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Ferroptosis in Critical Illness Myopathy and Ventilator-Induced Diaphragm Dysfunction: Mechanisms, Evidence Gaps, and Translational Perspectives

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ABSTRACT: ICU-acquired weakness, lengthy mechanical ventilation, difficult weaning from respiratory support, and delayed functional recovery can be largely attributed to critical illness myopathy (CIM) and ventilator-induced diaphragm dysfunction (VIDD). Ferroptosis is an iron-dependent form of regulated cell death driven by phospholipid peroxidation and failure of lipid-peroxide detoxification. This narrative review critically evaluates whether ferroptosis may contribute to CIM and VIDD and distinguishes direct evidence from mechanistic extrapolation. Core ferroptosis mechanisms include expansion of the labile iron pool, NCOA4-mediated ferritinophagy, impairment of the system xc⁻/glutathione/glutathione peroxidase 4 (GPX4) axis, ACSL4-dependent enrichment of oxidizable polyunsaturated phospholipids, and failure of complementary antioxidant systems such as FSP1-coenzyme Q. Critical illness and mechanical ventilation generate several ferroptosis-permissive conditions, including inflammation, altered iron handling, mitochondrial dysfunction, disuse, and oxidative stress. Nevertheless, direct causal evidence in human CIM and VIDD remains insufficient, and commonly used oxidative-stress markers are not specific for ferroptosis. The strongest future studies will combine tissue-specific iron and lipid-peroxidation measures, GPX4/SLC7A11/ACSL4/NCOA4-associated signatures, objective muscle-function outcomes, multi-omics profiling, and mechanistically informative rescue experiments. Ferroptosis should therefore be regarded as an emerging and testable contributor to critical-illness-associated muscle dysfunction rather than an established dominant mechanism.

1. INTRODUCTION

Critical illness myopathy (CIM) and ventilator-induced diaphragm dysfunction (VIDD) are clinically important components of intensive care unit-acquired weakness. CIM is characterized by diffuse weakness, reduced muscle excitability, preferential myosin loss, and variable muscle-fiber necrosis, whereas VIDD refers to the rapid loss of diaphragm force and mass associated with mechanical ventilation [1-7,29,31]. Skeletal and respiratory muscle dysfunction can develop early during critical illness and is associated with prolonged ventilation, longer hospitalization, impaired physical recovery, and adverse clinical outcomes [1-4,29].

Inflammation, immobilization, corticosteroid exposure, hyperglycemia, mitochondrial dysfunction, oxidative stress, and activation of ubiquitin-proteasome and autophagy-lysosome pathways are established contributors to CIM and VIDD [1,4-7,21,29,31]. Nevertheless, these mechanisms do not fully explain the heterogeneity or speed of muscle injury. Ferroptosis, first defined in 2012, is a regulated cell-death process caused by iron-dependent phospholipid peroxidation [8-10]. Its core biology intersects with several abnormalities found in critical illness, including disturbed iron homeostasis, antioxidant depletion, mitochondrial stress, and inflammatory signaling. Recent reviews of ferroptosis in critical illness and skeletal-muscle disease further support the biological plausibility of this intersection while emphasizing the continuing lack of direct human validation [28,30].

This narrative review synthesizes current evidence linking ferroptosis to CIM and VIDD, distinguishes direct evidence from mechanistic inference, and identifies priorities for experimental and clinical translation. Because the literature is emerging and heterogeneous, the purpose is hypothesis refinement and critical evidence mapping rather than quantitative estimation of effect.

2. LITERATURE SEARCH STRATEGY

A targeted PubMed/MEDLINE literature search was updated through 17 August 2026 to identify relevant clinical, experimental, and review literature. Search concepts were combined around “ferroptosis,” “critical illness myopathy,” “ICU-acquired weakness,” “ventilator-induced diaphragm dysfunction,” “mechanical ventilation,” “skeletal muscle,” “diaphragm,” “GPX4,” “SLC7A11,” “ACSL4,” “NCOA4,” “lipid peroxidation,” and “iron metabolism.” Reference lists of key mechanistic and clinical reviews were also used to identify foundational studies. Because direct ferroptosis studies in CIM and VIDD remain sparse, mechanistically relevant evidence from skeletal-muscle aging, muscular dystrophy, critical-illness biology, and diaphragm-disuse models was included when it informed biological plausibility or experimental design. Priority was given to primary studies, authoritative mechanistic reviews, and recent critical-care literature. The search was intentionally narrative rather than systematic; no meta-analysis or formal risk-of-bias assessment was performed. Reporting was structured to emphasize transparent literature sourcing, scientific reasoning, and evidence limitations in line with principles used to assess narrative reviews [33].

3. CORE MOLECULAR MECHANISMS OF FERROPTOSIS

3.1 Iron handling and initiation of lipid oxidation

The labile iron pool supplies redox-active ferrous iron that can amplify reactive oxygen species and lipid-radical formation. Increased iron uptake, impaired ferritin storage, reduced iron export, or ferritinophagy can expand this pool and lower the threshold for ferroptosis [8-10,17]. Iron is necessary but not sufficient: ferroptosis also requires oxidizable membrane phospholipids and inadequate detoxification of lipid hydroperoxides.

3.2 System xc⁻, glutathione, and GPX4

The system xc⁻ transporter supports cystine uptake and glutathione synthesis. GPX4 uses glutathione to reduce phospholipid hydroperoxides to non-toxic alcohols. Pharmacologic or genetic impairment of this axis permits lipid-peroxide accumulation and ferroptotic membrane damage [11,12]. Selenium is required for efficient GPX4 biosynthesis and activity, which provides a mechanistic basis for investigating selenium status in critical illness, but not for assuming clinical benefit from supplementation [26].

3.3 ACSL4-dependent phospholipid remodeling

ACSL4 and associated phospholipid-remodeling enzymes enrich membranes with arachidonic- and adrenic-acid-containing phospholipids that are susceptible to oxidation [13,14]. The abundance and localization of these substrates influence cellular ferroptosis sensitivity. This mechanism is particularly relevant to metabolically active muscle membranes and mitochondria, although muscle-specific mapping remains incomplete.

3.4 GPX4-independent protection

FSP1 suppresses ferroptosis by regenerating reduced coenzyme Q at cellular membranes, thereby trapping lipid radicals independently of GPX4 [15,16]. Additional defense systems, including mitochondrial dihydroorotate dehydrogenase and tetrahydrobiopterin pathways, further illustrate that ferroptosis sensitivity is controlled by overlapping antioxidant networks [10].

3.5 Relationship to other injury pathways

Ferroptosis can coexist or interact with apoptosis, necroptosis, autophagy, inflammation, and mitochondrial dysfunction. Ferritinophagy can increase redox-active iron, whereas inflammatory and metabolic stress may reduce antioxidant capacity [9,10,17]. In complex syndromes such as critical illness, a single cell-death label is therefore unlikely to explain all tissue injury.

3.6 Ferritinophagy, NCOA4, and supportive molecular readouts

NCOA4 is a selective cargo receptor for ferritinophagy, the autophagic delivery of ferritin to lysosomes for degradation and iron release [32]. Increased ferritinophagic flux can expand the bioavailable iron pool and thereby lower the threshold for iron-dependent lipid peroxidation. NCOA4 is therefore a mechanistically relevant candidate marker when ferroptosis is investigated in muscle. PTGS2 (COX-2) is also frequently increased in ferroptosis-associated experimental settings, but neither PTGS2 expression nor NCOA4 abundance alone is diagnostic of ferroptosis. These readouts should be interpreted together with labile iron, GPX4/SLC7A11 activity, ACSL4-associated lipid remodeling, oxidized phospholipids, compatible ultrastructural changes, and functional rescue [8-10,30,32].

4. FERROPTOSIS AND CRITICAL ILLNESS MYOPATHY

4.1 Established pathology of CIM

CIM develops in the context of severe systemic illness and is associated with myosin loss, reduced membrane excitability, altered calcium handling, mitochondrial dysfunction, and accelerated protein breakdown [1,4,21]. These abnormalities can produce profound weakness even when overt muscle necrosis is limited. Consequently, evidence of oxidative stress alone should not be interpreted as proof of ferroptosis.

4.2 Why critical illness may create a ferroptosis-permissive state

Systemic inflammation can alter hepcidin signaling and iron distribution, while organ dysfunction, transfusion, nutritional deficits, and oxidative stress may further disturb iron and antioxidant homeostasis. Mitochondrial dysfunction in CIM can increase redox stress and impair ATP-dependent repair [21]. Together, these changes provide a plausible environment for iron-dependent lipid peroxidation, but direct measurements of labile iron, oxidized phospholipids, GPX4 activity, and ferroptosis rescue in human CIM are still lacking [28].

4.3 Evidence from skeletal-muscle models

Experimental evidence supports ferroptosis in selected skeletal-muscle disorders. In a senescence-accelerated mouse model, aged muscle showed iron accumulation, lipid-peroxidation markers, reduced antioxidant capacity, and changes in the p53-SLC7A11 axis; ferroptosis inhibitors reduced injury in cultured muscle cells [18]. Iron overload and impaired iron handling have also been linked to dystrophic muscle pathology [19], and age-related muscle iron dysregulation has been increasingly recognized [20]. A recent synthesis of skeletal-muscle ferroptosis highlights convergent roles for iron handling, lipid remodeling, GPX4/FSP1-centered antioxidant defense, and organelle stress across multiple muscle disorders [30]. These observations strengthen biological plausibility but should not be treated as direct evidence for acute CIM, which has a distinct systemic and temporal context.

4.4 Interpretation of the current evidence

At present, ferroptosis should be considered a candidate amplifier of CIM rather than an established primary mechanism. Convincing demonstration would require a temporally coherent combination of iron dysregulation, phospholipid peroxidation, loss of ferroptosis-defense activity, compatible ultrastructural changes, and rescue by mechanistically distinct ferroptosis inhibitors without equivalent rescue by apoptosis or necroptosis inhibitors [8-10].

5. FERROPTOSIS AND VENTILATOR-INDUCED DIAPHRAGM DYSFUNCTION

5.1 Established mechanisms of VIDD

Mechanical ventilation can produce diaphragm weakness within hours to days. Human biopsy data demonstrate rapid diaphragm-fiber atrophy during controlled ventilation [22]. Oxidative stress, mitochondrial dysfunction, calcium dysregulation, calpain activation, autophagy, and ubiquitin-proteasome signaling contribute to reduced contractile function and protein loss

[5-7,23-25]. Contemporary critical appraisal further emphasizes that diaphragm dysfunction in critical illness reflects an interaction between ventilation-associated unloading or injurious effort and the systemic biology of critical illness, rather than a single uniform mechanism [31].

5.2 Mechanistic overlap with ferroptosis

VIDD includes several conditions that could facilitate ferroptosis: diaphragm inactivity, mitochondrial redox imbalance, membrane lipid oxidation, and potentially altered iron handling. However, commonly measured markers such as malondialdehyde, 4-hydroxynonenal, or total reactive oxygen species are not specific for ferroptosis. Direct VIDD studies demonstrating ACSL4-dependent phospholipid oxidation, GPX4 loss, labile iron expansion, and pharmacologic rescue by ferrostatin-1 or liproxstatin-1 are sparse.

5.3 Ventilation mode and diaphragm activity

Controlled ventilation generally causes greater diaphragm inactivity than assisted modes, whereas excessive inspiratory effort can also injure the diaphragm. The clinically relevant goal is therefore diaphragm-protective ventilation that avoids both over-assistance and under-assistance [5]. Any relationship between ventilation mode and ferroptosis remains hypothetical until mode-specific ferroptosis biomarkers are measured alongside diaphragm force and histology.

5.4 Regeneration and satellite cells

Muscle regeneration depends on satellite-cell survival, activation, and differentiation. Iron overload and lipid peroxidation can impair myogenic differentiation in experimental systems [18], providing a potential link between ferroptosis and impaired diaphragm repair. Direct evidence in diaphragm satellite cells from mechanically ventilated patients is not yet available.

6. SHARED AND DISTINCT FEATURES IN CIM AND VIDD

Table 1. Evidence framework for ferroptosis in CIM and VIDD

Domain	CIM	VIDD	Current interpretation
Iron dysregulation	Plausible in systemic inflammation; direct muscle measurements limited	Diaphragm-specific iron data limited	Supportive context, not diagnostic
Lipid peroxidation	Oxidative injury documented; ferroptosis-specific phospholipids rarely measured	Oxidative stress is established; specificity for ferroptosis is uncertain	Requires targeted lipidomics
GPX4/system xc ⁻	Limited direct human data	Limited direct human data	Priority biomarkers for future studies
Functional rescue	No established CIM clinical trials	No established VIDD clinical trials	Preclinical intervention studies required
Clinical certainty	Hypothesis-generating	Hypothesis-generating	Causality not yet established
NCOA4/ferritinophagy	Mechanistically plausible; direct CIM tissue data scarce	Direct diaphragm data scarce	Candidate iron-mobilization pathway; requires multimarker validation
Multi-omics signatures	Not yet established as a validated CIM signature	Not yet established as a validated VIDD signature	High-priority discovery and cross-tissue validation approach

CIM and VIDD share inflammation, disuse, oxidative stress, mitochondrial dysfunction, and rapid loss of muscle performance. Their initiating contexts differ: CIM reflects systemic critical-illness biology across peripheral and respiratory muscles, whereas

VIDD is specifically linked to ventilation-associated diaphragm loading and inactivity. These differences may influence iron handling, lipid composition, and the relative contribution of ferroptosis. The current evidence does not support assuming that the same ferroptosis pathway predominates in both conditions.

7. THERAPEUTIC IMPLICATIONS

7.1 Iron chelation

Iron chelators can suppress ferroptosis in experimental systems by reducing redox-active iron. In critically ill patients, however, iron is essential for erythropoiesis, mitochondrial enzymes, and immune function. Chelation could worsen anemia, infection risk, or organ dysfunction. Clinical use should therefore not be proposed without evidence of tissue iron excess and a favorable risk-benefit profile [17,28].

7.2 Radical-trapping antioxidants

Ferrostatin-1 and liproxstatin-1 are valuable experimental tools because they interrupt lipid-radical propagation. They are not established treatments for CIM or VIDD. Vitamin E and coenzyme Q-related antioxidant systems are biologically relevant to ferroptosis control, but broad antioxidant supplementation has not been shown to specifically prevent critical-illness muscle weakness [27].

7.3 GPX4-supporting strategies and selenium

Selenium supports GPX4 synthesis [26]. Because selenium deficiency can occur in critical illness, biomarker-guided correction is biologically reasonable; nevertheless, selenium supplementation cannot be described as a GPX4 activator with proven efficacy against CIM or VIDD. Dose, timing, baseline status, and toxicity require careful evaluation.

7.4 N-acetylcysteine and glutathione restoration

N-acetylcysteine (NAC) replenishes cysteine availability and supports glutathione synthesis, providing a biologically plausible means of strengthening glutathione-dependent antioxidant defense and limiting lipid-peroxide accumulation. Its relevance to ferroptosis is therefore mechanistically plausible, particularly where glutathione depletion contributes to impaired GPX4 function. However, NAC is a broad thiol antioxidant rather than a ferroptosis-specific inhibitor. Any protection of skeletal or diaphragm muscle by NAC should therefore be interpreted as evidence of redox modulation unless it is accompanied by a coherent ferroptosis signature and comparison with more mechanistically specific rescue strategies such as radical-trapping ferroptosis inhibitors [8-10,28,30].

7.5 Ventilation and rehabilitation strategies

The most clinically actionable approaches remain prevention of excessive diaphragm inactivity, avoidance of injurious respiratory effort, early mobilization when feasible, and optimization of nutrition and metabolic control [1,5]. These strategies may indirectly reduce ferroptosis-permissive stress, but their benefits should not be attributed to ferroptosis without specific mechanistic evidence.

8. RESEARCH PRIORITIES

Future studies should: (1) define tissue-specific ferroptosis signatures using labile-iron assays, targeted oxidized-phospholipid profiling, GPX4 activity, GSH/GSSG, SLC7A11, ACSL4, NCOA4, and complementary ultrastructural assessment; (2) pair molecular biomarkers with objective muscle outcomes such as diaphragm force, twitch pressure, electrophysiology, and muscle-fiber cross-sectional area; (3) use mechanistically distinct pharmacological and, where feasible, genetic rescue designs to distinguish ferroptosis from apoptosis, necroptosis, and nonspecific oxidative injury; (4) directly compare peripheral skeletal muscle and diaphragm within the same critical-illness model; (5) integrate transcriptomic and proteomic profiling to identify convergent ferroptosis-related pathways and candidate biomarkers across tissues and interventions; and (6) validate the most robust signatures in prospectively collected human tissue or minimally invasive biomarker studies. Single-cell and spatial approaches may further clarify which myofiber, immune, endothelial, or satellite-cell populations are most susceptible.

9. LIMITATIONS

This narrative review has important limitations. First, direct experimental evidence of ferroptosis in CIM and VIDD is scarce; much of the argument is extrapolated from aging muscle, muscular dystrophy, non-muscle critical-illness models, and general ferroptosis biology. Second, no universally accepted clinical biomarker panel distinguishes ferroptosis from other oxidative or necrotic processes. Third, the targeted narrative search was not a registered systematic review, did not use formal study-level risk-of-bias assessment, and may therefore be vulnerable to selection bias. Fourth, this article contains no original participants or experimental dataset; sample-size calculation and inferential statistical testing were not applicable. Finally, rapid evolution of the ferroptosis and critical-care literature means that mechanistic interpretations should be updated as tissue-specific human and intervention data become available. These limitations restrict causal interpretation and generalizability.

10. CONCLUSION

Ferroptosis is a biologically plausible contributor to critical-illness-associated muscle dysfunction because iron dysregulation, impaired antioxidant defense, phospholipid peroxidation, ferritinophagy, and mitochondrial stress intersect with established biology of CIM and VIDD. However, mechanistic overlap is not equivalent to causal proof, and direct evidence in human CIM and VIDD remains insufficient. The field now requires tissue-specific, multimarker studies that connect molecular ferroptosis signatures to objective muscle dysfunction and demonstrate mechanistically informative rescue. Comparative analysis of peripheral skeletal muscle and diaphragm, supported by integrated transcriptomic and proteomic profiling, may be particularly informative. Until such evidence is available, ferroptosis should be framed as an emerging mechanistic hypothesis and potential therapeutic target rather than a confirmed dominant pathway or a basis for routine ferroptosis-modulating therapy in critically ill patients.

GRAPHICAL ABSTRACT

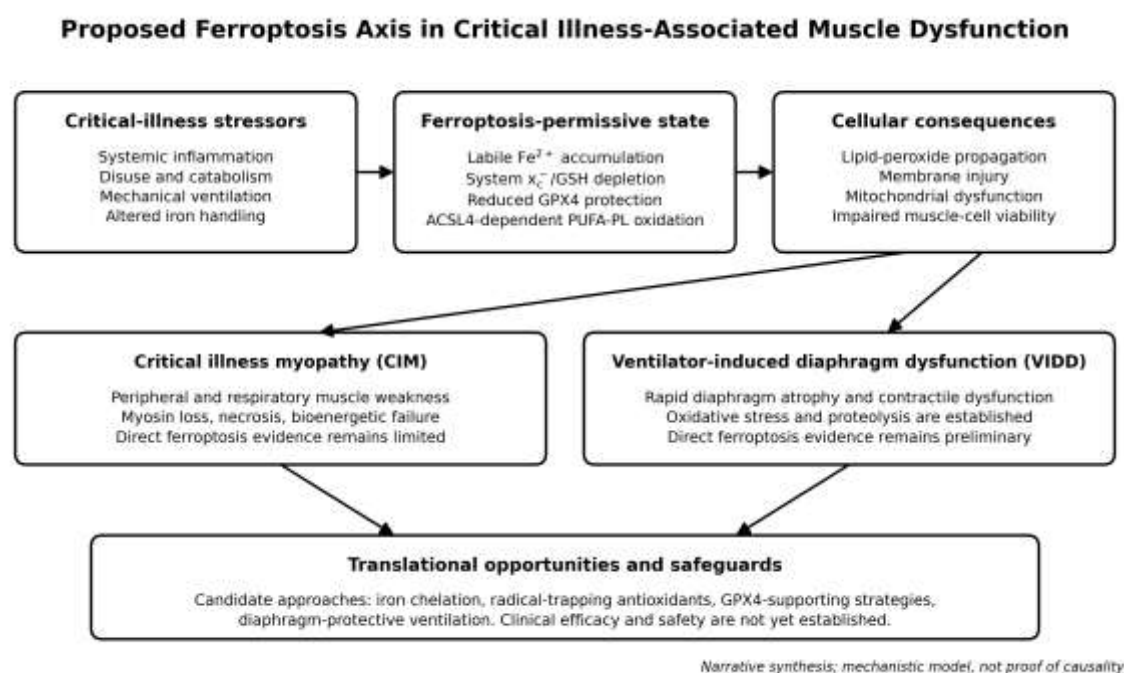


Figure 1. Proposed ferroptosis axis in critical illness-associated muscle dysfunction. Critical-illness stressors may create a ferroptosis-permissive state through altered iron handling, reduced system x_c^- /GSH/GPX4 protection, and oxidation of ACSL4-enriched polyunsaturated phospholipids. Lipid-peroxide propagation may then aggravate membrane and mitochondrial injury in CIM and VIDD. Solid arrows indicate the proposed sequence synthesized from current evidence; the diagram does not establish causality. CIM, critical illness myopathy; VIDD, ventilator-induced diaphragm dysfunction; GSH, glutathione; GPX4, glutathione peroxidase 4; ACSL4, acyl-CoA synthetase long-chain family member 4; PUFA-PL, polyunsaturated fatty-acid-containing phospholipid.

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AUTHOR CONTRIBUTIONS

Qian Zheng: Conceptualization, Methodology, Investigation, Visualization, Writing – Original Draft, Writing – Review & Editing.

Sarisak Soontornchai: Supervision, Validation, Writing – Review & Editing.

Somchai Bovornkitti: Supervision, Validation, Writing – Review & Editing.

Ya Wen: Supervision, Validation, Writing – Review & Editing.

All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest. Ya Wen is affiliated with San Biomedical Technology Co. Ltd.; the company had no role in the design, literature review, interpretation, writing, or decision to publish this manuscript.

ETHICS STATEMENT

Not applicable. This narrative review did not involve human participants, human tissue, or animal experiments performed by the authors.

Consent for publication: Not applicable.

DATA AVAILABILITY STATEMENT

No new datasets were generated or analyzed for this narrative review. The evidence summarized in this article is available in the published studies cited in the reference list. Articles indexed in PubMed can be accessed through the National Library of Medicine database, subject to the access conditions of the original publishers.

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