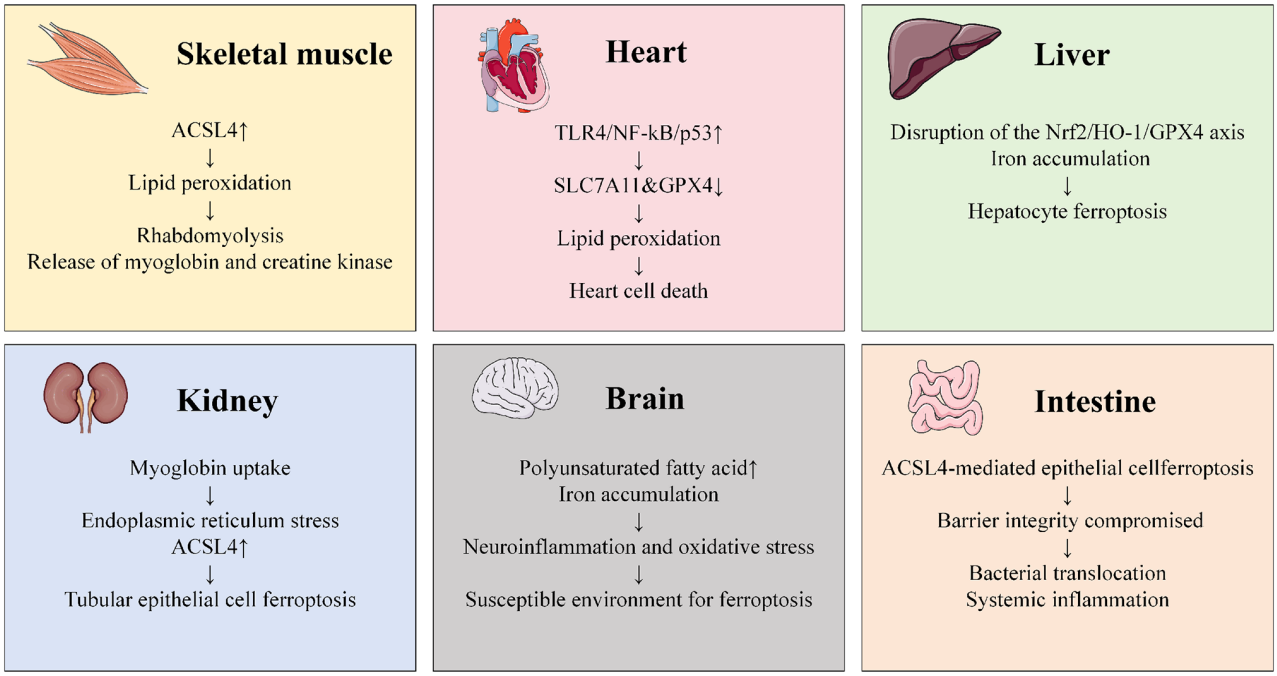


Figure 2. Organ-specific pathways of ferroptosis in heatstroke-induced multiple organ dysfunction. Heatstroke triggers organ-specific ferroptosis pathways contributing to multi-organ injury. In skeletal muscle, ACSL4 upregulation drives lipid peroxidation and membrane rupture, leading to rhabdomyolysis and the release of harmful contents like myoglobin. In the heart, activation of the TLR4/NF-κB/p53 pathway suppresses the cystine/glutamate antiporter SLC7A11 and inactivates GPX4, resulting in cardiomyocyte ferroptosis. Hepatic injury involves disruption of the Nrf2/HO-1/GPX4 antioxidant axis and iron accumulation. Renal tubular epithelial cells undergo ferroptosis primarily via myoglobin-induced endoplasmic reticulum stress and subsequent ACSL4 upregulation. The brain, rich in PUFAs and iron, is highly susceptible to ferroptosis potentiated by neuroinflammation, while intestinal epithelial cell ferroptosis may compromise barrier function, promoting bacterial translocation. These distinct yet converging pathways explain the synchronized failure of multiple organs. ACSL4, Acyl-CoA synthetase long-chain family member 4; TLR4, Toll-like receptor 4; NF-κB, nuclear factor κB; SLC7A11, Solute Carrier Family 7 Member 11; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; GPX4, glutathione peroxidase 4; PUFAs, polyunsaturated fatty acids.

injury (133,141). The dominant trigger is direct heat stress combined with mitochondrial ROS overproduction. The primary causal chain proceeds as: mitochondrial dysfunction → GPX4 failure → lipid peroxidation → cardiomyocyte ferroptosis. While TLR4/NF-κB signaling contributes, it is considered a secondary amplification loop rather than the principal driver.

*Neurological injury*. Central nervous system dysfunction is a defining feature of heatstroke (142). Evidence mixed from CHS and generic heat-stress models; direct

EHS-specific neurological data are limited. Brain tissue, rich in polyunsaturated fatty acids and iron, is highly susceptible to ferroptosis (22). Although research directly validating ferroptosis in brain cells in heatstroke models is still ongoing, ferroptosis has been recognized as a key pathological mechanism in various acute brain injuries (such as ischemic stroke and traumatic brain injury) (133,143,144). In heatstroke-associated brain injury, the TLR4/NF-κB signaling pathway is similarly activated, potentially indirectly inducing ferroptosis in neurons and glial cells by promoting lipid peroxidation and weakening antioxidant defenses (133). Therefore, it is reasonable to hypothesize that the impaired consciousness, cerebral edema and long-term neurological deficits caused by heatstroke are partly attributable to the occurrence of ferroptosis in brain tissue (28,143). The dominant trigger is the high intrinsic PUFA and iron content of brain tissue combined with excitotoxicity. The primary causal chain is: glutamate accumulation → System Xc-inhibition → GSH depletion → neuronal ferroptosis. TLR4/NF-κB activation and antioxidant weakening represent secondary modulatory pathways.

*Hepatic injury*. The liver often exhibits acute injury in heatstroke, where ferroptosis plays a critical role (145,146). Evidence mixed from EHS and generic heat-stress/drug-induced liver injury models. In models of acute liver injury induced by drugs (such as acetaminophen) or endotoxins (LPS), markers of ferroptosis (iron accumulation, elevated lipid peroxides and downregulated GPX4) are markedly increased, while ferroptosis inhibitors such as Fer-1 can effectively alleviate hepatocyte death and abnormal liver function indicators (146,147). The systemic inflammation, oxidative stress, and (I/R)-like injury associated with heatstroke may trigger hepatocyte ferroptosis by disrupting intracellular iron homeostasis and enhancing lipid peroxidation (148-150). Furthermore, expression changes of key proteins regulating ferroptosis (such as ACSL4 and the Nrf2/HO-1/GPX4 axis) in heatstroke-induced liver injury also support this mechanism (83,151). The dominant trigger is Kupffer cell iron overload combined with CYP2E1-mediated ROS generation. These initiate hepatocyte ferroptosis through direct lipid peroxidation and iron-catalyzed oxidative damage. Secondary pathways including Nrf2/HO-1/GPX4 axis disruption contribute to injury amplification but are not the primary initiators.

*Renal injury*. Acute kidney injury is a common and severe complication of heatstroke, to which ferroptosis directly contributes. Evidence is primarily from EHS models, given the central role of rhabdomyolysis-induced myoglobinuria in AKI. Research indicates that the large amount of myoglobin released following EHS can promote ferroptosis in renal tubular epithelial cells by inducing endoplasmic reticulum stress (ERS) and upregulating ACSL4. In clinical retrospective analyses, a serum myoglobin level ≥1,000 ng/ml can predict the occurrence of AKI and the 90-day prognosis in EHS patients. Animal and cell experiments further confirm that myoglobin exacerbates lipid peroxidation and ferroptosis in renal tubular cells under heat stress conditions, while using ERS inhibitors or ferroptosis inhibitors (such as baicalein) markedly attenuates renal injury (19,77). This suggests that ferroptosis is an important effector mechanism in heatstroke-associated AKI. The dominant trigger is myoglobin-heme iron released from rhabdomyolysis combined with direct tubular heat injury. The causal chain centers on heme iron overload and tubular oxidative stress driving GPX4 inactivation and lipid peroxidation in renal tubular epithelial cells. ERS and ACSL4 upregulation are secondary amplifying mechanisms.

*Intestinal injury*. Heatstroke often leads to gastrointestinal mucosal ischemia, impaired barrier function, and even gut-origin endotoxemia (152). Although direct research on intestinal ferroptosis in heatstroke is still limited, ferroptosis has been demonstrated as a key injury mechanism in intestinal I/R models. In intestinal I/R, upregulated ACSL4 expression promotes ferroptosis in epithelial cells, disrupts intestinal barrier integrity and facilitates bacterial and endotoxin translocation, thereby amplifying the systemic inflammatory response (153). Given the presence of intestinal ischemia, oxidative stress and inflammatory cascades in heatstroke, it is reasonable to infer that ferroptosis of intestinal epithelial cells may be involved in heatstroke-associated gastrointestinal dysfunction and the exacerbation of systemic inflammation (154). Direct evidence for intestinal ferroptosis in heatstroke remains limited; current understanding is largely extrapolated from I/R and sepsis models. Intestinal epithelial cells may be vulnerable due to high PUFA content and mucosal hypoxia during heatstroke, but causal claims require further experimental validation.

It is important to note that the evidence for intestinal ferroptosis in heatstroke is largely extrapolated from I/R and sepsis models, not from direct hyperthermia models. Enterocytes may be particularly vulnerable to hyperthermia-induced ferroptosis due to their high PUFA content in intestinal membranes, proximity to gut microbiota-derived LPS/DAMPs, and the unique hypoxic-ischemic environment of the intestinal mucosa during heatstroke. Direct evidence from hyperthermia-specific enterocyte models (such as Caco-2 cells at 43˚C, intestinal organoids) or large-animal heatstroke models with direct intestinal sampling is urgently needed. Until such studies are available, causal claims about intestinal ferroptosis in heatstroke should be interpreted with caution.

These pathological mechanisms of ferroptosis-driven organ injury in heatstroke are summarized in Table III.

## 4. Potential ferroptosis biomarkers of heatstroke

Early and accurate assessment of the severity and prognosis of heatstroke is crucial for guiding clinical management (121). Current clinical practice often relies on comprehensive scoring systems such as APACHE II or SOFA; however, these systems lack reflection of the specific pathological processes of heatstroke (155). Consequently, the development of specific biomarkers based on pathological mechanisms has become a research focus. Ferroptosis, an iron-dependent, lipid peroxidation-driven form of regulated cell death, may play a key role in multi-organ damage in heatstroke (73). Molecules associated with ferroptosis thus offer novel potential targets for assessing disease status (19).

Although no specific ferroptosis biomarkers have been fully clinically validated for heatstroke yet, based on existing research, the following categories of molecules show notable potential.

*Core regulatory genes and proteins*. Through single-cell transcriptomic analysis of peripheral blood mononuclear cells from heatstroke patients, researchers have screened potential

Table III. Ferroptosis-driven organ injury in heatstroke.

| Organ | Primary injury mechanism | Key evidence/biomarkers | (Refs.) |
|---|---|---|---|
| Skeletal muscle | ACSL4-mediated lipid peroxidation, rhabdomyolysis | Elevated serum CK and myoglobin; ameliorated by ACSL4 inhibitors | (19,72) |
| Heart | TLR4/NF-κB/p53 pathway activation, GPX4 inhibition | Ferroptosis in cardiomyocytes; protection by TLR4 inhibitors and Ferrostatin-1 | (65,133) |
| Brain | High PUFA and iron content, potential TLR4/NF-κB activation | Implicated in cerebral edema and neurological deficits; indirect evidence from other acute brain injuries | (28,126) |
| Liver | Iron accumulation, GPX4 downregulation, involvement of Nrf2/HO-1 axis | Elevated ferroptosis markers; ferrostatin-1 alleviates injury | (66,73) |
| Kidneys | Myoglobin-induced ERS and ACSL4 upregulation | Serum myoglobin (≥1,000 ng/ml) predicts AKI; ferroptosis inhibitors are protective | (19,72) |
| Intestine | Putative ACSL4-mediated ferroptosis in epithelial cells (analogous to I/R) | Contributes to barrier dysfunction, bacterial translocation, and systemic inflammation | (152-154) |

ACSL4, acyl-coa synthetase long-chain family member 4; CK, creatine kinase; TLR4, Toll-like receptor 4; NF-κB, nuclear factor-κB; GPX4, glutathione peroxidase 4; PUFA, polyunsaturated fatty acid; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; ERS, endoplasmic reticulum stress; AKI, acute kidney injury; I/R, ischemia/reperfusion.

diagnostic marker genes related to ferroptosis, such as *ACSL1*, *MAPK14*, *ALOX5AP*, *PROK2* and *DUSP1* (156). Measuring the mRNA levels of these genes or their encoded proteins in blood may reflect the activity of ferroptosis *in vivo*. Furthermore, assessing changes in the levels of core proteins such as GPX4 and ACSL4 in blood also holds potential value (157,158). In severe COVID-19 patients, decreased GPX4 is closely associated with ferroptosis activation, suggesting it might similarly serve as an important indicator under analogous oxidative stress conditions in heatstroke (158).

*Lipid peroxidation products*. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are end products of lipid peroxidation and their levels directly reflect the execution degree of ferroptosis (159,160). In critical illnesses such as sepsis and severe COVID-19, serum levels of MDA and 4-HNE are markedly elevated and positively correlate with APACHE II and SOFA scores (161-163). Although data from dynamic monitoring in heatstroke patients and its correlation with scoring systems are still lacking, detecting these products remains the most direct method for assessing the extent of oxidative stress and ferroptosis-related damage in heatstroke (164).

*Iron metabolism-related indicators*. Heatstroke is often accompanied by disordered iron metabolism. Changes in indicators such as serum iron, ferritin and transferrin may indirectly reflect the risk of ferroptosis (165). In severe inflammatory states such as COVID-19 and sepsis, hyperferritinemia is closely associated with disease severity and poor prognosis (166,167). Experimental studies also show that in exertional heatstroke models, serum myoglobin promotes ferroptosis in renal tubular epithelial cells by upregulating p53 and inhibiting SLC7A11 and GPX4 expression, suggesting that myoglobin could also serve as a ferroptosis-related biomarker for assessing renal injury in heatstroke (19,77).

*Other novel biomarkers*. Studies have found that proteins such as sRAGE and GDF-15 are closely associated with ferroptosis and organ damage in severe infections and inflammatory states (168-170). Furthermore, exosome-carried ferroptosis-related molecules (such as lipid peroxides and iron metabolism proteins) transmit death signals between cells and might represent a new direction for liquid biopsy (171-173).

It is important to distinguish between upstream triggers of ferroptosis and specific ferroptosis biomarkers. Myoglobin, released during rhabdomyolysis, is a marker of muscle injury severity, not a specific ferroptosis biomarker. It promotes ferroptosis by releasing free iron and catalyzing lipid peroxidation in renal tubular cells, but it does not reflect the core execution mechanisms of ferroptosis. True ferroptosis biomarkers should reflect the execution machinery, such as MDA/4-HNE for lipid peroxidation, ACSL4 for PUFA incorporation, or GPX4 loss for antioxidant failure. In the context of heatstroke, myoglobin should be classified as an upstream trigger and risk factor; rather than a 'core ferroptosis biomarker' and caution should be exercised to avoid biomarker over-interpretation. These potential ferroptosis biomarkers in heatstroke are summarized in Table IV.

*Research challenges and prospects*. Current research on ferroptosis biomarkers for heatstroke is still in its infancy, with most evidence derived from other critical illness models such as sepsis and COVID-19 (174,175). Future work requires prospective dynamic monitoring in heatstroke clinical cohorts, correlating the aforementioned biomarkers with traditional scores (APACHE II and SOFA) and organ function outcomes, and utilizing methods such as machine

Table IV. Potential ferroptosis biomarkers in heatstroke.

| Biomarker category | Example molecules | Potential clinical utility | (Refs.) |
|---|---|---|---|
| Core regulatory genes/proteins | ACSL4, GPX4, SLC7A11, ALOX5AP | Reflect pathway activity; potential for early diagnosis and prognosis | (134-136) |
| Lipid peroxidation products | MDA, 4-HNE | Direct indicators of ferroptosis execution; correlate with severity in other critical illnesses | (137-142) |
| Iron metabolism indicators | Serum iron, ferritin, myoglobin | Indicate iron overload state; associated with organ injury and outcomes | (19,72, 143-145) |
| Novel biomarkers | sRAGE, GDF-15, exosome-cargo molecules | Potential for liquid biopsy, reflecting intercellular communication and injury signals | (146-149) |

ACSL4, Acyl-CoA Synthetase Long-Chain Family Member 4; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; ALOX5AP, arachidonate 5-lipoxygenase-activating protein; MDA, malondialdehyde; 4-HNE, 4-Hydroxynonenal; sRAGE, soluble receptor for advanced glycation end products; GDF-15, growth differentiation factor 15.

learning to construct multi-biomarker predictive models (176). Simultaneously, intervention studies targeting key molecules in the ferroptosis pathway (such as GPX4, SLC7A11 and ACSL4) hold promise for providing new therapeutic strategies for heatstroke (156,177).

Ferroptosis-related readouts may provide incremental prognostic value beyond conventional markers (such as lactate, CRP, creatinine and transaminases) because they reflect the underlying mechanism of cell death rather than generic organ injury or inflammation. This mechanistic specificity could enable earlier intervention (before irreversible organ damage) and guide targeted therapy selection. The most plausible sampling window is 0-6 h post-cooling, during the peak of lipid peroxidation. Signal separation is most expected in patients with rhabdomyolysis (high iron load) or those with SOFA ≥4. A feasible validation approach would be a prospective cohort design with serial sampling (0, 6, 12 and 24 h) combined with machine learning models integrating ferroptosis markers (MDA, ACSL4 and GSH/GSSG) with SOFA/APACHE II scores to predict organ failure and mortality (178-182).

In summary, ferroptosis-related biomarkers (including core regulatory proteins, lipid peroxidation products and iron metabolism indicators) demonstrate significant potential value in assessing heatstroke severity. Through further clinical validation, these biomarkers are expected to enable early warning, severity stratification and prognosis prediction for heatstroke, providing essential tools for precision medicine.

## 5. Therapeutic potential of targeting ferroptosis in heatstroke

Given the pivotal role of ferroptosis in the pathological process of heatstroke, targeted inhibition of ferroptosis has emerged as a highly attractive novel therapeutic strategy (75,133). Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation, is markedly upregulated in multi-organ damage induced by heat stress, including rhabdomyolysis, myocardial injury, acute lung injury and neurological damage (75,77,133,183). Currently, various ferroptosis inhibitors have shown considerable potential for protecting against heatstroke-associated organ damage in preclinical studies (77,133).

*Ferroptosis-targeted interventions in heatstroke*. Ferroptosis inhibitors are primarily categorized into three classes based on their targets. Iron chelators, such as DFO, function by chelating excess intracellular free iron, thereby blocking the initiation of iron-catalyzed Fenton reactions at the source and inhibiting lipid peroxidation. DFO has been shown to mitigate ferroptosis-related injury in models such as intracerebral hemorrhage and I/R, providing a rationale for its potential application in heatstroke (127,184). Lipid peroxidation inhibitors, including Fer-1 and Lip-1, directly scavenge lipid radicals to interrupt the chain reaction. They have demonstrated significant cytoprotective effects in heatstroke cardiomyocyte models and acute lung injury models, reducing lipid peroxidation products such as MDA and 4-HNE while restoring the expression of key proteins such as GPX4 and SLC7A11 (75,185). Another approach involves agents that restore GPX4 function, which enhances the cellular capacity to clear lipid peroxides by supplementing GSH precursors or directly activating GPX4 (104). Furthermore, SIRT1 agonists can inhibit heat stress-induced ferroptosis in lung epithelial cells by deacetylating p53 and subsequently upregulating GPX4 and SLC7A11 (75).

Therapeutic strategies targeting ferroptosis have achieved notable success in preclinical models. Fer-1 markedly alleviated rhabdomyolysis, reduced serum creatine kinase levels and improved survival rates in a mouse model of heatstroke (77). In heat stress-induced cardiomyocyte injury, Fer-1 effectively mitigated ferroptosis markers and protected cardiac function (133). Lip-1 also exhibited protective effects in a heatstroke-associated acute lung injury model, reducing inflammation and blocking ferroptosis via inhibition of the TLR4/NF-κB signaling pathway (133). The ACSL4 inhibitor Rosiglitazone alleviated muscle damage in an exertional heatstroke model by inhibiting ACSL4-mediated lipid remodeling (77). Additionally, novel approaches such as curcumin-loaded nanovesicles have shown promise by attenuating heatstroke-induced neuronal ferroptosis in the hypothalamus via upregulation of the PCBP2/SLC7A11 axis,

Table V. Therapeutic strategies targeting ferroptosis in heatstroke.

| Representative agents/ interventions | Mechanism of action | Preclinical efficacy | Challenges and prospects | (Refs.) |
|---|---|---|---|---|
| Deferoxamine | Chelates free iron, inhibits Fenton reaction | Reduces ferroptosis-related organ injury | Optimization of timing and delivery required | (117,155) |
| Ferrostatin-1, Liproxstatin-1 | Scavenge lipid radicals, restore GPX4 expression | Protects heart, lung, and skeletal muscle | Poor bioavailability; nano-delivery systems under investigation | (70,156) |
| Rosiglitazone | Inhibits ACSL4-mediated lipid remodeling | Alleviates rhabdomyolysis and renal injury | Specificity and safety profile need further validation | (72) |
| Glutathione precursors, SIRT1 agonists | Boost GPX4 activity, enhance antioxidant defense | Attenuates ferroptosis in lung epithelial cells | Efficacy in multi-organ context requires clinical confirmation | (70,95,157) |
| Curcumin-loaded nanovesicles | Inhibits neuronal ferroptosis via PCBP2/SLC7A11 axis | Improves neurological outcome and survival | Carrier stability and targeting need optimization | (157,158) |

DFO, deferoxamine; GPX4, glutathione peroxidase 4; ACSL4, acyl-coA synthetase long-chain family member 4; SIRT1, sirtuin 1; PCBP2, poly(rC)-binding protein 2; SLC7A11, solute carrier family 7 member 11.

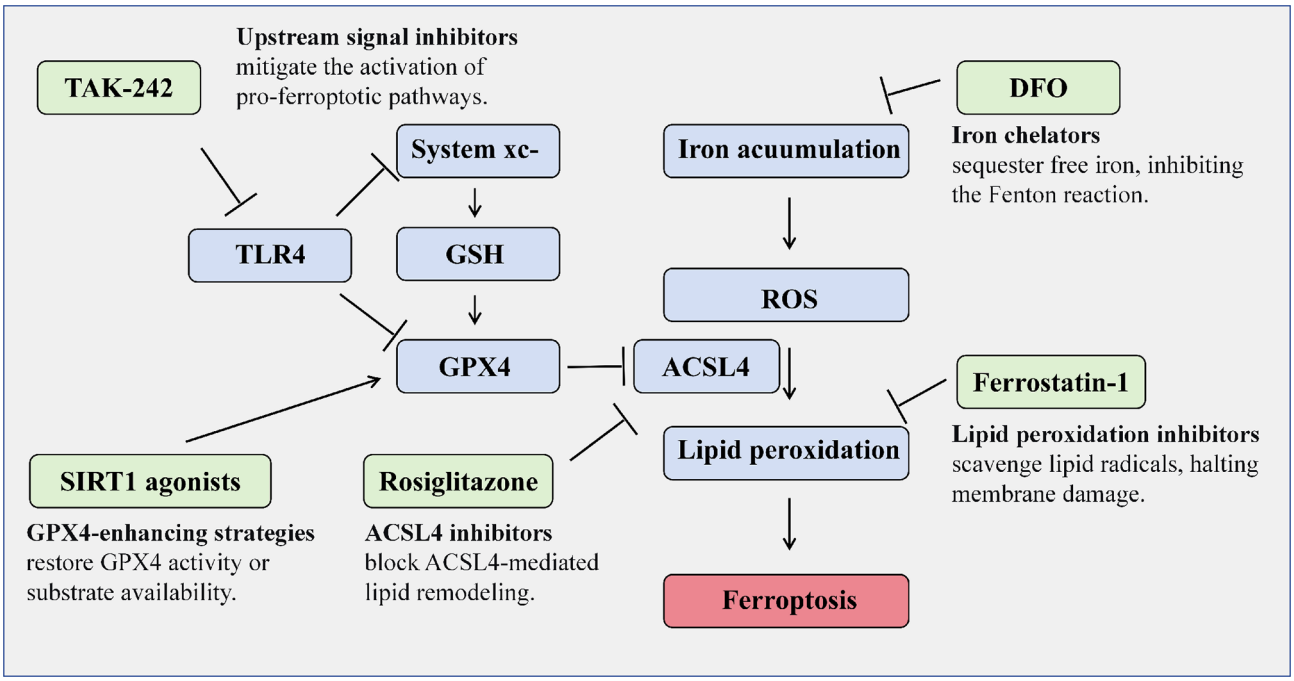


Figure 3. Therapeutic strategies targeting ferroptosis in heatstroke. Targeting ferroptosis offers novel therapeutic avenues. Interventions include iron chelators (such as DFO) to reduce iron, lipid peroxidation inhibitors (such as Fer-1, Lip-1) to scavenge radicals, and ACSL4 inhibitors (such as rosiglitazone) to prevent lethal lipid remodeling. Enhancing GPX4 activity (via SIRT1 agonists or glutathione precursors) restores antioxidant defense, while upstream TLR4 inhibition blocks pro-ferroptotic signaling. These strategies shift treatment from supportive care to mechanism-based intervention. DFO, deferoxamine; Fer-1, Ferrostatin-1; Lip-1, Liproxstatin-1; ACSL4, Acyl-CoA synthetase long-chain family member 4; GPX4, glutathione peroxidase 4; SIRT1, Sirtuin 1; TLR4, Toll-like receptor 4.

leading to improved neurological outcomes and survival (186). These data robustly indicate that ferroptosis inhibitors possess broad-spectrum protective potential against multi-organ damage in heatstroke and are promising as effective adjuncts to traditional therapies. The corresponding therapeutic targets are shown in Fig. 3 and these therapeutic strategies are summarized in Table V.

*Clinical timing and stratification of ferroptosis-targeted interventions*. Given the strong time-dependence of heatstroke management, ferroptosis-targeted interventions should be stratified by clinical timing and grouped into three tiers: i) Tier 1 (upstream stabilization, 0-1 h): Anti-inflammatory agents (such as Xuebijing) and endothelial stabilizers (such as epoprostenol) should be initiated during active cooling,

with measurable endpoints including coagulation markers (D-dimer and PT/INR) and endothelial injury markers (sTM and sICAM-1); ii) Tier 2 (Iron/lipid radical blockade, 1-6 h): Iron chelators (DFO) and lipophilic antioxidants (Fer-1 and CoQ10) should be initiated during the post-cooling phase, with endpoints including serum ferritin, MDA/4-HNE and AKI incidence; iii) Tier 3 (mitochondrial/antioxidant restoration, 6-24 h): Nrf2 activators (such as sulforaphane) and mitochondrial protective agents (such as MitoQ) should be initiated during the recovery phase, with endpoints including lactate clearance, GSH/GSSG ratio and neurological outcomes (Glasgow Coma Scale) (10,187-192). This stratification aligns with the pathophysiological trajectory of heatstroke and emphasizes that the therapeutic window for ferroptosis inhibition is narrow and organ-specific.

However, translating ferroptosis inhibitors from the laboratory to the clinic still faces multiple challenges. Key issues include the poor *in vivo* stability and low bioavailability of compounds such as Fer-1 and Lip-1, which limit clinical application, although strategies such as nanocarrier encapsulation are being explored to enhance their delivery (193,194). Determining the optimal therapeutic time window is also critical, as most studies indicate administration must occur early after heat stress for best efficacy (75). Furthermore, the potential of combination therapies, such as using ferroptosis inhibitors alongside apoptosis inhibitors, warrants investigation in heatstroke models, given the coexistence of different cell death pathways (15). Advancing clinical translation requires validating efficacy and safety in large animal models, developing reliable biomarkers for monitoring ferroptosis in patients, and ultimately designing randomized controlled trials targeting severe heatstroke patients (73).

A critical translational hurdle is the near-exclusive reliance on prophylactic administration in the current literature. Most preclinical studies administer ferroptosis inhibitors prior to the thermal insult (Fer-1 30 min to 2 h before heat stress), which does not reflect clinical reality. To date, only one study has systematically evaluated post-insult efficacy: He *et al* (77) administered Fer-1 at 0, 6, and 12 h after EHS onset in mice. Fer-1 given immediately (0 h) or at 6 h post-insult markedly improved survival and attenuated rhabdomyolysis, whereas administration at 12 h showed limited survival benefit but still reduced muscle injury. These data confirm that a therapeutic window exists but narrows rapidly after the insult. By contrast, Luan *et al* (19) demonstrated ferroptosis involvement in myoglobin-induced renal tubular injury using an *in vitro* heat-stress model, but did not evaluate pharmacological interventions *in vivo*. The scarcity of post-insult *in vivo* efficacy data, particularly for iron chelators such as DFO, represents a massive translational hurdle. Without evidence that ferroptosis inhibitors are effective when administered after heat exposure, their clinical utility in emergency settings remains unproven. Combination with rapid cooling, which may itself attenuate ferroptosis by reducing ROS production, represents the most realistic near-term strategy.

## 6. Conclusion

In conclusion, the accumulating body of preclinical evidence positions ferroptosis as an important and potentially targetable pathway contributing to heatstroke-related organ injury, alongside pyroptosis, necroptosis and apoptosis. This iron-dependent, lipid peroxidation-driven cell death represents one of several active, regulated processes that participate in multi-organ dysfunction, rather than a solitary or definitive mechanism. As detailed in the present review, the activation of specific signaling axes, most notably the Hippo-YAP-ACSL4 pathway, provides a plausible molecular link between heat stress into lethal lipid remodeling and cellular disintegration. The paradoxical role of the heat shock response, which can transition from a protective mechanism to a pro-ferroptotic trigger and the systemic collapse of antioxidant defenses, including the Nrf2 and FSP1 systems, may contribute to an environment that facilitates ferroptosis. The organ-specific evidence, from rhabdomyolysis and cardiac contractile dysfunction to acute kidney injury and potential neurological damage, suggests that ferroptosis acts as one convergent pathway among multiple injury mechanisms in diverse tissues.

The therapeutic implications of these findings are promising but require rigorous validation. Preclinical studies have demonstrated that a diverse array of ferroptosis inhibitors, including iron chelators such as DFO, radical-trapping antioxidants such as Fer-1, ACSL4 inhibitors and GPX4-enhancing strategies, can confer protective effects in animal models. However, these results should be interpreted cautiously: The translation from rodent models to human heatstroke remains uncertain, optimal dosing, timing and patient selection are undefined and clinical safety data are lacking. Ferroptosis-targeted therapy in heatstroke should therefore be regarded as a hypothesis-driven strategy requiring prospective clinical investigation rather than an established treatment modality.

However, the translation of this exciting preclinical promise into clinical reality is fraught with challenges and limitations, a number of which are inherent to the current state of research. A significant constraint is the heavy reliance on animal models, which may not fully recapitulate the complexity of human heatstroke, especially in vulnerable populations such as the elderly. The clinical data for ferroptosis in human heatstroke patients remain scarce, and the field urgently lacks validated, readily measurable biomarkers for real-time monitoring of ferroptosis activity in patients to guide therapy. Furthermore, practical hurdles concerning the pharmacokinetics of first-generation ferroptosis inhibitors, such as the poor stability and bioavailability of Fer-1, must be overcome through advanced drug formulation technologies such as nanocarrier systems.

Looking ahead, future research must be directed along several promising avenues. First, large-scale prospective clinical studies are imperative to dynamically monitor established and novel ferroptosis biomarkers (such as lipid peroxidation products, ferritin and GPX4 activity) and correlate them with disease severity and outcomes. Second, concerted efforts should focus on optimizing the delivery, stability and therapeutic window of ferroptosis inhibitors and exploring their efficacy in combination with other cell death pathway inhibitors or anti-inflammatory agents. Third, research should expand beyond the currently studied organs to investigate the role of ferroptosis in heatstroke-associated lung and gastrointestinal injury. Finally, the utilization of multi-omics technologies and sophisticated large-animal models will be crucial for validating targets and accelerating the development of effective, targeted therapies. In summary, while challenges

remain, the strategic inhibition of ferroptosis opens a new and highly promising frontier in the fight against heatstroke, with the potential to markedly alter its devastating clinical course and improve patient survival and long-term recovery.

Based on the evidence reviewed in the present study, the following concrete research gaps require attention: i) Temporal trajectories: No prospective studies have established the dynamic kinetics of ferroptosis markers (ACSL4, MDA and GSH/GSSG) in heatstroke patients during the first 72 h; ii) Compartment-specific evidence: Tissue-level ferroptosis has never been demonstrated in human renal tubules, brain endothelium, or intestinal epithelium during heatstroke; all evidence is from serum/blood or animal models; iii) Cooling-ferroptosis interaction: It remains unknown whether rapid cooling directly modulates ferroptosis pathways (such as by reducing ACSL4 activity or restoring GPX4 function) beyond simply lowering core temperature; iv) Drug-cooling interactions: No studies have evaluated whether ferroptosis inhibitors (Fer-1, DFO) interact with standard cooling strategies or vasopressor resuscitation; v) Organ-specific therapeutic windows: Whether different organs have different windows for ferroptosis intervention is unknown. Addressing these gaps will be essential for translating preclinical findings into clinical practice.

**Acknowledgements**

Not applicable.

**Funding**

The present study was supported by the National Natural Science Foundation of China (grant no. 82472241) and Peking Union Medical College Hospital Medical Foundation-Rui E Special Foundation for Emergency Medicine Research (grant no. PUMF01010010-2024-03).

**Availability of data and materials**

Not applicable.

**Authors' contributions**

HG and YC collected relevant literature and drafted manuscripts. HG and RY reviewed and made significant revisions to the manuscript. TZ and YC prepared figures and tables. YS and RY guided the preparation of this manuscript. All authors read and approved the final manuscript. Data authentication is not applicable

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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